

# Intracytoplasmic Sperm Injection



**Southern Ontario  
Fertility Technologies**

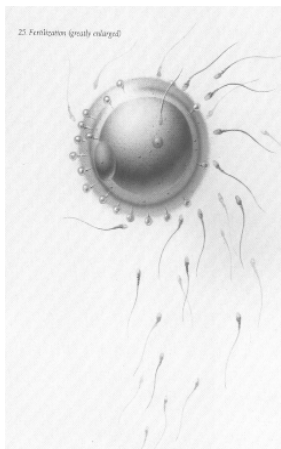
## Introduction

Intracytoplasmic sperm injection refers to the lab procedure in which a sperm is injected in the cytoplasm of an egg. It has been a breakthrough in the treatment of male infertility. Before ICSI, the treatment of male factor infertility was disappointing. Fertilization rates in IVF with severely decreased sperm quality were only half those obtained with normal sperm and nothing could be done for men with no sperm in the ejaculate.

## How ICSI is Done

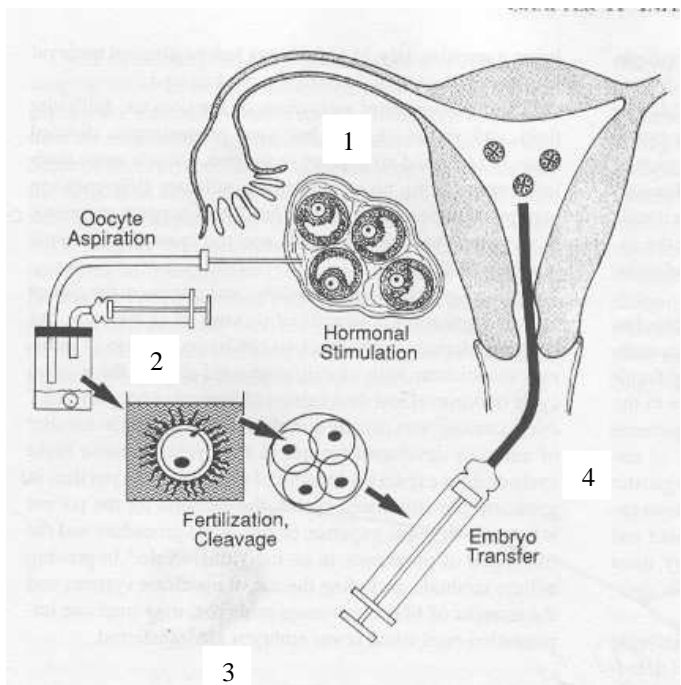
ICSI is performed in an in vitro fertilization cycle. A full information sheet is available on both funded and non-funded IVF. In-vitro refers to something occurring outside of the body, fertilization is the penetration of the egg by a sperm and the mixing of their genetic information. With IVF, the cycle is stimulated to produce multiple eggs. This is depicted below #1 in the diagram to the right. This is not by definition part of IVF but is necessary to improve the success of IVF. In fact, natural-cycle IVF is offered in some countries in the world but its success rate is lower than 5% per cycle.

Once multiple eggs have matured, they are retrieved from the body. This is also depicted in the diagram above next to #1. The next step is fertilization of the eggs with sperm. This is the step that gives IVF its name and is depicted beside #2 in the diagram above and in the picture opposite. In IVF cycles without ICSI, 50,000 to 100,000 sperm are placed with the egg in a Petri dish. One sperm will penetrate the egg and cause fertilization.



However, when this step is completed with ICSI, each egg is stripped of the cells that normally surround it (the nurse or granulosa cells). The egg is then held in a large pipette. A normal appearing sperm is caught and drawn into a smaller pipette. The small pipette is then used to puncture the egg and inject the sperm into the egg. This essentially bypasses the usual fertilization process.

**In IVF without ICSI many sperm are placed with the egg in a Petri dish. Fertilization occurs “naturally”, much the same way as it would occur in the body.**



Once the eggs are fertilized, they become embryos. These are cultured in the lab.

