

Intrauterine Insemination (IUI) With Letrozole (Femara) plus Injectable Fertility Medication



Introduction

Intrauterine insemination (IUI) is the deposition of sperm into the cavity of the uterus using a fine plastic catheter. It is also sometimes referred to as “sperm washing”. It is the simplest of the reproductive technologies. Some of the other infertility treatments such as in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) have a higher profile. Because of its simplicity, intrauterine insemination is much more affordable, less invasive and may be more effective overall, than the more intensive technologies.

IUI is believed to double to triple **the chance of pregnancy** in a cycle over and above anything else that is being done. This is probably especially true if mild male factor infertility is present. It is also extremely important if hostile cervical mucous exists.

Theoretically, IUI increases the chance of pregnancy by increasing the number of sperm entering the uterine cavity. We believe that when semen is ejaculated into the vagina that only 3-5% of the motile sperm navigate the cervical mucous to enter the uterine cavity. When sperm are washed, we can usually recover 20-50% of the moving sperm and these can be placed in the uterine cavity, thus making ten times the number of sperm available at this level.

The increased number of available sperm might not be the whole answer. Intrauterine insemination also involves detailed monitoring of the cycle using blood tests and ultrasound. Perhaps this precise monitoring also adds to the improved success.

Letrozole (Femara) is a pill. It is used to promote ovulation and therefore pregnancy. It is used at S.O.F.T. as an alternative to clomiphene citrate. Like clomiphene, it is believed to double the pregnancy rate per cycle and may be responsible for even greater improvements in women who are not ovulating. A detailed information sheet is available on letrozole and a detailed discussion on how it differs from clomiphene citrate is given below.

Injectable fertility medicine refers to products that supply follicle stimulating hormone (FSH). FSH cannot be given orally and therefore must be taken by daily injection. Many brand names have been marketed (Gonal-F DIN# 02244787, Puregon DIN#02231656 and Repronex DIN# 02247790) and the general trend has been to develop more purified products. FSH is the hormone produced by the pituitary that stimulates the ovary to make eggs. Clomiphene citrate initially “fools” the ovary to make more FSH and induces follicles to develop in a given cycle. When more FSH is added by injection, more of these induced follicles are encouraged to develop. This usually gives a much stronger and more sustained stimulation.

IMPORTANT NOTICE
Recently, the use of Femara for infertility has come into question. We do not believe that Femara is dangerous in any way and this is discussed in detail later in this information sheet and on a separate information sheet.

Both IUI and clomiphene citrate double the pregnancy rate. The addition of FSH is designed to make more eggs. Even if it doesn't make more eggs than clomiphene citrate alone, it probably helps to offset some of the negative effects clomiphene may have on the endometrium. IUI with clomiphene together may quadruple the baseline spontaneous pregnancy rate and therefore has become a standard infertility treatment. IUI and clomiphene with injectable fertility medicine probably gives an even greater increase over baseline but is usually chosen for couples with more persistent infertility (and therefore the baseline pregnancy rate may be lower).

The Pros and Cons:

This **is considered our medium stimulation protocol** and is effective treatment for idiopathic infertility, female-age related infertility, anovulatory infertility, endometriosis-associated infertility, mild tubal-factor infertility and mild male-factor infertility.

The advantage of this protocol compared to just letrozole is that usually more mature follicles (eggs) develop and the pregnancy rate is higher despite the fact it is used for a group of patients that have more severe infertility.

The disadvantage compared to letrozole and IUI is more expensive if it is not covered on a drug plan and there is a higher incidence of multiple births. The chance of twins is about 15% should a pregnancy occur. Triplets or higher multiple births are increased but not common occurring in about 1% of these successful cycles. Medication costs are also increased and monitoring of these cycles is much more intense.

The advantages of this protocol over a "full-stimulation" protocol with injectable fertility medication only are a lower drug cost and slightly lower chance of multiple births. In some circumstances the stimulation in response to this is better than to "full stimulation".

This has been a very successful protocol in older women.

It has been reported to be more successful than clomiphene and injectable fertility medications in some centers. In our hands it is at least equally effective.

A Description of a Spontaneous or Stimulated Cycle

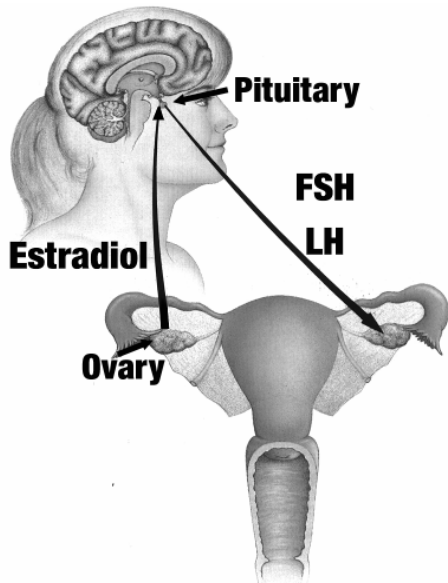
The menstrual cycle is described in terms of days - day one being the first day of vaginal bleeding requiring protection as long as it occurs by midnight. At this point most of the hormones are at very low levels. The cycle begins with **Follicle stimulating hormone (FSH)** being released by the pituitary and stimulating both egg-maturation and production of estrogen (estradiol). In a successful (ovulatory) cycle, the combination of FSH and estrogen facilitates a rapid release of Luteinizing Hormone (LH). This rapid, high level of LH is often referred to as the **LH Surge** and is thought to induce release of the egg (ovulation) about 34 to 36 hours after its peak.

