Infertility Studies Support Anastrozole, Letrozole

BY JANE SALODOF MacNEIL
Southwest Bureau

Los Angeles — New data from two pilot studies support the use of aromatase inhibitors to promote pregnancy in women with ovulatory dysfunction or unexplained infertility, according to poster presentations at the annual meeting of the Society for Gynecologic Investigation.

In the first randomized study to test anastrozole as an infertility treatment, women who took the aromatase inhibitor before undergoing intrauterine insemination (IUI) had a pregnancy rate comparable overall with those undergoing standard treatment with clomiphene and IUI. Anastrozole cycles appeared to offer an advantage, however, in that they led to more pregnancies in women with polycystic ovary syndrome and generated three times fewer follicles overall.

In the second study, women taking letrozole before undergoing in vitro fertilization (IVF) produced more oocytes and had higher pregnancy rates than those who were treated with a standard protocol of gonadotropins, although the differences between groups were not statistically significant. This study was a randomized feasibility trial in low responders who had failed previous treatments and were scheduled for an aggressive IVF protocol.

Christopher S. Sipe, M.D., lead investigator of the anastrozole study, said in an interview that he believes enough data exist for physicians to start prescribing aromatase inhibitors for infertility patients, but that few will without an indication for infertility from the Food and Drug Administration. "I think you can still use it, but I don't think a lot of people will with the medicolegal aspects in the field," said Dr. Sipe of the department of ob.gyn. at the University of Iowa Hospitals and Clinics, Iowa City.

Women who took anastrozole before undergoing IUI had a pregnancy rate comparable overall with those treated with clomiphene and IUI.

The anastrozole trial recruited 50 couples from the University of Iowa Infertility Treatment Center. Patients with tubal factor infertility or severe male factor infertility were excluded.

Women were randomized to receive 1 mg of anastrozole or 100 mg of clomiphene citrate on cycle days 3 through 7. All women received intramuscular injections of 75 IU of purified FSH on days 7 through 11.

On day 12, ultrasounds and measurements of serum estradiol were initiated and performed every other day. If needed, FSH injections continued until a follicle greater than 18 mm was observed and the patient received 10,000 U of human chorionic gonadotropin. IUI followed 36 hours later.

Overall, the cancellation rate was 16% and the pregnancy rate 18% with nine pregnancies achieved. Though the pregnancy rates of 16% with anastrazole and 20% with clomiphene were similar, Dr. Sipe said the trial was too small to draw conclusions.

Serum estradiol was lower with anastrazole, and the investigators proposed that the smaller number of follicles in those patients suggests the aromatase inhibitor could produce fewer multiple births. "This study did not have enough patients to look at the multiple pregnancy rate—you need 1,200 patients or so—but that is what we are thinking," Dr. Sipe said.

Perhaps the most provocative finding was in women with polycystic ovary syndrome. Anastrozole produced three pregnancies in this group, but clomiphene produced only one. A published study has also found these patients benefitted from letrozole (Fertil. Steril. 2001;75:305-9), so Dr. Sipe said the Iowa investigators plan further studies with anastrozole in this population.

Sonya Kashyap, M.D., worked on the letrozole study presented at the meeting while she was a fellow at the Cornell Center for Reproductive Medicine and Infertility, New York. Her group was able to randomize 55 patients, of whom 48 completed and were eligible for evaluation, according to Dr. Kashyap, now at the University of Ottawa.

The patients willing to enter the study were largely older couples who had nearly exhausted their options. Most fulfilled at least three of five entry criteria, only one of which was required for eligibility.

The study was not blinded but randomized patients by "concealment of allocation" to either a standard protocol of gonadotropins or letrozole before IVF. Physicians did not know which group patients would be in, and Dr. Kashyap maintained in an interview that the outcomes measured protected the study from bias once treatment began.

The final sample was small (26 women on the standard regimen and 22 on letrozole), and the primary outcome data were not statistically significant but trended in favor of the aromatase inhibitor. Compared with the control group, patients treated with letrozole had higher pregnancy rates per cycle started (3/22 vs. 1/26), per retrieval (3/14 vs. 1/16), and per transfer (3/13 vs. 1/14). ■

Infertility Work-Up Should Include Examination With TVL, Expert Says

BY KATE JOHNSON
Montreal Bureau

London — The modern infertility work-up should include a transvaginal hydrolaparoscopic exploration of the tubes and ovaries, said Stephan Gordts, M.D., of the Leuven (Belgium) Institute for Fertility and Embryology.

