Effect of letrozole at 2.5 mg or 5.0 mg/day on ovarian stimulation with gonadotropins in women undergoing intrauterine insemination

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Objective: To determine the effect of combined therapy of letrozole (2.5 mg or 5.0 mg) with recombinant follicle-stimulating hormone (FSH) in comparison with the administration of recombinant FSH alone in an intrauterine insemination (IUI) program.
Design: Retrospective study.
Setting: Assisted fertilization program in a specialized infertility center.
Patient(s): 110 women undergoing IUI and gonadotropin therapy.
Intervention(s): Recombinant FSH alone administered from day 3 or combined with letrozole, 2.5 or 5.0 mg/day, on days 3 to 7, and gonadotropins starting on day 7 of the menstrual cycle. Transvaginal ultrasound examinations were done until the dominant follicle reached 18 mm in diameter. Ovulation was triggered with 10,000 IU of human chorionic gonadotropin (hCG), and IUI performed 30 to 40 hours later.
Main Outcome Measure(s): Recombinant FSH dose required, number of follicles greater than 14 mm and 18 mm, endometrial thickness, pregnancy rates, miscarriages, and characteristics of newborns.
Result(s): Women treated with FSH and 5.0 mg/day of letrozole required a lower dose of FSH than the group co-treated with 2.5 mg/day of letrozole or with FSH alone. Throughout most of the follicular phase, the endometrial thickness was statistically significantly less in both letrozole cotreatment groups compared with the FSH control group. By the day of hCG administration, the endometrial thickness was comparable among all the groups. The pregnancy rates were the same with recombinant FSH alone or combined with letrozole.
Conclusion(s): In terms of cost-effectiveness, 5.0 mg/day of letrozole is more effective than the 2.5 mg/day in cotreatment with no adverse effect on pregnancy rate or outcome. (Fertil Steril® 2008;90:1818–25. ©2008 by American Society for Reproductive Medicine.)

Key Words: Letrozole, aromatase inhibitors, recombinant FSH, intrauterine insemination

Aromatase is the key enzyme that converts testosterone to estradiol (1). Aromatase inhibitors (AIs) are a series of compounds that were developed for the treatment of breast cancer, where AI was demonstrated to be more effective than the classic treatment with tamoxifen (1). More recently, AIs also have been used for applications outside cancer treatment (2–5), such as inducing ovulation in women who have failed with clomiphene citrate treatment (6). In this use, AIs have been demonstrated to be even superior to clomiphene citrate in effectiveness (3, 7); in fact, unlike clomiphene citrate, AIs have no antiestrogenic effect over the endometrium, which be an advantage for keeping the endometrium in optimal condition to maintain a pregnancy (8). Therefore, AIs constitute an excellent alternative to clomiphene citrate treatment as an ovulation inductor for the treatment of infertility, particularly in assisted reproduction programs.

When combined with recombinant follicle-stimulating hormone (FSH), letrozole, a third-generation aromatase inhibitor, modifies the follicular, hormonal, and endometrial dynamic in comparison with treatment with recombinant FSH alone. Recombinant FSH plus letrozole could have beneficial effects on the ovulatory and endometrial cycle (9, 10). The combination of 2.5 mg/day of letrozole with recombinant FSH also reduces the dose of recombinant FSH required for superovulation, thus lowering the cost of assisted fertility programs (11), particularly in women who have had a poor response to hormonal stimuli (8, 12).

A recent study demonstrated that the dose of 5.0 mg of letrozole resulted in a greater number of follicles and an improved rate of pregnancies per cycle than 2.5 mg/day (13). However, it is not known whether this pattern also would

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be observed when a different dose of letrozole is co-administered with recombinant FSH. Our study was designed to determine the differences in the effect of combined therapy of letrozole (2.5 mg or 5.0 mg) with recombinant FSH when compared with the administration of recombinant FSH alone in an intrauterine insemination (IUI) program. In a developing country, the use of 5.0 mg/day of letrozole could be an optimal dose for reducing the cost to patients with no adverse impact on endometrial thickness or pregnancy rate.

MATERIALS AND METHODS

Patients

This retrospective study is based on secondary data analysis obtained from the clinical records of women who attended a specialized infertility center (PRANOR, Assisted Reproduction Group) in Lima, Peru, from December 2004 to January 2007. The study was approved by the institutional review board of the Universidad Peruana Cayetano Heredia (code number 52252).

