
A LITTLE
BOOK ON IVF
MERCK

FOREWORD

There are different routes to parenthood. You might live alone or as a couple, same-sex or different sexes. Depending on the reason for your childlessness you may need treatment involving your own or your partner's eggs or sperm. Sometimes donated eggs or sperm are necessary, or both.

A little book on IVF describes how a method known as IVF (*in vitro fertilisation*) or test tube fertilisation takes place. It also describes insemination and treatment with pre-fertilised eggs, i.e. embryos. The book is aimed at people who have begun or are considering treatment. Anyone who wants to learn more about the different ways to get pregnant can also benefit from the booklet.

IVF is a successful method for treating childlessness regardless of the underlying cause.

This booklet was prepared in collaboration with Dr. Margareta Wood. Stina Järvholm, psychologist at the Department of Reproductive Medicine at Sahlgrenska University Hospital has contributed comments on psychological aspects. The booklet was revised and updated 30/09/2019 by Dr. Britt Friberg, Reproductive Medicine Center, RMC, Malmö and Livio Malmö.

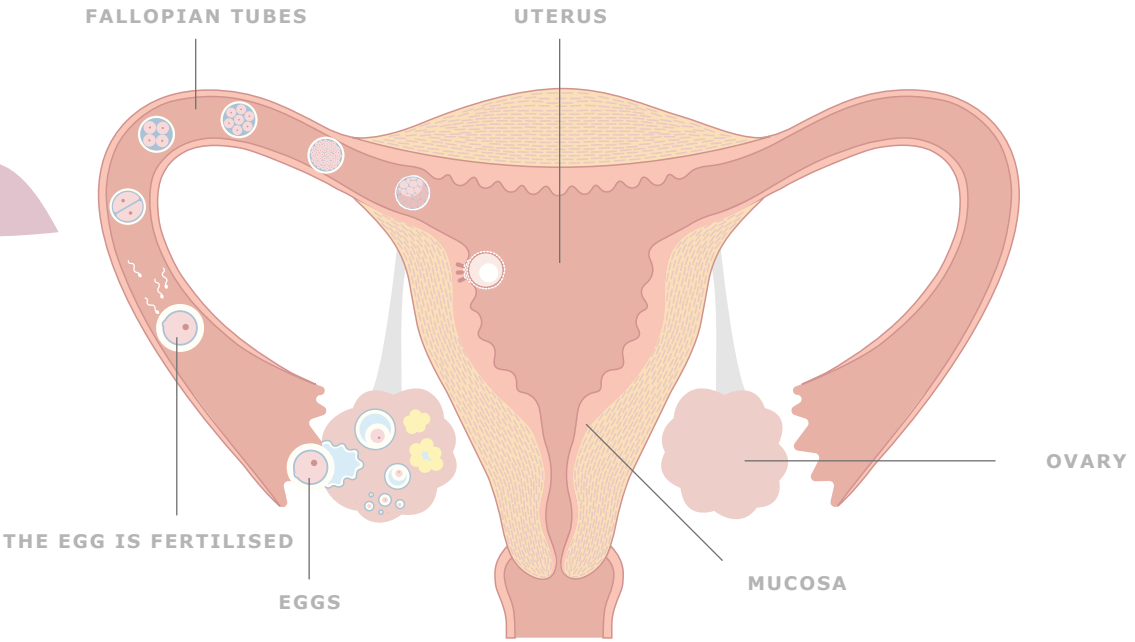
1. BEFORE TREATMENT

When you arrive at the IVF clinic for your first appointment, a doctor, midwife or nurse will talk about and discuss your upcoming treatment. The doctor will talk to you about the results of the examination. Sometimes a an additional examination may be necessary. You also get to discuss any previous treatments, illnesses and current medication. There will be a gynaecological examination of your uterus and ovaries by ultrasound. You can also use this opportunity to ask any questions and talk about your thoughts.

During your appointment, we plan a suitable date for your treatment, and run through the various stages step-by-step with you. It's important to follow the clinic's instructions. Do not hesitate to contact us if anything seems unclear. The more you are confident about a treatment, the better it will be.

In the case of couples, its not unusual for childlessness to have an impact on the relationship. Often, partners can have different needs when discussing infertility.
The situation may also affect their love life, which for a while will be more about reproduction than desire and pleasure.
Many couples also describe how their shared efforts have brought them closer together.

