When nature isn't enough: Assisted conception with Genea

Genea
WORLD LEADING FERTILITY

Genea would like to welcome you and make your assisted conception experience with us as comfortable, simple and stress-free as possible.

At what may be a time of great uncertainty there is one thing you can be absolutely certain of.

No clinic anywhere can offer you a better chance of success than Genea.

At Genea, we look at things from the point of view of our patients and we understand what a moving and profound time this is for them.

You will have your own Genea accredited specialist and nurse throughout your treatment – available to offer guidance and support 24 hours a day. So if you wake up in the middle of the night with a little worry, big problem or question, a fertility expert nurse is only a phone call away.

You will also have a support person and unlimited access to a counsellor throughout your treatment.

It may help when making what is a very emotional decision to consider this scientific information.

Genea virtually doubled success rates in the mid-nineties and continues to deliver advances today to improve outcomes.

We also invest more into research than any other IVF clinic in Australia.

We encourage you to visit the clinic and meet the scientists, nurses and other staff involved, to help you gain an insight into the science behind the scenes and to give you a sense of how we will look after you during the various stages of your treatment cycle.

We have designed this booklet to provide you with the most important information you'll need to help you better understand the fertility treatments available to you at Genea.

Prof. Robert Jansen's book Getting Pregnant is also a helpful resource to refer to along your journey.

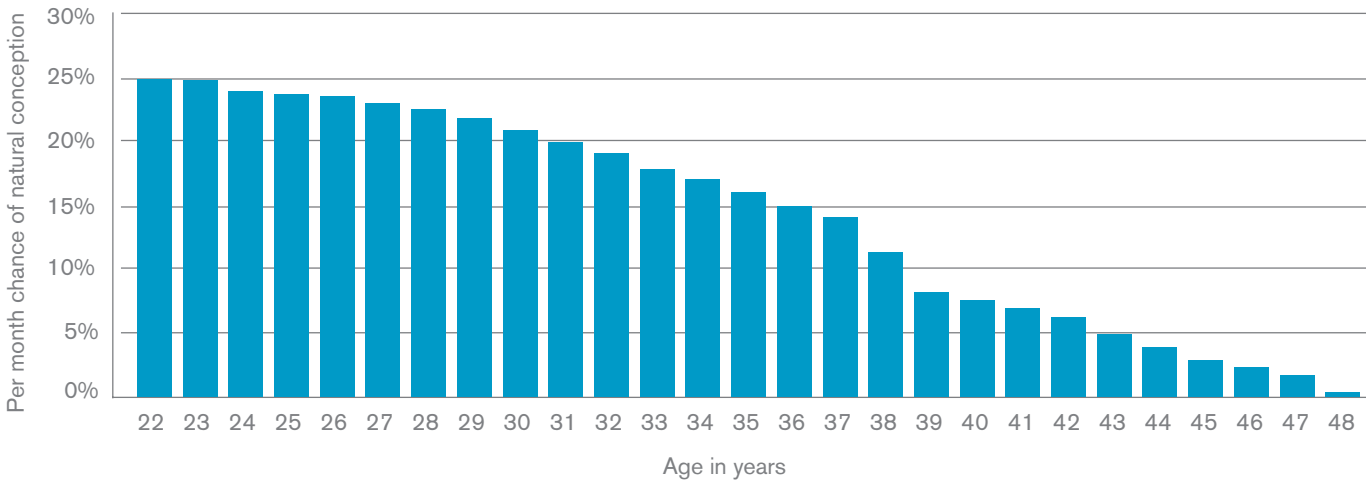
More detailed information can also be found at **genea.com.au**

Infertility

Infertility can be caused by:

- Irregular ovulation, or the failure to release eggs; or no eggs remaining in the ovaries
- Fallopian tube damage or obstruction, or some other anatomical problem
- Endometriosis
- Male factors – impaired or reduced sperm parameters; or no sperm in the ejaculation
- Immunological issues – the presence of anti-sperm antibodies in either partner
- No obvious cause (unexplained infertility)
- Female age – older eggs (especially beyond 38 years of age) have a lower chance of causing a successful pregnancy

The latter is crucial – as a result of ageing eggs, a woman's fertility drops progressively as she gets older.



Assisted conception

If there are significant problems uncovered in your investigations, if simple or other treatments have not lead to pregnancy, or even if there are no problems but time and age are advancing, assisted conception may be recommended by your doctor.

There are a number of different assisted conception treatments that are available to you, depending on the reason/s you're having trouble.

All of them aim to increase your chance of pregnancy by enhancing what happens in nature, through increasing the number of sperm that get to where the egg is, and/or increasing the number of eggs available for fertilisation.

The chance of pregnancy with any assisted conception technique will depend on:

- The woman's age
- The reason/s why pregnancy hasn't happened naturally
- The strength and quality of the embryos that a couple produce.

For couples experiencing infertility due to an extremely low (or zero) sperm count, no ovulation or completely blocked fallopian tubes – assisted conception will be the only way that pregnancy is possible.

Other couples with subfertility have a chance of becoming pregnant naturally, but that chance is reduced by factors such as a low sperm count, irregular ovulation, endometriosis, scarring of the fallopian tubes, fibroids, or the increasing age of the woman. In about 1 in 5 couples, no apparent explanation for subfertility can be found. For any of these subfertile couples, assisted conception can speed up the process of becoming pregnant.

The main techniques for assisting conception are:

- Assisted insemination (also known as intrauterine insemination, or IUI)
- Ovulation induction
- In vitro fertilisation (IVF) and variations of IVF.

Monitoring cycles: where timing is everything

All assisted conception techniques involve the monitoring of cycles to time procedures precisely. Developing follicles secrete increasing amounts of estrogen, particularly estradiol (E2). Blood tests that measure the level of E2 will detect a growing follicle.

Vaginal ultrasound examinations enable us to further monitor the ovarian response by counting and measuring the growing follicles as the E2 level rises. Once follicles reach 18-20 mm in diameter, they are big enough to produce a mature egg. At Genea, we try not to interfere with your day-to-day life. Blood tests and ultrasounds for cycle monitoring are done early in the morning, enabling you to get on with the rest of your day. We will give you your results by phone later in the afternoon.

