

The S.O.F.T. Rapid Diagnosis and Treatment Protocol for Women 38 to 43 Years Old

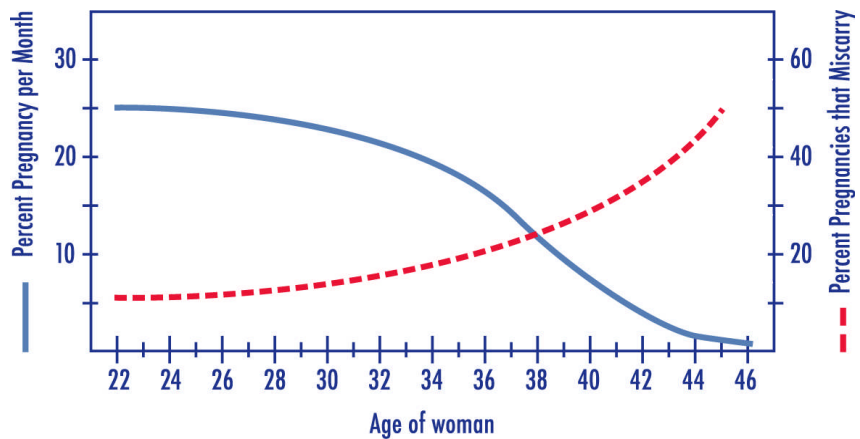


**Southern Ontario
Fertility Technologies**

Introduction

Normal menopause, where the ovary is unable to produce enough hormones to cause normal menstrual cycling occurs at an average age of 51 years old in most of the developed world. However, about 10 years before this, at age 41, is the average age of stopping the production of eggs which are capable of producing a pregnancy. Like most biological variable, this occurs over a bell curve. This means that a woman younger than this (I.E.-38 may run out but a woman of 43 may still have some viable eggs.

At the side is a graph indicating pregnancy rates per cycle (and miscarriage rates per cycle for women of different ages. As you can see from the graph, pregnancy rates, decrease with age and miscarriage rates increase with age. With normal age-related ovarian failure there is a gradual decrease, even in late 20's and early 30's but the rapid increase begins at about 34 and becomes worse each year.



Delay of Childbearing

In most of the developed world, there has been a tendency to wait to a later age to have children. There are good and probably unavoidable reasons for this. Educational and career opportunities have increased for men and women and this involves a focusing on this aspect for more early years in couple's relationship. In fact, in North America, the average age for women when they conceived their first child in 1970 was 24.6 years old. By 1999 this had risen to 29.1 years old. Fortunately, if you place these two numbers on the above chart, it does not make a great deal of difference for most of these women. However, in 1975 only 6% of women delivered at over age 34 but by 2005, 25% of women were delivering at over 34 years of age. Remember, the rapid increase in normal age-related pregnancy rate begins at age 34.

Age of Starting	% who are Successful	% Requiring Treatment
20-24	94	3
25-29	91	6
30-34	85	8
35-39	70	14
40-44	36	47

Percentage of Women Able to Have a Successful Pregnancy in Different Age Groups

Your Initial Consultation

At your initial consultation to S.O.F.T., you will be offered an approach which may seem overreactive and overwhelming. Our objective in this approach is to get the ball rolling as quickly as possible. You will be given information about the overall prognosis or chance of a pregnancy and the risks involved in pregnancies when you older. A separate information sheet on this subject is available. Then we will arrange to complete your fertility investigation, perform a clomiphene challenge test (which gives a little more information about ovarian reserve) and do your first infertility treatment in a single cycle.

S.O.F.T. Approach

Often in women 38 to 43, an approach which maximizes the information about ovarian reserve and begins treatment as quickly as possible is offered. On the initial consultation visit, any components of the **basic infertility investigation** which have not been done will be arranged. This includes the day 3 blood work, a semen analysis and a hysterosalpingogram. A prescription for clomiphene citrate 100 mg (2 tablets) per day from day 3 to 7 of the cycle will also be offered and a day 10 FSH level arranged. This is a **clomiphene challenge test**. In addition to this, we will arrange to do a **vaginal ultrasound on day 10, 11 or 12 of the cycle**. This is not part of the clomiphene challenge test but gives us good information about the response to clomiphene.

When the ultrasound is preformed, we are looking for follicles which are the cystic structures containing the eggs. If you are making follicles, we will offer to continue to monitor the cycle and complete it with intrauterine insemination. A separate information sheet is available on intrauterine insemination with clomiphene citrate.

