Use of letrozole versus clomiphene citrate combined with gonadotropins in intrauterine insemination cycles: a pilot study

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Objective: To compare the clinical outcomes between letrozole and clomiphene citrate (CC) in gonadotropin-combined intrauterine insemination (IUI) cycles.
Design: Prospective pilot study.
Setting: One university hospital and two private infertility clinics.
Patient(s): Ninety-three infertile couples eligible for superovulation and IUI.
Intervention(s): A letrozole dose of 2.5 mg/day (n = 66) or a CC dose of 100 mg/day (n = 27) was given on day 3–7 of the menstrual cycle, combined with human menopausal gonadotropin (hMG) at a dose 150 IU every other day starting on day 5.
Main Outcome Measure(s): The number of mature follicles, serum estradiol (E_2) and progesterone (P) levels, endometrial thicknesses on the day of human chorionic gonadotropin (hCG), and clinical pregnancy rates.
Result(s): The patients' clinical characteristics were comparable between the two groups. The number of mature follicles (3.2 ± 1.7 vs. 5.6 ± 2.4) and serum E_2 levels on the day of hCG (231.0 ± 179.8 vs. 1,371.7 ± 750.5 pg/mL) were significantly lower in the letrozole group. No significant differences were found in endometrial thickness measured on the day of hCG or clinical pregnancy rates (18.2% vs. 25.9%). The rate of patients with serum P levels >1.0 ng/mL on the day of hCG was significantly lower in the letrozole group (4.5% vs. 25.9%).
Conclusion(s): Letrozole produced a comparable pregnancy rate vs. CC in gonadotropin-combined IUI cycles. Our results should be confirmed in larger populations with proper randomization. (Fertil Steril® 2006;85:1774–7. ©2006 by American Society for Reproductive Medicine.)

Key Words: Letrozole, clomiphene citrate, intrauterine insemination

Clomiphene citrate (CC) is the most commonly prescribed agent for ovulation induction for the treatment of subfertility associated with oligo-ovulation (1), and could be used as a superovulation regimen for timed intercourse or intrauterine insemination (IUI) cycles, when favorably combined with exogenous gonadotropins.

Recently, aromatase inhibitor has been investigated as a potential ovulation induction agent (2). Because it does not deplete estrogen receptors in central and peripheral target tissues, it typically results in mono-ovulation, and it may have no negative impact on endometrium and cervical mucus (3, 4). However, IUI cycles sometimes need multiple follicular developments; therefore, aromatase inhibitor must be combined with exogenous gonadotropins for superovulation in IUI.

The superiority of aromatase inhibitor over CC has not been proven in gonadotropin-combined IUI cycles. Only one prospective pilot study has been performed to date, and the results show that letrozole cycles have a significantly higher pregnancy rate than CC cycles in gonadotropin-combined IUI cycles (5). These authors believed that their favorable outcomes could be attributed to a thicker endometrium and a lower level of serum E_2. However, the study primarily focused on possible reduction of gonadotropin dose by adding letrozole or CC to ovarian stimulation for IUI. Moreover, letrozole was administered from day 3 to day 7, and gonadotropins were started on day 7 (i.e., a sequential regimen). In contrast, CC was administered from day 5 to day 9, and gonadotropins were started on day 5 (i.e., overlapping regimen).

We recently conducted this prospective pilot study to compare clinical outcomes of letrozole with that of CC in gonadotropin-combined IUI cycles. In this study, we used fixed schedules for letrozole and CC and combined them with gonadotropins in an "overlapping" manner.

MATERIALS AND METHODS

This study was a prospective pilot study. The subjects were not randomized because this study was a preliminary trial. One university hospital and two private infertility clinics

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participated in this trial, and the patients were enrolled from January to September 2004. The Institutional Review Board of Hamchoon Women's Clinic approved the use of letrozole for ovarian stimulation.

Ninety-three infertile couples eligible for superovulation and IUI were recruited. All couples with a duration of infertility that lasted one year or more underwent a routine infertility workup. The mean age of female was 31.2 ± 2.6 years old (range 25–36); the mean duration of infertility was 3.5 ± 1.7 years (range 1–9). Tubal patency was confirmed by hysterosalpingography in all subjects. Semen parameters were interpreted by the World Health Organization (1999) criteria.

