Letrozole Warning Called 'Knee-Jerk' Reaction

BY KATE JOHNSON
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American and Canadian fertility experts have expressed surprise and disappointment about new warnings concerning the aromatase inhibitor letrozole and its off-label use in fertility treatment.

"This is a knee-jerk reaction without a proper review of the data," said Dr. Kutluk Oktay, referring to the Swiss company Novartis Pharmaceuticals' letter to health care professionals in Canada and the United States warning that the drug may be associated with congenital anomalies. Letters are also planned for all other countries where the drug is available, said a company spokesperson.

Novartis markets letrozole under the name Femara for the treatment of breast cancer. But worldwide the drug is used off label for ovulation induction, and has replaced clomiphene citrate in many intrauterine insemination programs because of its superior pregnancy success rates and ability to decrease gonadotropin requirements. Additionally, it is one of the only safe options for breast cancer patients wishing to undergo in vitro fertilization with ovarian stimulation to freeze embryos prior to their cancer therapy.

Although Femara's label has always stated a contraindication in premenopausal women because of "the potential for maternal and fetal toxicity," Novartis' renewed concerns about the drug's use in fertility treatment arose after a small, unpublished Canadian study was presented at the recent conjoint annual meeting of the American Society for Reproductive Medicine and the Canadian Fertility and Andrology Society, said company spokesperson Kim Fox.

Dr. Marinko M. Biljan, medical director of the Montreal Fertility Clinic, reported that among his patients, letrozole, used at the 5-mg dose for ovulation induction, was associated with an increased rate of serious fetal anomalies.

"We stopped using it at our center in September and we hope others will stop using it, at least at this dose," Dr. Biljan said in an interview.

An analysis of 150 babies born at his clinic after letrozole therapy (5 mg daily on days 3-7) found a 4.7% rate of major anomalies compared with a 1.8% rate in a control group of more than 36,000 babies born at a local "low-risk" hospital. As a result of this study, Novartis subsequently reviewed its safety database and found 13 reports of obstetric exposures to letrozole, of which 4 had adverse obstetric outcomes, said Fox.

Health Canada said three of the four adverse obstetric outcomes occurred in women who were exposed to letrozole as a result of infertility treatment, and the fourth exposure was a result of breast cancer treatment in the first and second trimesters of pregnancy. Two of the three infertility patients had spontaneous abortions, while the third gave birth to a baby who was diagnosed at 1 year with bilateral adrenal neuroblastoma, said Christopher Williams, a spokesman for Health Canada. The breast cancer patient who was exposed to letrozole during pregnancy gave birth to a female baby with a genital abnormality.

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Novartis has not studied Femara as an infertility therapy and so cannot comment on this, said Fox. But "because there were some adverse events reported it is important that we remind physicians about the appropriate use and warnings about Femara, regarding not only pregnancy and lactation, but also premenopausal status," she said.

Although the Food and Drug Administration is reviewing the matter, Health Canada has endorsed the Novartis warning. But several fertility experts with extensive experience using letrozole say the matter has been blown way out of proportion.

"There is a growing body of literature supporting the use of aromatase inhibitors in infertility therapy and the peer-reviewed literature is expected to support its continued use," said Roger Pierson, Ph.D., professor of obstetrics, gynecology, and reproductive sciences at the University of Saskatchewan, Saskatoon.

"The study reported by Dr. Biljan et al. has done more harm than good as the conclusions are not supported by appropriate data," he said. Dr. Robert Casper, one of the pioneers of letrozole in the treatment of infertility, said the Biljan study is seriously flawed because it has an inappropriate control group. "It compares young fertile with older infertile women," said Dr. Casper, professor of obstetrics and gynecology at the University of Toronto.

"An infertile control group would be more valid and the Canadian IVF database for last year showed an overall anomaly rate of 2.6% in over 1,600 deliveries. Using this number, Dr. Biljan's relative risk numbers would be quite a bit lower," he said. In addition, most of the major anomalies detected in the study's control group would have been referred to specialists prenatally and thus would not have shown up as adverse outcomes in the final analysis, he said.

Dr. Casper has reviewed his experience with more than 200 letrozole births and found no major congenital anomalies—which is "much below the expected rate" even in the general population, he said. Nevertheless, his clinic has stopped using letrozole as a result of the Novartis warning.

"Unfortunately this is going to negatively impact physicians and patients," said Dr. Oktay, of Cornell University, New York. Dr. Biljan believes the discrepancy between his results and those of others could be explained by his use of a higher than normal dose of letrozole (the more common dose is 2.5 mg daily on days 3-7).

