

Letrozole (Femara)



**Southern Ontario
Fertility Technologies**

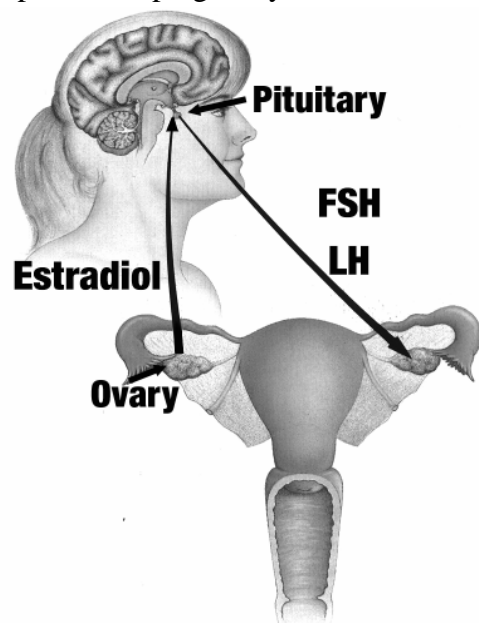
Introduction

Once the “basic” infertility investigation is completed, ovulation induction is often used to promote fertility. Up until recently clomiphene has been the standard of care for ovulation induction. However, **letrozole** is a new alternative to clomiphene. It is often used in Toronto, Montreal and here in the S.O.F.T. clinic and is now experiencing wider use. Because it is new, it is not as widely used and many physicians and pharmacists may not be aware of this use. It is not used if the fallopian tubes are blocked or if severe male factor infertility is present (similar to clomiphene) but it is usually worth a short trial in all other forms of infertility. For women who are **not ovulating** (producing an egg) every month, Letrozole may be the first treatment attempted or may be used as an alternative to clomiphene. However, Letrozole is also useful in couples with “**idiopathic**” infertility, **female age-associated infertility**, **mild male factor**, **endometriosis-associated infertility**, **mild tubal factor infertility** or **cervical factor infertility**. How many cycles of Letrozole will be suggested depends on the diagnosis, the previously attempted infertility treatments, the length of infertility, and the female partner’s age. Letrozole is effective for women who are not ovulating because it stimulates ovulation but it is also used in the other forms of infertility to mature more than one egg per month. It is sometimes used when clomiphene produces side effects. It may be successful in inducing ovulation in situations where clomiphene has failed either to cause ovulation or to produce a pregnancy. It is also often used when clomiphene causes a thin endometrium, which may interfere with implantation (attachment of the embryo to the uterine wall). More recently, we have found it very useful in combination with clomiphene and a separate information sheet is available on this.

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.

How It Works

Menstruation and ovulation are complex processes depending 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. **Follicle stimulating hormone (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 (see diagram). Blocking this



“feed-back” of estradiol in the early part of the menstrual cycle allows the production of more FSH and stimulation of the ovary. 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 therefore promotes ovulation (release of an egg) and perhaps the production of more than one egg.

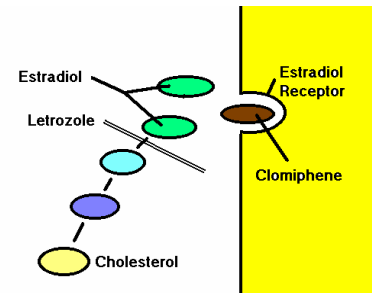
Letrozole vs. Clomiphene Citrate

Letrozole (Femara) works in a similar fashion to clomiphene but may have fewer detrimental effects on the endometrium. Letrozole usually is used in the treatment of estrogen-receptor positive breast cancer because it blocks estrogen production. In fact it has recently been in the news because clinical trials have shown it to be as good as or better for this use than tamoxifene. It is this ability of Letrozole to block estrogen production that makes it valuable as a fertility drug.

The difficulty with clomiphene citrate (which works by blocking the estrogen receptors) is that there are estradiol receptors at the level of the **endometrium and the cervical mucous**. When clomiphene occupies these receptors it may promote a more hostile cervical mucous and a less receptive endometrium. At lower doses of clomiphene, the promotion of ovulation or more eggs over-rides these effects but at higher doses and longer duration of use the balance may change. Different patient may also have different susceptibilities to these detrimental effects. Clomiphene remains in the body for a long time. One study indicated that small amounts are excreted in the urine and bowel movements up to 50 days after it is given. It is theoretically possible therefore that clomiphene may have cumulative negative effects on the cervical mucous and endometrium. Saying that, clomiphene is still the standard of care and has been demonstrated to be beneficial in the promotion of pregnancy in both ovulating and non-ovulating women.

