

INTRA-CYTOPLASMIC SPERM INJECTION (ICSI) AND ITS POSSIBLE EFFECTS ON HEALTH



Intracytoplasmic sperm injection (ICSI) is a technique used to help an egg become fertilised by directly inserting a sperm into the egg in the laboratory. This increases the chance of fertilisation when there are problems with male fertility, including low sperm count or problems with sperm function.

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The purpose of this document

VARTA provides independent information and support for individuals, couples, and health professionals on fertility, infertility, assisted reproductive treatment (ART) and the best interests of children born from ART.

This brochure is intended as a general introduction to this topic and should not be seen as a substitute for advice from doctors or other health professionals.

Information contained in this brochure was correct at the time of writing; however, as technology advances rapidly and new studies are conducted, it is important to check information with your fertility specialist.

Further information can be obtained from ART clinics and clinical genetics services.

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Common terms and their meanings

ART: Assisted reproductive treatment. Technological and other methods to achieve pregnancy.

Azoospermia: A condition in men where no sperm are found in the semen.

Chromosome: The gene packaging in a cell. Every cell has two copies of each chromosome – one from each parent.

Clinical pregnancy: A pregnancy confirmed by a blood test and ultrasound, usually performed at around six to eight weeks.

Cytoplasm: All the material within a cell other than the nucleus.

DNA: Deoxyribonucleic acid; molecule that contains the genetic code that determines the characteristics of the organism.

DNA fragmentation: Strands of DNA broken into smaller pieces.

Embryo: The stages of development of a fertilised egg up to 11 weeks gestation.

Fertilisation: The moment when the DNA from a sperm and egg combine.

Gamete: A mature reproductive cell, such as a sperm or egg (ovum).

Gene: Section of DNA that contains the instructions (genetic code) to make molecules and proteins. Every person has two copies of each gene – one from each parent.

Genetic abnormality: Missing or additional portions of DNA in the chromosomes within a cell, or an abnormal number of chromosomes.

Hypospadias: A malformation in boys where the urinary opening is not located at the head of the penis, but instead is found along the underside of the penis or, in rare cases, within the scrotum.

In-vitro: Literally means “in glass”. Refers to techniques being performed in laboratory containers such as petri dishes, test tubes and flasks.

In-vitro fertilisation (IVF): An assisted reproductive treatment where an egg and sperm are combined in the laboratory before being transferred to the woman’s uterus.

Male factor infertility: Infertility related to sperm count and/or motility and/or morphology, or ability to engage in intercourse or ejaculate.

Morphology: Shape and structure.

Motility: Ability to move.

Nucleus: The compartment inside a cell that contains the genetic material (DNA)

Oocyte: An immature egg cell, which matures into an ovum.

Oligospermia: Low sperm count (less than 15 million sperm/ml).

Ovum (plural ova): A mature egg. The female reproductive cell.

Semen: The fluid that is produced in the male reproductive tract that carries the sperm.

Spermatozoon (plural spermatozoa): Sperm, the male reproductive cell.

Testicular sperm aspiration (TESA): A method where sperm are collected directly from the testicles under anaesthetic.

Testicular sperm extraction (TESE): A method where a biopsy is collected from the testicles under anaesthetic to collect sperm.

Vas deferens: Tube that carries sperm from the testicles to the urethra for ejaculation.

Zona pellucida: The outer layer of the egg.

Zygote: The single cell formed by the combination of DNA from a sperm and an egg through fertilisation.

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What is intra-cytoplasmic sperm injection (ICSI)?

ICSI is an assisted reproductive technique where a single sperm is injected directly into an egg to assist fertilisation.

How is ICSI different from IVF?

In IVF, the eggs and several thousand sperm are placed together in a petri dish in the laboratory. The sperm are left to spontaneously find and fertilise the egg. Once a sperm has penetrated the outer layer of the egg, no other sperm can enter. Inside the egg, the sperm starts a reaction that causes the DNA of the egg and sperm to combine. This is the moment of fertilisation. The fertilised egg is then left to develop in the laboratory for two to five days.

In ICSI, the sperm does not have to travel to find the egg, or penetrate its outer layer. Instead, a single sperm is selected by the scientist and injected directly into the egg using a tiny needle. The following day the egg is checked to see if has been fertilised. The fertilised egg is then left to develop, just like in IVF.

