

Patient information Leaflet

Intracytoplasmic Sperm Injection (ICSI)

Intracytoplasmic sperm injection (ICSI) was introduced into clinical practice for certain types of infertility in 1992. The London Women's Clinic has offered ICSI since 1994.

The female partner undergoes the same drug regime and egg collection procedure as in standard IVF treatment. The male partner produces sperm, either in the normal way or through surgical retrieval.

ICSI uses sperm that would otherwise not be able to fertilise an egg, so the main difference between ICSI and IVF is what happens in the laboratory. In standard IVF treatment, many thousands of sperm are mixed with each egg and it is hoped that one of the sperm will penetrate the zona pellucida (outer shell of the egg) to begin the fertilisation process. When ICSI is used, a single sperm is injected directly into the cytoplasm of a mature egg. ICSI circumvents several steps in the natural fertilisation process, such as sperm-zona binding, zona penetration and fusion of the gametic cell membranes.

Any damage to the eggs is observed at the time of the injection procedure and the damaged eggs are not used. An average of 10% of the eggs is generally discarded. The eggs that fertilise are then allowed to develop over the next few days. Embryo transfer is carried out as in a standard IVF treatment cycle.

According to HFEA regulations, eggs that have failed to fertilise after 24 hours during a standard IVF procedure are not to be used in ICSI treatment. Only in exceptional circumstances is it allowed to transfer 'mixed embryos', resulting from ICSI as well as from IVF in the same treatment cycle.

ICSI is indicated when the sperm count is very low, when sperm cannot move properly or are in other ways morphologically abnormal and in cases of high levels of anti-sperm antibodies in the semen. ICSI may also be used when fertilisation has failed in previous IVF attempts, when there has been a repeatedly poor response to ovarian stimulation and when sperm have been surgically retrieved directly from the epididymis (PESA) or the testicles (TESA/TESE).

It is possible that the risks from ICSI are not fully understood and it is important to read the following information from HFEA if you are considering undergoing treatment.

The Human Fertilisation and Embryology Authority – Patient Information: ICSI

Introduction

The Human Fertilisation and Embryology Authority (HFEA) is the statutory body that regulates in vitro fertilisation (IVF) treatments including ICSI. One of the HFEA's responsibilities is to give advice and information to people seeking licensed fertility treatment. The HFEA has produced this information to explain some of the recent medical and scientific studies relating to the use of ICSI and the implications this may have for patients.

Before deciding upon a particular treatment, patients should have an opportunity to weigh up the benefits and risks of that treatment. Your treatment centre is required by law to offer you counselling about the implications of any proposed treatment. It is important that the counselling offered to you should include genetic implications, especially for men who have very few sperm (severe oligozoospermia) or no sperm (azoospermia) in their semen and men with Klinefelter's Syndrome. Pre-natal diagnosis may be of help in considering individual risks. The centre will also be able to provide you with information specifically about ICSI and answer any questions you have. This leaflet deals with general issues surrounding the ICSI technique.

ICSI was introduced into clinical treatment for certain types of infertility in 1992. ICSI is a type of IVF treatment that involves the injection of a single sperm straight into each egg. The fertilised egg (embryo) can then be transferred into the womb of the woman as in a normal IVF cycle. ICSI is a relatively new technique but has already helped many couples. The live birth rate for ICSI and conventional IVF are similar.

What does ICSI involve?

In conventional IVF the eggs and the sperm are mixed together in a dish and the sperm fertilise the eggs naturally. ICSI bypasses the natural processes involved in a sperm penetrating an egg and is therefore used when there are problems that make it difficult to achieve fertilisation naturally or by conventional IVF. Circumstances in which ICSI may be appropriate include:

- When the sperm count is very low
- When the sperm motility is low.
- When the abnormal forms are high
- When sperm has been retrieved directly from the epididymis (PESA) or the testicles (TESA/TESE), from the urine or by electro ejaculation
- When there are high levels of antibodies in the semen
- When there have been previous fertilisation failure

Patients who do not fall into these categories may wish to discuss any concerns about their treatment with their clinician.

Men who have very few sperm (oligozoospermia) or no sperm (azoospermia) in their semen, or who have high numbers of abnormal sperm that are unable to fertilise and egg, would

previously have had little or no chance of fathering their own genetic offspring. ICSI offers these men and their partners real hope of having a genetically related child.

What are the risks of ICSI treatment?

ICSI like IVF is an invasive procedure. However, unlike IVF, ICSI involves injecting a sperm directly into an egg, therefore allowing the use of sperm that may not otherwise be able to fertilise an egg. For these reasons, concerns about the potential risks to children born as a result of the ICSI have been raised, and several follow-up studies have been published.

The HFEA reviews the evidence on an ongoing basis. ICSI is still a relatively new technique and all children conceived using ICSI are still very young. Consequently, these follow-up studies involve relatively small numbers of children and do not include effects that may only be seen in older children or the next generation. The HFEA considers follow-up studies to be extremely important and would encourage patients to talk to their treatment centre about participation in such studies.