Intrauterine insemination (or assisted insemination)

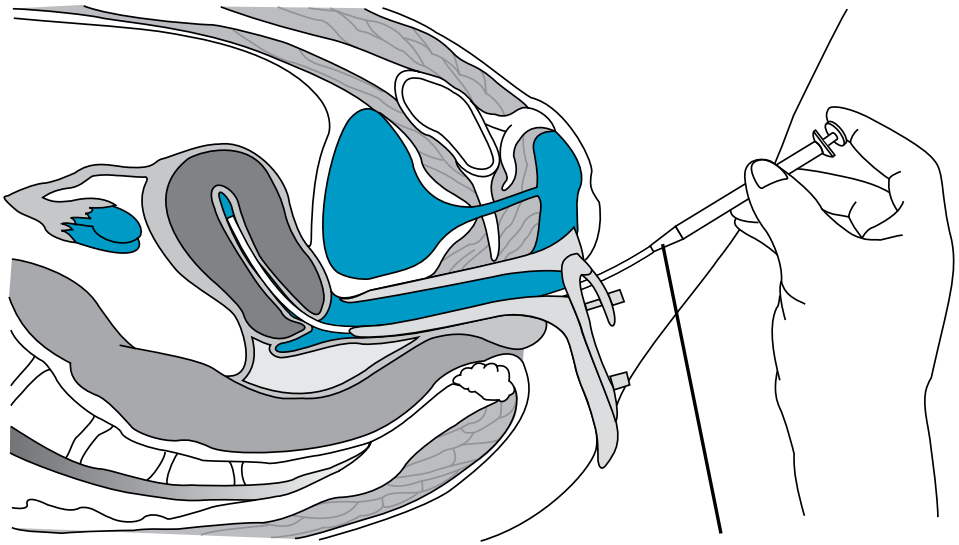
This technique is used in only a few circumstances, for example when:

- There is a physical problem with sexual intercourse
- Scarring of the cervix prevents sperm penetration
- Donor sperm is required.

When there is low sperm count, or if there is endometriosis, assisted insemination is not as effective as IVF. In addition, the fallopian tubes must not be blocked, nor is assisted insemination recommended when the cause of infertility is unknown.

Assisted insemination (AI) is a technique in which sperm are placed into a woman's cervix or uterus with a soft, thin plastic tube around the time of ovulation.

An insemination cycle might or might not include ovarian stimulation. The cycle is monitored with blood tests and ultrasounds so that the insemination can be timed precisely.



Sperm injected into uterus

Ovarian stimulation

Ovulation induction (OI) with controlled ovarian stimulation may be recommended for women who have normal tubes, and whose partners have a normal semen analysis, but who rarely or never ovulate.

For women who do ovulate regularly, stimulation can also be used to increase the chance of pregnancy by increasing the number of follicles that develop fully and, therefore, increasing the number of eggs that are ovulated during a cycle.

Two types of hormones may be used to stimulate ovulation: tablets of clomiphene citrate (Clomid® or Serophene®) and injections of follicle stimulating hormone, or FSH (Gonal-F® or Puregon®).

Clomiphene

Clomiphene (Clomid® or Serophene®) is often the first choice for stimulating ovulation because of its low cost and ease of use.

A synthetic hormone, clomiphene acts as an anti-estrogen, tricking the brain into producing higher levels of FSH than in an untreated cycle, which in turn stimulates ovarian follicular development. A course of tablets is given for 5 days, usually days 2-6 or 5-9 of the cycle.

Side effects can include thickening of the cervical mucus, vaginal dryness and hot flushes, while some women also complain of mood changes and irritability. Uncommonly there can be abdominal bloating, breast discomfort, nausea, a skin rash or dizziness. These symptoms usually pass after the 5 days of tablets finish.

Because it is an anti-estrogen, clomiphene can have a negative effect on cervical mucus and on the lining of the uterus, impairing conception and implantation. Pregnancy rates are 5% to 10% per month, or 35% to 40% over a six-month course of treatment.

FSH

Follicle stimulating hormone (FSH) is the hormone necessary for the multiple follicular development required in IVF. FSH may also be used in smaller doses for ovulation induction or ovarian hyperstimulation. The FSH is made in the laboratory and is identical to human FSH.

Because it is a protein that if taken orally would be digested in the stomach, FSH is given by injection under the skin, with a fine needle. There are two brands of FSH available in Australia – Gonal-F® and Puregon®. Both are self-administered with pen-like devices (similar to those used for insulin by diabetics).

Using FSH to induce ovulation for getting pregnant naturally, as opposed to through IVF, can be tricky because of the risk of stimulating too many follicles and having a multiple pregnancy. This is why the body's response is closely monitored with blood tests and ultrasounds.

When the lead follicle or follicles are the right size on ultrasound, ovulation is triggered with an injection of human chorionic gonadotrophin (hCG), which mimics the LH surge.

Ovarian stimulation

Even with the most careful monitoring, more follicles can reach maturity than desired. Intercourse should be avoided in this situation because of the high risk of twins, triplets or an even higher-order multiple pregnancy. If this looks too likely, either the ovulation cycle that has been induced will need to be cancelled or a suggestion might be made to carry out an IVF procedure.

Multiple pregnancy is the single greatest complication in using FSH injections for ovulation induction.

If pregnancy occurs, there is a 20% chance of twins. Triplets or higher occur in about 5% of pregnancies.

Infertile couples might think twins are a blessing, but complications are much more common in twin than singleton pregnancies (read more on this later).

Because it is identical to a hormone that a woman's body makes naturally, the side effects a woman experiences with FSH are really the expected effects of the injections. These include bloating as the ovaries are stimulated and mood changes as estrogen levels rise.

Pregnancy rates depend primarily on the age of the woman, and range from around 10% to 20% per month, or 40% to 50% over a six-month course of treatment in women under 38.

Other medication for ovarian stimulation

For patients undergoing IVF, other adjunctive medication might be used to assist follicle/egg development. A longer acting version of FSH which can reduce the number of injections (Elonva®) might also be recommended.

In vitro fertilisation (IVF)

Depending on a woman's age, anywhere between 1 and 30 follicles, known as 'recruits', will begin to develop in each menstrual cycle. Whatever her age, though, only one of these developing follicles will dominate and ovulate at the level of FSH that a woman produces naturally.

With IVF, the goal is to keep the level of FSH constant, and thus encourage more of the recruits to grow and to develop mature eggs, which are collected surgically under vaginal ultrasound guidance.

The eggs are then fertilised in the laboratory, cultured for several days, and then the embryo is transferred back into the woman's uterus. If there are additional embryos, they may be frozen and stored for later use.

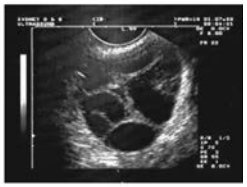
The steps in an IVF cycle are:

1. Stimulating the ovaries with injections of FSH
2. Preventing premature ovulation (the LH surge) by shutting down communication between the brain and the ovaries, so that the eggs are not lost before they can be collected
3. 'Triggering' ovulation by replacing the LH surge at mid cycle with an injection of hCG
4. Collecting the eggs and sperm
5. Culturing embryos in the laboratory
6. Transferring the embryo
7. Supporting the endometrium in the luteal phase with hCG or progesterone

Step 1:

Stimulating the ovaries with injections of FSH

Firstly, it's important to understand that no amount of FSH will stimulate more follicles than are available to be recruited. The dose needs to be enough to stop the usual competition that takes place among them, but once that threshold is reached there isn't a lot of control possible over the number of recruits that will grow. Secondly, using FSH injections does not use up follicles and their eggs any faster than they're already being used anyway.



They actually began their development months earlier. And the non-recruits – those that don't release mature eggs – are absorbed and lost.

More is not better when it comes to FSH dosing. If the dose is too high it can be damaging to the eggs and may also put a woman at risk of ovarian hyperstimulation syndrome.

The duration of FSH administration is also important. The normal length of the follicular phase generally needs to be made available to the growing follicles, which takes 11 days or more.

