**In Vitro Fertilization (IVF)**

This document is a part of your informed consent process. Both partners should read the entire document carefully.

In vitro fertilization (IVF) is a treatment for infertility which was first used in the 1970’s to assist couples facing infertility to achieve a pregnancy. It is now a common, successful therapy which is used worldwide.

These are the steps that occur in a natural pregnancy:

- The woman releases an egg (ovulates) on a monthly basis
- After intercourse, the sperm travels through the womb (uterus) into the Fallopian tube
- The egg is fertilized by the sperm in the Fallopian tube
- The fertilized egg (embryo) then moves into the uterus and attaches to the wall of the uterus (implantation)

A problem with any of these steps can lead to difficulty conceiving a pregnancy. IVF can help to treat many of these problems. Sometimes after fertility testing, there is still no explanation for the fertility problem. IVF can help to overcome infertility, even if there is no obvious reason.

**When might IVF be an appropriate treatment?**

IVF may be a good option for the following conditions:

- Blocked Fallopian tubes
- Low sperm numbers or motility
- Infrequent or absent ovulation
- Endometriosis
- Unexplained infertility
- Age-related infertility
- Failure of other fertility treatments such as IUI
What are the steps in the IVF process?

IVF helps to overcome fertility problems by giving medications to the woman to produce many eggs. The eggs are then removed from the ovary and fertilized in the laboratory with the sperm. The healthiest fertilized egg(s), or “embryo(s)” is then put back into the woman’s uterus.

IVF treatment involves the following steps:

1) **Suppression of the menstrual cycle**
   - The birth control pill is often given to suppress the woman’s own hormones so that the body is ready for the stimulation of the ovaries.

2) **Stimulation of the ovaries**
   - The goal of ovarian stimulation is for the woman to produce several mature eggs during the IVF cycle.
   - This is achieved taking a daily injection of follicle stimulating hormone or FSH (e.g. Gonal-F™). This is similar to the hormone the body makes each month to signal the ovary to produce a mature egg, however higher doses are given with the goal of several mature eggs developing.
   - This stage of treatment usually lasts 10-14 days. During this time, close monitoring with blood tests and vaginal ultrasounds is required. The first 5 days of treatment do not require close monitoring but after this time, testing will be done every 1-2 days to monitor progress.
   - The blood tests monitor the estradiol levels. This is the hormone produced by the ovary as it responds to the medication.
   - The ultrasound monitors the development of the lining of the uterus and ovarian follicles. The follicles are the fluid filled sacs in the ovary which contain the developing egg.
   - Frequent adjustments to the dose of medication may be required during this time.
   - Once the follicles reach a certain size, an injection (hCG or Suprefact™) will be taken to trigger the final maturation of the eggs.

3) **Inhibition of ovulation**
   - It is important to prevent ovulation from occurring during IVF. This process is called “down-regulation”. This is achieved by taking an injectable medication during ovarian stimulation called a GnRH antagonist (Cetrotide™, Orgalutron™)
   - This medication is generally started around the 6th day of ovarian stimulation and taken on a daily basis, between 10 and 11 am, until the last day of ovarian stimulation.
4) Egg retrieval

° Egg retrieval is performed 35-36 hours after the hCG injection.
° An intravenous line is started and medications are given for pain control.
° A transvaginal ultrasound probe is placed in the vagina.
° A thin, hollow needle is then passed through the top of the vagina into the follicles under ultrasound guidance. The fluid is suctioned out of the follicles and then examined under a microscope by the embryologist to identify and count the eggs.
° Very rarely, no eggs are found.
° The egg retrieval is performed by one of the physicians with the assistance of a nurse.
° The partner is encouraged to be present in the room during the egg retrieval.
° While the procedure itself is not painless, every attempt is made to ensure your comfort. The degree of discomfort varies between individuals.
° The egg retrieval takes approximately 10-15 minutes. Usually you will go home approximately 2 hours after the procedure.

