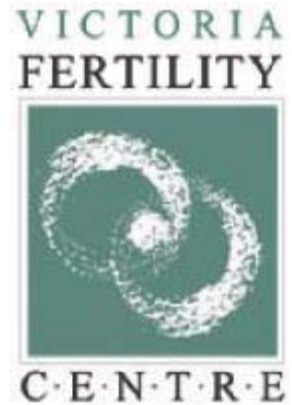


InfoSheet: IN VITRO FERTILIZATION (IVF)



In-Vitro Fertilization, or IVF, is a process designed to help women achieve pregnancy. There may be many reasons why a couple are unable to become pregnant, and a thorough investigation of both partners is appropriate before making any decisions about treatment.

The first baby born through IVF was Louise Brown, through the pioneering efforts of Drs Steptoe and Edwards, in 1978. Originally, IVF was designed to help women with tubal disease, but today IVF is able to help couples with many different problems achieve a healthy pregnancy.

Before explaining IVF it is important to have a basic understanding of the female menstrual cycle.

The Normal Menstrual Cycle

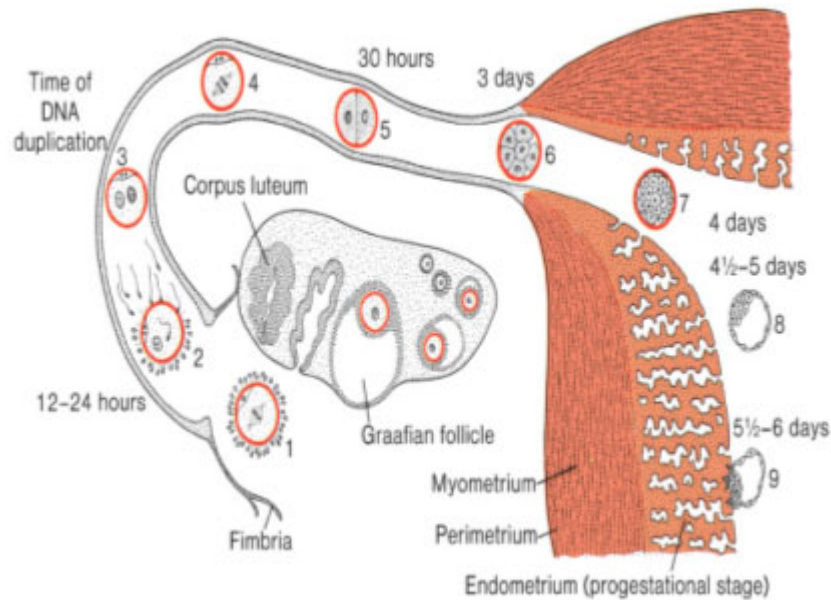
Women are born with a finite number of eggs. The ovaries are not like the testes in men. The testes are like sperm factories that continue to make fresh sperm all the time. The ovaries are more like "banks" of eggs. The ovaries are not autonomous (self-regulating), and need to be stimulated to function.

The ovaries are controlled by a hormone called FSH (follicle stimulating hormone) produced in the brain. At the start of each menstrual cycle the brain releases FSH and, in response, a number of eggs are "recruited" or withdrawn from the "bank". These eggs start maturing and each egg grows in a capsule of fluid called a follicle. A follicle is, in fact, a small cyst. Although many many eggs start on this journey, within a couple of days most will die and disappear, and only one or two will continue to grow and mature.

As the follicles grow they release a hormone called estradiol (estrogen). When the egg is almost mature, the rising estrogen level signals the brain to release a hormone called luteinizing hormone (LH). This hormone triggers ovulation, and it can be detected in a woman's urine the day before she will ovulate. LH is the hormone that is detected by ovulation predictor kits.

Around the time of ovulation, the rising estrogen levels act on the mucus at the cervix, making it stringy – like the white of an egg. Normally the cervical mucus is thick, and is designed to prevent any bacteria from getting in to the uterus from the vagina. The estrogen makes the mucus sperm-friendly so that the sperm are able to penetrate through the mucus and get into the uterus and then on to the fallopian tubes.