This means in one cycle, we are able to complete the basic infertility investigation, do several tests of ovarian reserve including an assessment of response to treatment and start a very effective treatment (IUI with clomiphene citrate). Once this is completed, we go from there.

A study in which I participated, demonstrated a very good pregnancy rate with medium stimulation intrauterine insemination (7% per cycle in women 40 to 42 years old) compared with IVF. Usually if several cycles of IUI just clomiphene or another ovulation induction agent doesn't produce a pregnancy, we will offer medium stimulation IUI. By this we refer to ovulation induction followed by injectable fertility medicines or just low dose injectable medicines combined with intrauterine insemination. Examples, which are documented with there, own information sheets are "Intrauterine Insemination with Clomiphene Citrate and Injectable Fertility Medication", "Intrauterine Insemination with Femara and Injectable Fertility Medicines" and "Intrauterine Insemination with Injectable Fertility Medications".

After several cycles of medium stimulation IUI, if a pregnancy has not occurred we will consider IVF. The IVF protocol will be designed to create maximum stimulation. If it produced three follicles (eggs) or more you will be given the chance to continue but if there are less than three follicles, you will be advised to convert your cycle to IUI. There is no charge for



A follicle

As you can infer from the description of our approach, we will give everyone a chance, even if the odds are very low. As long as you are fully aware of the odds, participation in a treatment is ultimately your decision. If you are not willing to try for miracles, they will not occur!

cancellation of the IVF cycle at this point. If your response to maximum stimulation is poor, we will usually advise donor eggs, adoption or discontinuation of your treatment.

Women who are older have an increased risk (> 50%) of not developing 3 follicles and therefore having their IVF attempt cancelled or converted to IUI. If three follicles are present, we will offer to continue IVF. Usually, if three follicles are present, we will get to the stage of embryo transfer. In fact, many experts feel transfer of a good quality embryo gives almost an equal chance of pregnancy regardless of age. Older women, however, have fewer eggs, develop fewer embryos and in general may have embryos that do not develop as well. Patients who achieved the stage of embryo transfer have a very reasonable chance of conceiving, regardless of their age. Cancellation after egg retrieval when there is no embryo to transfer only qualifies for a refund of \$200.00.

Completing the First Cycle with IUI

A complete information sheet is available on intrauterine insemination with clomiphene citrate. However, the basics are covered here for your convenience.

Ovulation induction appears to be very useful in older women. Ovulation induction involves taking pills to stimulate the cycle and promote ovulation. The most widely used form of ovulation induction is clomiphene citrate and **many studies have demonstrated clomiphene citrate to be useful in promoting pregnancies in women 38 to 43 years old**. A complete information sheet on clomiphene is available on our web page. Ovulation induction may be beneficial because it treats irregular cycles which often indicate **anovulatory cycles** (cycles which do not produce an egg) and shorter cycles (IE: 24 or 25 days instead of 28 days) that can often indicate **luteinized unruptured follicle syndrome** or **inadequate luteal phase**. Clomiphene may also promote the development of more than one egg per cycle. If an increasing percentage of eggs are defective, it is probably beneficial to have more than one available.

Intrauterine insemination (IUI) monitors the cycle and allows 10 times as many sperm as intercourse in the uterus at the time of ovulation may be additionally important in older woman because their older partner's sperm may not function as well and their eggs may be more difficult to fertilize. Increasing available sperm numbers may help to overcome this.

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**.

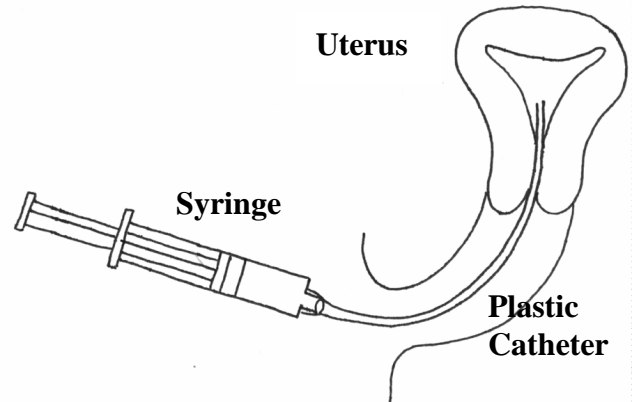
On the day of the insemination, the male partner must produce a semen sample. Masturbating into a sterile container does this. Most of the time, it is easier for the male to do this

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.

The preparation of the sperm for insemination takes 2 hours.