They had had several timed intercourses and were superovulated by CC with or without gonadotropins at least two times before enrollment. They had undergone IUI with or without superovulation for a maximum of up to five times before enrollment. We excluded couples when the female was >37 years old, had severe endometriosis (stage IV), or a basal serum FSH of >15 mIU/mL. The couples were also excluded when they had undergone IUI for more than five cycles.

The infertility factors of the subjects were identified as unexplained (n = 47), ovulatory (n = 13), tubal (n = 11), male (n = 5), uterine (n = 6), endometriosis (n = 5, stage III for all), and combined (n = 6).

The choice of letrozole or CC was decided according to the couple's preference after discussing the experimental nature of the letrozole. We used a fixed schedule for letrozole or CC, in combination with gonadotropin, in an "overlapping" manner.

Letrozole (Femara®, Novartis, New York, NY), in a dose of 2.5 mg/day (n = 66), or CC (Serophene®, Serono, Geneva, Switzerland), in a dose of 100 mg/day (n = 27), was given on day 3 to day 7 of menstrual cycle. In addition, human menopausal gonadotropin (hMG, Pergonal®, Serono) 150 IU was administered every other day, starting on day 5 until human chorionic gonadotropin (hCG) administration. When mature leading follicle(s) reached 19 mm in diameter and the urinary LH test was negative, urinary hCG (Profasi®, Serono) in a dose of 5,000 IU was given; IUI was then performed 36–40 hours later. When the urinary LH test was positive, IUI was performed the next morning.

The luteal phase was supported by oral micronized (Utrogestan®, Laboratories Besins International, Paris, France) or IM progesterone (Progest®, Samil Pharmaceutical Company, Seoul, Korea).

The primary outcome measurement was pregnancy rate. Clinical pregnancy was defined when an intrauterine gestational sac(s) was visible by ultrasonography. Our secondary outcome measurement was the number of mature follicles (17 mm or more in diameter), serum levels of E_2 and P, and endometrial thickness measured on the day of hCG administration.

Blood samples were collected on the day of hCG administration, and serum aliquots were immediately separated, then frozen at −80°C for determination of the E_2 and P levels. The concentrations of serum E_2 (TKE21, Diagnostic Products Corporation, Los Angeles, CA) and P (PROG-CTK-4, DiaSorin, Saluggia, Italy) were measured by a radioimmunoassay (RIA) kit.

Data were analyzed with SPSS for Windows 10.0.1 (SPSS Inc., Chicago, IL). The χ^2 test was used to compare proportions, and the Student's *t*-test to compare means. A *P* value of <.05 was considered statistically significant.

RESULTS

Female age, duration of infertility, number of previous IUI trials, and the profile of infertility factors were comparable in the letrozole and CC groups (Table 1). Although total doses of hMG were similar, the number of mature follicles and serum levels of E_2 on the day of hCG administration were significantly lower in the letrozole group. No cancelled cycles occurred due to excessive stimulation or cases of ovarian hyperstimulation syndrome. No significant difference was found in endometrial thickness measured on the day of hCG administration.

Clinical pregnancy rates were comparable in the two groups. However, one patient in both groups experienced twin gestation. One patient who received letrozole with hMG was found to have a tubal ectopic pregnancy.

A urinary LH test performed on the day of hCG administration was positive in two patients who received letrozole and in four patients who received CC (3.0% vs. 14.8%, *P*>.05). However, serum levels of P >1.0 ng/mL on the day of hCG administration were found in three patients receiving letrozole and in seven patients receiving CC (4.5% vs. 25.9%, *P*<.05).

DISCUSSION

When we began this study, only one prospective pilot study had been reported, and its results indicated that letrozole cycles were associated with a significantly higher pregnancy rate and thicker endometrium in gonadotropin-combined IUI cycles (5). However, that study was primarily designed to test the feasibility of reducing the gonadotropin dose by adding letrozole or CC for ovarian stimulation. Moreover, for letrozole cycles, a sequential regimen was used; in contrast, for CC, an overlapping regimen was used. Therefore, we tried to compare the outcomes of letrozole with CC, and thus we used a fixed schedule for both letrozole and CC in an overlapping manner in gonadotropin-combined IUI cycles.

We included 93 infertile couples who were proper candidates for superovulation and IUI, but they were not randomized due to the experimental nature of letrozole. However, the characteristics of patients were not different between the