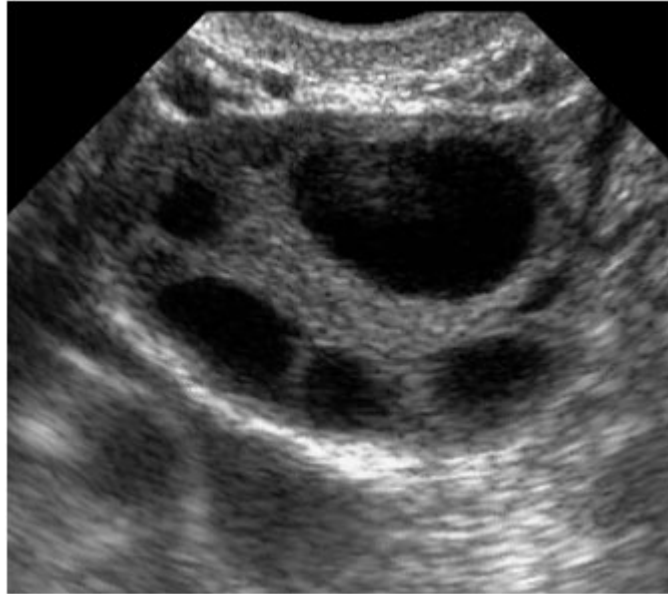
After ovulation the egg is picked up by the many tiny finger-like structures at the end of the fallopian tube called fimbria. A sperm will then fertilize the egg in the upper part of the tube. A fertilized egg is called a zygote and then, once it starts to divide, an embryo. The early embryo spends 3–5 days in the tube before it reaching the uterus where it will then implant in the uterine lining (the endometrium) and begins to grow.



What Happens in an IVF Cycle

During IVF you are given medications which manipulate your ovaries and the eggs being produced. The idea is to try and get several eggs to mature, not just one or two. The follicles where the eggs are developing can be monitored by ultrasound and by measuring your estrogen levels.

ULTRASOUND IMAGE OF OVARY CONTAINING FOLLICLES



When the eggs are mature, they are taken from the ovaries (using a fine needle which is passed through the vagina under ultrasound guidance) and handed to the embryologist. The eggs are then fertilized with your partner's sperm (or, in some instances, donor sperm).

The fertilized eggs (embryos) are then cultured under very strict conditions and examined each day by the embryologist to assess their progress. On the third day the embryos are assessed by the embryologist and a meeting is then held to discuss them. At this meeting we decide how many to replace inside the uterus (by a second procedure called an embryo transfer).

Sometimes more than one embryo will be transferred, and sometimes the other good quality embryos will be suitable for freezing for your later use. Our aim is to enhance the chances of pregnancy but limit the risk of multiple pregnancies.

Multiple Pregnancies

Although most couples are happy to accept a risk of twins, it is important to know that even twins carry significant risks (e.g. premature delivery, developmental abnormalities, toxæmia, gestational diabetes, etc, etc). So although in most cases the outcome with twins is good there are significantly increased risks of problems over "singletons".

Higher order multiple pregnancies such as triplets and quads carry extremely high risks – and we do everything we can to avoid these. If a pregnancy does occur with triplets or more we would encourage you to consider a selective reduction. This is a procedure done at 10–11 weeks' gestation, whereby the

number of fetuses is reduced to twins. It is like an amniocentesis, and does carry a risk – about 5 % – that the whole pregnancy could be miscarried. Ideally we try and avoid this scenario, which is upsetting to everyone.

Preparation for an IVF Cycle

In order to optimize results we recommend that you pay particular attention to both your physical and mental health both before and during the treatment phases. Both men and women are advised to stop smoking and drinking alcohol prior to treatment. We also recommend that women stop all caffeine as soon as they start medication and stay off it until the first pregnancy test. If pregnancy occurs we recommend no caffeine until 12 weeks' gestation.

Optimal weight is very important, and being underweight or overweight can adversely influence the success of a cycle. The ideal body mass index (BMI) is between 20 and 25, and a BMI over 30 will both significantly reduce the chances of conception and increase the chance of miscarriage.

