ORIGINAL STUDIES

Letrozole versus Clomiphene Citrate in Patients with Anovulatory Infertility

[1]Mandakini Parihar , [2]Dhiraj Gada, [3]PG Paul, [4]Shravanti Bhowmik

[1]IVF Centre, Chembur, Mumbai-400071, Maharashtra, India
[2]IVF Family Planning and Endocrinology Centre, Indore-452004, Madhya Pradesh, India
[3]Pauls, Hospital, Kaloor, Cochin-682 017, India Centre, Indore-452004, Madhya Pradesh, India
[4]Medical Advisor, Clinical Research, Sun Pharma Ltd., Mumbai-400093, Maharashtra, India

Correspondence: Mandakini Parihar, IVF Centre, Chembur, Mumbai - 400071, Maharashtra, India
Fax: 91-22-25233672; e-mail: mandakini.ivf.center@gmail.com

Abstract

Objective: To compare the effectiveness of letrozole and clomiphene citrate (CC) in patients with anovulatory infertility.

Design: Open, prospective, randomized, parallel group, multicentric, comparative trial.

Setting: Outpatient clinics of infertility centers in India.

Patient(s): Fifty-five patients with anovulatory infertility were recruited. Twenty-seven patients (59 cycles) were given letrozole and twenty-eight patients (68 cycles) were given CC. Both drugs were given orally on days 3-7 of menstrual cycle.

Intervention(s): Letrozole, CC, ovulation induction, vaginal micronized progesterone, IUI.

Main outcome measure(s): Occurrence of ovulation, endometrial thickness and pregnancy rates.

Result(s): Ovulation occurred in 77.9 % (46/59) of letrozole cycles and in 80.9 % (55/68) of CC cycles. The mean endometrial thickness on the day of human chorionic gonadotropin administration was 9 mm in letrozole group and 8.76 mm in the CC group. Pregnancy rate per cycle was 11.9 % (7/59) in the letrozole group and 8.8 % (6/68) in the CC group.

Conclusion(s): Letrozole and CC have comparable effectiveness in anovulatory infertility patients. Letrozole may be an acceptable alternative to CC as an ovulation-inducing drug.

Keywords: Letrozole, clomiphene citrate, anovulatory infertility, ovulation induction.

INTRODUCTION

Clomiphene citrate (CC), an antiestrogen is the treatment of first choice for induction of ovulation in women with anovulatory infertility. However, about 25% of such women do not respond to CC. Of the 75% who ovulate in response to CC, only 20-40% of them have a successful pregnancy. The use of letrozole has been known to induce ovulation in 75-80 % women.[1] In addition to this, the use of Letrozole has not been associated with the undesirable effects of CC.[2] Prompted by the efficacy of CC for ovulation, letrozole has been considered as the next candidate for induction of ovulation. Major clinical studies have reported successful induction of ovulation with Letrozole.[3-7] Subsequently, few clinical studies have been undertaken in India, the findings of which have been presented in the annual conference of The Federation of Obstetric and Gynaecological Societies of India held in January 2003.

The aim of this study was to compare the effectiveness of letrozole and CC for ovulation induction inpatients with anovulatory infertility.

MATERIALS AND METHODS

During the study period from December 2004 to July 2006, 55 patients with anovulatory infertility who attended the 3 outpatient clinics of IVF center, Chembur, Mumbai; IVF endocrinology center, Indore; and Pauls Hospital, Cochin in India. The study was approved by an independent ethics committee (Central ethics committee, Mumbai, India) and the Drugs Controller General of India.

In this prospective, open-label, multicentric study, each patient's treatment was determined centrally by block randomization, performed on *www. randomization.com.* Each site was allowed to enroll up to 25 patients.

The study population consisted of 55 patients 20-38 years of age with a diagnosis of anovulatory infertility established by standard criteria, a normal pelvic ultrasonography and bilateral

tubal patency. Patients with uterine or adnexal pathology, ovarian cyst, hyperprolactinemia, hypothyroidism, hyperthyroidism, diabetes mellitus, follicle-stimulating hormone (FSH) more than 9 mIU/mL (during early follicular phase), history of previous surgery related to genital tract, appendicitis, peritonitis, genital tuberculosis, impaired hepatic or renal function were excluded. One group of 27 patients received letrozole (2.5 mg/day, Letroz; Sun Pharma, India) and the other group of 28 patients received CC (50 mg/ day for new cases and 50 mg + previously tried dose with total dose not exceeding 200 mg/day; Ferotab; GlaxoSmithkline, India). Both the treatments were administered on days 3 to 7 of the menstrual cycle. Patients treated with CC in past were enrolled if they had not exceeded the dose of 100 mg/day in previous cycles. Patients were followed with follicular monitoring with transvaginal ultrasonography and with serial measurement of estradiol starting on day 8 of the menstrual cycle. Endometrial thickness was determined at the greatest diameter perpendicular to the midsaggital plane in the fundal region, including both layers of the endometrium.