Letrozole vs. Clomiphene Citrate

More commonly, IUI is combined with clomiphene citrate. Letrozole (Femara) works in a similar fashion to clomiphene but may have fewer detrimental effects on the endometrium. It is a very new treatment and many physicians and pharmacists will not have heard of this use of Letrozole used in this way. Letrozole usually is used in the treatment of estrogen-sensitive breast cancer because it blocks estrogen production. In fact, a recent clinical trial has indicated it may be better than tamoxifene and therefore it has got a lot of

press lately for this. It is this ability of Letrozol to block estrogen production that makes it valuable as a fertility drug.

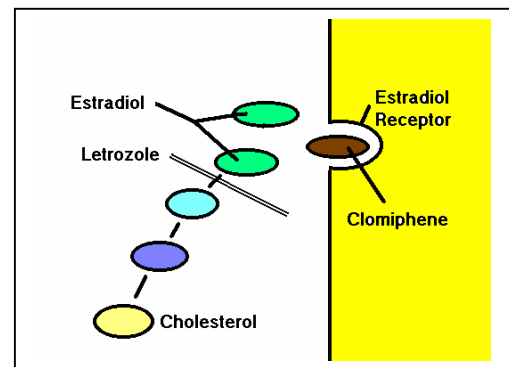
How Letrozole with Injectable Infertility Medication Works



Menstruation and ovulation are complex processes that depend on the action of hormones released from the ovary, pituitary and hypothalamus. An imbalance in the levels of these hormones can disturb normal ovulation and can contribute to infertility. As written before, **FSH** is released by the pituitary and stimulates both egg maturation and production of estrogen (estradiol). The estradiol “feeds back” to the pituitary to cause a decrease in the secretion of FSH. In a woman who is ovulating each month, the FSH and estradiol take turns turning off and on, much like the furnace and thermostat in your house. Clomiphene essentially works by fooling the body into thinking there is less **estrogen**. It does this because it has the same three-dimensional shape as estradiol. It occupies its receptor so that estradiol

cannot occupy the receptor. Estrogen needs to fit into the receptor to work. Therefore the estrogen does not feed back to the pituitary and the production of FSH is not turned off and more FSH is produced.

Letrozole blocks the last step (the aromatase enzyme) in the synthesis of estradiol. There is therefore reduced estradiol to feed back and turn the pituitary off and more FSH is made. This results in more stimulation of the ovaries and usually results in ovulation in a woman who has not been ovulating or in the production of more than one egg in a woman who is already ovulating.



Injectable fertility medications are preparations containing FSH. Historically, FSH was collected and concentrated from urine of menopausal women and was therefore called Human Menopausal Gonadotropins (HMG). Newer forms of FSH are now produced in cell cultures (recombinant technology) but all forms work in the same way. Many brand names have been marketed (Gonal F and Puregon and Repronex and the general trend has been to develop more purified products. The newer formulations have the advantage of subcutaneous injection.

In this protocol, one of these FSH is injected daily starting on day 6 of the cycle. With this protocol the combination of increased FSH production from the pituitary because of the letrozole and the extra-injected FSH should produce a stronger stimulus to the ovarian production of eggs and estrogen. We believe the clomiphene induces the follicles and the extra FSH allows more of them to mature.

We consider this protocol our **medium stimulation protocol** for IUI. It has advantages over letrozole alone in that it will often effect adequate stimulation when letrozole will not and, on average it will cause a higher number of eggs to develop. The

object of this drug protocol is to develop **3 to 5 eggs**. Because injectable FSH is very expensive, combining it with letrozole decreases the medication costs per cycle from \$3,000.00 to about \$600.00 per cycle.

How to Take Letrozole + FSH

Usually **two pills of** letrozole (2.5 mg X 2) are taken for five days beginning three days after the first day of menstrual bleeding (day 3 to 7 of cycle). More information on the use of letrozole is available from the S.O.F.T. letrozole or letrozole and IUI information sheets.

FSH is added on day 6 and is usually given by **daily or alternate-day injection**. The dose of FSH is individualized and depends on female age, response to previous treatment and other factors. Self-injection of FSH is taught to you, usually on day 6 in the first cycle of using this protocol. A separate information sheet is also available about self-injection of FSH.

What is IUI?

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”** and IUI are the same technology.