It is recommended that all women considering pregnancy take a prenatal supplement containing folic acid for at least a month or more before pregnancy, and then throughout the pregnancy. Materna is a popular prenatal vitamin. Folic acid has been shown to reduce the incidence of spina bifida and the ideal amount of folic that should be taken daily is 1 mg. Women in certain high-risk groups may need a higher dose to achieve the same protection. These include:

- Women who are overweight
- Diabetics
- Women who have had a child with spinal bifida, or who have a relative with spinal bifida
- Certain racial groups including Sikhs and women from some European countries such as Wales
- Women who take anti-epileptic drugs

These groups of women are recommended to take 4 mg of folic acid daily. You might be taking prescription drugs. Please make sure that you have discussed these with VFC before starting IVF treatment.

It is important to keep physically fit, although we would recommend that you moderate your exercise before an IVF cycle.

The Treatment Cycle - What to Expect

Although what follows is a "typical" approach – every treatment is individualized and this is therefore just an example.

Step 1

- History, physical examination, blood tests, sperm functional assessment, pelvic ultrasound
- Possibly hysteroscopy/laparoscopy
- Consultation with our reproductive psychologist
- Setting an individually-designed treatment plan
- Clinical orientation at VFC (with one of our Clinical Co-coordinators) to explain your treatment plan and make sure that you understand how to give injections and take medications

Step 2

- You maybe asked to take the birth control pill (the "Pill") for approximately 3 weeks. This suppresses the ovaries and the uterine lining (puts them to sleep). It also suppresses other hormones which in certain circumstances has a positive effect on outcome
- While on the Pill you will be asked to come to VFC for a Mock Embryo Transfer. You will be given an instruction sheet about this process. The reason for the Mock Embryo Transfer is to check that there will not be any problems transferring the very delicate embryos into your uterus.

Step 3

- After being on the Pill for 2 weeks, you will be started on a drug called a GnRH analogue. The commonly-used ones, Suprefact and Lupron, are given by injection once a day, preferably in the morning. This drug suppresses the pituitary gland in the brain, which prevents it releasing FSH and LH. This means that we can take complete control of the ovaries and uterus without any interference from the brain
- After being on the GnRH analogue for 7–10 days, you will be asked to stop the Pill – but you will continue to take the GnRH analogue. After stopping the Pill you will have a bleed (this is the lining of the uterus shedding).
- You will then have an ultrasound to check that the ovaries are "suppressed", i.e. that there are no follicular cysts on them. You will also have a blood test to check your estradiol level
- If everything looks good you will be ready to start the stimulation phase of your cycle

Step 4: Stimulation Phase (ovulation induction)

- You will continue with your GnRH analogue, aspirin and prenatal supplement
- You will be started on injections of gonadotrophins, FSH and LH, to stimulate your ovaries. The names of the commonly used drugs are: Gonal F, Puregon and Repronex (although there are others). During your orientation session you will have been taught how to mix and inject these hormones
- After approximately 7 days of stimulation you will have an estradiol (blood test) and ultrasound. The dosage of your gonadotrophin drugs might be adjusted at this stage

Step 5: The Follicles Are Ready

- When the follicles reach a certain size and your estradiol levels are right you will be ready for “triggering”. At this stage you will be asked to stop the GnRH analogue and FSH/LH (gonadotrophin) injections. You will be told then when to have an injection of another drug called hCG (trade names are Profasi or Pregnyl). The hCG “matures” the eggs and makes them ready for retrieval
- You will also be asked to start taking an antibiotic called Doxycycline. You will take this twice a day until the day of your embryo transfer taking the last dose of Doxycycline that evening.
- Your egg retrieval will be scheduled for exactly 36 hours after this injection