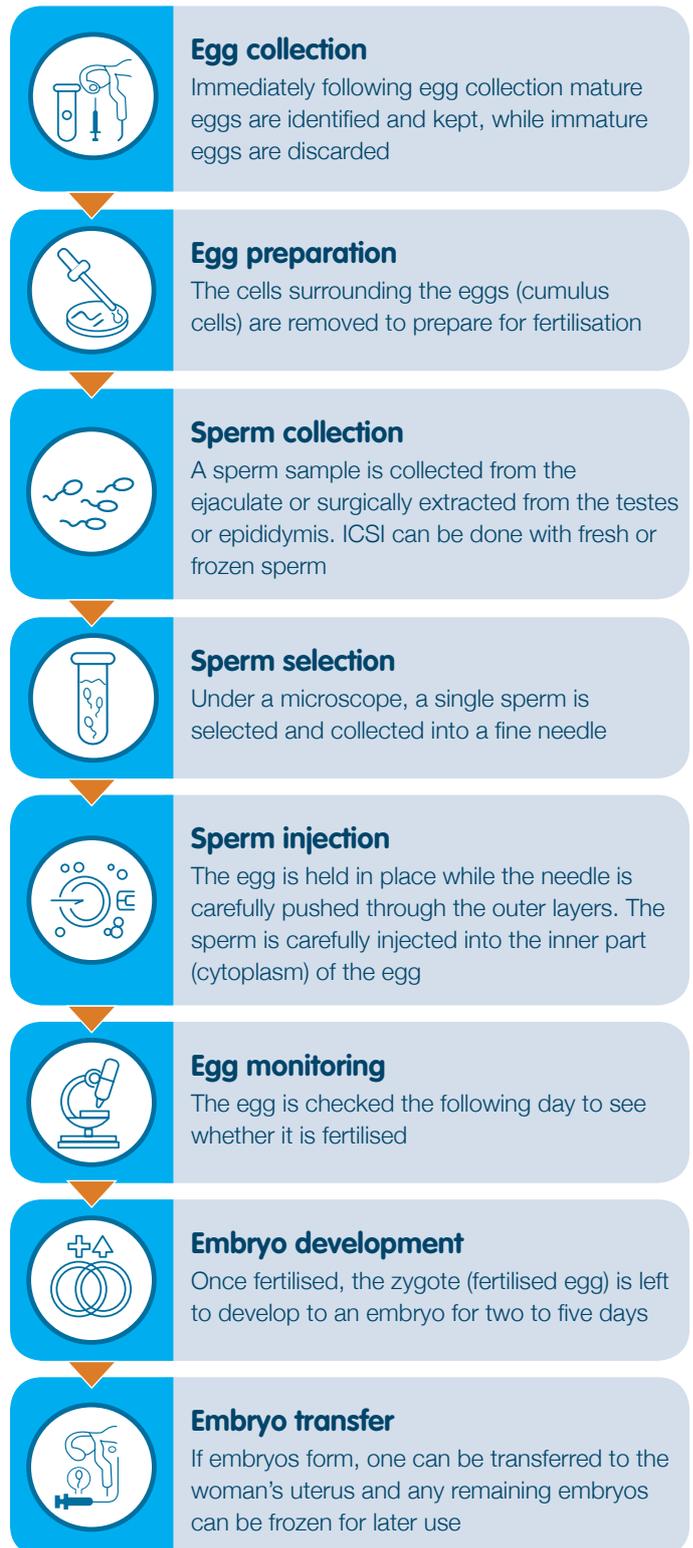
When is ICSI performed?

ICSI is most commonly used for male factor infertility, which includes low sperm count, low sperm motility (movement), poor sperm morphology (shape) and problems with ejaculation. ICSI is also used when men have anti-sperm antibodies. It may also be used in cycles involving frozen partner sperm, donor sperm, frozen eggs, or when no eggs become fertilised in a previous cycle with IVF.

For most men, sperm are collected from the ejaculate. In men with no sperm in the ejaculate (azoospermia) due to very few sperm being produced or a blockage in the tubes from the testis, sperm must be surgically collected from the testicle or epididymis under anaesthesia. ICSI is the only fertilisation option for these men. Such cases include men with a vasectomy or unsuccessful vasectomy reversal, or in those where sperm production is extremely poor yet a few sperm can be taken directly from the testis.

What does ICSI involve?

Eight steps used in ICSI



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Sometimes all embryos are frozen and replaced one by one in subsequent cycles.

Unfortunately, some eggs are damaged in the ICSI process and are unable to be used further. This occurs in less than two per cent of cases.

