
The Use of Femara (Letrozole) for Infertility

Introduction

Femara was first reported to be effective for ovulation induction in 2000. At the OFC we have had babies born as a result of treatment with Femara or Femara in combination with other drugs. In October of 2005, a group from 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 overall congenital abnormality rate was not different but that congenital abnormalities of the limbs and cardiovascular system were over-represented in the group using Femara.**

On 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 we have included the entire abstract (below).

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; Université Laval, Québec, 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.

There are several important things to point out about the abstract.

- 1) 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!
- 2) 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 their 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!
- 3) 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 sizes of the groups. 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 single rare congenital abnormality (1/1300) occurs in a small study group like the Femara pregnancy group (1/130) its 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 Dicletin both had articles written early in their 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 issued 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 suits that could result from pregnancies complicated by congenital abnormalities.

The Use of Femara in infertility

As stated earlier, Femara has been used extensively for several years by many fertility specialists in Canada and around the world. Since the presentation of the above abstract in 2005, a Canadian multicentre study of 911 babies born after letrozole or clomiphene citrate treatment was published in the infertility journal “Fertility and Sterility”. The authors found no increase in congenital anomalies in the Femara babies, and in fact, they observed a significant reduction in heart defects in the Femara babies compared to the babies born after their mothers were given clomiphene.

Initially they found that some women who would **not ovulate on clomiphene citrate** would respond to Femara and that the pregnancy rate using Femara was twice as high as clomiphene citrate.

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 injectable gonadotropins alone. An alternative is to use Femara alone, or in combination with injections of gonadotropins. We do not see a thin lining as a result of gonadotropins or Femara.

New Study by Legro and colleagues published in the New England Journal of Medicine in July 2014: Efficacy of Letrozole versus Clomiphene in patients with Polycystic Ovary Syndrome

Study design: Double-blind, multicenter, randomized control trial from February 2009 to January 2012.

Summary: Looked at 750 women aged 18-40 with PCOS, comparing letrozole and clomiphene head-to-head for ovulation induction. The primary outcome of the study was live birth during the treatment period, with secondary outcomes being ovulation and conception. The findings of the study were that those treated with letrozole had more cumulative live births than those receiving clomiphene (27.5% vs 19.1%), a statistically significant difference. Cumulative ovulation rates were also statistically significantly higher in the letrozole group at 61.7% compared to 48.3% in the clomiphene group. Between each type of treatment there was no statistically significant difference in adverse maternal effects or in congenital anomalies.

What does this mean: While the standard of care for ovulation induction in a PCOS population remains clomiphene, this trial does demonstrate that letrozole is indeed more effective both at inducing ovulation as well as increasing live birth rates than clomiphene. Given that the use of letrozole for ovulation induction is off-label, it is important to be cognizant of the potential risks raised by Health Canada. However, these risks must be balanced with the findings that in the very specific population of polycystic ovary syndrome, letrozole has been found to be more effective than the standard of care.

What Should Femara Users Do?

At OFC, we ask you to make an **informed decision** if you wish to use Femara. To use Femara, we must know and document that you have made this 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. We would like you to have read this information sheet accompanying scientific articles.

We have provided this information sheet to inform you and help you make a decision. If you have additional questions, we will try and answer them.