Washing the sperm 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. Unprepared semen cannot be placed in the uterine cavity as it contains many biologically active components such as prostaglandins. If these were placed directly into the uterine cavity, they would make the woman very ill. Several techniques are available and the one that produces the highest recovery of sperm will be chosen for you. At the end of the sperm wash, as many of the motile sperm as possible from the original sample are suspended in a salt and protein solution. This solution is formulated to resemble the fluid found in a woman’s fallopian tube. This process is not covered by OHIP and you will be **charged \$200.00**.

On the day of the insemination, the male partner must produce a semen sample. Masturbating into a sterile container does this. Most of the time, it is easier for the male to do this at home and bring the sample to the clinic. As you go through your monitoring, make sure if you want to do the sample at home that you have a bottle. If your sample is required the next day and you don’t have a sample bottle, don’t use a substitute bottle. Come to the clinic the next day to produce your sample. In situations of great distances or when there is concern about the sample, it should be produced at the clinic. A men’s room is available for this purpose. **Any sample delivered to the lab must have your name on it.** Unfortunately if you forget to put your name on the bottle, we cannot process it.

Some controversy exists about producing the sample **at home or in the clinic**. In fact, some infertility units will insist that the sample is produced on-site rather than at home. However, it has been our experience that sperm recovery rates are slightly higher from samples produced at home as long as they are properly transported to the clinic. To properly transport a sample, the specimen container should be placed under your shirt, next to your bare skin, as soon as possible after it is produced. This keeps the sample at about body temperature or a little bit lower. Samples transported in this way are usually stable for hours although we do encourage you to deliver your sample to the clinic as quickly as possible. Sperm are very sensitive to temperatures even slightly above body temperature so

transporting them in another method (heat packs, warm towels, on the dash board next to the car heater) can be disastrous!

The preparation of the sperm for insemination takes 2 hours. We will usually ask for the sample at 8 am and the insemination will be at 10 or 11 am. Once your sperm sample is in our lab, it is very stable. During the sperm wash and after preparation, it is kept in an incubator at just below body temperature. Except in very rare circumstances, (previously frozen sperm or in some male factor patients) the sample **will remain stable for hours** thus allowing convenient scheduling of the insemination.

When your insemination is done, you will be given some information about your sample. Sometimes all the numbers can be a little confusing!

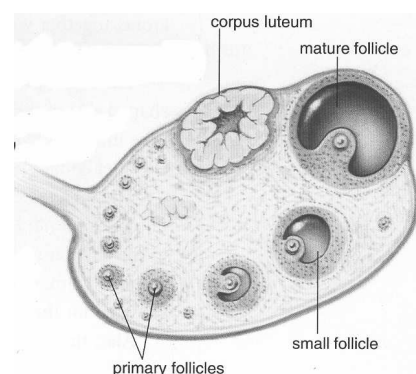
A basic semen analysis is always done on the sample. This includes the **volume** or amount of fluid, the **concentration** or number of sperm in each milliliter of ejaculate and the **motility** or percentage of the sperm that are moving. From these numbers we will calculate a **“total motile count”** which refers to how many moving sperm were in the original sample.

When your sample is washed we will calculate two more numbers. The first will be the **“total motile count” of the sample**. This is the number of moving sperm available for us to inseminate. This is the most important number for you as it determines (with other factors) the chance of a pregnancy from the insemination. (A discussion of this is available in the information sheet on male infertility) The last number we will tell you is the **percent recovery**. This is the percent of the moving sperm that are available for insemination compared to the moving sperm in the original sample. Usual sperm recoveries are 20%. Sperm recovery is not only based on our technique but as well on some characteristics of the sample. However, at S.O.F.T., we try very hard to get as many sperm for insemination as possible and our recoveries are often much higher.

Some controversy has existed in our medical literature about **the benefit of two inseminations as opposed to a single insemination**. In 2003, we completed a large study at S.O.F.T. to try to solve this question and we found some interesting results. In the next section of this information sheet the timing of the insemination and how we monitor you to determine exactly when to do your insemination is discussed. This is important to this discussion as it influences whether two inseminations will be helpful. Our findings were that two inseminations were most helpful when some male factor infertility is present and when the timing of the insemination is determined by the “LH surge” rather than an HCG injection. Male factor was deemed to be present if the total motile count of the insemination sample was less than 5 million sperm. The timing of the procedure and the benefit of two inseminations will be discussed in the next section. In general, we will suggest two inseminations instead of one if the first insemination contained fewer than 5 million sperm and your insemination was timed from a spontaneous LH surge. You will be charged \$250.00 for a double insemination.

Timing the Procedure

The success of IUI depends on timing it with **ovulation or release of the egg from the ovary**. Ideally, the insemination should be done at the exact time when the egg or eggs are being released from the



ovary. IUI cycles use **both blood tests and vaginal ultrasounds to determine when this occurs.**

The beginning of the cycle is referred to as “day 1”. “Day 1” is the first day of menstrual bleeding requiring more than a panty liner for protection. All hormone levels are very low and the ovary should contain only very small follicles. Follicles are small cystic structures which contain the eggs and produce the ovarian hormones. We can figure out how the cycle is progressing by measuring the growth of the follicle(s) and measuring the blood level of key hormones.

