Letrozole co-treatment in infertile women 40 years old and older receiving controlled ovarian stimulation and intrauterine insemination

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Objective: To investigate the effect of a combination of letrozole and gonadotropins in advanced reproductive age infertile women who were treated with IUI.
Design: A retrospective case control study.
Setting: A private practice affiliated with an academic institute.
Patient(s): Infertile women 40 years old and older who were treated with IUI and controlled ovarian hyperstimulation (COH) using either letrozole in combination with FSH (n = 90) or FSH alone (n = 69).
Main Outcome Measure(s): Pregnancy rates (PR), mature follicles, serum levels of E_2, P, LH, endometrial thickness, rates of cycle cancellation, and FSH dose.
Result(s): Pregnancy rates were comparable between the letrozole–FSH co-treatment group and the FSH alone group. Significantly fewer cycles were cancelled in the letrozole co-treatment group. The E_2 levels and the number of follicles were significantly higher in the FSH-only group. Serum levels of LH were significantly higher in the co-treatment group on cycle day 7. The P levels were significantly higher in the FSH alone group on the day of hCG administration.
Conclusion(s): Letrozole co-treatment compared with using FSH alone has significantly modified the cycle characteristics without reducing PRs and could be of potential benefit in IUI cycles in older infertile women. (Fertil Steril® 2009;91:2501–7. ©2009 by American Society for Reproductive Medicine.)

Key Words: Letrozole, FSH, controlled ovarian hyperstimulation, intrauterine insemination, advanced reproductive age

Reproductive age is the most critical factor in determining the outcome of female infertility treatment. A significant decline in fecundity occurs in women starting at the age of 35 years (1–4). Several factors account for obstacles and failures of fertility treatment with advancing female age including poor oocyte quality, reduction in follicular recruitment and follicular response to internal and external gonadotropins, and the decline in endometrial receptivity (5–8).

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In spite, increasingly more women are starting to seek pregnancy in their fourth decade (9). Assisted reproductive technology (ART) is believed to offer the best chance for pregnancy in these women (10). About 12% of IVF patients are 40 years old and older (11). Other treatment options recommended for this age group include IUI. However, IUI alone is thought not to be as effective in women aged more than 40 years old as it is in younger women (12, 13).

Controlled ovarian hyperstimulation (COH) combined with IUI (COH-IUI) is often used for the treatment of unexplained infertility, early stage endometriosis, and borderline male factor infertility (14). Although the increase in female age has a negative impact on the outcome of COH-IUI (15), it remains an appropriate initial choice for older women (16). Gonadotropins are required to achieve multiple follicular recruitment to improve the ultimate outcome of IUI in this particular group (17). In general, COH-IUI using gonadotropins resulted in higher pregnancy rates (PR) than timed intercourse (18), intracervical insemination (19), and IUI alone or superovulation alone (20–23).

Nevertheless, gonadotropins are costly medications that also produce supraphysiological levels of serum E_2 during the follicular phase, which could adversely affect implantation or result in ovarian hyperstimulation syndrome (OHSS) or multiple pregnancies (24).

Aromatase inhibitors have been increasingly used in COH protocols. Aromatase inhibitors are believed to work through both a central mechanism at the level of the hypothalamic-pituitary axis and through a peripheral mechanism at the level of the ovary. The blockade of conversion of androgens to estrogens (E) leads to a reduction of serum E levels and suppression of E negative feedback in the brain. Aromatase inhibitors also increase the intrafollicular androgen concentration with a concomitant increase in ovarian follicular FSH receptors (25).

The objective of the present study was to investigate the effect of adding letrozole, a highly potent nonsteroidal reversible aromatase inhibitor, to gonadotropins in COH-IUI cycles in a group of older infertile women at or more than 40 years old.

