

IN-VITRO FERTILISATION (IVF)

What is in-vitro fertilisation (IVF)?

IVF is a process by which eggs are fertilised by sperm outside of the womb (in-vitro). The embryo (fertilised egg) is then transferred into the womb to achieve pregnancy or is cryopreserved (frozen) for future use.

Why do I need IVF?

IVF is a major treatment in infertility when other methods of assisted reproductive technology have failed. IVF is indicated for you if:

1. You have blocked fallopian tubes.
2. Your spouse has male factor infertility, such as low sperm counts.
3. You have endometriosis (presence of the inner lining of the womb in places outside the womb for example in the ovaries or pelvis).
4. You / your spouse have sub-fertility.
5. You have problems with ovulation (release of the egg from the ovary) e.g. in polycystic ovarian disease.
6. You are of advanced maternal age.
7. You wish to conceive using donor sperm.
8. Other indications deemed medically suitable by your doctor

The success rate for pregnancy varies with different couples. The percentage of pregnancies per embryo transfer is around 34 – 42.5% and the live birth rate is about 25 – 31%.

What does it involve?

Prior to IVF, you and your husband would need to undergo screening for infectious diseases. You would also undergo an ultrasound assessment of the pelvic organs, assessment of the cavity of the womb, trial cannulation (insertion of a catheter into the vagina and cervix to find the path into the womb) if necessary, and a mapping of your hormonal profile to assess your ovarian reserve so as to have a gauge of how well you might respond to hormonal medication.

Hormones and other medications may then be administered to increase the number of eggs available for harvesting by stimulating the development of multiple follicles (which contain the eggs) in the ovaries. This process may take 2 to 3 weeks, and regular transvaginal ultrasound scans are performed to assess response to this treatment. On rare occasions where the ovary is deemed unlikely to respond to this, the eggs are harvested based on your natural cycle instead. We refer to this as natural cycle IVF.

The eggs are retrieved by the use of an ultrasound-guided needle, either transvaginally or transabdominally, from follicles in the ovaries. This is an outpatient procedure, where a sedative and painkiller is usually given to make you relax and go into a light sleep. This will last for about half an hour to an hour. Usually, the husband will have to submit a fresh semen sample in person, unless there are stored frozen sperm. The eggs are then incubated with the sperm in a dish in the laboratory to allow natural fertilisation in conventional IVF. Alternatively Intra-Cytoplasmic Sperm Injection (ICSI), which is explained separately in the attached consent form for ICSI, can be performed where a single sperm is injected into the egg to assist in fertilisation. The resulting

embryo(s) is incubated in the laboratory where the embryologists will select the most suitable embryo(s) for transfer.

The embryos may be transferred between Day 2 to blastocyst stage of embryo development depending on the medical team's decision, e.g. by considering the quality and number of embryos available. As the embryos develop from Day 2 to blastocysts, the number of embryos will be reduced. The purpose of culturing the embryos to blastocysts stage is to allow selection of better embryos and may result in the reduction of the number of embryos available. To transfer the embryo to your uterus, the embryo is placed in a catheter which goes through the vagina and the cervix. The Singapore Ministry of Health permits a maximum of 2 embryos to be transferred at any one time, and the process takes about half an hour. Rarely, under special circumstances, 3 embryos may be transferred (e.g. in women at least 37 years of age with poor quality embryos or previous failed IVF cycle). Embryos that implant successfully will result in a pregnancy. If there are any good quality embryo(s) remaining, the patient can choose to have them frozen for future use, donated, or be disposed.

The completion of an IVF cycle varies generally from 4 to 7 weeks. Eggs that are not fertilised and embryos that are not transferred or cryopreserved due to abnormality or poor quality will be disposed.

What precautions must I take for the procedure?