Regardless of dose, both Dr. Oktay and Dr. Casper said that the short half-life of letrozole makes it biologically implausible that the drug could cause anomalies, since it is discontinued before conception occurs.

However, according to the FDA, "although the terminal elimination half-life is said to be 2 days, steady state is not reached for 2-6 weeks—and steady-state levels are maintained over extended periods."

Dr. Oktay said one would expect fetal exposure to letrozole to result in abnormal sexual development. Indeed, Novartis's one record of second trimester exposure did result in a child with genital abnormalities. But the cases resulting from preconceptual exposure (two spontaneous abortions and one bilateral neuroblastoma) are not obviously drug related, and in some cases could be explained by factors related to infertility, he suggested. Similarly, in Dr. Biljan's study, none of the adverse outcomes were related to abnormal sexual development. ■

Clinical Capsules

Tegaserod Therapy in Women With IBS

A large, international trial found that tegaserod was significantly more effective than placebo for irritable bowel syndrome with constipation.

Dr. Jan Tack, of the Centre for Gastroenterological Research, University of Leuven (Belgium), and coauthors worked with physicians from 20 countries to randomize 2,660 female patients; 2,135 received tegaserod (6 mg twice daily) and 525 took the placebo for the initial treatment phase of 1 month.

After a treatment-free interval, the researchers re-randomized 983 patients (488 tegaserod, 495 placebo) who qualified for repeated treatment because they responded to the first treatment and then had a recurrence of IBS symptoms (Gut 2005;54:1707-13).

The researchers found that patients treated with tegaserod had better work productivity and quality of life than did placebo patients during both the initial therapy and repeated treatment. The drug, marketed as Zelnorm by Novartis, was initially approved in 2002 for IBS with constipation in women.

Due to subsequent concerns about overuse, the label advises physicians and patients to "periodically assess the need for continued therapy."

Drinking Tea May Cut Ovarian Ca Risk

Tea consumption appears to reduce a woman's risk of developing epithelial ovarian cancer, reported Dr. Susanna C. Larsson and Dr. Alicja Wolk of the Karolinska Institute, Stockholm.

The researchers used dietary data collected from 66,651 Swedish women between 1987 and 1990 to examine a possible link between tea consumption and later development of ovarian malignancy.

They identified incident cases of invasive epithelial ovarian cancer that occurred over the intervening 14-17 years using a national cancer registry. A total of 301 of the women developed ovarian cancer.

Tea drinking was inversely correlated with the disease, so that the incidence of ovarian cancer decreased as the quantity of tea drinking increased. Women who drank at least two cups of tea daily showed a 46% lower risk of ovarian cancer than did those who did not drink tea (Arch. Intern. Med. 2005;165:2683-6).

These results closely replicate the findings of the Iowa Women's Health Study, which reported a 47% lower risk of ovarian cancer in women who drank tea weekly. "To our knowledge, the Iowa Women's Health Study is the only other prospective study that has examined the relationship between tea consumption and ovarian cancer risk," Dr. Larsson and Dr. Wolk said. Polyphenols that are abundant in both green and black teas "have been extensively studied as cancer chemopreventive agents," they added.

Catechins, theaflavins, thearubigins, and flavonols have been shown to inhibit carcinogenesis in laboratory and animal studies. It is possible that these polyphenols protect against cancer by their antioxidant effects. Some researchers have posited that they may also inhibit cell growth, induce apoptosis, or inhibit tumor angiogenesis, the investigators noted.

Puberty Feeds Body Dissatisfaction

Pubertal changes were more likely to trigger body dissatisfaction in white girls than in African American girls in a study of 331 girls, reported Tiffany Floyd, Ph.D., in a poster presented at the annual meeting of the Association for Behavioral and Cognitive Therapies.

Previous studies have shown that body dissatisfaction during puberty is more common among girls than among boys—because pubertal changes conflict with the idealized image of the thin female—and that this increase in body dissatisfaction may promote depression.

However, additional research has shown that larger female body types are more desirable and acceptable among African Americans than they are among whites, wrote Dr. Floyd, of City College, New York, and her colleagues.

The study included girls in grades 4 through 9, with an average age of 12 years. Approximately 50% of the girls were African American.

Overall, white girls reported significantly more body dissatisfaction than did African American girls. Although pubertal status did not directly predict depression in either group, pubertal status significantly predicted body dissatisfaction among white girls in a linear regression analysis, which in turn predicted depressive symptoms.

Pubertal status failed to predict body dissatisfaction among African American girls, but body dissatisfaction significantly predicted depressive symptoms independent of pubertal status.

The girls were assessed using the Children's Depression Inventory, the Body Dissatisfaction Scale, and the Pubertal Development Scale.

—From staff reports