Our bodies make estradiol from cholesterol through a series of chemical changes involving enzymes. The last chemical change involves the **aromatase enzyme**. Letrozole blocks the aromatase enzyme and therefore the production of estradiol. The possible advantage of Letrozole is that it has a half-life of 45 hours (the length of time required for the body to eliminate one half of the drug). It does not build up in the body and may avoid the negative effects produced by clomiphene. However, even though Letrozole does not block the receptors and doesn't accumulate, it may cause a longer depression of estradiol in some individuals than desired. This can sometimes be avoided by prescribing the Letrozole earlier in the cycle.

In general, letrozole demonstrates the same improvement in pregnancy rate as clomiphene. Studies in our clinic demonstrate about a 5% pregnancy rate per cycle when used with “timed intercourse”. At present Letrozole may be used as the first line but is more commonly used when clomiphene fails to cause ovulation or causes thinning of the endometrium. Preliminary observations are very positive and in the future, Letrozole may become a first line drug as an alternate to clomiphene.



Several observations have been made early on with the use of letrozole which may be interesting for our patients.

When we monitor for intrauterine insemination, the **endometrial thickness and appearance** are always assessed. Many papers in our literature have indicated higher pregnancy rates in cycles where the endometrial thickness is greater than 6 mm and appears as a “triple layer” (like the picture directly to the right). Our initial observations are that this occurs much more commonly with letrozol than clomiphene. In fact early observations in 500 cycles of intrauterine insemination indicate an endometrial thickness of over 6 mm in 96.5% of cycles with letrozole compared to only 81.5% of cycles of clomiphene. A triple layered endometrium was observed in 94% of letrozole cycles as compared to 78% of clomiphene cycles.

Some of the **temporary side effects** of clomiphene such as hot flashes and pelvic bloating or fullness appear to be less with letrozole than with clomiphene. However, in a very small group of women (<1%) who are sensitive to low-estrogen headaches, these may be more severe with letrozole. Letrozole, in higher doses, also seems to cause a very unique kind of fatigue or tiredness. This is described by our patients as being a very pleasant feeling of “really being ready for bed” as apposed to a drugged tiredness.

The people in Montreal who used letrozole a great deal have reported very few multiple pregnancies. This has been our experience with low doses but not with high doses. When we are monitoring for intrauterine insemination, letrozol tends to produce fewer follicles than clomiphene. **In most cycles in fact it produces only one follicle.** However, at higher doses or combined with injectable fertility medications it can produce multiple pregnancies. At the usual starting doses this risk is probably lower than clomiphene; so far in our program there has been only one twin pregnancy in 84 pregnancies with letrozol at the lowest doses. However, there has been one triplet pregnancy when letrozole was used at a triple dose.



Endometrial appearance by ultrasound using letrozole.

How to Take Letrozole

Letrozole very new so the best way to take it has not been fully established. Initially it was taken as a pill(s) for five days beginning three days after the first day of menstrual bleeding (**day 3 to 7 of cycle**). The first day of the cycle is considered the first day of bleeding sufficient to require sanitary protection as long as it occurs before midnight. Letrozole may be started after medication (**provera**) is given to bring on a period.

Sometimes Letrozole will be prescribed for only one or two days early in the cycle. For example, in women who do not ovulate, even with higher doses of clomiphene or letrozole, four or five tablets of letrozole may be given on day 2 and 3 of the cycle only. Also in individuals where the suppression of estradiol occurs more profoundly and for longer in the cycle, it may be prescribed earlier.

The lowest dose of letrozole we give is 7.5 mg (or three tablets) on day three. This is enough to cause ovulation to occur in many anovulatory women and also seems to

improve the pregnancy rate over no medications and results in a very low incidence of twins in our intrauterine insemination program (1 in 74 pregnancies).

If ovulation doesn't occur, the dose of letrozol is increased in a stepwise fashion similar to clomiphene. The limiting factor to how high the dose can go seems to be very individualized. Once the maximum dose for an individual is exceeded, a profound inhibition of estradiol production occurs such that it does not recover in the cycle.

Cost of Letrozole

Letrozole at the lowest dose is usually about **\$30.00**. Many drug plans that do not cover infertility medications do cover letrozol because it is not widely recognized as a fertility drug yet. However, if the drug plan does count it as a fertility medication, it is important to note that some **drug plans** cover a given number of cycles of infertility treatments. Letrozole does not work for everybody and you may have to move on to more expensive medication. Before submitting Letrozole to your drug plan, check exactly your coverage.