During culturing, the number of cells in the embryo increases and this is depicted beside #3 in the diagram on the first page. Once the embryos have cell divided, they are transferred back into the woman's uterus hopefully to implant and produce a baby. This is depicted beside #4 in the diagram on the last page.

### Indications

ICSI is of course indicated for **“significant” male factor infertility**. The definition of “significant” and the cutoff values for when ICSI will be suggested are vary widely from clinic to clinic and even from physician to physician within the same clinic. This will be discussed in detail when you are considering an IVF cycle.

There are clinics in which everybody gets ICSI. This is justified in those circumstances by the fact that it eliminates the rare situations in which no fertilization occurs. The disadvantage of this approach is that ICSI costs a great deal of money and exposes the eggs to trauma that may not be necessary. Unexpected lack of fertilization is rare (2%) and rescue ICSI (ICSI done after no fertilization is recognized) can be very successful.

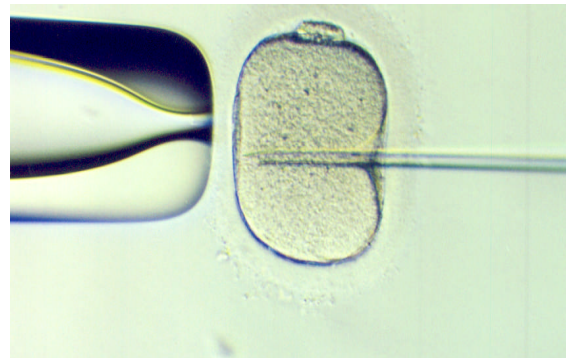
Our approach at S.O.F.T. is to use ICSI only in situations where there has been poor fertilization in previous IVF cycles or if the sperm recovery in previous intrauterine insemination cycles (IUI) has been consistently below 10 million.

In some circumstances we will suggest splitting the eggs retrieved between half ICSI and half conventional IVF. This is usually suggested when the sperm recoveries in previous IUI cycles have sometimes been below 10 million or there have been some semen analysis below the WHO cutoff criteria. The disadvantage of “half-and-half” is that it is the same price as ICSI for all the recovered eggs but the advantage is it usually will clear up any uncertainties about whether ICSI was necessary or not. This is valuable if future cycles are necessary but it also allows for us to just know if it was part of the problem.

### Costs

ICSI has to be done with an IVF cycle because the eggs have to be available outside of the body to perform ICSI. **Costs, therefore not only involve the ICSI procedure but also the IVF cycle and the cost of the drugs used to stimulate the IVF cycle.**

In Ontario, women with bilateral tubal obstruction are covered for IVF. In this situation, the IVF cycle will be covered but the ICSI procedure is not. Funded IVF is available through our clinic in co-operation with Mount Sinai Hospital in Toronto. The cost of the ICSI procedure is



**ICSI – The Egg Is Held By A Larger Pipette. A Smaller Pipette With a Sperm Is Poked Into The Egg and the Sperm Is Injected directly Into The Cytoplasm Of The Egg.**

\$1,500.00 and an administration fee for the IVF cycle is \$1,650.00 for a total of \$3,150.00. We can also do funded IVF through the ISIS clinic in Mississauga and the IVF cycle is \$3000.00 and the ICSI is \$1000.00 or a total of \$4,000.00. If the cycle is not funded, it is done through the ISIS clinic in Mississauga. **The IVF cycle is \$4,500.00 and the ICSI is an additional \$1,000.00 for a total of \$5,500.00.** The only other costs that might be encountered are **\$\*850.00 for embryo freezing and \$200.00 for assisted hatching** if it is required.