Sperm selection

Where possible, sperm are chosen based on their physical appearance (size and shape) and their motility (movement). In general, healthy sperm have an oval shaped head and a long, extended tail, allowing them to move vigorously. However, these visible features do not guarantee the sperm are genetically normal.¹

Some clinics use an extra step to help select sperm for ICSI. This can be based on physical structure under a high-powered microscope, or binding of sperm to materials such as hyaluronan gel (a substance similar to one found naturally surrounding the egg). These sperm selection methods can add to the cost of ICSI, yet there is no conclusive evidence they increase the chance of having a live baby.²⁻⁵

Does selecting sperm for ICSI bypass natural selection?

In spontaneous conceptions, it is generally believed the fastest and fittest sperm is the first to find and fertilise the egg. This sperm has managed to get past all the natural barriers to fertilisation: it has travelled the long distance through the female reproductive tract and competed with all the other sperm to be the first to fertilise the egg.

A degree of natural selection also occurs in IVF. This is because many sperm are added to each egg in the laboratory. While these sperm do not have to travel to find the egg, they still compete with the other sperm to be the first to get through the outer layer.

A concern with ICSI is that there is no natural process for sperm selection. In ICSI, a single sperm is selected by the embryologist, who injects it straight into the egg. Although care is taken to choose sperm based on their appearance and movement, this may not result in selection of the healthiest sperm. Theoretically, if the selected sperm has a chromosomal or genetic abnormality, this could affect the embryo. Potentially, this may result in fertilisation failure, abnormal embryo development, failure to implant, miscarriage or lead to a child with genetic defects. It is impossible to see chromosomal or genetic abnormalities through a microscope.



In ICSI, the sperm are injected directly into the egg using a very fine needle.

Does ICSI improve success rates compared to IVF?

The chance of a successful pregnancy and healthy baby following either IVF or ICSI depends on many factors including age, reason for infertility, genetics, lifestyle (e.g. smoking, weight), and quality and number of embryos reaching the blastocyst stage. For more information on these factors, see the VARTA website www.varta.org.au.

Fertilisation rates: ICSI typically results in quite high fertilisation rates (around 50-80 per cent). However, fertilisation does not guarantee that the embryo will develop further, or result in a pregnancy or live birth of a healthy baby.

Pregnancy and live birth rates: Following fertilisation, there is no difference in the chance of pregnancy or live birth between IVF and ICSI when used for male factor infertility⁶. For other causes of infertility, pregnancy and live birth rates with ICSI appear lower than with IVF.^{6,7} If more than one or two embryos develop, they can be frozen and used in subsequent cycles. This adds to the chance of having a baby after ICSI and IVF.⁸

What are the possible risks of ICSI on the pregnancy?

For IVF, ICSI and spontaneously-conceived pregnancies, older maternal age, obesity, and smoking all increase the risk of pregnancy complications and adverse birth outcomes. If you are proceeding with treatment, you should discuss potential pregnancy-related risks with your fertility specialist, who can provide advice relevant to your particular circumstances.

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The risks of pregnancy loss and adverse birth outcomes after ICSI must be viewed in the context of how often problems occur in spontaneously-conceived pregnancies in Australia.

Current Australian data for all pregnancies and births show that approximately:

- one in six pregnancies will miscarry
- one in 145 babies will be stillborn
- one in 12 babies will be premature
- one in 25 babies will have a birth defect
- one in 500 babies will die around the time of birth
- one in 400 children will have cerebral palsy and be disabled.

Most pregnancies conceived by ICSI proceed without complications. However, compared to spontaneous conceptions, both IVF and ICSI carry a small increase in the risk of still birth, premature birth, low birth weight and multiple birth.^{9, 10}

Studies show that the risk of miscarriage after ICSI is around 20% which is the same as after IVF.⁶

What are the possible risks of ICSI for the child?

The vast majority of babies born as a result of ICSI are healthy and have no short or long-term problems. When health effects are found, it is difficult to determine whether these are due to the underlying health problems that contribute to infertility, the egg and/or sperm retrieval processes, or the ICSI procedure.

Birth defects

A summary of studies conducted between 2000 and 2016 reported around one child in 14 conceived by ICSI have a birth defect.¹¹ This is similar to the rate seen after IVF,¹² but higher than in the general population, where birth defects occur in one in 25 children. Defects include chromosomal conditions, cardiovascular defects, abnormalities of the urogenital system (including hypospadias), neural tube defects, cleft lip or cleft palate, and malformations of the gastrointestinal and musculoskeletal systems.¹¹

Development

In studies where children conceived with ICSI are compared to other children, no differences are found regarding when they reach developmental milestones, their growth, vision, hearing, motor function (movement), cognitive function (language and memory skills) or in rates of cerebral palsy^{13,14}. An improved understanding of other health endpoints in ICSI conceived children will be gained with further study.