MATERIALS AND METHODS

Study Design

This was a retrospective case control study conducted at Toronto Center for Advanced Reproductive Technology, affiliated with the Division of Reproductive Sciences, Department of Obstetrics and Gynecology, University of Toronto, Canada.

Selection of Study Subjects

In this study we analyzed the data of 142 infertile women 40 years old and older who underwent 258 consecutive cycles of COH and IUI. We compared two groups of patients. Group I ($n = 90$) included women who received the aromatase inhibitor letrozole in combination with FSH. Patients who received FSH alone were included in group II ($n = 69$). The rationale, mechanism of action, and the off-label nature of this indication of aromatase inhibitors were initially explained to all patients before the treatment.

Assessment and Outcome Measures

We analyzed the baseline clinical and cycle characteristics of patients in both groups including age, cause of infertility, number of treatment cycles (completed and cancelled), and causes of cycle cancellation, as well as the dose of FSH and the overall cost of medication in both groups. We considered PR as the primary outcome measure. In all patients, the presence of an intrauterine pregnancy and number of gestational sacs were confirmed by ultrasound performed when β-hCG levels were >2,000 mIU. Follicular development, serum levels of E_2, LH, and P, and the endometrial thickness were analyzed as secondary outcome measures.

Treatment Protocols

Patients in group I received letrozole (Femara; Novartis Pharmaceuticals, East Hanover, NJ) starting at a dose of 2.5 mg daily from cycle day 3 to day 7, in conjunction with FSH injections (Gonal-F; Serono, Oakville, Canada or Puregon; Organon, Scarborough, Canada) (50–100 IU/day) started on day 7 of their stimulation cycle until the day of hCG administration. The dose of letrozole was increased to 5 mg daily in cases of poor response to stimulation (unable to produce two follicles $\geq$15 mm in diameter). Group II patients received FSH injections alone (50–100 IU/day), starting on day 3 of the stimulation cycle. The dose of FSH was variable according to the patient's response. Injection of 10,000 IU of hCG (Profasi, Serono or Pregnyl, Organon) was given to all patients to trigger ovulation when they had at least two mature follicles with a mean diameter of 15 mm. Medroxyprogesterone acetate (Provera; Pfizer, New York, NY) 10 mg daily for 10 days was prescribed for anovulatory women to induce withdrawal bleeding before the stimulation protocol. The initial choice of the stimulation protocol and the dose of medications were based on the clinical profile of the patient, as well as response to prior treatment cycles.

Cycle Monitoring and IUI

All stimulated cycles in both studied groups were monitored with transvaginal ultrasound for follicular development and endometrial thickness starting at baseline on day 3 of the cycle, then on day 7 or 8, one of the days from 9–11, and on the day of hCG administration. Follicle size was reported as the average of two dimensions, measured from the outer wall of one side of the follicle to the inner wall of the other, in the most rounded configuration. Endometrial thickness was measured in the plane through the central longitudinal axis of the uterus at a point of maximum distance between the echogenic interfaces of the diameter.

Serum FSH was measured at baseline on day 3 of the cycle. Serum E_2, LH, and P levels were estimated at all four visits. An LH surge was defined as an increase in LH level more than 100% during the mean of the preceding 2 days.

A single IUI was performed 36–40 hours after hCG administration if no endogenous LH surge occurred. If an endogenous LH surge was detected on the day of hCG administration, IUI was performed in the following 2 days. Of prepared semen, 0.5 mL with motile spermatozoa was injected into the uterine cavity, approximately 0.5 cm below the fundus. A standard sperm preparation is used in our institution for all IUI procedures, as detailed in our previous report (26).

Data Collection and Statistical Analysis

Data were tabulated using Microsoft Excel version 7 (Microsoft Corporation, Redmond, WA) and analyzed using the Statistical Package for Social Sciences Program (SPSS) (version 13, Chicago, IL). Continuous data were described in terms of mean and SD. The Mann-Whitney U test was used to analyze continuous independent variables, whereas the χ^2 test was