<p>Before starting any infertility treatment, make yourself familiar with the details of your drug plan!</p>

The Success Rate When Not Ovulating

Letrozole is very effective at promoting ovulation in women where the reason for not ovulating is miscommunication between the pituitary and the ovary (usually referred to as polycystic ovary syndrome or PCOS – separate information sheet available). Letrozol will not work for women with pituitary or ovarian failure. These different causes of not ovulating will be evaluated with your initial infertility investigation. Between **50 - 90%** of women who take Letrozole will ovulate. Not everyone will be successful with the lowest dose (7.5 mg on day 3). Your doctor will begin with this dose but will increase the daily dose by to 2.5 mg day 3 to 7 of the cycle. A dose of 5 mg, and 7.5 mg day 3 to 7 or 7.5 or 10.0 mg on day 2 and 3 may be tried. Approximately **50%** of women who ovulate will become pregnant, usually within the first three to six cycles. A maximum of six ovulatory cycles / pregnancy are indicated before other infertility treatments are considered.

The Success Rate with Other Causes of Infertility

In couples with “idiopathic”, mild male-factor, endometriosis-associated, mild tubal-factor, or cervical-factor infertility, Letrozole can be used to stimulate a higher pregnancy rate. The exact mechanism by which letrozol increases the pregnancy rate is not known. However, it is associated with a **doubling to tripling** of the monthly pregnancy rate.

How Long To Try Letrozole?

Letrozole is indicated for a maximum of **six ovulatory cycles** in patients who are not ovulating. How we determine whether ovulation occurs or not is covered later in this information sheet. Once six ovulatory cycles have been documented without a pregnancy, it becomes increasingly less likely that Letrozole alone will be successful and it is probably time to consider a different treatment.

Letrozole is indicated for a maximum of **12 cycles for other forms of infertility**. The reason for this is that most research indicates that a benefit (higher chance of pregnancy) cannot be demonstrated past 12 cycles of ovulation induction and it is time to add something else to the treatment.

In many situations you may be advised to do **less than the suggested number of cycles**. With an increased length of infertility or in older women, fewer cycles may be suggested as time may necessitate moving on to a more intensive treatment earlier. Fewer cycles may also be suggested with certain diagnoses such as mild male-factor or mild tubal-factor infertility as these may be associated with a lower chance of success with Letrozole.

You should try _____ cycles of letrozole.

In a few circumstances, **more cycles than mentioned above may be recommended**. If Letrozole has produced a pregnancy but it has unfortunately ended in miscarriage it will often be tried again. In anovulatory women who cannot afford more intensive treatment or for patients whose endometriosis has been treated at the time of laparoscopy more cycles may be considered.

Lastly, the exact number of cycles of letrozole to be tried will be modified by **how you feel about it**. Letrozole is usually attempted first because it is inexpensive, easy (less time consuming), and requires less intervention. Side effects are very few (to be discussed) and the risk of multiple pregnancies is lower than many other infertility treatments. However, if your particular preference is to avoid Letrozole, this will be discussed and respected.

Timing of Ovulation and Intercourse

Release of the egg(s) usually occurs day 12 to 15 of the cycle. If a pregnancy does not occur, menstruation will probably occur day 27 to 32 day cycle. The average cycle length on Letrozole is 27 days.

Intercourse should occur **whenever you feel like it**. One of the more stressful aspects of infertility is that intercourse tends to become regimented and only for the purpose of conceiving. There is no good evidence that having intercourse, even frequently outside of the “fertile window” will decrease the chances of pregnancy. In fact, on the contrary, there is good evidence that couples that **have more frequent intercourse become pregnant faster**.

There is also no evidence that any particular sexual frequency clustered at ovulation is better. Advice has been given in the past that intercourse every two days will allow a higher sperm count. It is true that when we request a semen analysis, you are asked to abstain for 48 hours so that we can estimate the maximal sperm count. However, ejaculation into the vagina allows the number of sperm in the female to

One of the misconceptions about infertility is that intercourse should be only every other day in order to maintain a high sperm count. An example might help to clarify this. A couple has intercourse in the morning and 100 million sperm are deposited in the vagina. The couple then has intercourse later that same day and only 75 million sperm are deposited in the vagina because the sperm count is decreased by the earlier ejaculation that day. However, there are now 175 million sperm in the vagina, thus increasing the total number of sperm where it counts!

be additive and of different ages. We believe sperm live in the female reproductive tract about 48 hours. If intercourse occurs **at least every other day from the 10th to the 20th day of the cycle** there should always be sperm available when the egg is released.