He pioneered transvaginal hydrolaparoscopy (TVL) in 1998 (later, another group named the procedure "fertiloscopy") and said he's since abandoned tubal assessment by hysterosalpingogram (HSG).

Whereas the HSG can explore tubal patency only, "with TVL you have a more complete exploration of the patient," he told this newspaper.

Speaking at the annual congress of the International Society for Gynecologic Endoscopy, Dr. Gordts explained that TVL can evaluate both the inside and outside of a patient's reproductive organs and can evaluate adhesions and endometriosis by incorporating hysteroscopy, transvaginal hydrolaparoscopy, salpingoscopy, and tubal patency testing.

TVL can be done in an ambulatory setting, under local anesthetic, and requires only an oocyte aspiration room, rather than a full operating theater. The procedure is performed with the insertion of a needle transvaginally into the pouch of Douglas followed by infusion with saline. An endoscope can be introduced, allowing visualization of the outside of the uterus, the ovaries, and the distal part of the fallopian tubes. The scope can be introduced a few centimeters into the distal end of the fallopian tube for evaluation of the ampulla and the inside of the distal tube. A biopsy can reveal the presence or absence of normal cilia movement.

At the same time, a hysteroscope can be passed through the cervix, allowing evaluation of the inside of the uterus, and infusion of dye through the fallopian tubes to assess their patency.

The presence of saline makes adhesions and subtle endometriotic lesions float, allowing for easier identification. "This pathology is often masked under the high intraabdominal pressure of laparoscopy," Dr. Gordts said.

Although it's primarily a diagnostic procedure, TVL can be used to perform adhesiolysis, treat mild to moderate endometriosis, and drill ovaries in patients with polycystic ovarian disease.

Unlike Dr. Gordts, Jacques Donnez, M.D., said he believes there is still a place for HSG in the fertility work-up—and the combination of HSG and TVL might offer the most thorough tubal assessment.

Although TVL can visualize a few centimeters of the inner distal fallopian tube, and evaluate patency by confirming spillage of dye infused through the cervix, it offers no other information about the status of the proximal tube, said the professor and head of gynecology at Catholic University of Louvain in Brussels.

"You can see if the dye is not going through, but if this happens you have no idea of the location of the blockage or if there is some diverticuli or anomalies in the proximal tube," he said in an interview.

HSG can identify the location of proximal blockages, some of which can be easily catheterized. ■

Smoking, Estrogen Bad Combination for Alzheimer's

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

Miami Beach — The risk of Alzheimer's disease declines by almost half among postmenopausal nonsmokers who use estrogen therapy, but nearly doubles among those who both smoke and use estrogen therapy, Rosebud O. Roberts, M.B., said in a poster presented at the annual meeting of the American Academy of Neurology.

Dr. Roberts, an epidemiologist at the Mayo Clinic, Rochester, Minn., also found that early estrogen therapy might be a predictor for Alzheimer's in postmenopausal women; in contrast, estrogen therapy taken later in life appears to be more protective. But these conclusions may have more to do with premenopausal estrogen levels than postmenopausal estrogen therapy, she said in an interview.

"What I suspect is that smoking may lead to lower estrogen levels premenopausally, which could lead to brain neurons that are less viable and more likely to die early. Those who initiate therapy earlier probably have less [endogenous] estrogen, and more symptoms, while those who initiate therapy at a later age—because they had fewer symptoms or less severe symptoms—probably had more premenopausal estrogen."

She and her associates conducted a case-control study that included 216 women with natural menopause who developed Alzheimer's disease during 1985-1989. They were compared with 210 cognitively intact controls who had similar ages at menarche and menopause.

A similar percentage of women in both groups used estrogen therapy for at least 6 months (11.6% of cases, 14% of controls). Of the 54 women on estrogen, the 25 with Alzheimer's started estrogen therapy earlier than the 29 controls (50 years vs. 53 years), and had a shorter lag time between menopause and the initiation of estrogen therapy (1 year vs. 4 years). Estrogen users had a 20% reduced risk of Alzheimer's disease, but this was not statistically significant.

The investigators did see significant differences in estrogen therapy and the risk of Alzheimer's disease between smokers and nonsmokers, however. The odds ratio of Alzheimer's was 1.93 in smokers who used estrogen therapy and only 0.54 in nonsmokers who used estrogen therapy. In nonsmokers, estrogen therapy of more than 3 years' duration showed a significant protective effect, reducing the risk of Alzheimer's by almost 70%.

"It is in women who don't smoke where we see the beneficial effects of [estrogen therapy]," she said. ■