The first thing that happens in the cycle is that the pituitary gland produces **follicle stimulating hormone (FSH)**. This causes a follicle, or in the case of a stimulated cycle, more than one follicle to grow in the ovaries. The follicle(s) produces **estrogen** in increasing levels as it grows. In most cycles the estrogen increases each day and we measure this increase during the critical time of the cycle. Another hormone, Luteinizing hormone (LH) stays low during the first part of the cycle. However, once the estrogen reaches a certain level or a follicle becomes a certain size; a **LH surge** occurs (a doubling or tripling of the level). The LH surge is then used to time the insemination. In spontaneous cycles the LH surge usually occurs on day 12 or 13, however, in clomiphene-stimulated and cycles with clomiphene and injectable fertility medication, the LH surge is usually delayed until day 14 or later. Once the LH surge has occurred the estradiol level usually drops. In fact, with our monitoring, we can determine if we are at the beginning or end of the LH surge by the estradiol level. If it is still rising, we are at the beginning of the LH surge; if it has dropped from the previous day, we are at the end. The peak of the LH surge occurs 34 to 36 hours before the release of the eggs.

If a spontaneous LH surge is used to time your insemination, insemination will be done the day after the surge is detected (therefore about 10 hours, if it was the peak of the surge, before egg release). However, if your cycle requires an HCG injection to release the eggs, the injection should be given about 10 pm the night and the insemination will be the day after next (about 36 hours after the injection, therefore just about when the egg(s) are being released).

Cycle Day	Estradiol E ₂	LH	Follicle Size (mm)
Day 1	50	4	2
Day 3	100	3	5
Day 6	200	4	8
Day 8	300	3	11
Day 10	450	4	14
Day 11	600	3	15
Day 12	750	6	17
Day 13	900	5	19
Day 14	1050	7	21
Day 15	1200	12	23
Day 16	1250	75	24
Day 17	850	20	24

The dynamics of a cycle with letrozole and injectable fertility medication is presented in this table. **This table is an example only and individual cycles may vary widely.**

Usually, blood tests (estradiol and LH) are performed daily from day 11 or 12 of the cycle. In the cycle, the estradiol should increase slowly and the LH should stay consistently low until one day it rises dramatically. The **“LH surge”** refers to a rapid release of luteinizing hormone from the pituitary gland before ovulation occurs and is reflected in the LH blood test by a doubling or tripling of the baseline level. The insemination is performed the day after the “LH surge”. If the follicle(s) have grown to a good size (16 mm and over) or you get to day 16 of the cycle and a LH surge has not occurred, we will suggest **an HCG injection**. An HCG injection is an artificial LH surge. By using HCG we prevent extended monitoring of your cycle and cycles in which an egg or eggs are produced but not released. A

LH surge does not always occur in cycles being monitored for IUI. This can happen even if there is normal egg development. In natural cycles this has been named “luteinized, unruptured follicle syndrome” and is thought by some to contribute to some infertility.

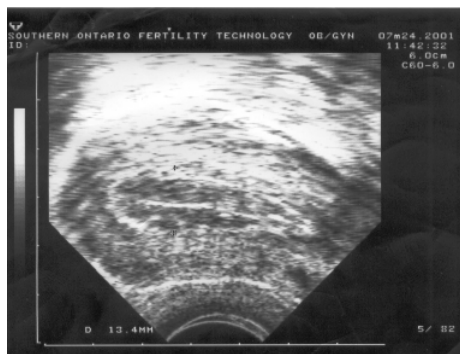
Unfortunately, the results of **the blood test required for this monitoring have to be available the same day**. This usually requires them to be done at S.O.F.T. We have been able to arrange same-day blood testing in some cities (IE Windsor, Kitchener and Sarnia). This can only be done on weekdays and on days that you don’t have to have an ultrasound. If you are interested in doing some of your blood testing in these labs, you should speak to the nurse about it on your first day of monitoring. This is usually reliable, but S.O.F.T. cannot take responsibility for the result being sent to us the same day. This can make doing an IUI cycle very stressful and fatiguing. We try to make this less stressful by performing the monitoring blood tests at the clinic (one stop shopping!). Also, instead of rigidly having to do the tests first thing in the morning, they can be done as late as 1 pm on most weekdays.

Blood testing, ultrasounds and inseminations may need to be performed 7 days a week at the clinic. For this purpose, S.O.F.T. is open from 7:30 am to 1 pm weekdays and 8:30 am to 10 am on weekends. On weekends and holidays only the back door of the building will be open.