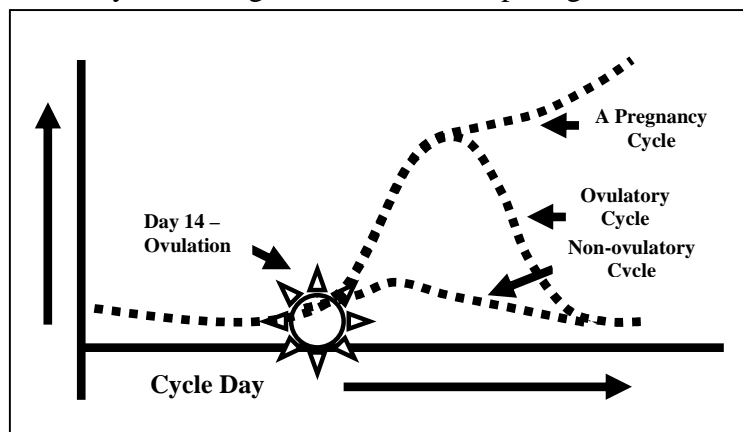
In rare circumstances when intercourse is not possible frequently (illness or work commitments which require separation of the partners), detection of ovulation may be important to time intercourse. In this circumstances, basal body temperature charts or urine based ovulation detection kits (I.E. Clearplan Easy or Ovukit) may be used. Probably intrauterine insemination would be helpful in these circumstances (information sheets available).

Determining If Ovulation Occurs

It may not be critical to determine when ovulation occurs but it is important to determine whether ovulation is occurring. If menstrual period starts about 27 or 32 days after the first day of the last period, then ovulation has likely occurred. In this program, we prefer to confirm ovulation with "luteal phase progesterone". Because there appear to be rapid responders and slower responders to letrozole we may have to modify when you check your progesterone level. The first cycle this should be done day 21 or 22 of your cycle. Once we have seen the pattern of your response (rapid or slower) we may ask you to change this. If this information sheet has been given to you at the clinic with a prescription for letrozole, you should also be given a lab requisition with 6 months repeats of your progesterone level. This can be done in at a lab nearest your home or in the clinic if you live close to us. If the desired testing day falls on a Sunday, the test can be done the Monday morning. The results will automatically be sent to the clinic and arrive about a week later. **It is probably only important to know the progesterone level if letrozol is not producing the usual cycle lengths.** Progesterone level of 16 or greater indicates ovulation. A progesterone level of less than 16 indicates that ovulation did not occur or did not occur at the usual time.

For example, if your period was 27 to 32 days in length and the progesterone is 16 or greater, you probably released an egg (ovulated). If another cycle of letrozol has been prescribed, you should repeat the same cycle as long as it is within the pre-agreed number of cycles. If your period was outside this range and/or the progesterone was less than 16 and your pregnancy test is negative, you probably didn't ovulate or didn't ovulate at the usual time. We will likely advise you to increase your letrozol dose. If the letrozol dose has already been increased, we may change your medication or do something to make letrozol work better. Call S.O.F.T. (519-685-5559) for instructions.

The clinic only calls you if your progesterone is less than 16. If we don't call you, then the progesterone level was likely over 16. In this case you will have to call the clinic if



Call S.O.F.T. (519-685-5559) for instructions. The clinic only calls you if your progesterone is less than 16. If we don't call you, then the progesterone level was likely over 16. In this case you will have to call the clinic if

you want to know your exact level. Higher is not necessarily better although occasionally very high progesterone levels may foreshadow a pregnancy. That is not because a higher progesterone indicates a better ovulation but because in a cycle were a pregnancy occurs, the progesterone continues to rise rather than having the usual “bell curve shaped” rise.

If your period does not come in 35 days, call the clinic or your family doctor for a lab requisition for a pregnancy test. If your BHCG is positive, please call S.O.F.T. for an early pregnancy ultrasound.

What If Ovulation Does Not Occur?

If you had regular cycles and letrozol was given to you to promote the production of a pregnancy but appears to have caused you not to ovulate it may not be the right medicine for you. Usually we will abandon the use of letrozol in favor of another treatment. Sometimes we will try it a second time but monitor a cycle with blood tests and ultrasound, much like we monitor for intrauterine insemination. This will tell us exactly what is happening to your cycle and allow us to choose alternate treatments. Information on how this monitoring is done is available in the information sheet on intrauterine insemination with letrozol.

Some women, who are not ovulating naturally, will not ovulate with Letrozole. If you don't ovulate with the lowest dose of Letrozole, a higher dose will be tried. Usually, the highest dose that is attempted is 7.5 mg from day 3 to 7 of the cycle.

If this happens, some treatments are available to make them more sensitive to Letrozole or alternative medications such as tamoxofene may be tried. A new combination of Letrozole and clomiphene has been very successful for us at S.O.F.T. and an information sheet is available specifically on this treatment.

