

The Use of Femara (Letrozole) for Infertility



**Southern Ontario
Fertility Technologies**

Introduction

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.

In October of this year, a group from Laval, Quebec reported on 150 pregnancies born as 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 just to the right. 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**

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, Montreal, PQ, Canada; Universite' Laval, Que'bec, 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.

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 44 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 are all very concerned but none of us have noted an increased congenital abnormality rate. Two of my colleagues in Toronto and Montreal plan to investigate and publish our combined femara pregnancies (about 500) as soon as we can confirm and analyze the data. Our preliminary observations are very reassuring.

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 do 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 ?

Most 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 should 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 analyzed our data and combining it with colleagues in Toronto and Montreal to investigate more pregnancies. This was published in our premier fertility journal and will perhaps give additional reassurance. However, congenital abnormalities are rare and even this additional data will not be able to prove there is not as risk.

The abstract of that article is included 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.

So there is the evidence in great detail and you must decide.

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