Please inform your doctor if you have any medical illnesses. Before the procedure, please inform your doctor if any of the following are applicable:

1. You have a history of allergy or reaction to any medications, drugs, or food
2. You have a history of bleeding or clotting disorders
3. You are taking drugs (e.g. Aspirin, Clopidogrel, Warfarin, and Rivaroxaban) or supplements (e.g. Cordyceps, Ginkgo Biloba, and Lingzhi), that thin your blood, as these substances may affect blood clotting and increase the risk of bleeding. If you are taking any of these, your doctor will advise you accordingly.
4. Ensure that your medical condition(s), if any, is/are under control.

What are the risks and complications of the procedure?

The IVF cycle may need to be abandoned due to the following reasons:

- 1) Too many follicles developing
There is an approximate 3 – 8% risk that too many follicles may develop. The cycle may need to be abandoned because of risk of developing Ovarian Hyperstimulation Syndrome [OHSS (refer to below)].
- 2) Insufficient follicular development or no oocyte retrieved
Follicular development is unpredictable. The risk of none or insufficient follicular development is around 2%. In such an event, the treatment cycle may have to be abandoned before the eggs can be retrieved. The risk that no eggs are recovered at the point of egg retrieval is about 1%.
- 3) Poor or no fertilisation or poor embryo development
This occurs rarely. If this occurs, the cycle may be abandoned. In some patients, we would offer an ICSI (Intracytoplasmic sperm injection) in a subsequent cycle
- 4) Failure or difficulty in transferring embryos

Embryo transfer could sometimes be difficult or unsuccessful due to anatomical variations. This may require the patient to wait for a fuller bladder, or the doctor to use a stiffer catheter and/or require the doctor to use a tenaculum (instrument to hold the cervix). Sometimes, you may require sedation. Failure to transfer the embryos is extremely rare.

A. Risks and complications associated with hormone stimulation

1) Ovarian Hyperstimulation Syndrome

There is approximately a 1% risk of the patient suffering Ovarian Hyperstimulation Syndrome (OHSS), which may result in kidney failure, deep vein thrombosis (formation of blood clots in the leg veins) and pulmonary embolism (dislodgement of blood clots in the lungs). Pulmonary embolism is potentially life threatening. To minimise the risk of deep vein thrombosis and pulmonary embolism, blood thinning medication may be given if OHSS develops. Sometimes, to avoid the possibility of OHSS, the embryos are frozen and transferred at a later time when the risk of OHSS has resolved.

2) Multiple gestational pregnancy (12 –18% based on number of embryo transferred)

All the embryos transferred may result in successful implantation and hence, multiple gestational pregnancy may occur (pregnancy with twins or more). It is also possible for an embryo to split into two and result in identical twins. This may pose certain risks to the foetus(es) and mother, such as the following:

- Risks to the foetus(es) include increased risk of miscarriage, preterm labour and prematurity, attendant complications which require care in intensive care unit (ICU) such as respiratory distress, brain damage, including loss of life.
- Risks to the mother include higher risks of morning sickness (nausea and vomiting), miscarriage needing a caesarean section, preterm delivery, hypertension, anaemia, and diabetes. The mother will also be at greater risk of social, psychological and financial stress during and after delivery. You are advised to see the Medical Social Worker and/or Psychiatrist if necessary.

3) Adverse drug reaction

Some patients may experience unwanted, uncomfortable, and sometimes dangerous effects from the medications used (adverse drug reaction). Although uncommon, this may necessitate admission to the hospital for further observation or treatment

B. Risks and complications associated with Oocyte Retrieval and Embryo Transfer

1) Bleeding

Due to the nature of the procedure, bleeding could occur. Although uncommon, this may require blood transfusion, hospitalisation for further observation and/or treatment.

2) Infection

Infections following egg retrieval are not common. Severe infection may require hospitalisation for intravenous antibiotics or surgical treatment. This may complicate your reproductive treatment and lower the chances of successful conception.

3) Perforation of the uterine wall

This could occur during the introduction of the catheter when transferring the embryo(s). This may be treated conservatively and/or with an antibiotic course, and hardly ever require surgery.

4) Injury to nearby organs

In the process of egg retrieval from the ovary, the needle may injure nearby organs. Rarely, during embryo transfer, there may be perforation of the uterine wall. This rare complication may require hospitalisation for intravenous antibiotics or surgical treatment.