Step 6: Egg Retrieval

- You will be asked to do the following the day before your egg retrieval:
 1. Have a normal supper the night before retrieval, but nothing to eat after midnight
 2. Continue to take the antibiotics as directed.
 3. On arrival, you will be asked to empty your bladder and change into a nightgown
 4. You will then be given acupuncture for half an hour. This helps you relax, and also helps control the discomfort during the egg retrieval
 5. After the acupuncture you will be introduced to the RN (Registered Nurse) who will assist with your procedure. The RN will take you through to the Procedure Room, an intravenous line will be started, and you will be hooked up to an ECG and Oxygen Saturation Monitor
 6. Your legs will then be positioned in stirrups – just like when you have a Pap smear
 7. A speculum will be introduced in to the vagina so that it can be cleaned thoroughly with sterile saline. Local anesthetic is then injected in to the vagina wall

8. During this time you will be given some medications called Fentanyl and Midazolam to control discomfort. These drugs will make you feel drowsy and relaxed. You will also be given an intravenous antibiotic to reduce the risk of infection
9. A vaginal ultrasound probe is then inserted into the vagina. A needle is passed alongside the probe, through the vagina wall into the ovaries, and the follicles are aspirated and their fluid collected in test tubes. The fluid is immediately examined by our embryologist. The eggs are identified, placed in culture medium and stored in an incubator. This whole procedure takes about 15 minutes
10. At the end of the procedure the probe is removed and you will rest until you are ready to go through to the Recovery Room. There you will rest until you feel ready to go home. During this time you will be offered a drink and some cookies
11. You will need to be escorted home by your partner or a friend. You must not drive for 24 hours after egg retrieval
12. After your egg retrieval, unless you are using frozen/donor sperm, your partner will be asked to produce a fresh semen sample at VFC
13. The sperm are then washed and prepared in the laboratory by our embryologist
14. The eggs are then inseminated either by mixing the sperm and eggs together (standard IVF) or by ICSI (ICSI stands for Intracytoplasmic sperm injection and involves injecting a single sperm into each egg). ICSI is performed only if we have concerns about the sperm and their ability to fertilize an egg. In either case, fertilization actually occurs several hours later
15. After egg retrieval you will be asked to start your progesterone to prepare the uterine lining for the embryo transfer which will take place on the third day after the egg retrieval. Progesterone is usually given in one of two ways:
 - a. Prometrium: This comes in 100mg tablets which are inserted into the vagina. The usual dose is 200 mg (2 tablets) 3 times daily
 - b. Progesterone in oil: This is given by intra-muscular ("IM") injection, the usual dose is 50 mg per day. These injections might need to be given at VFC – or by your family doctor – daily

Step 7: The Short Wait....

This is the 3-day period between egg retrieval and embryo transfer.

- The day after egg retrieval you will be telephoned to tell you how many eggs have fertilized. The fertilized eggs (zygotes) are cultured under carefully controlled conditions for 3 days. Zygotes should divide into 2 cells

later on the first day and are then called embryos. On the morning of the second day the embryos should have 4 cells each, and 8 cells by the morning of the third day

- During these three days you may do everyday activities – but you will be asked to refrain from
 - Intercourse
 - Swimming or hot tubs
 - Coffee and alcohol
- You should continue with your prenatal vitamins. You should continue with the progesterone preparation until told otherwise

Step 8: Day 3 – The Embryo Transfer

- On the day of embryo transfer you will be asked to come to VFC at the specified time
- You should drink 2 glasses of water an hour before your transfer – ideally we would like your bladder to be half full but not uncomfortable
- We will discuss the embryos, their quality and confirm how many to transfer and freeze
- You will be shown to the Procedure Room, and given acupuncture for 30 minutes
- An ultrasound will then be done to check how full your bladder is
- When ready, your legs will again be placed in some stirrups, a speculum introduced into the vagina and the cervix cleaned with saline
- With an ultrasound probe on your tummy a fine catheter will then be passed through your cervix and the embryo(s) injected in to the uterus
- You will then be asked to lie quietly for at least 20 to 30 minutes
- After this you will be allowed to go home. You should rest quietly for the rest of the day – but don't worry, the embryos won't fall out

Step 9: The Long Wait....

This is the 12-day wait between your embryo transfer and the expected date of your next period (which hopefully won't come for many months!).