At Genea, we usually check a woman's estrogen level after 3 or 4 days of stimulation. If there does not seem to be much response, the dose of FSH can be increased. If the response has been too brisk, the dose of FSH can be reduced gradually.

Women have their first ultrasound after 5 to 8 days of stimulation. Ultrasonographers and nurses, who are very familiar with follicle tracking perform the ultrasound examinations. The need for further monitoring will be determined by a woman's individual response, and can require blood tests and ultrasounds every other day until the follicles reach 17-20 mm in diameter, large enough to contain a mature egg.

Step 2:

Preventing premature ovulation (the LH surge) by shutting down communication between the brain and the ovaries so that the eggs are not released before they can be collected

GnRH analogs are a group of drugs closely related to the natural hormone gonadotrophin releasing hormone (GnRH), a hormone produced by hypothalamus in the brain that controls the release of FSH and LH by the pituitary gland. There are two types of analogs – agonists and antagonists – that prevent an LH surge in different ways. GnRH agonists first cause a flare of FSH and LH as they stimulate and then inhibit, or down regulate, the pituitary. There are two agonists available in Australia – a nasal spray called Synarel® and an injection called Lucrin®. There is an extra cost for these agents.

GnRH antagonists are a newer class of injectable medication with the advantage that they drop levels of FSH and LH without first causing the flare, meaning they are given for a much shorter period of time. They are usually started around the fifth day of FSH stimulation. The antagonists, marketed in Australia as Cetrotide® and Orgalutran®, are also effective in preventing the LH surge and in leading to pregnancy. Cycles involving these agents are usually much shorter in length and many women find them more convenient and better tolerated.

They may also be of value in women who produce only a low number of eggs in an IVF cycle (particularly older women). Which drug your Genea doctor prefers to use will depend on factors such as age, previous response to treatment and convenience.

Step 3:

‘Triggering’ ovulation by replacing the LH surge at mid cycle with an injection of hCG

It’s not presently possible to use synthetic LH to mimic the natural surge, as the duration of action of currently available LH is too short. Using hCG (human chorionic gonadotrophin) to replace the natural LH surge sets in motion everything that makes ovulation happen, causing the egg in the mature follicle to be fertilisable and loosening it from the wall of the follicle so that it comes out with the follicular fluid at egg retrieval. It takes just over 38 hours for ovulation to occur after an injection of hCG. Eggs are mature and can float free from about 34 hours after hCG, giving a four-hour ‘window’ for egg retrieval, which is typically scheduled 36 hours after the hCG trigger. hCG is marketed either as Pregnyl®, a powder that must be mixed or Ovidrel®, delivered in a pre-filled syringe. Intercourse must be avoided from Day 3 of FSH stimulation, as not all of the eggs might be collected.

There is then a small chance of spontaneous conception, which increases the risk of a multiple pregnancy when an additional embryo is transferred.

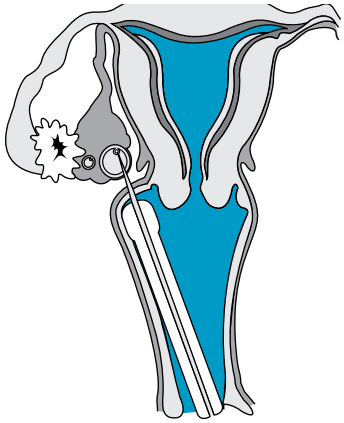
Step 4:

Collecting the eggs and sperm

Egg collection

Egg collection involves the aspiration or collecting of the fluid that contains the egg from the pre-ovulatory follicle. The procedure is carried out through the top of the vagina to either side of the cervix, and is guided by a transvaginal ultrasound.

The vast majority of egg collections at Genea are performed under local anaesthetic with mild sedation.



Some women may prefer a general anaesthetic and we can usually accommodate this wish, but we cannot guarantee this option if egg collection falls on a weekend. There are a number of advantages in being awake for the procedure, including:

- It is an amazing and special experience to see your eggs collected and sorted on the TV monitor
- Partners can be present and also see and experience the procedure
- It takes less time to recover
- General anaesthesia will cost extra.

The ovaries are scanned, just as they are during follicle tracking. Local anaesthetic is then placed in the wall of the vagina around the ovaries. The follicle/s are then aspirated using a needle passed through the wall of the vagina beside the cervix and into the ovary.

Patients and their partners watch the procedure on the ultrasound monitor. As the follicles are emptied the collected fluid is passed to the embryologist, who begins locating and extracting the eggs, transferring them to special plastic dishes ready to be incubated. The microscope that the scientist uses is attached to a video camera, so you can watch it all happen. During the procedure all that a woman is generally aware of is some pressure on the ovary, followed by an ache that subsides. About 1 in 20 women will experience significant pain, although it is usually very short in duration.

There's often a small amount of bleeding from the wall of the vagina. Other complications such as: major bleeding; damage to an internal organ; or infection; are possible, but rare.

After the follicles have been emptied they often fill up again with fluid, so the feeling of fullness may return.

Some women also complain of a cramping sensation for a few days following egg collection. This can be relieved with paracetamol (with or without codeine).

Sperm collection

Soon after egg collection the male partner has his role to play and will be asked to proceed to one of our collecting rooms. It is also possible to collect at home, if you live within an hour of the lab. Sperm can be frozen in advance of the day of egg collection if you anticipate difficulties.

Genea scientists look for two things in a sperm sample – freshness, and the quality of sperm. To ensure that the sperm is fresh we recommend ejaculation on the same day as the hCG trigger.

To maximise the quantity of sperm, ejaculation should then be avoided until after the egg collection.

Step 5:

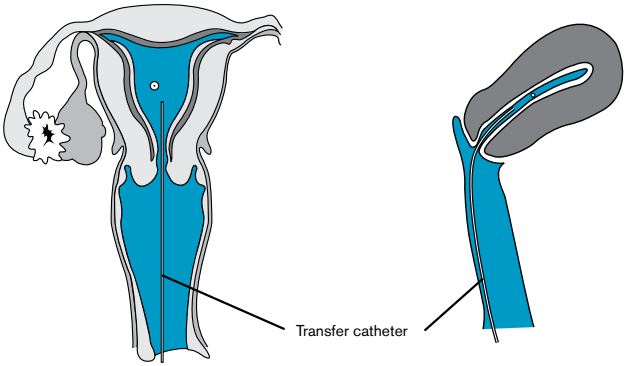
Culturing embryos in the laboratory

The eggs and sperm are brought to the laboratory where the eggs will be fertilised and the embryos cultured for 5 days. Please refer to the section overleaf "World-leading science" for details of what happens in the lab.

Step 6:

Transferring the embryo

An embryo transfer to the uterus is usually straightforward and painless: no more (or less) uncomfortable than having a Pap smear. After a speculum is placed in the vagina, a fine plastic catheter that has been loaded with the embryo is passed through the cervix into the uterus.



Many people think that the uterus looks like it does in diagrams with a cave-like interior in which the transferred embryo can rattle around and even fall out! In reality, the endometrial cavity is a potential space.

In fact, the front and back walls of the uterus are in contact like two slices of bread with jam in the middle; the embryo is like a raspberry seed wedged in between. No matter what you do, it won't fall out!