Medications for a cycle of IVF usually run between **\$2,800.00 and \$6,000.00.**

**For your convenience, S.O.F.T. carries a supply of most of the drugs that we use for infertility treatment. These can be sold to you at our cost plus a very small handling charge with no dispensing fee. In most cases this will make them less expensive than from pharmacies. A receipt will be given for tax purposes or for reimbursement from your insurance company. Procedures or drugs can be paid for with VISA, MasterCard or Debit. The small “profit” we make on these drugs is used to keep other fees at a minimum. You can use your prepaid drug coverage for medications at any pharmacy. We often recommend Commissioners Pharmacy as it is close, works closely with us and is knowledgeable about our drugs and procedures.**

Information sheets with more detail about funded and non-funded IVF are available.

### **Risks and Benefits**

The disadvantage of ICSI is the cost of the procedure and the “intensity” of the treatment for the female partner. If male factor infertility is the only reason for doing IVF and ICSI, the female member of the couple is subjected to intensive treatment, potential risks and side effects, when the fertility problem belongs to the male. At S.O.F.T., we will emphasize that infertility is a **couple’s problem** and should not be considered the fault of the male or the female. However, how both the male and female feel about this issue will be explored.

ICSI bypasses fertilization. We remove the selection which may occur during the fertilization process and therefore allow more congenital malformations. Several large studies have indicated an increase in the number of congenital problems in children born from IVF and IVF with ICSI. Most experts feel this is probably due to the couples who need IVF or IVF and ICSI having a higher genetic load to begin with and that it is not caused by either the IVF, drugs used to stimulate the IVF or the ICSI. There has been debate in the medical literature for some time that ICSI is associated with an increase in sex chromosome abnormalities. If there is an increase in this it is small. Some forms of severe male infertility may have a genetic basis and this will be outlined in detail below. One concern we have is that the genetic defect responsible for the man’s infertility may be transmitted to his child after successful infertility treatment.

In cases of extremely low or zero sperm counts, genetic testing and counseling may be recommended.

**A karyotype is a lab procedure** which looks at the number and structure of the chromosomes. An extra Y chromosome, for example can cause no sperm in the ejaculate but the male appears normal in all other ways. Other less complete additions or deletions of chromosomes can also cause male infertility. Men with complete chromosome additions or deletions are not candidates for ICSI. However, men with small deletions or additions of chromosomes can be candidates and are subject to a 50% risk of passing this abnormality on to their offspring.

A **cystic fibrosis gene mutation** analysis which a genetic test is looking mutations in the gene for cystic fibrosis is usually performed. To have cystic fibrosis, a person needs to have two copies of an abnormal cystic fibrosis gene. These men usually have severely decreased or no sperm in the ejaculate but they also exhibit the symptoms of cystic fibrosis. Men who carry only one abnormal cystic fibrosis gene usually will have minimal or no symptoms of cystic fibrosis but will have severely decreased or absent sperm counts. They will usually be found to have bilateral congenital absence of the vas deferens (the tube carrying the sperm from the testicle). Unfortunately, this cannot usually be repaired. They are referred to as carriers of the cystic fibrosis gene. This is believed to be present in approximately one person in twenty-five or 4% of the population.

When a man is found to be a carrier of the cystic fibrosis gene, it is **imperative that his female partner be tested for carrier status**. Remember, she will have no symptoms but has a 4% chance of being a carrier. If she tests negative, she is probably not a carrier but exclusion testing is not 100% as some of the rarer abnormalities in the cystic fibrosis gene will be missed. However, the risk is felt to be very low. If the female is a carrier, there is a 50% risk that the offspring will be a carrier and a 25% chance that they will inherit two copies of the gene and therefore have cystic fibrosis. This is usually considered an unacceptable risk and other (donor insemination) reproductive technologies are employed. Pre-implantation genetic diagnosis can be used and is available at the ISIS clinic but is expensive. If the female partner is not a carrier, the risk is that 50% of the offspring will be carriers of the defective gene. If the child is male, he will likely have the same infertility problem as his father. If the child is a girl, she will be a carrier, which poses a genetic risk to her children but she will likely have no symptoms.

A **Y chromosome micro deletion** study (a lab procedure which looks specifically for small missing pieces of the long arm of the Y chromosome) is often done in severe male infertility. A Y chromosome micro deletion will be passed on to all male offspring but none of the females.