Up to 60% of women with polycystic ovary syndrome have **insulin resistance**. Insulin resistance occurs when the body is required to produce more insulin to keep the blood sugar normal than usual. It is not diabetes but predisposes to diabetes later in life. If your cycles are irregular or you have a family history of diabetes, you will likely be tested for insulin resistance with your day three blood work done for your initial workup. Treatment of this with metformin (500 mg three times per day) will often make ovulation more likely to occur with Letrozole. Recently, several reports have indicated that metformin treatment may be beneficial even if the initial insulin resistance testing is within normal limits. An information sheet is available on decreased ovulation.

Sometimes combinations of drugs will be tried. One combination we have found successful in the clinic, as mentioned above, is Letrozole with clomiphene. Using the two drugs together appears to harness the ovulation induction ability of both while keeping the side effects of each to a minimum.

Other specific medications may be used in circumstances were there is increased production of androgens from the adrenal glands. A recent study has demonstrated that dexamethazone can be used to decrease the adrenal glands production of male hormones in the first half of the cycle to promote ovulation.

Ovarian cattery or drilling at the time of laparoscopy may also be considered. Ovarian cautery or drilling has been demonstrated to cause the resumption of normal ovulation or cause an improved response to clomiphene in many patients. Although this sounds crazy, it works very well. It was discovered serendipitously like many things are

in medicine (see box). More information is available on laparoscopy and ovarian cauterization in the information sheet on laparoscopy.

Occasionally, women who are ovulating spontaneously will react unusually to Letrozole. Instead of causing them more vigorous ovulation, it will cause them not to ovulate. If this occurs we will often monitor a cycle with blood tests and ultrasound, much like we monitor for intrauterine insemination. This will tell us exactly what is happening to your cycle and allow us to choose alternate treatments. Information on how this monitoring is done is available in the information sheet on intrauterine insemination with Letrozole.

Polycystic Ovary Syndrome was called Stein-Leventhol Syndrome after two gynecologists who first investigated women who did not ovulate. They took wedge biopsies from the ovaries of these women. However, they found that when they did the biopsies, the women would often start to ovulate! This is now believed to work because it decreases the intra-ovarian male hormone level and can be more easily done by burning the surface of each ovary in 6-10 places during a laparoscopy.

Determining If Pregnancy Has Occurred

If a period does not occur after **35 days** from the first day of your last period, a **pregnancy test** should be done. If this information sheet has been given to you at the clinic with a prescription for Letrozole, you may also be given a lab requisition for *BHCG* (blood pregnancy test). If not, call S.O.F.T. (519-685-5559) or your family doctor to order the test. Pregnancy tests are done seven days a week at S.O.F.T. so it is often ***“worth the drive to London”***. If you are pregnant, the test will be positive but may take a few days to get to our office. If you would like to know the results of your test faster, you may wish to write “copy to your family doctor or local gynecologist” in the forth box down on the left hand side of the requisition. Pregnancy tests run at S.O.F.T. are usually reported the same day. If you are pregnant, you will be offered a vaginal ultrasound at the clinic to evaluate the pregnancy and especially to diagnose a twin pregnancy. If you are not pregnant and your period is delayed, it is unlikely that you have ovulated. You should contact the clinic so that medication to bring on a period (Provera 5 mg X 5 days or other options) and the dose of Letrozole can be increased for the next cycle. If ovulation has not occurred on a given dose of Letrozole, that dose should not be continued; a higher dose should be prescribed or other forms of treatment employed.

What If It Doesn't Work

Letrozole is often considered the first line of infertility treatment. It is worth trying in almost any couple as long as at least one fallopian tube is open and extremely severe male-factor infertility is not present.

However, Letrozole doesn't always work. Many options may be considered but the most common is the **intrauterine insemination**. This may originally be combined with Letrozole or stronger medications.

Side Effects

The major side effect of Letrozole is an increase in the frequency of multiple births especially at higher doses. **Twins may not occur any more frequently than in**

spontaneous cycles at the lowest dose but do at higher doses. The number of multiple pregnancies with letrozol seems to be very dose dependent. If very high doses of letrozol are required to produce ovulation, triplets can occur but are still very rare. All in all, the risk of multiple pregnancies is probably equivalent or less than clomiphene 5 to 8%.

Letrozole may cause the ovaries to become larger as they are making more eggs but this occurs less than with clomiphene. This does not cause pain but you may be aware that there is more going on in that area of your body. Usually any new pelvic sensations are due to normal ovulation occurring in a woman who has not experienced this before because she has been anovulatory. However, abnormal **enlargement of the ovaries** can theoretically occur (this hasn't been observed in our clinic yet). This is very rare and can be easily diagnosed in the clinic with a vaginal ultrasound. If it does occur, it will respond to withdrawal of the drug for a cycle or two.