Freezing embryos

After ovarian stimulation and egg pick-up, there are often more embryos than the one needed for transfer in that cycle. If there are healthy-looking embryos left over from the IVF cycle they may be placed in cryo-storage.

By freezing these embryos you have the chance to attempt pregnancy more than once after only one stimulated cycle. Note that not all unused embryos are suitable for freezing.

Freezing and storing embryos reduces the amount of hormone treatment you receive and also the number of times your ovaries are stimulated. Some people have two or three embryo transfers after just one stimulated cycle.

Frozen embryo cycles involve either monitoring your menstrual cycle for ovulation and transferring the embryo at the right time or using sequential medication to mimic the hormones of a natural cycle.

Step 7:

Supporting the endometrium in the luteal phase with hCG or progesterone

The effects of the hCG injection wear off within a week and the ovaries may not produce enough progesterone on their own to support a pregnancy. Extra doses of hCG (Pregnyl®) or progesterone (in the form of pessaries or Crinone® gel) are required until the outcome of the cycle is known.

A pregnancy test is not reliable until 16 days after egg collection. This can be the most nerve-racking time of the whole treatment cycle. Many people will feel simultaneously elated (there's a new chance of pregnancy) and deflated (there is much less to do compared with before the egg retrieval, there is less information and, unless you have specific questions, there is much less contact with people at the clinic).

"The two week wait"

Once all the stages of the IVF cycle have been completed, there's nothing more to be done than wait for the time to pass before the results – whether or not the pregnancy has started – are known.

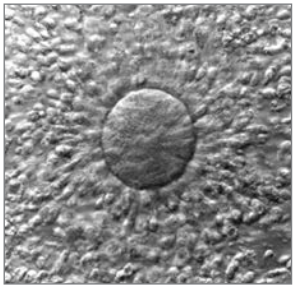
Some refer to this time as the dreaded "two week wait", because such a protracted period of uncertainty after so much forward activity can be stressful. Our counsellors, nurse coordinators and your doctor are all available to help during this time.

You might also find it helpful to record your thoughts and feelings at this time, as well as to note any questions or concerns you want to raise with your doctor or nurse coordinator.

World-leading science

At the time of egg collection, our scientists will hope to see mature eggs with smooth borders and a corona of cumulus cells around them. Immature and postmature eggs have irregular borders and not very good cumulus.

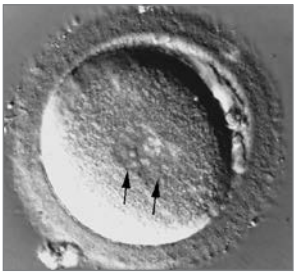
Immature egg



Mature egg

IVF

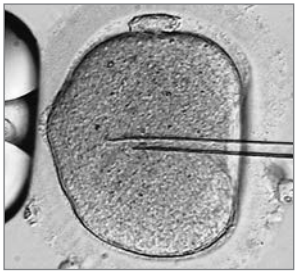
In conventional IVF, about 50,000 to 100,000 washed sperm are left in a small plastic dish with the eggs. The sperm spend the next few hours getting through the layers of cumulus cells, and hopefully one sperm will successfully fertilise the egg. By the next day – some 15 hours after introducing the sperm to the eggs – the scientists will check to see if the eggs have fertilised by looking for the presence of pronuclei. In normal fertilisation there should be two pronuclei – one from the sperm and one from the egg. Not all eggs will fertilise normally, which is common. We consider it a good result if 80% of the eggs collected have two pronuclei on Day 1.



Fertilised egg with two pronuclei

ICSI

Intracytoplasmic sperm injection (ICSI) can be used to fertilise eggs when there is thought to be a decreased chance of fertilisation occurring with conventional IVF, either because of problems with low sperm numbers or low sperm motility, or because of other barriers to the fertilisation process such as sperm antibodies or previous failure to fertilise through IVF. A single sperm is injected into each egg. The sperm is selected mainly on the basis of its normal shape and size.

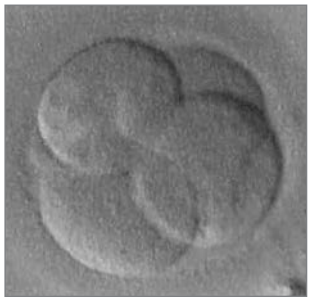


The ICSI process

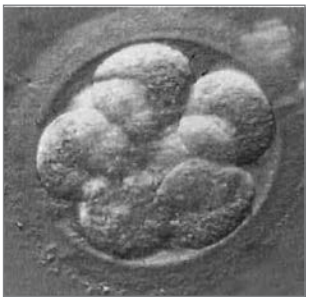
World-leading science

Blastocyst culture

Genea was the first fertility clinic in Australia to introduce single embryo transfers and routine Day 5 embryo transfers. Many clinics routinely transfer more than one embryo to try to increase success rates, but our technology allows us to achieve world-leading success rates with single embryo transfer.

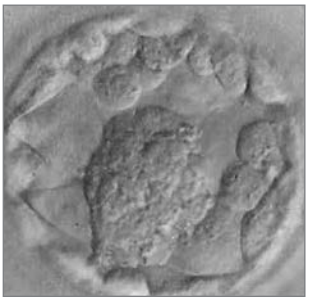


Day 2 - 3-4 cells



Day 3 - 6-8 cells

Day 4 - morula



Day 5 - blastocyst

Once fertilisation has occurred the embryo will divide and rapidly increase in cell number over the next few days. By Day 4, the cells have divided rapidly but the embryo has not yet increased in size. It is now 'compacting' (you can't distinguish the cells) and is called a morula.

If the embryo survives to Day 5 – the blastocyst stage – it will contain between 75 and 100 cells. It is a 3-dimensional ball of outer cells (the trophectoderm) surrounding a fluid-filled cyst in which an inner group of cells, the inner cell mass can be seen. The trophectoderm will go on to form the placenta, membranes and umbilical cord, while the inner cell mass will become the baby.

We cannot tell the difference between a 'good' embryo and a 'bad' embryo just by looking at them.

Embryos at the best of times are busy transforming and repairing themselves, so can develop fragmentation (which is when small bits of cells are pinched off during division) or vacuoles, which are small spaces within the substance of the cells.

The significance of these changes is not known and many fragmented and vacuolated embryos can go on to form perfectly healthy pregnancies.

While many embryos can survive 2 or 3 days to reach the 4-8 cell stage, only the strongest will have the ability to keep developing into a blastocyst and then a baby.

One way of identifying the better embryos, therefore, is to let them grow a little longer in the laboratory and to transfer them at the blastocyst stage. It is a good way of determining which embryos have the most developmental potential.

World-leading science

An embryo needs two things to reach Day 5.

Energy

An embryo's energy supply comes from tiny structures inside its cells called mitochondria.

The embryo needs to survive on the energy produced by the mitochondria it inherits from the egg until it has implanted and formed a placenta. Because all the mitochondria in an embryo come from the egg they are inherited from the mother.

And because women are born with all their eggs for their lifetime already formed, the mitochondria in your eggs are as old as the eggs themselves.

Chromosomes

Embryos must also have the right genetic makeup to develop normally. In humans, genes are contained in 23 pairs of chromosomes.