5) Fertilization

° Following the egg retrieval, the male partner will be asked to produce a semen sample. The semen is then prepared to separate the healthy, moving sperm. If you are using frozen sperm, the sample will be thawed at this time.
° There are 2 methods of fertilization (IVF and ICSI). Your physician will recommend a method of fertilization based on your history and test results.
° In vitro fertilization (IVF) – If in vitro fertilization is recommended, the prepared sperm and the egg are incubated together overnight. The following day, the eggs are examined for evidence of fertilization.
° If ICSI (intracytoplasmic sperm injection) is recommended, the sperm and eggs are prepared. The embryologist then chooses a healthy looking sperm and injects it into the egg.
With both methods, fertilization occurs in approximately 75% of the eggs. Rarely, fertilization is absent or very poor.

The embryos are left to grow for a total of 3-5 days to allow early development to occur so that the healthiest embryo(s) can be placed in the uterus.

6) Luteal phase support

After the egg retrieval, you will begin taking vaginal capsules, tablets or gel which contains progesterone (Prometrium™, Crinone™). This mimics the hormonal changes that naturally occur after ovulation to prepare the uterus for the arrival of an embryo.

This is continued until 10 weeks if you are pregnant.

7) Embryo transfer

On the 3rd or 5th day after the egg retrieval, the embryo transfer is performed.

The procedure is relatively quick and painless. A speculum is placed in the vagina (like when you have a Pap test). A soft, narrow catheter is then placed in the uterus and the embryo(s) is gently transferred in to the uterine cavity.

The number of embryos transferred depends on a number of factors which will be discussed with you, but depends mainly on the woman’s age:

- < Age 35  1-2 embryos
- Age 36-37  1-2 embryos
- Age 35-39  2 embryos
- > Age 39  2-3 embryos

Embryos that are not transferred will be allowed to develop until the 5th-6th day. If they appear to be developing well, they will be frozen (cryopreserved) for future use.

Two weeks after the embryo transfer, a sensitive blood pregnancy test will be performed and if it is positive, an ultrasound will be arranged 2-3 weeks later to confirm a healthy pregnancy.

Intracytoplasmic Sperm Injection (ICSI)

Normally with IVF about 60,000 sperm are placed with each egg in a fertilizing dish. Usually about 70-80% of the eggs will fertilize normally. However, in men with low sperm count, motility, or morphology (abnormal looking sperm), the chance that the eggs will fertilize is much lower.
Intracytoplasmic sperm injection (ICSI) is a laboratory procedure developed to help infertile couples undergoing IVF for severe male factor infertility. It involves the injection of a single sperm directly into the cytoplasm of a mature egg. Only mature eggs can be injected. Usually about 75-80% of eggs are mature at the time of retrieval. Fertilization occurs in approximately 75% of injected eggs. After the ICSI procedure, embryo culture and development is the same as with IVF. There is a small chance that the ICSI procedure may damage the egg, resulting in lack of fertilization or embryo development. Lack of fertilization may also be due to either sperm or egg abnormalities that cannot be identified under the microscope. Sperm for ICSI can be obtained from ejaculation, percutaneous epididymal sperm aspiration (PESA), or testicular sperm aspiration (TESA).

When is ICSI recommended?

- Very low numbers of motile sperm
- Very abnormal looking sperm (abnormal morphology)
- High levels of antisperm antibodies
- Prior or repeated fertilization failure with standard IVF
- Frozen sperm limited in number and quality
- Obstruction of the male reproductive tract – sperm obtained by PESA or TESA
Advantages and Disadvantages of Intracytoplasmic Sperm Injection

ICSI allows some infertile couples the possibility of achieving a pregnancy that they would otherwise not have had. Before ICSI, severe male factor infertility was seldom treated successfully and the only alternatives were donor insemination or adoption.

Disadvantages of ICSI are the additional cost, and the invasive nature of the procedure. About 10-15% of severe male factor infertility is known to be related to genetic abnormalities. Some of these men may also have an increased chance of being a genetic carrier for cystic fibrosis. Genetic testing for some men and their partners may be recommended prior to undertaking this procedure.