Some of the **temporary side effects** like hot flashes and pelvic bloating or fullness appear to be less with letrozol than with clomiphene. However, in a very small group of women (<1%) who are sensitive to low-estrogen headaches, these may be more severe with letrozol. Letrozol, in higher doses, also seems to cause a very unique kind of fatigue or tiredness. This is described by our patients as being a very pleasant feeling of "really being ready for bed" as apposed to a drugged tiredness. **Hot flashes** are the most common side effect while you are taking the drug. This occurs because Letrozole works by temporarily decreasing the production of estradiol - less estrogen can simulate symptoms of menopause.

Other adverse reactions, occurring less frequently (1% or less of patients), include breast tenderness, headache, nervousness, dizziness, nausea and vomiting and fatigue.

Safety

Femara was first used for ovulation induction about 5 years ago. Its use was first reported by a group from Toronto headed by Dr. Robert Casper. Not long after this, we began using at S.O.F.T. In the five years at S.O.F.T., over 200 babies have been born and many more pregnancies are ongoing as a result of treatment with femara or femara in combination with other drugs.

THE RECENT CONTRAVERSITY
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 here and on a separate information sheet is available that discusses this issue in great detail.

In October, 2005 a group from Laval, Quebec reported on 150 pregnancies born as

The Outcome of 150 Babies Following the Treatment with Letrozole or Letrozole and Gonadotropins. M. M. Biljan, R. Hemmings, N. Brassard. Montreal Fertility Centre, Montreal, PQ, Canada; St. Mary's Hospital, Montréal, PQ, Canada; Université Laval, Quebec, PQ, Canada.

OBJECTIVE: Letrozole is a medication widely used for secondary breast cancer prevention. Recently, this aromatase inhibitor has been used for ovulation induction. In this analysis we report the outcome of 150 babies born as a result of treatment with either letrozole alone or a combination of letrozole and gonadotropins at the Montreal Fertility Centre.

DESIGN: Retrospective analysis.

MATERIALS AND METHODS: This analysis includes patients with unexplained infertility and patients with polycystic ovarian disease. As a control group we used patients delivered at "St. Mary's" hospital in Montreal between 1995 and 2004. The choice of the hospital was deliberate, as "St. Mary's" hospital delivers mostly low risk babies.

RESULTS: During a period of 25 months 171 babies were born as a result of the use of letrozole or letrozole and gonadotropins. Twenty one babies were lost for follow-up. One hundred and fifty babies were compared with a data-base of normal deliveries containing 36,050 deliveries. The median age (M) of treated patients was 35.2 years (interquartile difference (IQD) 31.4-37.9). We had 110 singleton and 20 twin pregnancies. All twin pregnancies apart of one were conceived following the treatment with letrozole and gonadotropins. The incidence of vaginal bleeding was 36.7% in the first trimester, 7.3% in the second trimester, and 1.3% in the third trimester. Seventy-seven non-diabetic singleton pregnancies were delivered at term. There was no difference in weight between this group and the control. Twenty patients had gestational diabetes. Seventeen patients with gestational diabetes delivered at term. When compared with controls these babies were of a significantly lower birth weight than controls ($p=0.002$ 95%CI 11.3-136.6). **Incidence of all malformations was not different between the two groups** ($p=0.25$ 95%CI 0.78-4.71). However, the incidence of locomotor malformations ($p=0.0005$ 95%CI 2.64-27.0) and cardiac anomalies ($p=0.0006$ 95%CI 3.30-58.1) was higher than in the control groups.

CONCLUSION: The results of this study show that use of letrozole in ovulation induction should be controlled until more data on outcomes of pregnancies is obtained.

a result of femara or femara and injectable fertility medications. They found that the babies were born with a significantly **lower birth weight** than a control group of babies delivered in the same hospital. They also found that **the congenital abnormality rate was not different but that congenital abnormalities of the limbs and cardiovascular system were over-represented in the group using femara.**

November 17, 2005, Novartis, the company that makes Femara issued a contraindication for the use of femara in women with premenopausal endocrine status

(therefore women who might use it for infertility treatment), in pregnancy, and/or lactation due to the potential for maternal and fetal toxicity and fetal malformations.

The Evidence

The evidence against femara came in an oral presentation from which I have included the whole abstract on the preceding page. There are several important things I would like to point out about the abstract.

First and most importantly, the article **does not demonstrate an increased abnormality rate in the femara group compared to the control group.** The baseline congenital abnormality rate we expect in all births independent of how the pregnancies were conceived is about 3%. We would therefore expect 4 or 5 congenital abnormalities in 150 babies. This is exactly what was found!