An incorrect number of chromosomes leads to failure of an embryo to implant or to progress to a normal birth. Pregnancy is a great filter of abnormal embryos.

When chromosome analysis is performed on cells from Day 3 embryos, studies have shown that only one third will have the normal number. If an embryo progresses to Day 5 and becomes a blastocyst, it has a two-thirds chance of being chromosomally normal.

90% of chromosomally abnormal pregnancies will miscarry in the first trimester. 93% of chromosomally normal pregnancies will continue to term.

Preimplantation genetic diagnosis (PGD)

Genea was the first clinic ever to introduce preimplantation genetic diagnosis (PGD) successfully for Day 5 embryos.

We are now the most successful PGD clinic in the world, offering testing for over 170 chromosome and genetic conditions with virtually twice the chance of a healthy baby for each embryo transferred. In a normal IVF cycle the embryologist chooses which embryo will be transferred to the uterus based on a visual observation as they develop. Preimplantation genetic testing or diagnosis (PGD) allows the Genea scientists to base the choice on the results of genetic tests on the embryos to exclude those that contain an obvious genetic abnormality. Testing can involve a count of the chromosomes and/or a molecular examination for a particular gene or mutation. Either way, the testing can increase both the chance of a genetically normal pregnancy and your chance of having a baby.

Who can benefit from PGD?

PGD may be recommended for people who:

- Are affected by or carry a known genetic disease
- Have had recurrent miscarriages
- Need to choose the sex of their baby.

Genea is continually evaluating the possible benefit of more routine PGD in increasing IVF live birth rates generally.

What happens in PGD?

The biopsy

PGD requires the biopsy or removal of cells from each embryo for analysis. At Genea, our advanced embryo culture techniques allow us to wait until the embryos have reached the optimum fifth day of development when they can have a hundred or more cells, and then remove three to four at a time. Other clinics conduct the biopsy at Day 3 of the embryos' development when they consist of just six to eight cells, and only a single cell is removed, greatly reducing the number of opportunities for success and leading to a higher proportion of the embryo being taken away. By waiting until embryos have reached the blastocyst stage, Genea scientists can select cells from the trophectoderm, the part of the embryo that will go on to form the placenta. The inner cell mass, the part that will become the baby, is not touched.

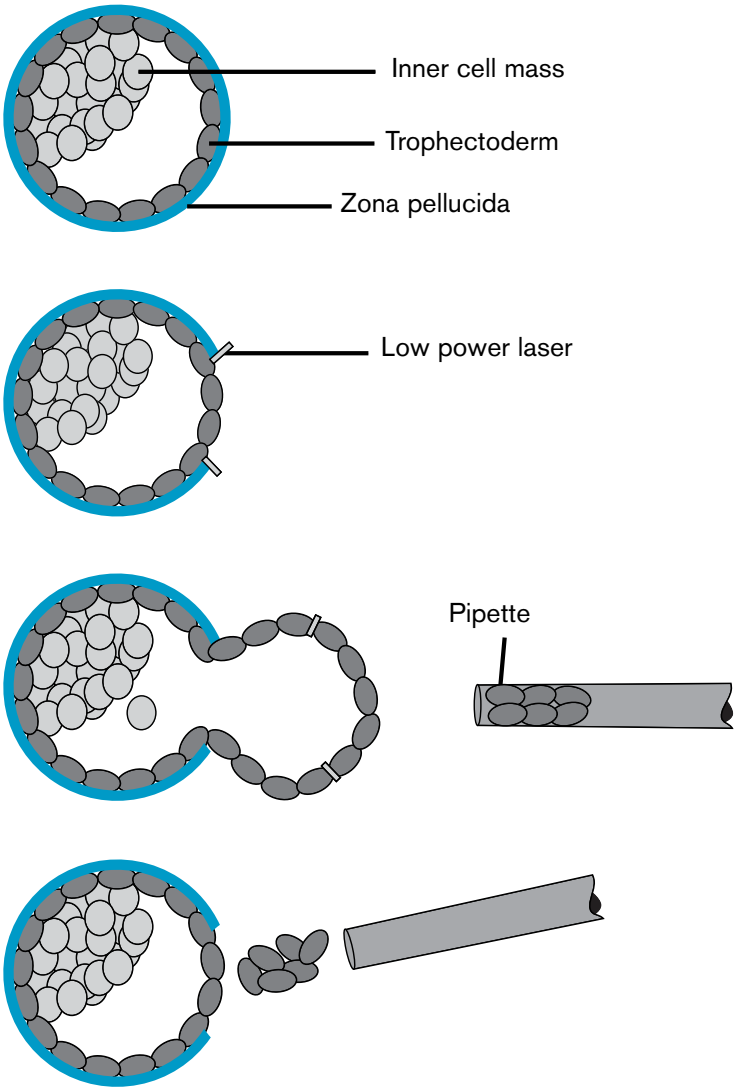
The analysis

Genea scientists can use a number of different methods to analyse the biopsied cells. Comparative genomic hybridisation (CGH) is used to count the number of certain chromosomes and to observe how they are arranged. CGH is also used to identify the sex of an embryo, as it can determine if there are two X chromosomes (usually a girl) or an X and a Y chromosome (usually a boy). If the problem is at a gene level rather than chromosome it is more common to use PCR. PCR makes millions of copies of a part of the DNA code, which allows us to see whether this part of the DNA in the sample is normal or mutant.

Interpretation

Even in the blastocyst, the embryo's cells are not in the final form they will have as a fetus and placenta after implantation. PGD for chromosome counting (preimplantation genetic 'testing' rather than true 'diagnosis') is a screening procedure that reduces the chance of Down syndrome or having a miscarriage, for example. But whilst CGH is highly accurate, it does not completely eliminate these possibilities. So even if you have PGD, you should still have the usual first trimester screening tests you and your obstetrician would otherwise consider.

Embryo biopsy



Being prepared: things to be aware of with IVF

This guide is intended to help you understand what you can expect to encounter during your treatment. That also includes having an understanding that things don't always go according to either desire or plan. While some of these problems are only temporary, others can take a considerable emotional and physical toll; and occasionally there are dangers.

Ovarian hyperstimulation syndrome (OHSS)

It's normal for the ovary to produce fluid in the abdomen as a follicle grows, and to bleed at ovulation.

And it's normal for a corpus luteum to form in the ovary and become cystic in the second half of the cycle. Pain can accompany ovulation and the formation of the corpus luteum, while premenstrual tension can cause bloating, irritability, depression and breast pain. When the ovaries are stimulated to increase the numbers of follicles, as occurs in IVF, all these events and their symptoms can be more pronounced than you might expect in a natural cycle.

Our years of experience at Genea tells us that 1 in 30 stimulations is accompanied by enough pelvic pain in the luteal phase to cause a woman to want to rest in bed for a day or two (mild OHSS).

In about 1 in 250 stimulations, a hospital rest results, mainly for observation and to enable us to give adequate relief of pain (moderate OHSS).

In about 1 in 1000 stimulations however, there's enough fluid in either the abdomen or the chest to be of serious medical concern. Severe OHSS increases a woman's chance of developing a blood clot which is potentially life threatening. Things to watch out for are: vomiting, diarrhoea, and shortness of breath. Contact Genea if you experience any of these.