Vaginal ultrasound monitoring of IUI cycles is also be important. It is employed in clomiphene cycles on day 11 or 12 to determine how many potential eggs are developing and to ensure that the endometrium is of adequate thickness. (Vaginal estrogen may be prescribed if the lining is too thin.) Follicles that may go on to ovulate are usually 11 mm or more in diameter by your first monitoring day. If all follicles are smaller than this it may mean that you will not ovulate in this cycle. If the follicles are very large, it may mean that they are left over from the last clomiphene cycle or



Ultrasound of an ovary with many small follicles but one central follicle, which has become larger



Ultrasound of a uterus, which demonstrates a triple layer endometrium of adequate thickness

that you are going to ovulate earlier than usual in this cycle. Ultrasound is also important in cycles where a spontaneous LH surge does not occur and helps to determine when HCG should be given. In clomiphene cycles where a spontaneous LH surge does not occur by day 16 or sometimes earlier if the follicles are large, HCG (Profasi HP, Pregnyl) can be given to create an artificial LH surge. Follicles that are 16 mm or greater in diameter probably contain a mature egg. It used to be thought that if follicles got too large, they may not be good. However, we now know that even large follicles 30 to 34 mm can produce a pregnancy.

When we decide exactly when to give HCG, the size of the follicles, the day of the cycle and the estradiol level are all taken into account. If you have a spontaneous LH surge, “Mother Nature” makes the decision for us.

Whether your insemination is timed by an LH surge or HCG is also important as far as considering one or two inseminations. In our 2003 study, mentioned before, we found that the only group that statistically benefited from a double insemination was the group with male factor (less than 5 million to inseminate) and those whose insemination was timed by an LH surge. This makes some sense as with an LH surge, the insemination would occur before and after the release of the eggs. With HCG, the insemination would occur at the time of egg release and 24 hours after. The second one may than be too late.

The Procedure

Once the sperm washing is completed a small plastic catheter attached to a syringe is used to inject the sample. No preparation is required before the procedure is performed. Breakfast can be eaten normally and medication is not necessary before or during the procedure. You can drive yourself.

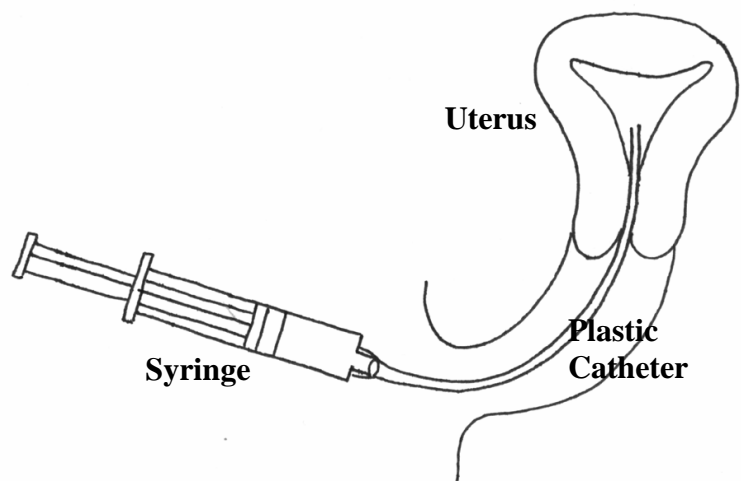
A speculum is placed in the vagina (similar to a Pap smear) and the catheter is fed

up through the cervix (the opening to the uterus) and into the endometrial cavity. Once the tip of the catheter is in the endometrial cavity, the washed sample is injected.

On the day of the insemination, the male partner must produce a semen sample. Masturbating into a sterile container does this. Most of the time, it is easier for the male to do this at home and bring the sample to the clinic. However, in situations of great distances or when there is concern about the sample, it can be produced at the clinic. **Any sample delivered to the lab must have your name on it and be in a sterile bottle.** Unfortunately if you forget to put your name on the bottle, we cannot process it. We will try our best to make sure you have a sterile bottle at the time you need it. The preparation of the sperm for insemination takes 2-3 hours. We will usually ask for the sample at 8 or 9 am and the insemination will be at 10 or 11 am.

Sample Safety

One of the most common worries of couples undergoing IUI is getting the wrong sample. **This is also of great concern to us at S.O.F.T. To ensure there is no mix-up of samples, we will never accept a sample that is not clearly labeled with your name.** During the processing of your sample, it never leaves a container that does not have your name clearly marked on it. All containers used are disposable sterile containers and a double



check is made when the sample is transferred from one container to another. As we are preparing to do your insemination, you will be asked to check your name on the container.

Sexual Intercourse during Your Cycle

If we are using the male partner's sperm, we would like to inseminate with the greatest number of sperm possible. Sperm counts decrease if intercourse has occurred recently. Therefore we ask you to refrain from intercourse for one or two days before your insemination. This just means not to have intercourse after we have called to tell you that your LH surge has occurred. If HCG is ordered, do not have intercourse after you are called.