Early research on infants born after IVF/ICSI suggests a slight increased risk of some chromosomal abnormalities, particularly sex chromosomal abnormalities. For this reason, couples conceiving a pregnancy through ICSI should discuss the option of prenatal testing (e.g. amniocentesis) with their physician. Male infants may be at risk for future fertility problems, similar to their father. Couples wishing to proceed with IVF/ICSI accept these small risks.

Alternatives to ICSI

ICSI is a complex procedure requiring the female partner to undergo a full IVF cycle. Some couples with severe male factor infertility may prefer the alternatives of donor insemination or adoption. Couples with a short duration of infertility may decide to continue to try to conceive on their own for a period of time before enrolling in the IVF/ICSI program.

Assisted Embryo Hatching (AH)

At least 90% of patients that start the IVF process will have an embryo transfer. Unfortunately even in the best IVF programs, many of the transferred embryos do not implant. This has resulted in a great deal of research into methods to improve the implantation rate. One of these methods is assisted embryo hatching (AH).

What is assisted embryo hatching?

The developing embryo is surrounded by a soft shell called the zona pellucida (ZP). The embryo must hatch out of this shell before it can implant, similar to a chick hatching out of an egg. Certain circumstances may be associated with excessive hardening or thickening of this shell. The AH procedure involves partial zona dissection (PZD). On the day of embryo transfer, a slit is made in the zona using a dissection needle. This creates a weakness in the zona, which makes hatching easier.
Indications for assisted embryo hatching

Assisted embryo hatching is not required for all embryos. It can only be performed on day 3 embryos. Your physician will discuss if AH should be considered in your situation based on the following possible indications:

- Frozen day 3 embryo transfer (FET) – the process of embryo freezing and thawing may thicken the zona pellucida, therefore it is recommended that all couples undergoing day 3 FET consider AH.
- Maternal age >38
- Elevated day 3 FSH level
- Previous unsuccessful IVF cycle with good quality embryos
- Embryos with thickened ZP under the microscope

Advantages of Embryo Hatching

Embryos that undergo assisted hatching show a small increase in implantation rate, therefore increasing the chance of a successful pregnancy.

Disadvantages of Assisted Embryo Hatching

There is a very small chance that the procedure may cause damage to the developing embryo. There is no guarantee that embryos that have undergone assisted hatching will implant. There are a few reports of a small increased incidence of monozygotic twinning (identical twins) associated with AH.

Risks of IVF

- **Medication side effects** - Exaggeration of symptoms that frequently occur during the menstrual cycle, such as feeling of heaviness or bloating in the pelvis, mood changes, headaches, breast tenderness, and decrease in energy level may occur.

- **Ovarian Hyperstimulation Syndrome (OHSS)** - Gonadotropin medications stimulate the ovaries to mature and produce eggs. At the same time the ovaries increase in size, and this may cause abdominal or pelvic discomfort. After the treatment cycle the ovaries will return to their normal size after a few weeks. In approximately 3-5% of cycles an exaggerated reaction called Ovarian Hyperstimulation Syndrome (OHSS) occurs. OHSS results in ovarian enlargement. Blood vessels around the ovaries become “leaky” causing fluid to collect in the abdominal and/or chest cavities. These symptoms may require close observation and/or hospital care. OHSS symptoms tend to last longer if the cycle has resulted in a pregnancy. Most of the cases of OHSS
can be managed by rest, plenty of fluids and mild pain relievers. Ovarian twisting (torsion) is another very rare complication associated with severe OHSS. The enlarged ovary, by twisting, cuts off its own blood supply, and this may require emergency surgery for removal of the ovary.

° **Multiple pregnancy** - Twin pregnancies occur in 1-2% of naturally-conceived pregnancies. Women conceiving with IVF have a 20-25% chance of having a multiple pregnancy, the vast majority of which are twins. Triplets or higher order pregnancies can occur, but are much less frequent; only 1-3% of pregnancies.