- You will be instructed to continue with the progesterone and prenatal vitamins – and any other medications that might be necessary
- You will be given a requisition to have a pregnancy test on a specified date. During this time we would encourage you to:
 - Avoid intercourse
 - Restrict exercise to everyday activities only
 - Get lots of rest
 - Think positively!!!

Expectations

It is important to be well-informed and have realistic expectations. Some important points are:

- Not every follicle contains an egg. So, if for example 10 follicles were identified by ultrasound prior to retrieval, it would be realistic to hope for 5 – 7 eggs
- The number and quality of eggs can also be predicted to some extent by the levels of estradiol
- Not every egg is good quality – so not every egg fertilizes. We expect a fertilization rate of about 80%
- Not every fertilized egg develops into a perfect embryo
- On Day 3 our embryologist assesses the embryos according to very strict criteria to help us decide which embryos to choose for transfer
- Not every embryo that is not transferred is suitable for freezing. Poorer quality embryos are unlikely to survive freezing and thawing – and may be discarded
- The table below gives some idea of IVF/ICSI cycles for average patients

Table: An example of the outcome from an IVF cycle. These may vary significantly, and there are not always embryos available to freeze.

Follicles	Eggs collected	Mature eggs	Eggs fertilized	Quality embryos	Embryos transferred	Embryos frozen
○						
○						
○						
○	⦿					
○	⦿	⦿				
○	⦿	⦿	⦿			
○	⦿	⦿	⦿			
○	⦿	⦿	⦿	⦿		
○	⦿	⦿	⦿	⦿	⦿	
○	⦿	⦿	⦿	⦿	⦿	⦿

Schematic Summary of an IVF Cycle

Birth control pill for 2 weeks

–

Add Suprefact – and continue the Pill – for 1 week

–
Stop the Pill – continue Suprefact
Expect vaginal bleed – continue Suprefact only
–
Ultrasound and estradiol (blood test)
If satisfactory, start HMG (Gonal F, Puregon, Repronex)
–
After 7 days of HMG, repeat ultrasound and estradiol
Further monitoring until follicles are “ready”
Trigger with hCG (Profasi or Pregnyl)
–
Egg retrieval – Fertilization – Embryo culture
–
Embryo transfer
–
Pregnancy test

Risks and Possible Complications Related to Superovulation and IVF/ICSI

1. Cancelled Cycles

A cycle might be cancelled for a variety of reasons, the most common of which are either an under- or over-response to the fertility drugs. We do our best to predict the ovaries' likely responses to the fertility drugs, and choose a dosage that is most appropriate to your individual characteristics. The ovaries are assessed pre-IVF by doing a Day 3 FSH level, and by examining them using ultrasound. Your weight and age are also important considerations.

Older women, elevated FSH levels, and previous poor response to stimulation are all factors that may predict a poor response to these medications. In these situations, a protocol will be selected to try and get the most from your ovaries. However, sometimes there is such a poor response that the cycle has to be abandoned.

On the other hand, sometimes the ovaries over-respond. Women at risk for this are those with polycystic ovarian syndrome (PCOS), and women who are overweight and not menstruating regularly.

One of the potential complications from over-responding is a condition called ovarian hyper-stimulation syndrome (OHSS). This is a potentially dangerous condition that results from the estrogen levels being too high. This causes the membranes between fluid compartments in your body to become too permeable, resulting in

fluid leaking into body cavities such as the peritoneal cavity (abdomen) and the pleural spaces (chest, around the lungs). OHSS also tends to result in the fluid volume in your blood vessels (the “intravascular volume”) falling, leading to a hypercoagulable state – in other words, you may be more prone to blood clots and stroke.