2. WHAT HAPPENS

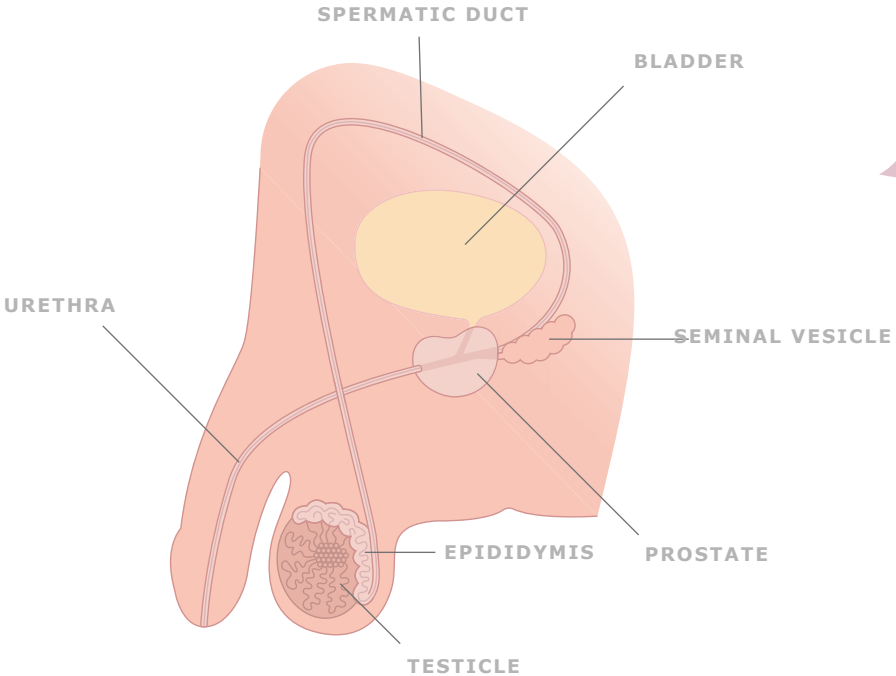


Women usually ovulate once a month

The egg detaches from the ovary and is captured by the fallopian tube. The sperm cell and egg meet in the fallopian tube, where fertilisation takes place

The fertilised egg, the embryo, continues to develop before attaching to the uterine lining after 5-6 days

IN NATURAL CONCEPTION?



Sperm formation takes place in around 70 days in the testicles

The sperm cell are stored and mature in the epididymides

Upon ejaculation, sperm is discharged from the epididymis with a secretion from the prostate and seminal vesicles

3. HORMONE STIMULATION
(FSH STIMULATION)

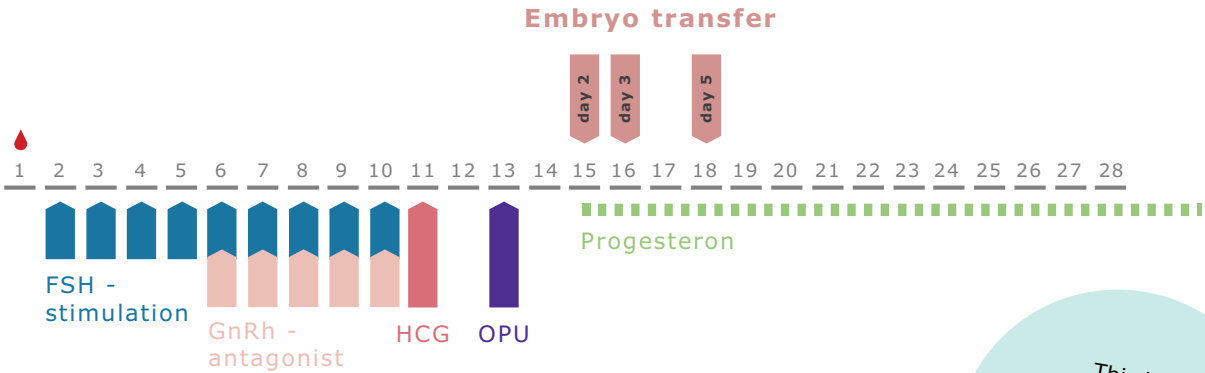
In the natural menstrual cycle, rarely more than one ovarian follicle releases an egg.
In IVF treatment, we want to fertilise several eggs, so we provide hormone stimulation to get more than one ovarian follicle to develop.

It's important that the body's own hormone production does not trigger early ovulation.
We use drugs to regulate the body's signals in different ways to externally control ovarian follicle development. The treatment options are known as the **short** and **long** protocols.