OHSS is a self-limited condition and the ovaries will almost always completely recover. The signs and symptoms will get worse before they get better if there has been a successful conception, because the natural production of hCG will then be added to the injected hCG and keep the ovaries stimulated and enlarged for an extra few weeks.

Rarely (about 1 in 5000 cases) an enlarged ovary can twist on itself, cutting off its blood supply and causing excruciating pain that necessitates immediate hospital admission.

Cycle cancellation

We occasionally find that the ovaries fail to stimulate, and cancelling the cycle may be recommended. Less than 5% of cycles are cancelled.

A cycle might be cancelled because:

- Your follicles are not responding to hormone treatment, or might ovulate prior to trigger
- Your follicles are over-responding to the hormones, risking hyperstimulation
- Uterine problems such as fibroids or polyps are unexpectedly detected on ultrasound
- Personal reasons.

If you're at risk of hyperstimulation or if a problem is discovered in the uterus, your doctor might suggest that you have a 'freeze-all' cycle rather than cancel the cycle completely. In a freeze-all cycle, the eggs are collected and fertilised then cryo-stored. Because pregnancy or further hormone injections will worsen the risk of ovarian hyperstimulation syndrome

(OHSS), a freeze-all cycle is a safer option. This gives the ovaries time to settle down before attempting pregnancy at a later date.

When returning for the frozen transfers there is no need to have any stimulation of the ovaries at all.

Multiple pregnancy risk

At Genea, we'd like to help you grow your family one healthy baby at a time. So as a rule, we only transfer one embryo. The risk of a twin pregnancy after a single blastocyst transfer is around 2%. In certain circumstances, such as older age of the woman or previous unsuccessful treatment, we will consider transferring two embryos.

If you've had trouble conceiving, the idea of having two babies at one time might seem like a blessing. However, severe prematurity is much more likely, leading to abnormalities and developmental delay, and the death rate of twins between 5 and 9 months of pregnancy is 6 times that for single baby pregnancies, while the mortality rate from IVF twins following birth is 4.5% or nearly 1 in 20.

In 2002, Genea undertook a study in a special subset of couples who had several high quality embryos suitable for both transfer and freezing. We compared the 'take home baby' rate in women under 38 who had two embryos transferred during the fresh cycle with those who had one embryo transferred fresh. Both groups later had frozen embryo transfer cycles if they needed them. The end result was the same: approximately 70% of women in both groups took home a baby after one stimulated cycle. However, five babies died from premature delivery among the IVF treatments where fresh embryos had been transferred two-at-a-time.

Risks of medications

Since ovarian stimulation medications were first used decades ago, there has been concern that their use might increase the risk of cancer. Several large studies have now found that the rates of cancers among women who have used infertility drugs are not significantly different from the rest of the population. There is no evidence to date that the drugs used in assisted conception cause either breast or ovarian cancer.

No fertilisation; no embryo development; no implantation

Fertilisation can fail, and fertilised eggs can fail to divide or undergo cleavage properly. The reason can lie with the sperm (usually fertilisation failure rather than cleavage failure), with the egg, or both. And sometimes it can lie with the lab.

Fertilisation can fail when not enough sperm attach to the egg's surrounding coat. This can happen because the number of healthy sperm is too low, or because there are antisperm antibodies that prevent sperm from attaching.

Either way, future cycles can overcome this problem by using ICSI. In addition, fertilisation and/or cleavage might fail if the follicles from which the eggs were extracted had begun to fail prior to egg collection. This can be an inherent problem with the ovaries or it can result from suboptimal stimulation.

Most embryos that fail to implant and/or fail to result in a baby (even though they might look normal in the lab) fail through a combination of intrinsic and extrinsic shortcomings. Intrinsic shortcomings might be based on insufficient metabolic energy or an abnormal chromosome count. Extrinsic shortcomings might occur during follicular stimulation or during laboratory handling.

Stresses associated with infertility

IVF treatment can be stressful and intrusive. There are various reasons for this including:

- Demands of stimulated treatment (daily injections, the need for blood tests early in the day, ultrasounds etc)
- Stresses associated with procedures (having an invasive procedure; the discomfort sometimes experienced; providing a semen sample on the day of the egg pick-up)
- Stresses associated with periods of waiting (such as waiting for fertilisation results; pre-embryo checks; and the long wait between transfer and pregnancy test, then the wait for the pregnancy test result)
- The possibility of treatment not being successful.

Luckily, stress itself does not jeopardise the chance of IVF working. Many people have remarked that they have felt worn down by the stresses and the losses associated with infertility. It's not uncommon for people to experience grief in response to the many losses experienced, as well as other emotional responses such as depression and anxiety. With this in mind, you should be aware that Genea provides counselling services that can greatly assist in managing this emotional impact.

Strategies for coping

Talking to supportive friends or family members can be helpful for some people, while others find it only adds to their burden. Some people have found distraction to be a useful coping strategy – pursuing activities or hobbies that require their full attention – in order to 'take time out' from the process of treatment.

Other people have reported that engaging in activities that gives them a sense of achievement was of some benefit. Some people learn specific relaxation techniques, for example yoga or meditation, to help them manage some of the stresses, while also reducing muscle tension and general anxiousness.

Others have reported that being able to talk to one of the nurse coordinators, who can answer questions and provide reassuring support, was helpful to them.

Counselling

At Genea we have a team of dedicated professional counsellors who are available to see you before, during or after treatment. People undergoing infertility treatment often wonder why, when or whether they should seek counselling. The treatment process can mean that some couples experience a roller coaster of emotions depending on the length of treatment and its outcome. The understandable stresses associated with impaired infertility can start to impact on all aspects of one's life. Undertaking counselling is one strategy to help manage these stresses.

Dealing with infertility can be isolating and lonely particularly if you have chosen not to confide in anyone about your treatment. It is also not uncommon for partners to react to infertility very differently and this can put a strain on any relationship. Maintaining a sense of balance and equilibrium at this time can be difficult. Sometimes, just finding out how others cope and whether your reactions are 'normal' can alleviate some anxiety.

You can choose to see a counsellor with your partner or alone. We also provide telephone counselling if you are not able to come for a face-to-face session. There is usually no charge for the counselling service provided to Genea patients. There is a charge for counselling that precedes egg donation, sperm donation, or surrogacy.

At regular intervals throughout the year, the counselling department runs Mind/Body groups for women,

to teach stress management and relaxation within a supportive environment. Other information seminars are also held several times a year.

Please visit **genea.com.au** for details of forthcoming groups or events. The counsellors can be contacted via the main Genea telephone number and welcome hearing from you.

Informed consent

There are many things you must be aware of before starting assisted conception treatment, all of which cannot be detailed here. The general risks and hazards associated with assisted conception and IVF are reviewed thoroughly in a separate document (printed on pink paper so you'll recognise it).

Before you start treatment with Genea you must sign forms in which you confirm that you have read these 'pink sheets' and the consent forms themselves. It's important to us that you are completely comfortable with your treatment and that you decide to go ahead with it only on a fully informed basis.