Clearly, more studies are needed, but the use of ICSI has been potentially linked with certain genetic and developmental defects.

- Possible inheritance of genetic and chromosomal abnormalities:

Inheritance of cystic fibrosis gene mutations: Some men who have no sperm in their semen are found to have congenital bilateral absence of the vas deference (CBAVD). In this condition, the tubes that carry sperm from the testes to the penis are missing. Two thirds of men with CBAVD are also carriers of certain cystic fibrosis mutations. Men with CBAVD and their partners may therefore wish to undergo genetic testing before proceeding with ICSI. Your treatment centre should be able to give you more information and counselling about the implications of genetic testing.

Sex chromosome defects and the inheritance of sub-fertility: A small proportion of sub-fertile men have parts of the Y chromosome missing (deleted). Certain genes on the Y chromosome have been shown to be involved in the production of sperm, and deletion of these genes may be responsible for some men having few or no sperm in their semen. Consequently, using sperm with such deletions to create an embryo may result in the same type of sub-fertility being passed from father to son.

Abnormal numbers or structures of chromosomes: The sex chromosomes (X & Y) in particular may be associated with infertility in both men and women, and babies born from ICSI treatment may have a slightly increased risk of inheriting these abnormalities. Studies have found that up to 3.3% of fathers of ICSI babies have abnormal chromosomes. It is estimated that up to 2.4% of the wider population have a chromosomal abnormality.

- Novel chromosomal abnormalities

The complexity of the process of egg and sperm production means that even if an individual possesses a normal number of chromosomes, their gametes could potentially have an abnormal number. It is not possible to detect beforehand which eggs or sperm have chromosomal abnormalities, and gametes that might not have been able to participate in natural fertilisation could therefore be used in ICSI. Babies born after ICSI have been

reported to have new chromosomal abnormalities in up to 3% of cases. The rate in the general population is around 0.6%.

- Possible developmental and birth defects

There is not yet any clear evidence whether ICSI results in higher rates of birth defects. The number of babies reported to have major birth defects, such as cleft palate, is between one and five % in both the general population and in babies born following ICSI. Studies suggest that minor abnormalities occur in up to 20% of ICSI babies, compared to up to 15% of the population. For example, one recent study has shown a three fold excess risk in the rate of the relatively rare problem hypospadias following ICSI. More studies are needed in order to gain further insight into these possible effects.

- Possible risks during pregnancy

Miscarriage: With ICSI it is possible that abnormal gametes, which would not usually be able to produce a viable embryo, could be used. This may increase the chance of an abnormal embryo being formed. However, most abnormal embryos will not implant into the womb and grow, but some might, leading to a possible higher risk of miscarriage. It has been reported that the risk of miscarriage increases in proportion to the severity of male infertility.

Medical and scientific information changes rapidly and the HFEA endeavours to keep patients and clinicians up to date with all relevant developments to help patients review their treatment options.

GLOSSARY

Azoospermia – complete absence of sperm in the ejaculate

Electro ejaculation – the use of electrical stimulation to aid production of a semen sample in impotent or paralysed men

Epididymis – coiled tubing outside the testicles which store sperm

Gametes – male sperm and female eggs

Hypospadias – congenital abnormality, affecting male offspring, in which the opening of the urethra is misplaced or malformed.

Klinefelter's syndrome – men with an extra X chromosome (47XXY)

Oligospermia – low numbers of sperm in the ejaculate.

PESA – (percutaneous epididymal sperm aspiration) sperm retrieved directly from the epididymis using a needle.

TESA – (testicular sperm aspiration) sperm retrieved directly from the testes using a needle.

TESE – (testicular sperm extraction) sperm retrieved from a biopsy of testicular tissue.

This HFEA information about ICSI was last updated in June 2006.

PATIENT INFORMATION SHEET

SCORING OF EMBRYOS

The day of you ET will be dependant on the number and quality of your embryos. To help the embryologist choose the correct embryos for the transfer, the embryos are scored according to a number of different factors:

1. Number of cells
2. Size and colour of these cells
3. The amount of fragmentation that has occurred whilst the cells have been dividing

The number of cells that we expect your embryos to be is shown below:

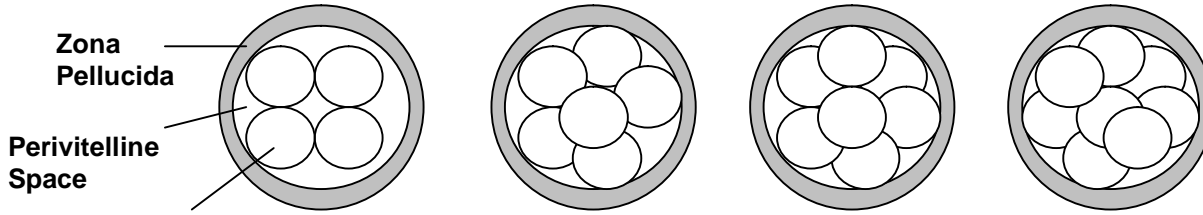
Day 1	1 cell
Day 2	2-5 cells
Day 3	6-9 cells
Day 4	Morula stage 30 cells
Day 5 or 6	Blastocyst 100-150 cells

Before the transfer an embryologist will explain what has happened since your egg collection. This explanation will include the grade of each of your embryos and explain why the embryo received that grade.