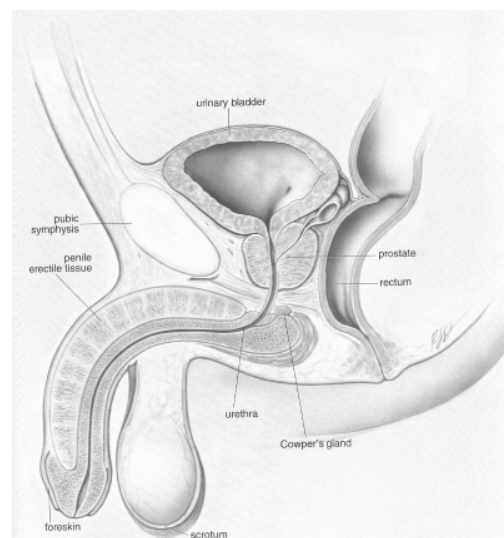
ICSI may be associated with an increased incidence of identical twinning especially when it is used with transfer of day 5 embryos or blastocysts. He incidence is small, probably less than 1% of cycles.

More **abnormal fertilizations** occur with ICSI. For example, the egg may be fertilized by two sperm. Fortunately, this abnormal fertilization can be recognized under the microscope and be discarded. The number of abnormal fertilizations is more than compensated by the increased number of normal fertilizations usually promoted by ICSI.

The advantage of ICSI is that it makes it possible to produce pregnancies for couples where the male partner has very few sperm. In fact the percent pregnancy per cycle with IVF and IVF with ICSI is almost identical. This means that ICSI compensates almost completely for the male factor.

### **ICSI Combined With Sperm Retrieval**

Not only has ICSI made pregnancies available to men with very low sperm counts but also men with no sperm in their ejaculate. If a man is found to have no sperm in his ejaculate, he may not make sperm (testicular failure) or he may have blockage of the ducts which deliver sperm to the ejaculate.



**Blockage of the ducts** that allow the sperm to be mixed with the secretions from the seminal vesicle and prostate before they are ejaculated can occur from a developmental failure, infection, surgery or trauma. As detailed earlier, many men in this situation are carriers of the cystic fibrosis gene. Cystic fibrosis usually expresses itself as a chronic, debilitating lung disease often leading to premature death. It is one of the most common “autosomal recessive” inherited diseases. To have the disease an effected person needs to have two copies of the “bad” gene. However, one copy of the gene appears to express itself in some males as blockage of the male ducts.

**Testicular failure** refers to the situation where not enough sperm are made by the testicles to appear in the ejaculate. This can be caused by developmental problems, genetic problems, infection and other problems. Testicular failure is seldom absolute. Many times a few sperm can be found in a testicular biopsy. Sometimes these sperm are not fully matured but can still be used successfully for ICSI.

Sperm can be retrieved from the testicle or epididymous by a number of techniques. Often, if there are no sperm or few sperm in the ejaculate, a **testicular biopsy** is done to see if any sperm are present in the testicle. Many times if this is done before an IVF with ICSI cycle, sperm can be frozen for use later.

Sperm retrievals differ based on three characteristics. The first is whether they are done so that **fresh sperm** can be used for IVF with ICSI (therefore the same day as the egg retrieval) or at sometime before the egg retrieval so that they must be **frozen** and thawed to be used on the day of retrieval. The scientific literature does not indicate clearly if there is an advantage to the pregnancy rate using fresh sperm. The advantage of using pre-frozen sperm is convenience and avoiding a procedure on both the male and female on the same day.

The second difference is whether the procedure is an **open surgery or aspiration of sperm through the skin of the scrotum** using a syringe and needle. Open surgery is often required if very few sperm are present (testicular failure). The disadvantage of this is the risks and discomfort of a surgical procedure. Sperm obtain through the scrotal skin is referred to as “per-cutaneous”. The advantage of this is avoidance of the surgical procedure and usually less post-procedural pain.