There are several ways to identify this condition (OHSS), and precautions that can be taken to prevent serious complications. If, during the stimulation phase of the cycle, too many follicles start growing, and the estrogen levels get too high, different options become available. This situation usually only becomes dangerous if the hCG is given, or if pregnancy occurs. The different options include:

- Coasting – stopping the FSH drugs and waiting for the estrogen levels to come down before giving hCG.
 - Retrieving and fertilizing the eggs, but then freezing all the embryos for later use; so that pregnancy will not occur until the ovaries and estrogen levels have had a chance to settle down.
 - Cancelling the cycle completely.
- Common symptoms associated with OHSS include bloating, nausea, abdominal pain, shortness of breath, vomiting and low urine output. Many cases are mild and respond to simple measures such as fluid manipulations.

2. Surgical Complications from the Egg Retrieval

Potential complications from this procedure include the following:

- Internal bleeding
- Infection
- Damage to internal organs such as the bladder, bowel or ureters

These are all very uncommon.

3. Ovarian Complications

After IVF the ovaries become swollen and tender. They can be very uncomfortable and can occasionally twist or bleed. Very rarely it might be necessary to do a surgical procedure to untwist them or stop them bleeding.

4. Multiple Pregnancy

It is our duty to do the very best to achieve pregnancy while also

reducing the risk of multiple pregnancy. Even twins carry significant risks, some of which are listed below:

- Increased social or domestic stress with child raising.
- Increased chance of premature delivery, with all the associated risks such as cerebral palsy, learning disorders, low birth weight, congenital anomalies, etc.
- Increased pregnancy risks, such as toxæmia (high blood pressure), gestational diabetes, anaemia, operative delivery, miscarriage, post-partum bleeding, etc.

Some of the ways to reduce the risks of a multiple pregnancy include:

- Limiting the number of embryos transferred
- Transferring only one embryo
- Selective reduction

5. **Long-term Risks of Cancer**

There have been concerns raised over the years that there might be long-term cancer risks associated with the use of fertility drugs.

One study in Washington State revealed that an unusual number of women with cancer had used a fertility drug called Clomiphene. However, subsequent studies that have been done are more, reassuring. There are many other factors that might be associated with an increased risk of ovarian cancer, one of which is infertility itself.

Recently, some studies have suggested a possible increase in the risk of breast cancer associated with the use of FSH (e.g. Gonal F, Puregon, Repronex), although once again the findings across all relevant studies are inconclusive.

At this present time the Cochrane review does not support an association between IVF, Fertility drugs and breast or ovarian cancer.

The bottom line is that there may be a risk, and these drugs should be used responsibly, on each occasion maximizing the chance of a pregnancy so as to reduce long-term (repeated) exposure.

6. **Risks of IVF and ICSI to Children**

So far, the studies done looking at children born after IVF and ICSI have been very reassuring. There is some evidence that children born after IVF/ICSI might have a slightly lower birth weight than children conceived naturally.

Recent evidence suggests that there might be a slightly higher risk of congenital abnormalities in children born after ICSI, but not IVF. It should be remembered that all babies born (i.e. naturally conceived babies) have a 4–6% risk of some form of congenital abnormality. These should not be confused with the genetic problems that increase with maternal age. Common congenital abnormalities include such things as club foot, cleft palate, extra digits, hernias, etc, which are not related to maternal age. However, it must also be remembered that babies born after IVF and ICSI are far more carefully scrutinized than babies conceived naturally.

Nonetheless, it is important that you are aware that there is a likelihood that a male sperm problem, if it is something you were born with, will probably be transmitted to your sons via the Y chromosome.

Having said all this, for the most part, the information available is reassuring.

7. Miscarriage

Miscarriage can occur in up to 10–20% of pregnancies, depending on maternal age. The rate of miscarriage may be higher with IVF/ICSI than in natural conception cycles, although this could be influenced by personal history and health. There may also be an increased risk of ectopic pregnancy, especially if there is a history of damaged fallopian tubes.

Dealing With Bad News – A Failed Cycle or Obtaining Fewer Than Expected Eggs or Embryos

Unfortunately, one has to be realistic about IVF success rates. It is recommended that dealing with a failed cycle be discussed beforehand, and that plans are made for receiving the pregnancy test result on the appointed day. A failed cycle often leave women with feelings of frustration, sadness and even despair. This is why we encourage all our patients at VFC to meet with our reproductive psychologist at the start of a treatment cycle.