In the **short protocol,** the ovaries are stimulated without prior suppression.
Hormone treatment begins in conjunction with menstruation, and a few days into the treatment, a drug is administered to regulate the body's ovulation signal.
The **long protocol,** uses a pretreatment (suppression) in the form of a nasal spray to put the ovaries into a resting phase. This can be described as a temporary menopause.
The low hormone levels may cause headaches, mood swings and tiredness.
Other symptoms include increased sensitivity to heat and dry mucous membranes.
This inconvenience will diminish once hormone stimulation begins and the ovarian follicles begin to grow.

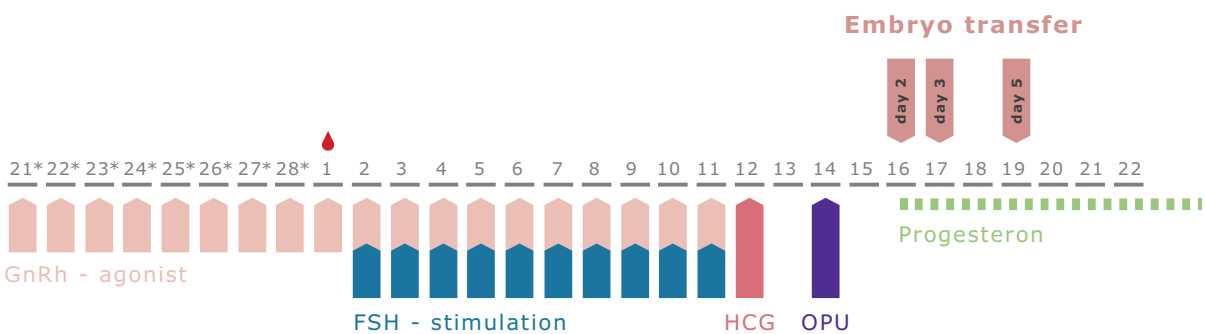
Treatment time for the short protocol is around 2 weeks, and 4-5 weeks for the long protocol.

Short protocol - GnRH antagonist



This is nothing to worry about. The nurse will run through the protocol thoroughly with you.

Long protocol - GnRH agonist



* The number of days until menstruation, which indicates suppression, varies. The start of hormone stimulation following menstruation also varies.

4. STIMULATION & INJECTION TECHNIQUE

The purpose of hormone treatment is to stimulate the ovaries and cause more ovarian follicles to grow to produce mature eggs. The hormone is injected under the skin in the same way diabetics inject insulin. This simple technique is taught in peace and quiet at the clinic. Injections should take place at around the same time every day.

After a few days from the start of hormone injections under the short stimulation protocol, you also begin the injections that prevent ovulation.

In the long protocol, you continue with the nasal spray throughout the hormone treatment.

The stimulation is monitored by ultrasound to see if the given dose of hormone produces growth in the expected number of follicles. The dose and treatment times depend on the individual, as does the number of visits to the clinic. When the ovarian follicles are sufficiently large, a drug is injected to prepare for final egg maturity.

During the latter stage of hormone stimulation, your tummy may feel bloated and tender due to an accumulation of fluid and the size of your ovaries.


After instruction, you can administer your own hormone injections.