Long term reproductive health and fertility

The oldest children conceived through ICSI for male factor infertility are only now reaching adulthood. Studies of male offspring in adolescence and adulthood show:

- normal pubertal development^{15, 16}
- normal Sertoli and Leydig cell function (the cells in the testes that regulate sperm development and release testosterone)¹⁶⁻¹⁸
- normal testosterone levels¹⁸
- lower average sperm counts and lower sperm motility.¹⁹

A better understanding of the reproductive health effects will be gained as more children conceived through ICSI reach adulthood.

What are the possible risks of ICSI to the male partner?

In most men, sperm for ICSI is collected from the ejaculate, with no risks to them. In some infertile men, sperm cannot be collected from the ejaculate. When this happens, sperm for ICSI may be retrieved surgically either by needle biopsy of the testicles under local anaesthesia, or open biopsy under general anaesthesia. These procedures are associated with minor risks related to the operation itself and use of anaesthetics. Local bleeding or infection occurs in less than one per cent of open biopsies; needle biopsies carry an even lower risk of complications. However, in rare cases, severe bleeding may occur with the risk of losing the testis.

Some men with severely reduced sperm production have low testosterone levels, or risk developing testosterone deficiency later in life. Biopsies of the testes can, on occasion, further reduce testosterone production, resulting in the need for lifelong testosterone replacement therapy.

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FAQs

Does ICSI damage the egg?

While all care is taken during the ICSI process, there is a small chance (less than two per cent) that the egg will be damaged and unable to be used for further treatment.

Does ICSI increase the risk of birth defects?

In a summary of all studies carried out between 2000 and 2016, birth defects were observed in up to seven per cent of children conceived by ICSI and IVF, which is higher than seen among children conceived spontaneously (four per cent). Many factors may be responsible for this increase, such as the underlying cause of infertility or the procedures used to retrieve eggs and/or sperm.

Can frozen sperm be used for ICSI?

Yes. Both frozen (thawed) and fresh sperm can be used.

Can embryos be frozen after ICSI?

Yes, there are often more embryos than can be transferred after a treatment cycle. These can be frozen for use in later cycles.

Should I use ICSI before trying IVF?

Clinical guidelines point to ICSI being used for severe male factor infertility or when previous IVF attempts have been unsuccessful. For other causes, ICSI does not improve the chance of fertilisation, pregnancy or a live birth. ICSI usage rates, however, have increased markedly in recent years and now exceed 75 per cent in many clinics. This is probably due to the belief that ICSI gives more reliable fertilisation rates than IVF. The decision to use ICSI will depend on your personal circumstances and should be discussed with your fertility specialist.

Why doesn't ICSI guarantee fertilisation if the sperm and egg are manually combined?

Fertilisation happens when the DNA of the egg and sperm combine. This does not always happen despite the sperm being injected directly into the egg. Fertilisation can depend on other factors, including the quality and maturity of the egg and sperm.

How long before I know if fertilisation has occurred following ICSI?

Your fertility specialist will be able to tell you within 24 hours if the ICSI process has resulted in fertilisation.

Does washing the sperm and processing the eggs before ICSI affect the embryo?

These procedures are necessary for ICSI. The sperm are washed to enable identification of the healthiest looking sperm. The cells from around the egg are removed to allow the embryologist to check the maturity of the egg and inject the sperm in the right place. There is no evidence that either of these procedures harm the developing embryo.

Does ICSI cost more than IVF?

Yes. A highly experienced embryologist and special equipment are required to perform ICSI. It is therefore more expensive. Costs vary between clinics.

Can I have half my eggs fertilised by ICSI and the other half by IVF?

Some clinics offer this as an option just in case IVF does not result in fertilisation. In general, ICSI is not needed unless there is male factor infertility. However, the best method to fertilise the eggs will depend on your personal circumstances and should be discussed with your fertility specialist.

Remember, there is no such thing as a bad question to ask your fertility specialist. They are there to help you.

Assisted reproductive treatment is a very personal experience and it is important you understand the procedure and your options. It can take a while for this information to sink in. Asking questions and seeking help from both fertility specialists and your own support people can reduce some of the stress through this challenging time.

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VARTA

Victorian Assisted Reproductive
Treatment Authority

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Phone: + 61 3 8601 5250

Email: varta@varta.org.au