Aromatase Inhibitors Show Promise in PCOS

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TORONTO — Aromatase inhibitors could someday replace clomiphene citrate as the first-line treatment for infertility in patients with polycystic ovary syndrome, Dr. Robert F. Casper said at the annual meeting of the Endocrine Society.

Aromatase inhibitors don't have some of the drawbacks of clomiphene citrate such as a long tissue half-life, high multiple pregnancy rates, and peripheral antiestrogenic effects, he said.

"All of these problems result in a lower pregnancy and live birth rate than you'd expect from the very good efficacy of clomiphene citrate for ovulation induction," said Dr. Casper, professor of obstetrics and gynecology at the University of Toronto.

Aromatase inhibitors such as letrozole, on the other hand, have a relatively short half-life and result in predominantly monofollicular ovulation when used alone. The drug also results in increased follicular sensitivity to follicle-stimulating hormone (FSH) and does not have adverse effects on the endometrium or cervical mucus.

And aromatase inhibitors are safe for use in ovulation induction, despite a well-publicized report in 2005 that letrozole results in an increased risk of congenital abnormalities, he said. Dr. Casper has a licensing agreement with EMD Serono, of Geneva, which is currently testing an aromatase inhibitor for use in treating infertility.

Many physicians may be reluctant to prescribe letrozole off-label for the treatment of infertility in patients with polycystic ovary syndrome (PCOS), Dr. Casper said, because of warnings from the drug's maker. In November 2005, Novartis, which markets letrozole as Femara for the treatment of breast cancer, issued a letter to physicians warning that that the drug is contraindicated in women with premenopausal endocrine status, in pregnancy, and during lactation because of the potential for maternal and fetal toxicity and fetal malformations.

The warning was based largely on a study presented at the American Society of Reproductive Medicine meeting in 2005 in which researchers examined the outcomes of 150 babies who were born following treatment with letrozole, or letrozole and gonadotropins, compared with a database of about 36,000 deliveries in a low-risk maternity hospital. The researchers, led by Dr. Marinko M. Biljan of the Montreal Fertility Center, found no difference in overall malformations but an increased incidence of locomotor and cardiac malformations in the letrozole group, which was statistically significant.

But there are some problems with the design of the study that call the results into question, Dr. Casper said. For example, the control group was composed of spontaneously conceiving patients without infertility. "It is actually well known that women with infertility, especially women with unexplained infertility, have a higher malformation rate in their babies than women who conceive naturally," he said.

In addition, two recent studies appear to contradict the findings presented in 2005, according to Dr. Casper. Between 2003 and 2005, Dr. Casper and his colleagues examined 911 pregnancies at five clinics in Canada. The four-arm study included patients who received letrozole, letrozole plus FSH, clomiphene citrate, or clomiphene plus FSH. All of the women in the study were undergoing either intrauterine insemination or timed intercourse, and all were monitored in the same fashion.

The researchers found no difference in the overall malformation rate between clomiphene citrate and letrozole. However, they did find a higher rate of cardiac abnormalities in the babies born to the group of women receiving clomiphene citrate. The children of women in the two clomiphene citrate groups had a combined 1.8% rate of cardiac abnormalities, compared with a combined 0.2% rate among women in both letrozole groups, which was statistically significant (Fertil. Steril. 2006;85:1761-5).

In a follow-up study at the McGill Reproductive Centre and the Toronto Centre for Advanced Reproductive Technology, Dr. Casper and colleagues looked at pregnancies occurring after patients received letrozole and clomiphene for ovulation induction. They compared women taking these drugs with an age-matched control group of spontaneous pregnancies in Toronto. They found no difference in overall malformation rates among the three groups, Dr. Casper said. The follow-up study has not yet been submitted for publication. ■