The second thing I would like to point out about the article is that they did find a **significantly lower birth weight in the femara pregnancy group** than the control

group. At first this may appear like another bad side effect of femara. However, femara has a half life of 45 hours. The half life of a drug is the time it takes the body to eliminate half of the drug. It is difficult to understand how a drug that would be gone from the body by the time implantation occurs could cause a difference in the birth weight almost nine months later. A more feasible explanation for this is that there was something else different between the control group that was used and the femara pregnancy group.

Notice that the **control group was “the babies delivered at St. Mary’s Hospital between 1995 and 2004.** These were not infertility patients. The article goes on to say that the age of the infertility patients was 35.2 years. The average age of women having babies in Canada in 1999 was 29.1 years old. Therefore the femara group was likely older. Twenty of the 130 pregnancies were twins. This is a rate of just over 15% compared to 1.25% in the general population. The article goes on to describe the incidence of vaginal bleeding in all three trimesters. The numbers are not compared to the control population but these numbers do appear very high. Twenty (15.4%) of the femara pregnancies were complicated by gestational diabetes. This is a higher number than would be expected in the whole population.

Therefore the **femara pregnancy group differed from the control group** in that they were older, had more bleeding during there pregnancies, more twins and more gestational diabetes. These differences or something else different about the control group is probably a more likely explanation for the higher birth weight in this group. These differences might be more likely to explain a higher congenital abnormality rate than the use of femara but remember there wasn’t a higher abnormality rate!

The control group differed in **one more important way** from the femara pregnancy group. There were 130 pregnancies in the femara group and 36,050 in the control group. Remember that the main concern from this article was that some congenital abnormalities (limb and cardiac) were over represented in the femara pregnancy group. This may only be an artifact of the difference in sample sizes. The control group is 277 times as large. Congenital abnormalities are rare (3% of pregnancies). Specific congenital abnormalities are even rarer, perhaps less than one in 1300. I picked 1300 not because that is the rate of specific abnormalities but to help me make this point.

If a rare congenital abnormality (1/1300) happens in a small study group like the femara pregnancy group (1/130) it frequency automatically appears 10 X as great. Several medications which have later proven to be safe have been caught in this trap. Clomiphene citrate and diclectin both had articles written early in there use that suggested over-representation of specific congenital abnormalities. Both have gone on to be demonstrated safe by over 50 clinical studies each.

The Contraindication

As a result of the article discussed above, Novartis, the company that makes femara issues a notice which was dated November 17, 2005 and mailed to physicians. This announced a “Heath Canada Endorsed Important Safety Information on Femara”. The notice went on to say that femara is contraindicated in women with premenopausal endocrine status, in pregnancy, and/or lactation due to the potential for maternal and fetal

toxicity and fetal malformations. Women with premenopausal endocrine status would include anyone trying to become pregnant.

The contraindication is not new. It was included in the product monograph on femara dated March 22, 2004. Novartis, like other pharmaceutical companies is committed to the safe use of its medications. Also, a formal notice re-stating the contraindication is good public relations and certainly a safety precaution against any potential law suites that could result from pregnancies complicated by congenital abnormalities.

The Use of Femara at S.O.F.T.

As stated earlier, femara has been used extensively for five years at S.O.F.T. We have over 200 completed pregnancies and many more on-going pregnancies that were promoted using femara by itself or in combination with other medications.

S.O.F.T., as you will know if you are a current or former patient keeps very close tabs on its successful pregnancies. We have not noticed an increase in complicated pregnancies, miscarriages or congenital abnormalities in our femara pregnancy group.

Since the Novartis announcement I have been in contact with a number of my senior colleagues about the issue. We recently have investigated and published our combined femara pregnancies (about 500) and an abstract of that article is included below.

Femara has been very useful at S.O.F.T.

Initially we found that some women who would **not ovulate on clomiphene citrate** would respond to femara. Dr. Robert Casper has found the pregnancy rate using femara to be twice as high as clomiphene citrate. We have found it to be at least as good.

We presented our first 100 pregnancies using femara and intrauterine insemination in 2004. In this presentation we demonstrated a **twinning rate** about the same as natural conceptions as long as lower doses of femara were used. Therefore low dose femara is often used when it is important to avoid a multiple pregnancy.

Clomiphene citrate promotes ovulation but is very hard on the endometrium (lining of the uterus). When **endometrial thinning** is demonstrated by vaginal ultrasound in response to clomiphene, we will often switch to femara.

It has also been found at S.O.F.T., that **combining clomiphene and femara** will often cause ovulation in patient who has **not ovulated with maximum doses of clomiphene**. We have also found this combination tends **to promote multiple follicles or eggs** and we have used it in patients undergoing intrauterine insemination that would traditionally go on to injectable fertility medications. Injectable fertility medication is very expensive, so it has been valuable to do this for patients who so not have drug plans. Next year we plan to present our first 100 pregnancies using clomiphene and femara with intrauterine insemination.