5) Failure of embryo implantation

Even after the embryo(s) has been transferred, it may fail to implant into the uterus, and hence pregnancy may not occur.

C. Risks and complications inherent in any pregnancy

1) Risks associated with older patients

Pregnancy rate is lower for women above 40 years old and there is a higher risk of developing complications, such as hypertension, diabetes, or delivery requiring caesarean section. For women above 35 years old at the estimated date of delivery, there is also an increased risk of genetic anomalies in the foetus, e.g. having a baby with Down's Syndrome.

2) Risks of ectopic pregnancy, miscarriage and foetal abnormality

There is also a risk of ectopic pregnancy, i.e. pregnancy occurring outside the normal cavity of the uterus (2 – 11%). Compared to natural pregnancies, there is also a higher rate of miscarriage (12 – 30%) and a higher risk of foetal abnormality (5.5%). This is thought to be due to the underlying problems in a subfertile couple rather than the IVF procedure itself.

What can I expect after the procedure?

Usually medical leave is prescribed for approximately two weeks from the date of embryo transfer until the blood pregnancy test is taken. During this time, it is advisable to avoid intercourse or vigorous exercise. However, complete bed rest is discouraged. Hormonal medication will be prescribed to support the pregnancy.

You may experience spotting vaginally before the blood pregnancy test is done. This may be due to the embryo(s) implanting in the womb or impending menses.

What are my options?

1. The option of no treatment.
2. Surgery in endometriosis (the tissue growth beyond or outside the uterus resembling the inner lining of the uterus). Endometriosis is known to cause subfertility and surgery will be to remove cysts in the ovaries or affected tissue. However endometriosis can recur and repeated removal of cysts may reduce remaining ovarian tissue and ovarian reserve.
3. Laparoscopic ovarian drilling, injection to stimulate ovulation, or lifestyle changes to achieve weight loss in some cases of Polycystic Ovarian disease. Polycystic Ovarian disease is a common cause of anovulation (i.e. difficulty with egg release) and usually fertility drugs would have been used as the first line of treatment.
4. Use of donor semen in men who have no or extremely low sperm count in ejaculation or after failed surgical retrieval.
5. Use of donor egg in women who have poor ovarian reserve or response to IVF stimulation.
6. Intrauterine insemination in mild male factor infertility where fallopian tubes are patent.
7. Child adoption when it is deemed the chances of success of IVF are very poor or not acceptable.
8. You can discuss the options in more detail with your doctor.

INTRA-CYTOPLASMIC SPERM INJECTION (ICSI)

What is intra-cytoplasmic sperm injection (ICSI)?

ICSI is an *in vitro* fertilisation procedure in which a single sperm is injected into the cytoplasm (centre) of the egg using a very fine glass needle. This bypasses the natural selection process and the sperm is selected by the embryologist.

Why do I need this procedure?

ICSI is most commonly used to overcome male infertility problems and may be used where:

1. The sperm count is very low
2. The sperm quality is not sufficiently high enough for IVF insemination technique
3. The sperm has been retrieved surgically directly from the epididymis (a coiled tube where sperms are matured) or the testicles, from the urine, or by electro ejaculation
4. There have been previous fertilisation failures or there is low fertilisation rate
5. The sperm tests suggest possible fertilisation problems
6. When only a few eggs are retrieved, ICSI can be used to achieve a higher percentage of fertilised eggs.

What does it involve?

ICSI involves injecting a sperm directly into a harvested egg, therefore allowing the use of sperm that may not otherwise be able to fertilise an egg. ICSI is currently the most effective treatment for sub-fertility, with fertilisation rates of 60 – 70%, depending on the quality of the sperm used.

What precautions must I take for the procedure (ICSI)?

Please inform your doctor if you have any medical illnesses. Before the procedure, please inform your doctor if any of the following are applicable:

1. You have a history of allergy or reaction to any medications, drugs, or food.
2. You have a history of bleeding or clotting disorders.
3. You are taking drugs (e.g. Aspirin, Clopidogrel, Warfarin, and Rivaroxaban) or supplements (e.g. Cordyceps, Ginkgo Biloba, and Lingzhi), that thin your blood, as these substances may affect blood clotting and increase the risk of bleeding. If you are taking any of these, your doctor will advise you accordingly.