The only way to reduce the chance of a multiple pregnancy is to limit the number of embryos transferred back to the uterus. In most women ≤ age 37, there is little difference in the chance of pregnancy when 1 vs. 2 embryos are transferred; however the chance of a multiple pregnancy increases dramatically when more than 1 embryo is replaced.

While many couples who have been struggling with infertility may welcome the opportunity to have more than one baby at a time, it is important to realize that twins are a high risk pregnancy, and triplets or higher are extremely high risk for both mother and babies.

**Risks to babies/children from a multiple pregnancy include:**

° Preterm delivery (70% of twins, 96% of triplets)
° 5 times higher risk of cerebral palsy
° Lung, eye and bowel disease
° Learning difficulties
° Stillbirth or death shortly after birth

**Risks to the mother from a multiple pregnancy include:**

° Diabetes in pregnancy
° High blood pressure in pregnancy
° Higher chance of requiring a caesarean section

° **Ectopic pregnancy** - Ectopic pregnancies are pregnancies that develop outside the usual location in the uterus, usually in the fallopian tube. While ectopic pregnancies occur in 1% to 2% of spontaneous pregnancies, in IVF cycles the rate may be slightly increased. This type of pregnancy is abnormal and cannot result in the delivery of a baby. The greatest concern is that if left untreated, the tube may burst resulting in severe, life-threatening bleeding in the abdomen.
Ectopic pregnancies can be treated with medications or surgery. Rarely, a tubal pregnancy occurs at the same time as an intrauterine pregnancy; this condition is known as heterotopic pregnancy and may be difficult to diagnose.

- **Birth defects** - Until recently, it was felt that the chance with IVF/ICSI of having a baby with a birth defect was the same as if the baby was conceived naturally: 2-3% for major defects, and 5-6% for minor defects. Recent research however, suggests a possible increased risk (up to 8%) of birth defects in babies conceived through IVF/ICSI. It is not clear whether the possible increased risk is due to the IVF procedures, the medications used, or if it is related to the population (i.e. infertile couples) being studied. This research is not conclusive, and many other studies are ongoing that will eventually give us more information.

- **Premature birth and lower birth weight babies** - There appears to be a slight increased chance that a baby conceived through IVF/ICSI will be born prematurely, or may have a lower birthweight. This is especially true for multiple pregnancies (twins, triplets, etc.), but also applies to singleton (one baby) pregnancies. It is therefore important for the physician caring for your pregnancy to know that you conceived with IVF.

- **Fertility drugs and the risk of ovarian cancer** - Nulliparity (i.e. never having had a baby) increases the chance of developing ovarian cancer, while pregnancy and use of the birth control pill decreases the risk. At present, there is no conclusive evidence that fertility drugs (gonadotropins) increase the risk of ovarian cancer.

- **Cycle cancellation** - Each woman responds differently to ovarian stimulation. Sometimes the response is too fast or too strong, and the physician supervising the cycle may feel that it is better to stop the medications to avoid excessive risk, particularly of OHSS. Likewise, sometimes the response to medications is less than expected, and the physician may recommend cancelling the cycle, or converting it to a superovulation/intrauterine insemination (IUI) cycle, if appropriate.

- **Risks of egg retrieval** - This procedure has a very low rate of complications. As with any other procedure, there is a very small risk of infection. Antibiotics are given to you and your partner prior to the procedure in order to minimize any risk. There is a risk of bleeding at the site of vaginal puncture, which is usually promptly stopped with local pressure. There is also a small risk of internal bleeding which may necessitate surgery. There is a chance of a reaction to the sedatives or pain medications.

**Elective single embryo transfer (eSET)**

Elective single embryo transfer (eSET) is a new technique being used to reduce the risk of conceiving a multiple pregnancy following IVF treatment. It has been shown that in couples who have the best chances of achieving a pregnancy, the chance of pregnancy is similar when either 1 or 2 embryos are transferred. In order to maximize the chance of a pregnancy, the embryos are evaluated on the third day of development. If the embryo quality on day 3
is good, they will be allowed to develop in the lab until day 5 when they reach the blastocyst stage. This allows the selection of the healthiest embryo and improves the chance of pregnancy. Any remaining normal embryos will be frozen for future use. Most, but not all, couples will have extra embryos to freeze.