What Should Femara Users Do?

Many clinics have decided to discontinue the use of femara until the current issues are sorted out. This is a very reasonable option for any of our patients currently on it. We will try to formulate a treatment plan for you without the use of femara. Clomiphene citrate has been used since 1963 and has been proven safe in numerous

clinical studies. Remember, it was incriminated in the promotion of specific congenital abnormalities early in its use but these were disproved after more widespread use.

At S.O.F.T., **we will allow you to make an informed decision** to continue using femara. To do this, you must read this document and make an informed decision after weighing all the available evidence. You must know that the number of pregnancies resulting from femara is too few to give absolute reassurance that it is safe. I would like you to have read this information sheet and any other information that you can find.

In June, 2006 we collaborated with colleagues in Toronto and Montreal to investigate more pregnancies. This resulted in a paper published in Fertility Sterility (our premier journal) and will perhaps give us additional reassurance. The abstract of the paper is presented below:

Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate.

[Fertil Steril.](#) 2006 Jun;85(6):1761-5.

[Tulandi T](#), [Martin J](#), [Al-Fadhli R](#), [Kabli N](#), [Forman R](#), [Hitkari J](#), [Librach C](#), [Greenblatt E](#), [Casper RF](#).

OBJECTIVE: To evaluate the incidence of congenital malformations among offspring of mothers who conceived with clomiphene citrate (CC) or with letrozole treatment for infertility. DESIGN: Retrospective study. SETTING: 5 fertility centers in Canada. PATIENTS: 911 newborns from women who conceived following CC or letrozole treatment. INTERVENTIONS: Examination of medical files of both mother and newborn, and cross-checked with the parents by telephone calls. MAIN OUTCOME MEASURES: Identified major and minor congenital malformations, birth weight, age of the mother, and type of treatment that led to the conception. RESULTS: Overall, congenital malformations and chromosomal abnormalities were found in 14 of 514 newborns in the letrozole group (2.4%) and in 19 of 397 newborns in the CC group (4.8%). The major malformation rate in the letrozole group was 1.2% (6/514) and in the CC group was 3.0% (12/397). One newborn in the letrozole group was found to have a ventricular septal defect (0.2%) compared to 4 newborns in the CC group (1.0%). In addition, the rate of all congenital cardiac anomalies was significantly higher (P: 0.02) in the CC group (1.8%) compared to the letrozole group (0.2%). CONCLUSION: **There was no difference in the overall rates of major and minor congenital malformations among newborns from mothers who conceived after letrozole or CC treatments.** However, it appears that congenital cardiac anomaly is less frequent in the letrozole group. The concern that letrozole use for ovulation induction could be teratogenic is unfounded based on our data.

Letrozole and Timed Intercourse Cycle – Day By Day

Cycle Day	Instructions	Patient Notes
Day 1	This is the first day of menstrual bleeding requiring protection (as long as the bleeding occurs before midnight)	
Day 1 (cycle 1)	Call for hysterosalpingogram (only if asked)	
Day 3 (cycle 1)	“Day 3 blood-work” (only if asked)	
Day 3-7 Day 3 only Day 2 & 3 only	Take Letrozole as prescribed.	
Day 2 to 13	Hysterosalpingogram (only if asked)	
Day 10 to 20	Have intercourse a minimum of every two days.	
Day 21 or 22	Go to the S.O.F.T. or a commercial lab and for serum progesterone. Because responses and cycle lengths may vary, this may need modification depending on the cycle length.	
Day 35	If your period does not begin, go to the lab or S.O.F.T. for a BHCG (pregnancy test).	
Day 54-56	If pregnancy test positive, an early pregnancy vaginal ultrasound	

When you're 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. After your ultrasound you are still considered our patient. Especially early in your pregnancy, if you have any concerns, perhaps because you have had bleeding or pain, we are more than happy to repeat your ultrasound.

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

Is Letrozole Right for You?



**Normal “luteal day 40”
ultrasound of a single
pregnancy**

Who knows? All the epidemiological data has been discussed earlier in this information paper but epidemiological studies describe the results in large groups of patients. This data will be used to decide how many cycles of letrozole should be used. However, individuals get pregnant and it has been my experience that in individuals there is a **key to obtaining a pregnancy**. It is not always possible to predict what that key is. Sometimes, “just letrozole” has produced some remarkable results. Therefore unless the fallopian tubes are blocked or there are very few sperm, letrozol is worth trying at least once.

James Martin MD ©

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Check out our web page at www.soft-infertility.com