What are the risks and complications of the procedure?

Some eggs may not survive the injection process and not all eggs collected will be of a high enough quality or achieve sufficient maturity to be suitable for ICSI.

It has been suggested that certain genetic and developmental defects are linked to babies born from ICSI treatment. These include:

1. The inheritance of sub-fertility due to sex chromosome defects. A small proportion of sub-fertile men have parts of the Y chromosome missing.
2. Couples who have difficulty conceiving may have abnormal numbers or structures of chromosomes. Babies born from ICSI treatment may have a slightly increased risk of inheriting these abnormalities.

3. Chromosomal abnormalities. Gametes (sperms and eggs) that might not have been able to participate in natural fertilisation could be used in ICSI. Babies born after ICSI have been reported to have chromosomal abnormalities in up to 3% of cases. The rate in the general population is around 1%.
4. Possible developmental and birth defects. There is not yet any clear evidence whether ICSI results in higher rates of birth defects. Studies suggest that foetal abnormalities occur in up to 5.9% of ICSI babies, compared to 4.1% in spontaneously conceived babies. For example, one recent study has shown a threefold excess risk in the rate of the relatively rare problem hypospadias (a condition in which the opening of the urethra develops abnormally) following ICSI using sperm from men with severe male factor.
5. Possible lower semen parameters for males born after ICSI.

What are your options?

1. The option of no treatment.
2. Conventional IVF where the eggs are incubated with the sperm in a dish in the laboratory to allow natural fertilisation.

Declaration: IVF and ICSI

1. We have read this information sheet and confirm that we understand the nature, purpose, risks, complications, and alternatives with regard to the following and consent to undergo the following "Procedure" **In-Vitro Fertilisation (IVF) and Intra-Cytoplasmic Sperm Injection (ICSI)**
2. We understand that no more than 2 embryos are transferred at any one time (with the exception of Point 3).
3. We understand that a maximum of 3 embryos (Day 2 or Day 3) may be transferred if the wife fulfils the following conditions:
 - a) the wife is at least 37 years of age AND
 - b) the wife has undergone at least 1 previous failed stimulated assisted reproductive cycle or there is no good quality embryo available
4. We declare that we are still legally married up to the point of embryo transfer and if there is any change in status, we will update the Hospital (the SingHealth institution where the Procedure is performed).
5. We acknowledge that we have had a full discussion and confirm that we understand the nature, purpose, risks and alternatives with regard to the Procedure.
6. We acknowledge that the risks and complication(s) listed are not intended to be exhaustive. We have had an opportunity to ask for more information about (i) the above-mentioned risks and complications; (ii) the risks and complications in general; and (iii) specific concern(s) of relevance to us.
7. We acknowledge that this consent does not assure that an embryo transfer will occur, that the embryo(s) will survive the thawing process or that the thawed embryo(s) will be of sufficient quality to warrant a transfer. We also consent to the Hospital freezing the embryos.
8. We consent to any other treatment and monitoring procedures deemed necessary; and further or alternative procedural measures as may be found to be necessary during the course of the Procedure.
9. We consent to the administration of sedation/anaesthesia as well as the use of drugs and medicines as may be deemed advisable or necessary for this Procedure.
10. We acknowledge that no representation has been made to us that the Procedure will be performed by any particular Medical Practitioner.
11. We hereby consent to undergo the Procedure.
12. We understand that all treatment details and outcome resulting from this Procedure will be notified to the Ministry of Health, Singapore, for the purpose of statistical reporting and research. We consent to the release of such information to the Ministry of Health.
13. We undertake to notify the Hospital of any birth(s) resulting from IVF/ICSI and related procedures within 28 days of delivery).
14. We understand and agree that the Procedure will be performed by the appropriate SingHealth institution and the Patient will be admitted and/or registered as a patient of that SingHealth institution.