Data were collected from records of patients who had had primary infertility of diverse etiology (anovulation, endometriosis, male factor infertility, and unexplained infertility) and who underwent controlled ovarian stimulation with recombinant FSH alone or combined with letrozole (2.5 or 5.0 mg/day) for IUI.

Criteria of Inclusion

The criteria of inclusion were patients with infertility of at least 1 year duration, aged <40 years, with patent tubes on hysterosalpingogram or laparoscopic assessment, and a normal uterine cavity, plus the presence of at least 10 million of motile sperms/mL in the male partner's assessment.

Groups of Study

This study comprised 110 women who underwent 124 IUI cycles. The patients were divided in three different treatment groups: group 1 received a combination of 2.5 mg/day of letrozole for 5 days plus recombinant FSH; group 2 received a combination of 5.0 mg/day of letrozole for 5 days plus recombinant FSH; and group 3 received recombinant FSH alone (control group). Group 1 was 26 patients who had 30 stimulation cycles. Group 2 was 48 patients who had 55 stimulation cycles. Group 3 was 36 patients who had 39 stimulation cycles.

Endometriosis was diagnosed by laparoscopy, male factor infertility was diagnosed according to the World Health Organization (14) criteria for normal semen, and the diagnosis of unexplained infertility was based on exclusion of male and female factors. Ovulation was documented by follicular monitoring with transvaginal ultrasonography.

All patients underwent a maximum of two cycles of insemination protocols. The dosage of medication was based on the clinical profile of the patient, including age, weight, and duration of infertility. The initial dose of recombinant FSH was of 50 IU in four cases, 100 IU in 34 cases, and 150 IU in one case, and in both letrozole treatment groups the dose was 50 IU in 18 cases, 100 IU in 64 cases, 150 IU in two cases, and 200 IU in one case. The dose was adjusted according to the follicular monitoring. None of the women had received letrozole before.

Treatment

In group 1, letrozole (Femara; Novartis Pharmaceuticals AG, Basel, Switzerland) was given at a dosage of 2.5 mg daily from day 3 to 7 of the menstrual cycle, followed by the recombinant follicle-stimulating hormone (FSH) injection starting on day 7 until the day of the human chorionic gonadotropin (hCG) administration. Group 2 received a combination of 5.0 mg of letrozole daily from day 3 to 7 of the cycle plus recombinant FSH starting on day 7 until the day of hCG administration. In group 3, recombinant FSH (Puregon; Organon Oss, The Netherlands) injections started on day 3 of the menstrual cycle until the day of hCG administration.

Human chorionic gonadotropin (Pregnyl; Organon Oss, The Netherlands; 10,000 IU IM) was given to trigger ovulation when the mean diameter of the dominant follicle reached $\geq$18 mm.

Examinations

Transvaginal ultrasound examinations were done before the beginning of the treatment on day 3 of the cycle as well as on days 7, 9, 10, and 11 of the cycle and more often if needed. During the ultrasound examination, the number of follicles >8 mm, >14 mm, and >18 mm, the diameter of each visible follicle, and the endometrial thickness (maximum distance between the echogenic interfaces of the myometrium) were measured. The endometrial thickness was measured in the plane through the central longitudinal axis of the uterus. The ultrasound examination was done by the same ultrasonographer, using the same ultrasound equipment (General Electric; Voluson 730 Expert; General Electric Healthcare, Waukesha, WI).

The values of serum FSH and estradiol were measured on day 3 of the cycle for all of the women. Information about sperm concentration, sperm motility, and sperm morphologic features of the partners also were collected. For this study, a concentration $\geq 20 \times 10^6$/mL, motility grade a + b $\geq$50%, and morphology $\geq$30% normal forms were considered normal values (14).

Intrauterine Insemination and Outcomes

Intrauterine insemination was performed 30 to 40 hours after hCG administration. Clinical pregnancy was confirmed by fetal cardiac pulsation 5 weeks after a positive pregnancy test. The study concluded with the confirmation of the delivery of a newborn.

The main outcome measures included the number of follicles >14 mm and >18 mm, the total dose of recombinant FSH used in all the groups, and the endometrial thickness