The third difference is whether the sperm are aspirated from the testicle or the epididymous.

If sperm retrieval is necessary it usually costs \$1200.00.

### **Alternatives to IVF with ICSI**

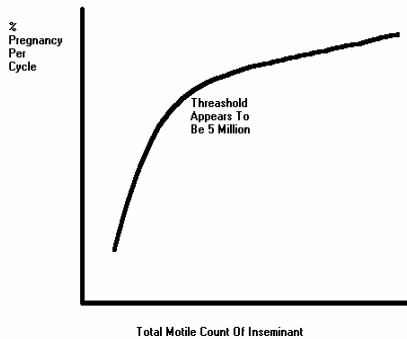
Once a diagnosis of male factor infertility is made several treatment options are available depending on the severity of the problem. Detailed information on most of these technologies is available at the clinic or on our web page at [www.soft-infertility.com](http://www.soft-infertility.com).

### **Improving the Sperm Count**

Improvement in sperm count can occur! A full consideration of this is worth it in less severe cases. Surgery for varicocele or the S.O.F.T. potion has produced dramatic results for some couples. A detailed discussion of these options is available in the male infertility information sheet.

### **Intrauterine Insemination (IUI)**

For less severe forms of male factor infertility, were count, motility or morphology is decreased from expected levels, **sperm washing and intrauterine insemination (IUI)** may be an option.



We believe IUI helps with mild to moderate male factor infertility because it improves the number of sperm available in the uterine cavity. The success of intrauterine insemination with male factor infertility depends on the number of motile sperm, which can be recovered in the washed semen sample. Experience with this technique as well as from the medical literature suggests that recovery of 2 million or less sperm gives a pregnancy rate of 3.5%. Although this seems very low, the chance of a spontaneous pregnancy in these circumstances is probably

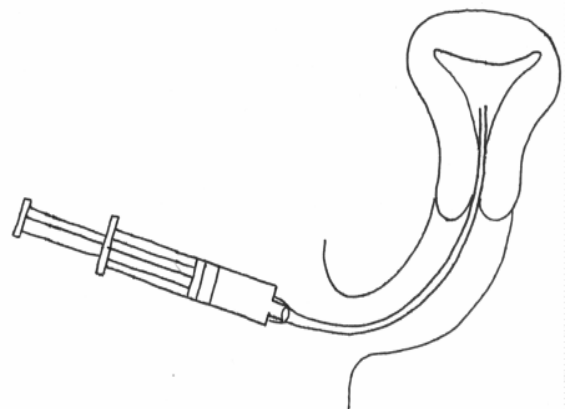
close to zero. Recovery of 2 to 6 million sperm gives a pregnancy rate of 6 to 7% per cycle and recovery of more than 7 million sperm gives pregnancy rates of up to 15%. A threshold seems to occur, were once 5 million sperm can be isolated, that everybody's chance is about equal (see the graph presented just above this text). Generally, we would prefer to do inseminations with 5 million sperm or more. However we feel that intrauterine insemination is worth doing for couples as long as 1 million sperm can be recovered. Although the pregnancy rate at this level is not as high, it still improves the chance over intercourse alone A pregnancy has occurred at a sperm recovery of 0.16 million. If below 1 million sperm are recovered, intrauterine insemination may be postponed while we try with the "S.O.F.T. potion" to improve the sperm count or IVF with ICSI may be recommended.

**It is generally believed that 3-5% of the sperm ejaculated into the vagina are able to navigate the cervical mucous and end up in the uterine cavity. Usually when the sperm is washed, we can recover 30-50% of the moving sperm and place these in the uterine cavity.**

**Intrauterine insemination** is the deposition of sperm into the cavity of the uterus using a fine plastic catheter at the time of ovulation. Before semen can be injected into the uterine cavity it must be "washed". **"Sperm washing"** is the process of separating the sperm from the rest of the seminal fluid that makes up 95% of the volume of the ejaculate. This is done in the lab. Several techniques are available and the one that produces the highest sperm count will be chosen for you. This process is not covered by OHIP and you will be **charged \$200.00**. This makes IUI a very affordable treatment for most couples.