5. EGG RETRIEVAL

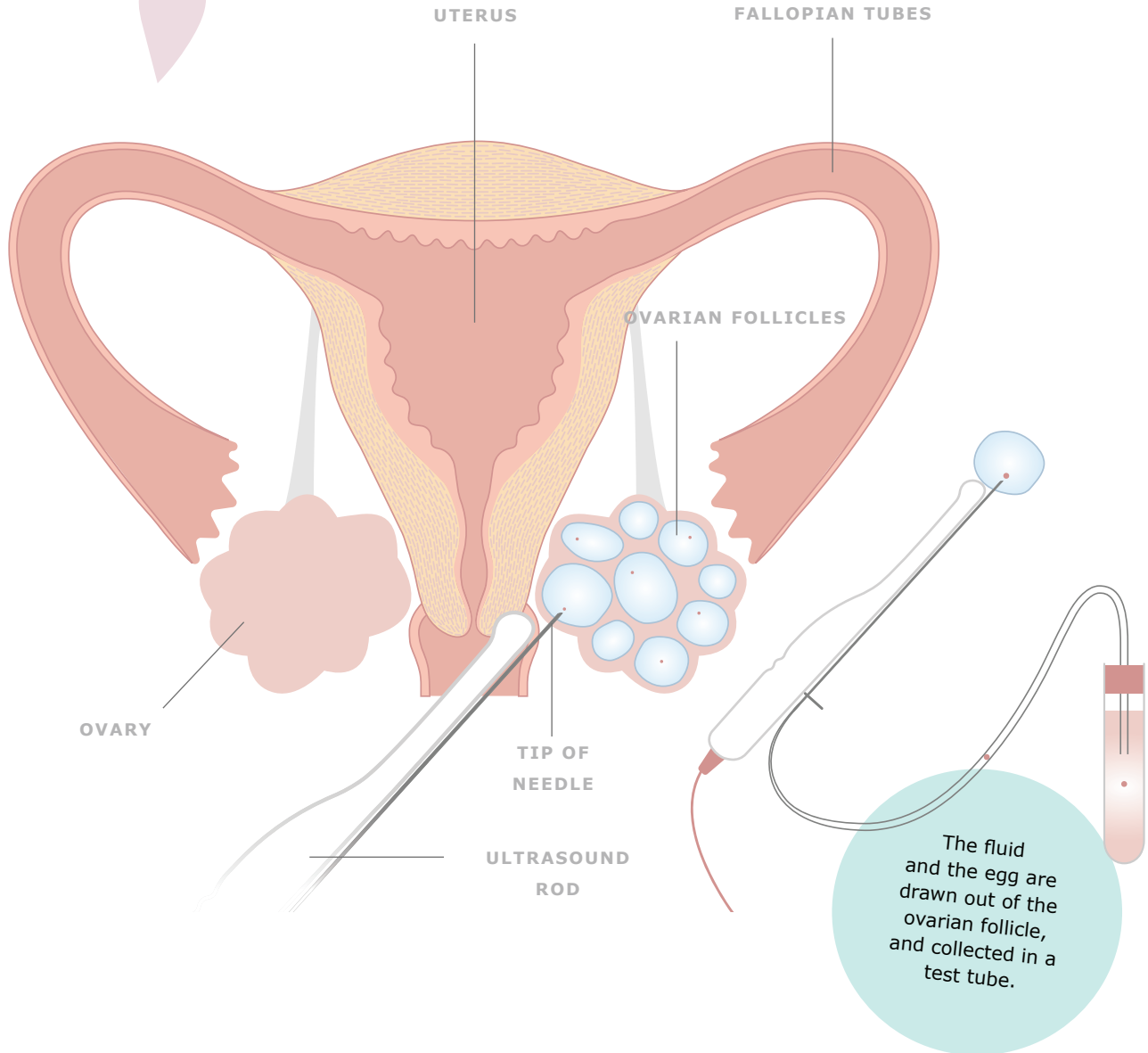
You come to the clinic in the morning of the day for egg retrieval. Couples come together.

If necessary, the woman may be given a pill to help her relax before the procedure. She will be awake during egg retrieval, but will be given a painkiller in the crook of the arm and a local anaesthetic in the vagina. Egg retrieval should not cause any pain. Using ultrasound via the vagina, as with the checks during the stimulation phase, the doctor is able to see the fluid-filled ovarian follicles. Using a thin needle connected to the ultrasound rod, fluid is drawn out and examined under a microscope by the embryologist.

Each follicle cannot contain more than one egg, but sometimes contains only fluid. The eggs are placed in a dish in a warming cabinet whose environment seeks to resemble the body's own.

The man provides a sperm sample on the day of egg retrieval. First, the sperm sample is analysed and the number of sperm cells and their motility is assessed. Next, the sperm cells are processed to sort out the best. Lastly, the sample is diluted with a nutrient solution and stored in an incubator (warming cabinet) before the sperm cells are brought together with the eggs later that same day.

Sometimes the plan is to fertilise eggs using frozen sperm cells. In this case, they are thawed on the day of egg retrieval and brought together with the eggs.


UTERUS
FALLOPIAN TUBES
OVARIAN FOLLICLES
OVARY
TIP OF NEEDLE
ULTRASOUND ROD
The fluid and the egg are drawn out of the ovarian follicle, and collected in a test tube.

6. FERTILISATION & CULTIVATION

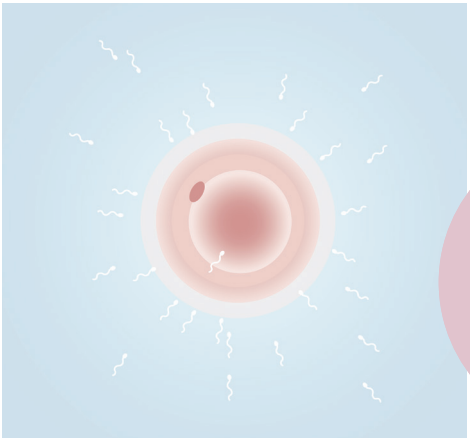
If sperm quality is normal, a **standard IVF** is performed, i.e. sperm cells and eggs are brought together in a dish where the eggs are fertilised unaided.