If you have questions or concerns, please raise them with your doctor or your nurse before you sign your forms.

World-leading success

Here is an example of how our world leadership translates into success. In a study of patients under 36 who came to us having failed to fall pregnant at other clinics, 66% took home a baby.

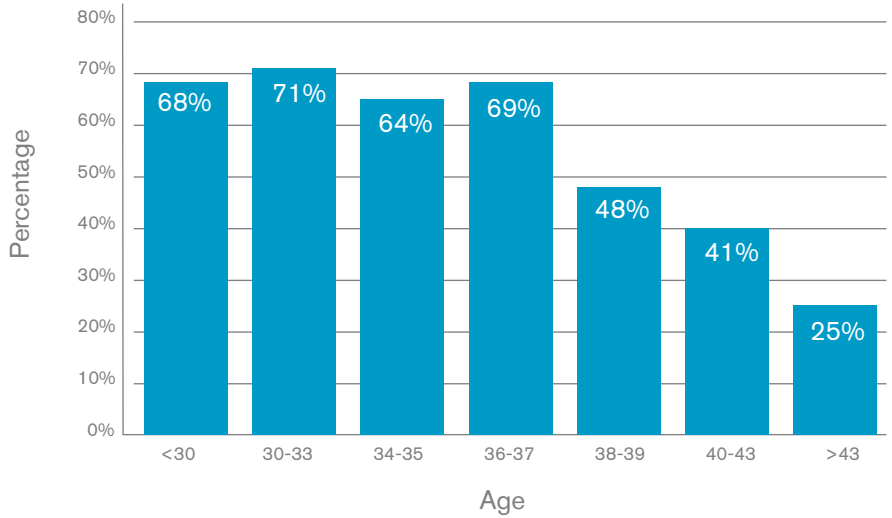
These were patients who had not been able to fall pregnant at other clinics – and nearly seven out of ten of them were successful with us.

What's more, because of our world-leading science and care, close to 100% of our patients who fall pregnant do so within three cycles. And women under 38 with high grade embryos have a 65% chance of having a baby from just one egg collection.

This is critically important. Patients at other clinics can undergo large numbers of cycles over a long period of time. This is financially and emotionally draining and at Genea we find it completely unacceptable.

It is reassuring for our patients to know that not only can no clinic worldwide offer them a better outcome than Genea, no clinic can offer a more timely outcome.

90 per cent of patients who have a baby do so within three or less cycles of IVF. Overall, almost 60 per cent of our patients - regardless of age - will have a baby.

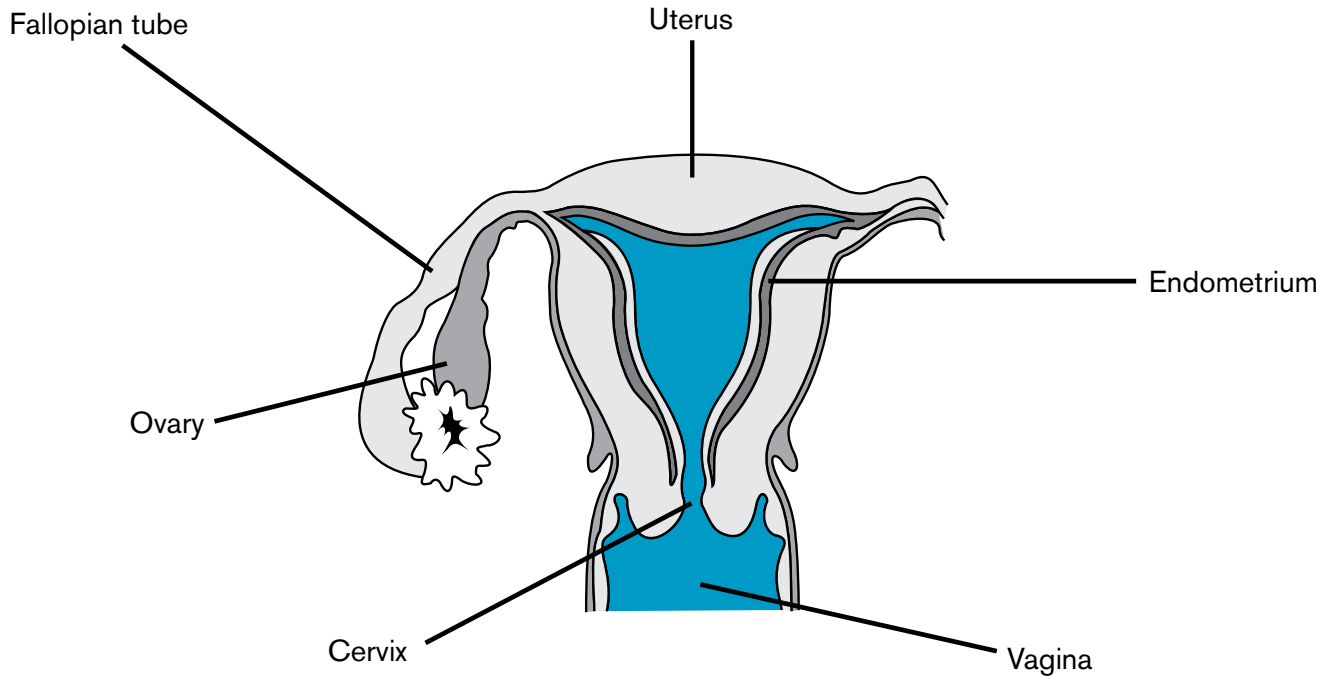


These figures are based on all the couples who started IVF at Genea clinics during a five-month period in 2009, who were followed through their IVF journey and shows the percentage of those women who now have a baby.