Intrauterine insemination is usually combined with some form of stimulation for the female partner. This may be as simple as clomiphene citrate or can be as complicated as a full IVF-type stimulation protocol. Information sheets are available for S.O.F.T. covering the different stimulation protocols.

Intrauterine insemination cycles involve careful monitoring of the cycle so that the insemination can be done at the time of ovulation. Some controversy exists as to



whether two inseminations may improve the chance of a pregnancy over one. Last year we completed a large clinical trial at S.O.F.T. to try and settle this question. The trial indicated that in general, two inseminations do not give superior results over one insemination. However, in the subgroups where there is male factor present (defined as a sperm recovery of less than 5 million) and when insemination was timed by a spontaneous LH surge rather than giving an HCG injection, there was an improvement. In fact, if both of these factors were present, the improvement in pregnancy rate was almost 5%. A double insemination is available at S.O.F.T. for \$250.00.

## **2) Donor Insemination**

Having a baby through donor insemination usually does not involve complex medical technology but does require you to make some very important decisions that aren't involved in many of the other technologies. The important decisions you make about this technology will affect not only you, but also generations to come.

Donor insemination is intrauterine insemination using semen obtained from a donor. It is one of the most commonly used reproductive technologies but receives very little publicity. Although there are other infertility treatments such as in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) for severe male-factor infertility, donor insemination is often used because it is more affordable.

Anonymous donor insemination is the most common form of donor insemination. Purchase of donor semen and other services are arranged between the sperm bank and yourself. Exact pricing for these things are available from the sperm bank but in general samples cost about \$450.00 to \$500.00. Additional costs can include shipping and additional donor information.

Known donor insemination is available but is even a more difficult decision process than anonymous donor. It is not necessarily a less costly undertaking as all the Health Canada Guidelines for donor insemination must be followed, At S.O.F.T. we encourage you to think about this very carefully. Counseling is available and may be very useful in this circumstance. You might want to consider legal advice and the development of an agreement with the potential donor.

Costs from the S.O.F.T. clinic are only washing the specimen to prepare it for intrauterine insemination (\$200.00). Other costs are covered by OHIP.

Success rates with donor insemination range from 10% to 20% per cycle depending on stimulation protocol and whether any female infertility factors are present.

Full information sheets are available from S.O.F.T. about IUI and DI.

## **Success Rates**

The chance of success can be measured in many different ways. However, the most meaningful method quotes the chance, if treatment is started, that a baby will be taken home. IVF has a usual per-cycle rate of **30 to 46% per cycle. ICSI pregnancy rates are exactly the same as IVF as the ICSI procedure bypasses fertilization and takes the male factor out of the equation.** The pregnancy rate is very sensitive to female age and elevated FSH. Your own chance of success will be estimated for you prior to undergoing the IVF cycle. If a pregnancy occurs, the chance of **miscarriage is 20 - 25% and of ectopic pregnancy is 3%.** The

miscarriage rate in IVF is not different from that in spontaneous pregnancies but the ectopic rate is twice the baseline rate as many women using this technology have damaged Fallopian tubes.

The number of embryos you will be advised to transfer in your IVF cycle will depend on your age, previous reproductive history, and the quality of the embryos, the number of embryos available for transfer or freezing, and the number of days that the embryos have been cultured since the egg retrieval. The goal is to maximize the chance of pregnancy and minimize the chance of multiple pregnancies. If more embryos are available than can be transferred, you will be offered **embryo freezing**. A separate fee of \$850.00 is charged for this. Embryos have an 80 - 90% chance of surviving the freeze-thaw and can be transferred later in spontaneous cycles with vaginal progesterone for maximizing the preparation of the endometrial lining. The chance of success with frozen embryos varies from 17 to 25% per try.

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