If sperm quality is impaired, a micro injection known as a (*intracytoplasmic sperm injection)* **ICSI** is used. The method involves drawing the sperm into a thin glass pipette and inserting it into the egg. An egg measures 0.1 mm, and sperm cells are much, much smaller.

In a condition known as azoospermia, some men do not have sperm in the sample, and they can be helped by a small surgical procedure.

Under local anaesthetic, sperm cells are retrieved from the epididymis or testicle using a thin needle, before microinjection into the egg. On rare occasions it may be necessary to surgically open a testicle to retrieve sperm cells.

A check the day after egg retrieval determines how many of the eggs have been fertilised. The embryos – the fertilised eggs – are grown in an incubator where they are monitored by the embryologist for 2-6 days. The incubator has an environment that mimics the uterus.

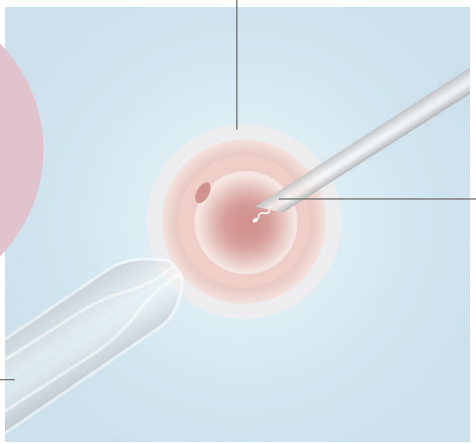


Standard IVF

The sperm cells and eggs are brought together in a dish.

ICSI

A sperm cell is injected into the egg.



7. EMBRYO TRANSFER

One, or in rare cases two, embryos are transferred to the uterus. This occurs on day 2, 3 or 5 of development depending on the day deemed to offer the best chance of pregnancy. A full bladder often facilitates transfer and provides a better ultrasound image. The doctor introduces a thin catheter via the cervix and places the embryo in the uterus.

The procedure is quick and should not be unpleasant or painful.

The empty ovarian follicles are transformed to become corpus luteum which produces the hormone (*progesterone*).

Supplementary progesterone is given to aid the uterine mucosa and make it more receptive to the embryo. Many women worry about losing the embryo, but it is well protected in the womb regardless of movement or exertions. Nature determines whether cell division continues allowing the embryo to implant in the uterine lining.