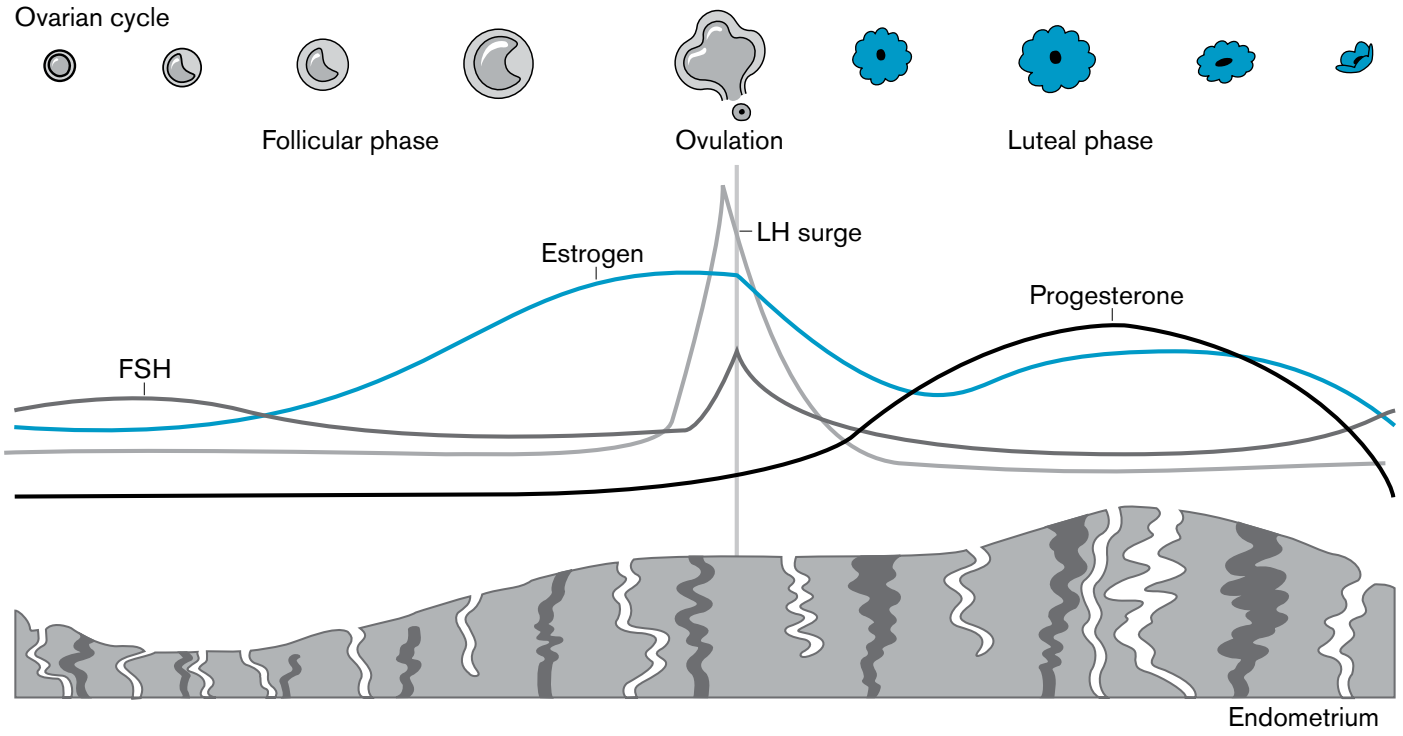
Useful diagrams

Your Genea accredited doctor might use these diagrams in explaining the processes of natural and assisted conception. For more information about the process of human fertility and a more detailed explanation of the many medical words and phrases that arise, visit **genea.com.au**

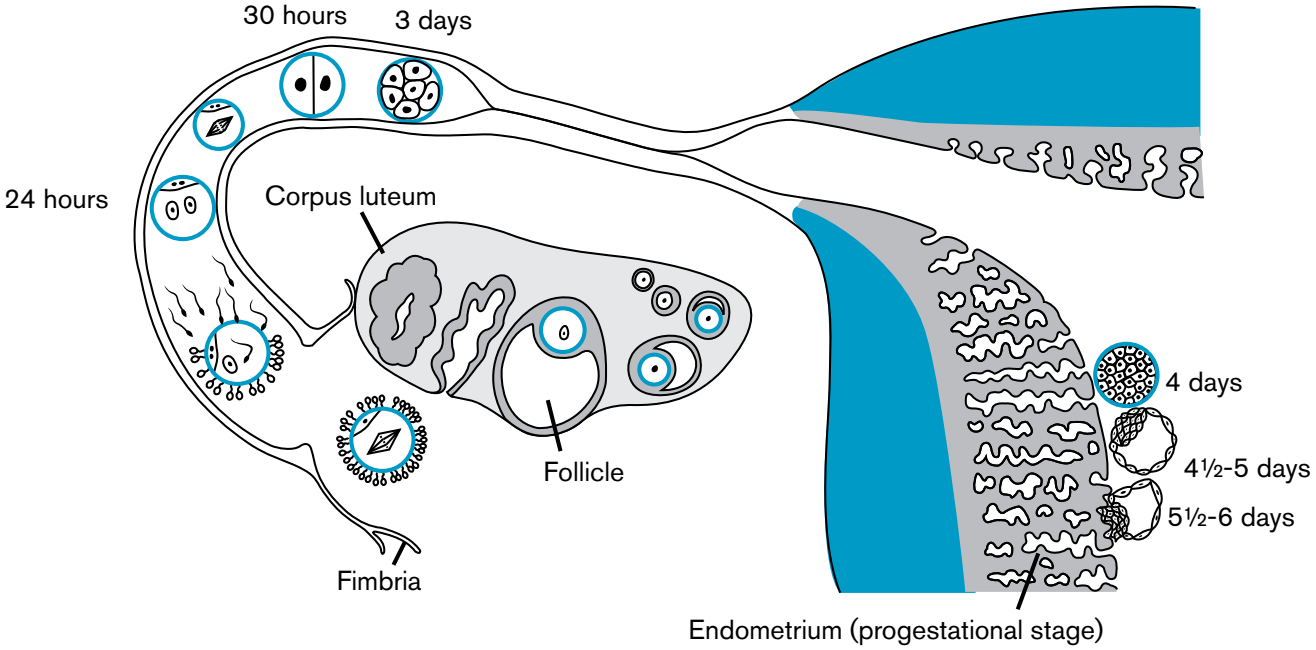
Uterus and fallopian tubes



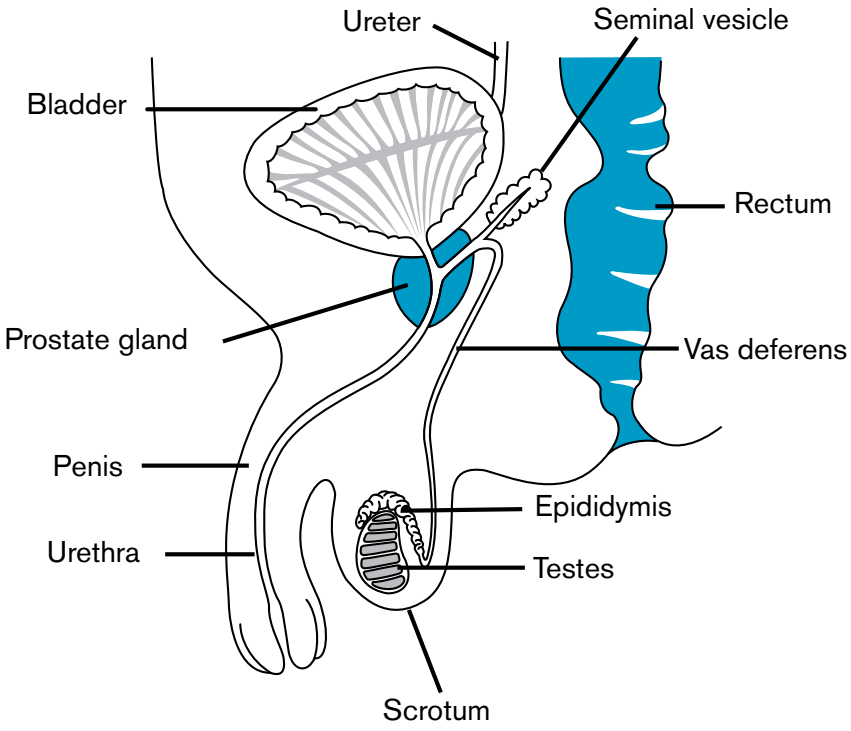
Menstrual cycle



Fertilisation and embryo development in nature



Male reproductive system



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