After the insemination has occurred we encourage you to have intercourse as often as possible over the next 24 hours. Ovulation has occurred and it seems logical to add as many sperm as possible. During other parts of the cycle, we encourage you to have intercourse as frequently as possible because it is good for your relationship and probably helps to maintain or increase the sperm count.

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. With this treatment the pregnancy is **15-20% per cycle**. If more than 5 eggs develop, the chance of a multiple pregnancy occurring is increased. In couples with extremely persistent infertility, the risk of multiple pregnancy will be discussed in detail and you will be asked to make a decision with us. Couples who have an extremely high risk of multiple pregnancy will have to abandon the cycle or you **may be offered conversion to the IVF program**. Women who develop even more than 5 eggs are sometimes not converted to IVF if they are older, have an elevated FSH, or have a long duration of infertility with many failed treatments. Conversion to IVF is only possible if a spontaneous LH surge has not occurred. A new injectable medicine, a GNRH antagonist (ganirelex or Orgalutran TM) is now available to block the LH surge and is effective as long as it is used early enough in the cycle. In IVF, the number of embryos transferred can be controlled, helping to limit multiple pregnancies.

15-20% doesn't seem very high but remember a 25 year old couple having intercourse at the time of ovulation has only a 15-25% chance each cycle

Time and Expense

The decision to use letrozole and an injectable medication with IUI is usually only undertaken if the infertility diagnosis mandates it or when simpler therapies have been exhausted. When choosing this treatment, we have crossed the boarder between low-tech and **hi-tech treatment**. Intensive monitoring is required to minimize complications and maximize the chance of pregnancy. This may mean up to daily blood testing and vaginal ultrasounds in each cycle. Some of the blood testing can be arranged in one's home city but most blood testing is done in London because the results are required the same day. These blood tests and the vaginal ultrasounds are done at the S.O.F.T. clinic to minimize as much as possible the traveling and time commitments. However, for those living out of London, this can still involve many early mornings and a great deal of driving.

Medications for one of these cycles usually run about **\$300.00 to \$800.00** depending on the dose of FSH. Many drug plans cover this but some do not. Additional expenses may include time lost from work, transportation, and accommodation.

Letrozole should cost about **\$50.00** at the 100 mg / day dose. Injectable fertility medications cost **\$75.00 to \$150.00 per daily dose**. Usually about 3 or 9 of these are required or we may prescribe a “Puregon pen” or a Gonal F multidose vial. If HCG is required for an artificial LH surge, it costs about **\$90.00**. The sperm washing costs **\$200.00** but fortunately the ultrasounds, blood tests and insemination are covered by OHIP.

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.

Side Effects

The major side effect is an increase in the frequency of multiple births. **Twins occur in about 10%** and **triplets in 1%** of these pregnancies.

Enlargement of the ovaries always occurs. However, in less than 1% of cycles the ovaries are stimulated too much. If too much stimulation occurs, fluid may leak from the ovaries into the abdominal cavity and result in a condition referred to as **Ovarian Hyperstimulation Syndrome**. The intense monitoring that takes place is to try and minimize the incidence and most people taking the regimen are not at risk for it.

Other adverse reactions, occurring less frequently include local injection-site tenderness, abdominal bloating, fluid retention, breast tenderness, headache, mood swings, nervousness, dizziness, nausea and vomiting and fatigue. These are usually confined to the treatment cycle and are self-limiting.

IUI is **extremely safe!** I have never seen a serious complication.

When the sperm are injected into the uterine cavity or as the catheter passes the narrowest part of the cervical canal, many women will experience **mild, short-duration cramping**. Sometimes, fluid will leak from the vagina right after the insemination is done. This is not the sperm coming out! Once the sperm are in the uterus, they will not come out. The fluid is usually a combination of the warm tap water used to heat and lubricate the speculum and some vaginal secretions that come out when we open the vagina with a speculum.

Sometimes **spotting** will occur after the insemination. This happens because of an injury to a small blood vessel on the cervix at the time of the IUI. It will resolve by itself and does not decrease the chance of pregnancy.

Occasionally (less than 1 in 200-500 inseminations), a reaction will occur to the semen when it is placed in the uterine cavity. We believe this occurs because small amounts of “prostaglandins” remain with the sperm despite the washing process and is referred to as a **‘prostaglandin reaction’**. Some women may also be more sensitive to small traces of these

prostaglandins. If this reaction occurs it can be easily treated and steps can be taken with the next insemination to minimize the chance of recurrence.

Rarely (less than 1 in 3,000-10,000 inseminations), an **infection** can be introduced into the uterine cavity during the insemination. This will present as increasing pelvic pain in the day or two after the insemination. A vaginal discharge, fever or chills sometimes accompany it. If any of these symptoms occur after an IUI, you should contact our program immediately. Prompt treatment will usually lead to an uneventful recovery.

Safety

No large study, similar to those of clomiphene, has been possible yet as letrozole has only been used for ovulation induction since 1999. However, letrozole has so far appeared very safe. Please read a detailed account of the issues surrounding the safety of femara before using it. Theoretically it should be even safer than clomiphene as it is eliminated from the body more rapidly. In fact, by the time ovulation occurs in most cycles almost no letrozole is left!