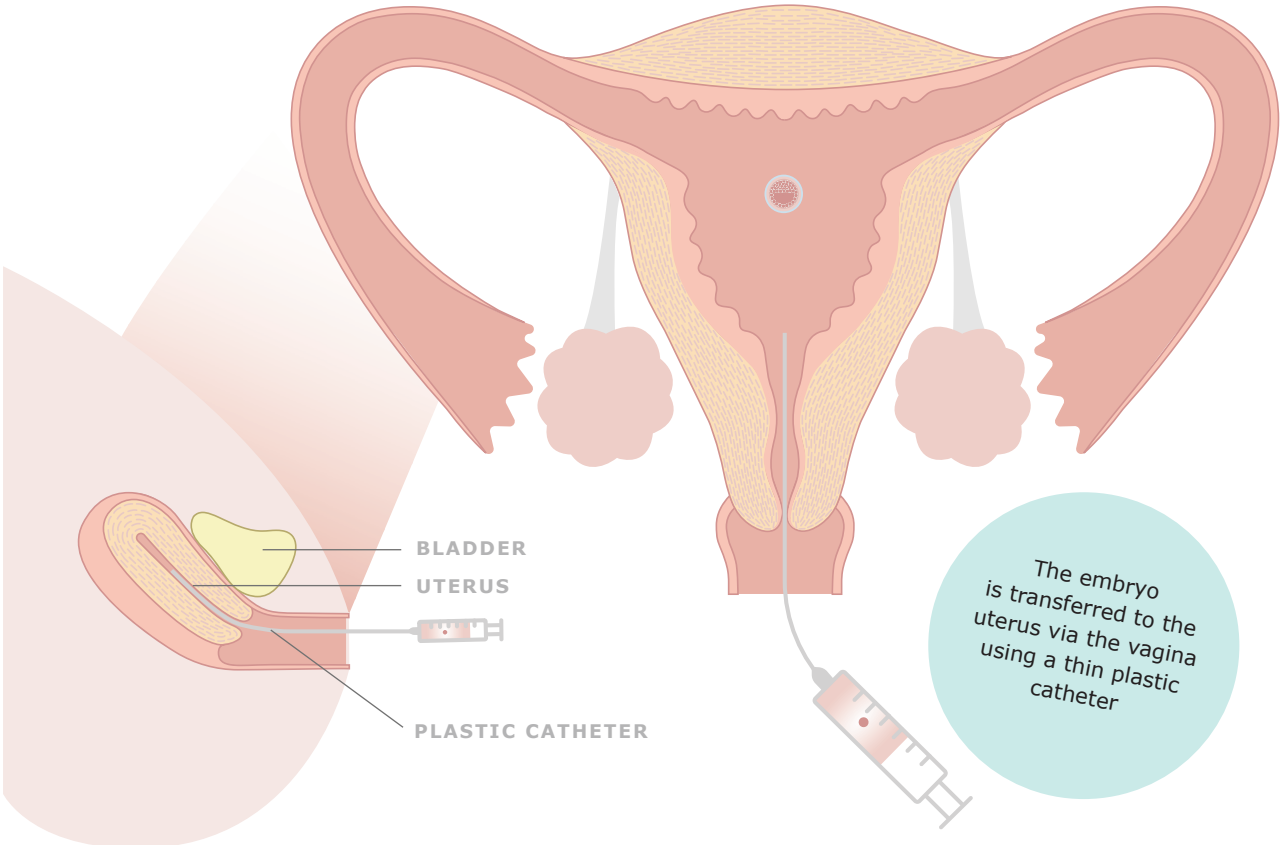
FREEZING EMBRYOS

If there are surplus, good-quality embryos, they can be frozen for storage. Under Swedish law, embryos may be stored for 10 years.

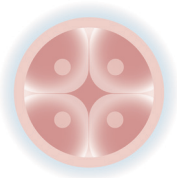
Embryos frozen after treatment are the joint property of the couple. Both parties must give their approval before transfer may take place.

In the case of embryos frozen after treatment with donated gametes, special regulations apply to transfer.

If the woman has regular periods and ovulation, transfer is carried out during a natural menstrual cycle. If periods are irregular and there is no ovulation, hormonal support will be given.

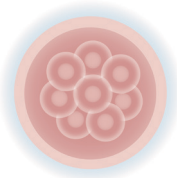


DAY 2



Embryo with 4 cells

DAY 3



Embryo with 8 cells

DAY 5

Blastocyst

8. DONATION

For women living alone or in a female same-sex relationship, your eggs can be fertilised using donated sperm. Pregnancy using donated sperm might also be necessary in a different-sex relationship.

If you lack eggs, or if it has prove difficult to fertilise eggs satisfactorily, egg donation is an option. Sometimes donated eggs and sperm are both necessary to achieve pregnancy, in which case both eggs and sperm can be donated. Eggs that have already been fertilised, i.e. embryos, may also be donated.

Treatment using donated sperm for IVF follows the same procedure as when sperm comes from the partner. However, donor sperm cells are always stored in a freezer before they are used. They are thawed before fertilisation of your egg. Sometimes, treatment using thawed, donated sperm is done by insemination. In this case, a thin catheter is inserted into the uterine cavity, and the sperm is then injected.

In pregnancies using donated eggs, the donor undergoes stimulation and egg retrieval. The eggs are fertilised either in conjunction with egg retrieval or after thawing. You will receive hormone treatment before embryo transfer so that the uterine lining is well prepared to receive the embryo. You continue taking these hormones until you know you are pregnant and for a few more weeks into the pregnancy.

The doctor performs embryo transfer in the same way as if the eggs were your own, regardless of whether one or both gametes are donated.

Important to know. A child born following donation, irrespective of whether the egg, sperm cell or both were donated, has the right to find out who the donor(s) is/are. This opportunity is provided when the child reaches maturity, which is considered to be around 18 years of age.

9. PREGNANCY

Most people describe the time from treatment to pregnancy test as long and sometimes stressful. Follow the clinic's directions on the date for the test and inform the clinic of the results.

The first ultrasound examination takes place three weeks after a positive test. By then it is usually possible to see if there is an amnion and foetus in the uterus.

10. DISCONTINUED TREATMENT

Sometimes stimulation must be discontinued following an ultrasound examination. If there are too few developed ovarian follicles , it may be better to discontinue hormone stimulation.

Another reason can be where a given dose of hormone causes far too many ovarian follicles to grow. If there is a risk of hyperstimulation, treatment may be discontinued and resumed later at a lower dose. In some cases, egg retrieval treatment and fertilisation is completed after the hormone dose is reduced. If the patient feels well, and is considered to be at low risk of hyperstimulation syndrome, a fresh embryo can be transferred during the current cycle, otherwise good quality embryos are frozen for transfer after hyperstimulation symptoms have abated.