**Good candidates for eSET are:**

- < 38 years old
- Are attempting IVF/ICSI for the 1st or 2nd time
- Have at least 4 good quality embryos on day 3 of development

Your physician will discuss eSET with you further during treatment.

**Embryo Freezing (Cryopreservation) and Storage**

Embryo freezing and storage (cryopreservation) consists of placing embryos at a very low temperature and storing them for prolonged periods in liquid nitrogen. During freezing, chemical solutions (cryoprotectants) replace water, protecting embryos from damage by ice formation. When embryos are thawed, water replaces cryoprotectants.

**Why are embryos frozen?** - To avoid an excessively high risk of multiple pregnancies, only 1 or 2 embryos are placed into the uterus during an In vitro fertilization (IVF) cycle. However, it is quite possible that there more healthy embryos are available. In this case embryo freezing is an option, since the frozen embryos can be thawed and transferred to the uterus at a later date. Embryos must meet certain criteria with respect to quality to be frozen. Not every couple will have excess embryos to freeze.

**At what stage are embryos frozen?** - Embryos can be frozen at either the 6-8 cell stage (day 3) or blastocyst stage (day 5 or 6). In our clinic, most embryos are frozen as blastocysts.

**Advantages of embryo freezing** - Without the option of embryo freezing, excess embryos cannot be stored for prolonged periods, and must be either placed into the uterus (transferred) or discarded. Embryo freezing provides an alternative to discarding excess embryos. Frozen embryos can be thawed and transferred following minimal preparation with medications, and without ovarian stimulation. There is no evidence that the freeze-thaw process will increase the probability of having an abnormal child. Birth defects (major or minor) occur in 4-6% of the general population.

**Disadvantages of embryo freezing** - The embryos may not survive the freeze–thaw process. Each cycle of cryopreserved embryo transfer represents both a new opportunity for conceiving, or another source of disappointment if no pregnancy occurs. The chance of pregnancy is about half that of a fresh IVF cycle. Initially, partners might be in complete agreement about embryo freezing and storage, but later they may disagree on what to do with the embryos. It is important for you to discuss these issues ahead of time.
How long will embryos be frozen? - Embryos will be stored for as long as you wish. You will be required to pay a yearly storage fee. Each year you will be given the option to continue storing the embryos. If you do not wish to store the embryos any longer, you will be given the option to discard the embryos or to donate the embryos to the lab for education or research.

What happens if the couple wants the frozen embryos discarded? - The embryos will be discarded after both partners provide a signed written authorization.

What happens in the event of separation or divorce? - The embryos that are cryopreserved are intended for use as a couple. In the event that a couple separates or divorces and remaining frozen embryos are in storage, it is recommended that each partner notify the physician immediately. Frozen embryos will remain in storage until the couple reaches a mutual decision about their disposition.

What happens in the event of death? - If both partners die while the embryos are in storage, the embryos will be discarded immediately. The couple must decide prior to treatment the disposition of the remaining embryos, in the event that one partner dies. This must be included in your will.

What happens if the storage fee for the embryos is not paid regularly? - It is your responsibility to maintain the yearly storage fees. You must contact the clinic with your new contact information if you move. If you have not received the yearly invoice, you should contact the clinic. If there is an outstanding payment, we will make every effort to contact you, but if neither partner can be found, or if the storage fee is not received, the embryos will be discarded.

Emotional aspects of Infertility - Infertility can be very stressful for couples. Hope and anticipation alternate with disappointment and despair. Men and women experience these emotions in different ways, which can often lead to more stress. It is important to prepare yourself for the possibility of both a successful, and an unsuccessful outcome. If you are struggling with the emotional stress of infertility, please do not hesitate to discuss this with one of the physicians or nurses. We help you to access professional counselling services.