THE RECENT CONTRAVERSY
Recently, the use of Femara for infertility has come into question. We do not believe that Femara is dangerous in any way and this is detailed on the femara and femara for fertility information sheets.

Injectable fertility medications were first introduced a few years after clomiphene. They are tricky medications to use as they can easily cause multiple pregnancies. No study, however has linked the use of injectable fertility medications with an increase in birth defects. Recently, an increase in congenital abnormalities has been found with children born after IVF and ICSI (in vitro fertilization and intracytoplasmic sperm injection). However most experts in the field believe this is due to the increased genetic load in these couples which has already in many cases contributed to their infertility. There is no evidence that it is caused by the medications.

IUI has never been associated with any increase in congenital abnormalities.

Initial Instructional Visit:

When we began the programs at S.O.F.T. we had you schedule a separate instructional visit to make sure you understood how everything worked. Now we will usually give you this information sheet before you start and answer any questions during your first cycle. We have found that by reading this instruction sheet, most patients are very informed about what they are doing. However, the staff is always happy to answer any of your questions and clear up any confusion.

Also, during your first cycle, both you and your partner will have to do program blood work. Program blood work involves blood tests on both members of the couple, testing blood types, rubella status and for infectious diseases such as hepatitis and HIV. These tests are done for all couples doing IUI (or any other reproductive technology) and are mandated by our professional organizations. A uterine measurement (trial run of the insemination procedure) was done prior to your first insemination in the past. This is no longer done as it was found not to be helpful.

An important part of our teaching which is usually done on day 6 of your first cycle with injectable infertility medications at a brief meeting with our nurses is teaching you to

give your own injections. Injecting yourself may seem very overwhelming at first but 99%+ of patients are able to do this.

Injection of an FSH Preparation:

Injection of an FSH preparation can be easily taught to you so that you can do it yourself. This can be done during the first part of the cycle. Often we will have you attend briefly on day 6 of your cycle and the nurses will give your first injection and use it to teach you how to give the remaining injections. This is also the time when we supply you with an auto injector (with Gonal F) or pen (with Puregon) if you need one. Both these are supplied free of charge by the companies who make the medications.

Some FSH products (Repronex) come with a vial of the medication in powdered form and a vial of liquid to dissolve it. The liquid is drawn into a syringe so that it can be injected into the vial with the powdered medication. Once the powdered medication is dissolved, the liquid mixture is drawn back into the syringe for injection or to be injected into another vial of the powdered medication depending on the desired dosage. The skin is then wiped with an alcohol swab, the area to be injected is pinched, the needle is put through the skin at 90 degrees, the liquid is injected, the needle withdrawn and pressure applied. More complete instructions are available on a separate information sheet.

Injection of HCG:

As was discussed earlier in this instruction sheet, if a spontaneous LH surge does not occur but adequate sized follicles have developed, an injection of HCG will be ordered. You can inject this medicine and instructions will be given at the time that the injection is suggested for your cycle. An instruction sheet is available which describes the injecting technique in detail.



HCG injections are available in the clinic. Often during monitoring we will decide that if a spontaneous LH surge does not occur that day that you should take HCG. If you have not already filled a prescription for HCG we will send you home with the medication. If you do not need it, you can keep it for a few cycles and when you no longer require it (hopefully, you're your pregnant) you can bring it back. We will return your money minus a small restocking fee as long as it is not opened.

If you're IUI Cycle Doesn't Work???

Even if everything works well in your cycle, the chance of a pregnancy is still only 10 to 15%. Our overall pregnancy rate in all IUI cycles is 13.8%. Most of our research indicated that any given protocol in IUI maintains the same chance of pregnancy per cycle for 6 cycles. Therefore, if everything has been perfect, a repeat of the same cycle may be suggested if pregnancy does not occur.

Your cycle is evaluated at the time of your insemination. At that time changes in the medication for IUI, additional treatments such as laparoscopy, or moving on to another technology such as in vitro fertilization (IVF) may be suggested. Usually IUI will work for most patients. A common question that is asked after an IUI cycle that has not resulted in a pregnancy is: "Everything went so well – why didn't I get pregnant???" There are two basic reasons for this.

The first is that human beings are the most infertile species on earth! A couple in their 20's with no infertility factors will only get pregnant in 20 to 25% of their cycles. This % drops as they get older.

The second reason is that infertility diagnosis is extremely incomplete. We can test the basic hormones involved, make sure the tubes are open and count the sperm. We can even do laparoscopies and sperm function testing. However, there are so many other steps to getting pregnant that we cannot test.