It is rare for egg retrieval not to yield any eggs. It can happen that no egg is fertilised or that eggs fail to continue dividing. If this happens, the doctor will inform you about possible causes and the possibility of new treatment attempts.

Should you and/or your partner wish to discontinue treatment for any reason, please contact your clinic to discuss how best to do this.

11. RISKS & SIDE EFFECTS

THE WOMAN

If the woman has many ovarian follicles, there is a risk of hyperstimulation *(OHSS – Ovarian Hyperstimulation Syndrome)*. This occurs in 1-2% of cases in conjunction with in vitro fertilisation. A different type of ovulation injection is sometimes given to reduce the risk of hyperstimulation, and instead of transferring the embryos after egg retrieval, they are frozen. Embryo transfer is then carried out during a subsequent menstrual cycle. Hyperstimulation causes too many ovarian follicles to grow; the abdomen swells, it hurts and breathing feels heavy. Sometimes it is necessary to discontinue treatment before the eggs are retrieved, but usually the symptoms do not occur until after egg transfer. In the case of hyperstimulation, measures vary according to severity. Usually, rest and outpatient checks are sufficient, but sometimes hospital care is necessary. The pregnancy is not adversely affected.

Miscarriages are not more common following assisted conception than with normal conception.

In rare cases, ectopic pregnancies *(extra uterine pregnancies)* occur following IVF. The embryo placed in the uterus migrates into the fallopian tube and implants. The symptoms of an ectopic pregnancy are bleeding and pain.

While ovarian infections following egg retrieval are rare, it is important to detect them and treat them with antibiotics.

Studies so far have not shown an increased risk of developing cancer over time following hormone treatment.

THE MAN

Bleeding or infection following the retrieval of sperm cells from the testicle or epididymis using a needle are rare.

Surgical procedures for sperm cell retrieval from the epididymis or testicle can be repeated many times without impairing sperm cell quality.

12. LIKELIHOOD OF BECOMING PREGNANT

In ideal conditions during natural conception, the likelihood of becoming pregnant is 20-25% per menstrual cycle. The likelihood of becoming pregnant through in vitro fertilisation varies. You (both) should discuss matters with your doctor for an individual assessment.

A variety of factors have a bearing on the likelihood of having children:

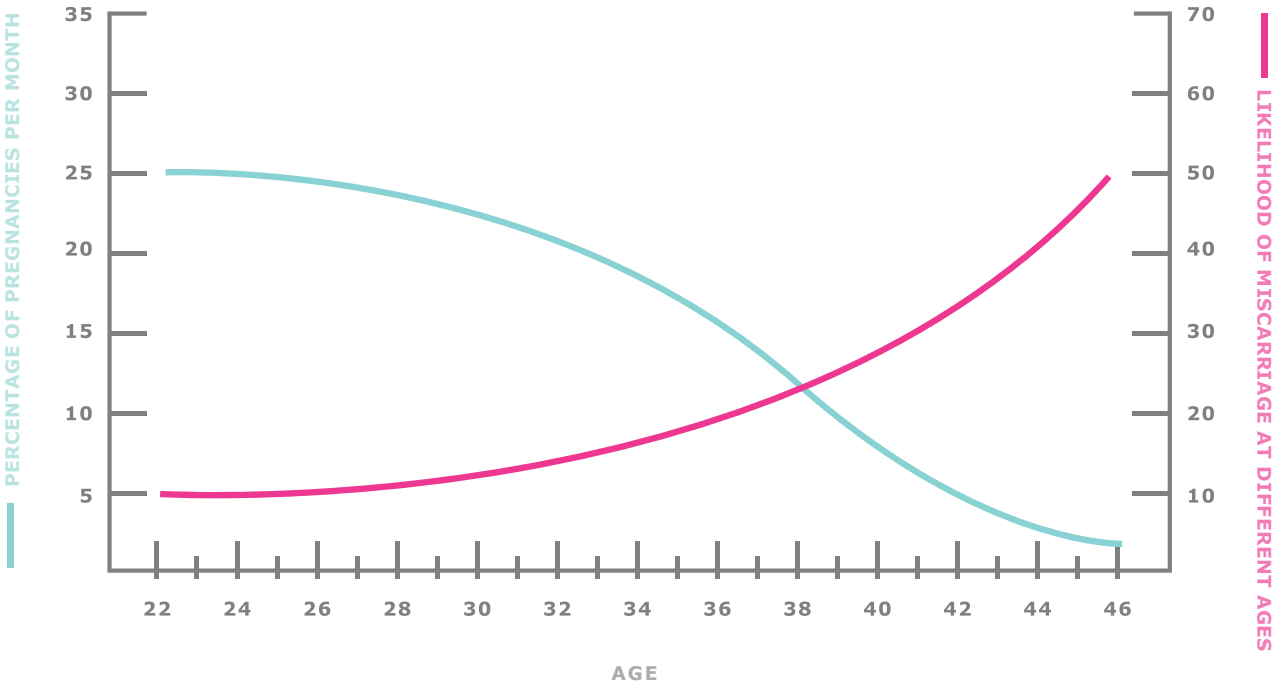
- The women's age
- How long you've been trying
- The causes of infertility
- The number of previous treatments
- Lifestyle factors