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GRADE 1 EMBRYOS

These embryos have cells of an even size, consistent colour and have no fragmentation. Grade 1 embryos have the best implantation rates and will also be considered for cryopreservation (freezing).

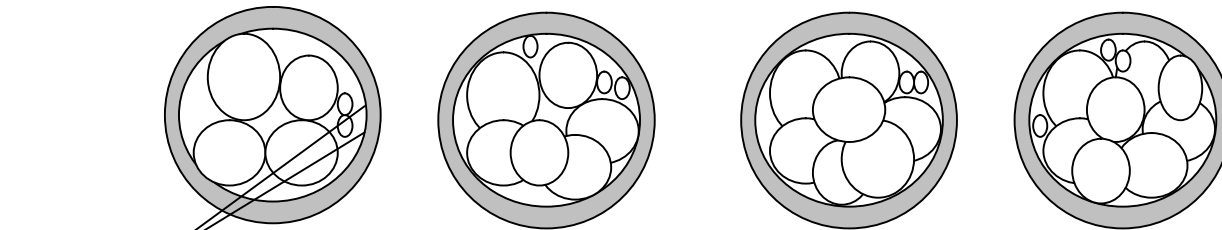


Blastomere (Cell)

Grade 1 embryos (4 cells, 6 cells, 7 cells, and 8cells)

GRADE 2 EMBRYOS

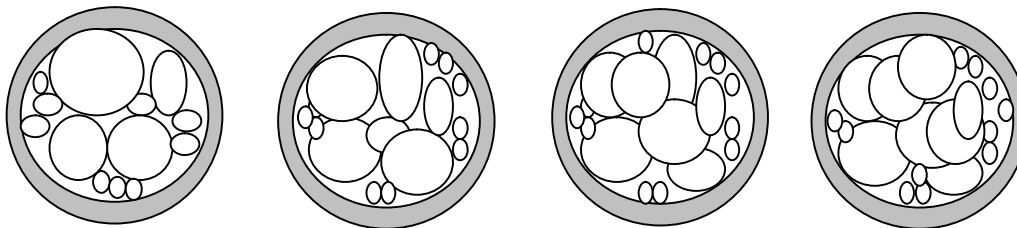
These embryos may have slightly uneven cells, slight fragmentation or both. Like grade 1 embryos, they are good quality embryos with slightly decreased implantation rates.



Grade 2 embryos (4 cells, 6 cells, 7 cells, and 8cells)

GRADE 3 EMBRYOS

These embryos have even more uneven cells, more fragmentation or both. The implantation rate for these embryos is probably not as good as for grade 1 or 2 embryos. These embryos have poor implantation rates and are not usually considered for cryopreservation as their survival rate is poor following freezing/ thawing.



Grade 3 embryos (4 cells, 6 cells, 7 cells, and 8cells)

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BLASTOCYST TRANSFER

In select cases we are culturing embryos to the blastocyst stage before transferring them into the uterus. The blastocyst transfer is still a relatively new procedure.

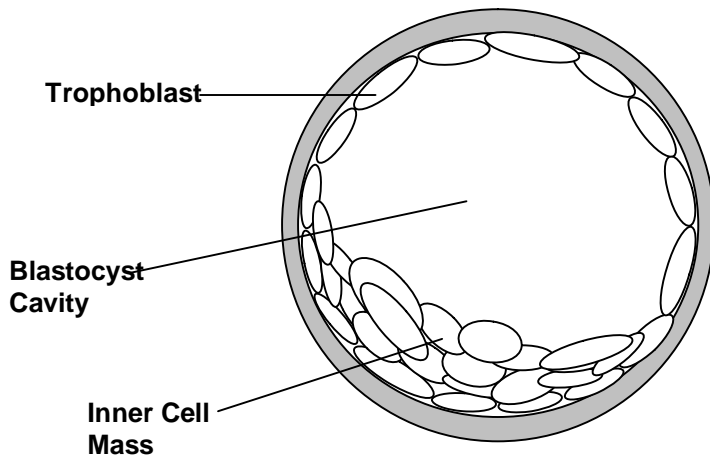
Good quality embryos reach this point usually on day 5 after fertilisation; however, some may take until day 6.

The benefit of a blastocyst transfer is that implantation rates are higher due to two reasons:

1. The transfer timing is more physiological (on day 3 the embryo is in the fallopian tube),
2. The embryo has proved its strength (viability) by surviving in the laboratory for 5 days.

But it should be remembered that sometimes embryos do not survive to day 5 even if they are grade 1. This is important to consider before deciding to have a blastocyst transfer.

The London Women's Clinic routinely performs embryo transfers on day 2 and day 3 and we achieve pregnancy rates equal to those with blastocyst transfer.



A Blastocyst

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