Our basic approach to this is to eliminate as many of these unknown steps as possible and increase the number of chances. Therefore, the first treatment usually offered to couples is ovulation induction. This eliminates some of the unknowns as far as, "is ovulation fully occurring?" and usually provides more than one egg per cycle. The next step is usually IUI. This eliminates such steps as: "are sperm (and how many) getting through the cervical mucous?", "When is ovulation occurring?" and provides 10 X as many sperm at the endometrial level. The last step is usually the IVF process which takes many of those unknown steps out of the body and allows us to observe them.

At S.O.F.T., the decisions about your treatment will be made with you. You should never feel reluctant to ask questions or suggest things you have read about or found on the internet. We are always willing to discuss them with you and after all, you know your body best!

When you are Pregnant

After a positive pregnancy test, you will be asked to attend the clinic about 40 days after your insemination for a vaginal ultrasound. By this time we should be able to clearly see the gestational sac (bag of waters) inside the uterus. A multiple pregnancy can also be diagnosed.

It also is possible to diagnose problems with the pregnancy such as a miscarriage or ectopic pregnancies.

Although a perfectly normal ultrasound cannot guarantee a normal pregnancy because it cannot predict the future, it is very reassuring. At least 90% will go on to be normal.

When the ultrasound is done, your due date will be calculated and a report will be sent back to your referring physician informing them of your pregnancy and asking them to take over your obstetrical care.

It is at this time we will also remind you of the **Clinic Rules**. Rule one is you have to send us a birth announcement and rule two is that you have to bring the baby to visit us.

Default Instructions:

Our clinic is run very efficiently but with a very small staff. We will do everything possible to facilitate your treatment and answer any of your questions. However, to make things run smoothly, we have developed "default instructions". This means that **unless we call you and tell you differently, the usual order of instructions should be followed.**

Below is a day-to-day description of an IUI cycle with clomiphene and injectable fertility medication with the default instructions. Remember, this is the default. Your cycle may be very different and yet perfectly normal. For example, some patients will have large



Normal "luteal day 40" ultrasound of a single

follicles on the first day of monitoring. Sometimes in this situation we will just suggest HCG the next day if a surge does not occur. Sometimes, the follicles will be very small on the first day of monitoring and we will advise you to take one or two days off before continuing the monitoring.

The day-to-day instructions will remain the same unless S.O.F.T. calls you with a change.

The table indicates the default instructions. If an extra ultrasound is indicated, HCG should be given, a spontaneous LH surge has occurred or we want you to cancel your cycle, this will be discussed at your visit or we will telephone you. **If you do not get a telephone call or have not been instructed differently in the clinic, follow the table.**

For example, if you came for blood and ultrasound on day 11 and the largest follicle was only 12 mm, we would tell you to take a day off from monitoring because for an LH surge to occur you need a 16 mm or greater follicle. In contrast, if you came on day 11 and your follicles were all large (16 to 25 mm), we might ask for only blood work the next day and give you HCG if you didn't have the LH surge.

Cycle Monitoring – Day By Day

Cycle Day	Instructions	Patient Notes
Day 1	Call S.O.F.T. (519-685-5559) and inform us that your cycle has started if day 1 is the weekend, call Monday)	
Day 3	Baseline bloodwork and/or vaginal ultrasound Only if ordered.	
Day 3-7	Take letrozole in prescribed dose	
Day 6	Start daily or alternate-day injections Your first cycle may require a visit to the clinic in order to learn injection techniques	
Day 11	Blood and ultrasound	
Day 12 and 14	Daily blood testing (looking for an LH surge)	
Day 13 and 15	Blood and ultrasound If no LH surge and good size follicle(s), inject HCG	
Insemination	Next day if LH surge detected HCG given at 10 pm and insemination will be the day after next Insemination usually between 10 – 11 am	
Semen Sample	Samples should be delivered to the clinic at 8 am on weekdays and 8:30 on weekends and holidays Your Name Must Be On the Sample Bottle	
Day 14 after insemination	If no menses, serum <i>B</i> HCG	
Day 40 after insemination	If pregnancy test positive, an early pregnancy vaginal ultrasound	

A Last Comment:

Any infertility treatment can be **frustrating!** We often refer to the emotional rollercoaster of infertility as hopes are increased by good responses to treatment, only to be dashed by a negative pregnancy test.

A 25-year-old couple having intercourse at the time of ovulation and having no infertility factors has only a 15 to 25% chance of a pregnancy. This makes humans' the most infertile species on earth!



The IUI program you have been referred to has a success rate of 10 to 15% per cycle of treatment. This is encouraging but **still leaves 85 to 90% of couples not pregnant each cycle.** If a cycle doesn't result in a pregnancy, this is disappointing **but doesn't mean that the treatment needs to be changed.** Most studies indicate that IUI with clomiphene remains equally effective for 6 cycles. Your treatment is constantly under review even if everything appears perfect. Usually, if you are not pregnant after 6 cycles it is time to move on and more medication or a change of technology can be considered.

James Martin ©

S.O.F.T.

555 Southdale Rd. East, Suite 107,

London, ON, N6E 1A2

Tel: (519) 685-5559

Check out our web page at soft-infertility.com