The woman's age plays a major part in how fertile she is. A woman's egg supply is present from birth and no new eggs are formed. The eggs age, and decrease in quantity and quality. The older a woman gets, the more difficult it is to become even with IVF, and the risk of miscarriage increases.

LIFESTYLE FACTORS

- Smoking
- Excessive exercise
- Obesity/Underweight

The graph shows the likelihood of becoming pregnant from regular intercourse and the risk of miscarriage in women of various ages



Reference: Reproductive Ageing: Guidelines for First Line Physicians for Investigation of infertility Problems (Canadian Fertility and Andrology Society, 2004)

A FEW LAST WORDS...

Undergoing in vitro fertilisation is demanding, and it usually takes more than one treatment. If the treatment does not result in pregnancy, it may lead to disappointment. An emotional roller coaster with highs and lows of uncertainty, difficulty planning ahead and hope that the next attempt will be successful.
In discussions following a treatment without a positive pregnancy test, many want to resume attempts as quickly as possible. Bear in mind the physical and psychological importance of a period of rest in order to have the strength to continue.

When a treatment is unsuccessful, it can be helpful to talk to someone not involved, and even when treatment leads to pregnancy it may give rise to mixed feelings and the need for increased support.

Staff at the clinic are used to meeting singles and couples in your situation before, during and after treatment. You can also talk to a counsellor or psychologist. It may be helpful to formulate and come to grips with your feelings together or individually.

Try to be hopeful; we live in times where the impossible has become possible. There are constant advances, and IVF as a method is ever more successful.

A LITTLE GLOSSARY

azoospermia *absence of sperm in the semen*

blastocyst *embryo cultivated for 5 days*

cervix *neck of the womb*

coitus *sexual intercourse*

corpus luteum *(yellow body) - transformed ovarian follicle after ovulation*

ejaculate *semen*

embryo *fertilised and divided egg*

endometriosis *uterine mucosa outside the uterine cavity*

endometrium *the mucous membrane lining the womb*

epididymis *a duct behind the testicle*

ET *Embryo transfer*

follicle *a sheath surrounding the egg*

FSH *follicle stimulating hormone - affects ovarian follicle growth*

gametes *eggs, sperm*

GnRH agonist *administered to block the woman's own hormones*

GnRH antagonist *administered to prevent ovulation*

gonadotropin *collective name for the pituitary hormones FSH and LH*

hCG *human choriongonic adotropin - pregnancy hormone*

ICSI *microinjection of a sperm into an egg*

implantation *an embryo adheres to the uterus mucus*

incubator *warming cabinet*

IVF *in vitro fertilisation - test tube fertilisation*

LH *luteinising hormone – causes ovulation, among other things*

luteal phase *time following ovulation or embryo transfer*

myoma *uterine muscle fibroid*

OHSS *hyperstimulation*

OPU *Ovum Pick-Up – egg retrieval in IVF*

ovarium *ovary*

ovulation *release of an egg from the ovary*

PESA *fluid and sperm cells drawn out of the epididymis with a thin needle*

progesterone *the hormone produced in the corpus luteum that makes the uterine mucus membrane more receptive to the embryo*

testis *testicle*

TESA *testicular tissue extracted with a thin needle and examined under a microscope to find sperm*

TESE *testicular tissue extracted using a surgical procedure. If a microscope is used for the extract, it is known as micro-TESE*

testosterone *male sex hormone*

tuba uterina *fallopian tubes*

uterus *the womb*

ectopic pregnancy *ectopic pregnancy - embryo that develops outside the uterus*

ovulation injection *hCG injection*

oestradiol/oestrogen *female sex hormone*

MY OWN NOTES

"A little book on IVF" is part of the informational material produced by Merck concerning involuntary childlessness.

Merck AB
Box 3033, SE 169 03 Solna
Phone +46 8-562 44 500

www.merck.se

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