Once the sperm washing is completed a small plastic catheter attached to a syringe is used to inject the sample. This is done in a clinic examining room. 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. You are usually asked to remain lying down for 10 minutes after the catheter and speculum are removed. We will usually set a timer for you. You may then resume for full activities. As far as we know, there is no physical activity that makes it less likely for you to get pregnant. However, we do encourage you to make love in the next 24 hours as frequently as you can as this cannot possibly hurt and may be beneficial.

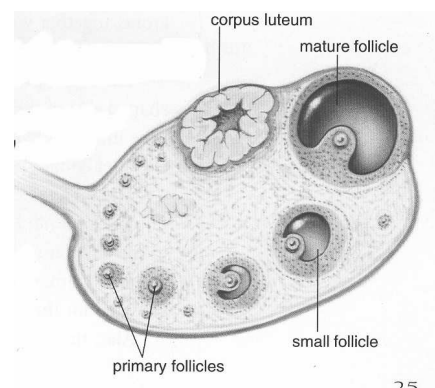


The semen sample has to be delivered to the clinic before the insemination (7:30-8 am on weekdays and 8:30-9 am on weekends and holidays (unless you are instructed differently) as the sperm washing procedure takes 2 hours. Inseminations are usually done between 10 am and 11 am but usually different times can be arranged if this is difficult for you to schedule

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** and these will be started if your day 10 ultrasound demonstrates that you are making follicles.

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 clomiphene-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 cycles, the LH surge is usually delayed until day 14 to 16. 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 egg(s).

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).

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

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

Usually, blood tests (estradiol and LH) are performed daily from day 11 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.

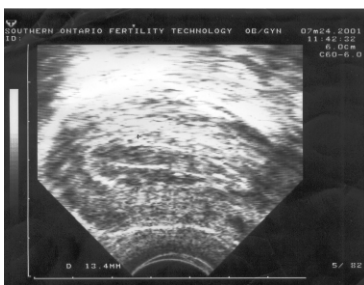
Blood testing, ultrasounds and inseminations may need to be performed 7 days a week at the clinic. For this purpose, S.O.F.T. is open from 7:30 am to 1 pm weekdays and 8:30 am to 10 am on weekends. On weekends and holidays only the back door of the building will be open.

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 that you are going to ovulate earlier than usual in this cycle. Ultrasound is also important in cycles were a spontaneous LH surge does not occur and helps to determine when HCG should be given. In clomiphene cycles were 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 to 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.



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



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

Default Instructions:

More information is available on the information sheet on intrauterine insemination with clomiphene citrate. Some of that information is duplicated here.

To make things run smoothly, we have developed “default instructions” for IUI. 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 with the default instructions. Remember, this is the default. Your cycle may be very different and yet perfectly normal.

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.**

Your cycle begins on day 10. That is the day we need to repeat your FSH level to complete the clomiphene challenge test.

Cycle Monitoring – Day By Day (Default Instructions)

Cycle Day	Instructions	Patient Notes
Day 1	Call and ask for a hysterosalpingogram (if ordered). Clinic number is 519 685-5559	
Day 3	Baseline blood. (will include FSH which is the first part of the clomiphene challenge test) Semen analysis (if ordered)	
Day 3-7 (5-9)	Take clomiphene citrate 200 mg.	
Day 10	Blood and ultrasound (blood should include an FSH level)	
Day 11-15	Continues only if a follicle is seen Daily blood testing until LH surge Often we will ask for another ultrasound but the default is none	
Day 11 – 16	If an LH surge occurs (with good follicle(s)) insemination is scheduled the next day (you will be called)	
Day 16	Blood and ultrasound	
Day 16 or 17	If no LH surge and good size follicle(s), inject HCG (will be discussed at ultrasound)	
Insemination	Next day if LH surge detected Or if HCG is given at 10 pm - insemination will be the day after next (I.E,-36 hours) Double insemination in rare circumstances	
Semen sample	Samples should be delivered to the clinic at 8 am on weekdays and 8:30 on weekends and holidays	

	You may be asked to produce your sample in the clinic (default is at home) Your Name Must Be On the Sample Bottle	
14 days after insemination	If no menses, a serum <i>B</i> HCG is done A repeat BHCG is requested in 48 hours if the first is positive.	
When available	If BHCG is negative, schedule an appointment with one of the physicians	
40 days after insemination	If pregnancy test positive, an early pregnancy vaginal ultrasound	

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Check out our web page at soft-infertility.com