Human chorionic gonadotropin (hCG) 10,000 IU, subcutaneous (SC) injection was used to trigger ovulation when at least one follicle exceeding 18 mm in diameter was noted. Single IUI was performed in all patients 40 to 44 hours after administration of hCG. Vaginal natural micronized progesterone (800 mg/day) was given from day of ovulation till the expected day of next menstrual period. Serum β-hCG was measured 5 days after the first missed menstrual period. Babies born from women who conceived during this study were evaluated for congenital malformations.

The statistical package True epistat was used for statistical analysis. The χ^2 test and Fisher's exact test were used to analyze the frequencies of nominal variables in cross-tables. Student's *t* test was used to compare parametric data of two groups. The type I error was set at 0.05. Sample size determination was based on the percentage of ovulations induced per cycle. A sample size of 96 cycles (48 cycles in each group) was targeted to detect a difference of 30 % between the two groups, with a (type I error) set at 0.05 and 80 % power. As each patient was to be treated for 3 cycles, 32 women would provide 96 cycles.

RESULTS

The two groups were comparable regarding the baseline characteristics, including age, cause and duration of infertility, hormone profile (prolactin, thyroid stimulating hormone, luteinizing hormone and FSH). Fifteen patients did not complete all 3 treatment cycles.

Patients in the letrozole and CC groups had 59 and 68 cycles, respectively. All patients were scheduled for IUI. Ovulation occurred in 77.9 % (46/59) of the cycles with letrozole and in 80.9 % (55/68) of the cycles with CC (P = 0.27), respectively. Spontaneous ovulation occurred in 4.4 % (2/59) of the cycles with letrozole and none of the cycles with CC (P = 0.20).

The mean endometrial thickness on hCG day in letrozole and CC groups were 9 mm and 8.76 mm, respectively. However, endometrial thickness was < 7 mm in 10.2 % (6/59) of the cycles with letrozole and in 17.7 % (12/68) of the cycles with CC (P = 0.34).

Pregnancy was achieved in 11.9 % (7/59) of the letrozole cycles and 8.8 % (6/68) of the CC cycles (P = 0.64). 4 (57.1 %) abortions occurred in the letrozole group and 1 (16.7%) in the CC group (P < 0.0001). The remaining pregnancies reached term; no multifetal pregnancy was observed in either group. No congenital malformations were seen in babies born from women who conceived. Patients did not report any significant adverse effect while taking letrozole or CC.

DISCUSSION

The first line treatment for ovulatory disorders for more than 40 years has been CC. Lower than expected pregnancy rates with CC have been attributed to peripheral anti-estrogenic effects, mainly on the endometrium and the cervical mucus. CC is easy to use and results in ovulation in most patients (60 to 90%), but the pregnancy rates as reported in literature from studies conducted outside India are disappointing (10 to 40%).[2] Aromatase inhibitor letrozole is orally administered, easy to use and with minor side effects.[8,9]

This first controlled study in anovulatory infertility in India with a total of 127 treatment cycles was conducted to compare Letrozole 2.5 mg and CC 100-150 mg in ovulation and pregnancy rates. The weakness of our study is that it is not double-blind. Other than this, both patient groups were comparable with respect to the ovulation rate, endometrial thickness and pregnancy rate.

The ovulation rates were approximately 80 % with letrozole and CC. This is not in agreement with literature for CC with reported ovulatory rates of ~ 45%.[1,10,11] The occurrence of 2 spontaneous ovulations in the letrozole group may not be of clinical significance as it is routine to induce ovulation with hCG in treatment regimens for infertility. Although mean endometrial thickness was comparable among the letrozole and CC groups, it was less than 7 mm in a higher percentage of CC treated than letrozole treated patients. Comparative endometrial thickness with letrozole and CC is equivocal across published studies.[1,2,5,6,12]

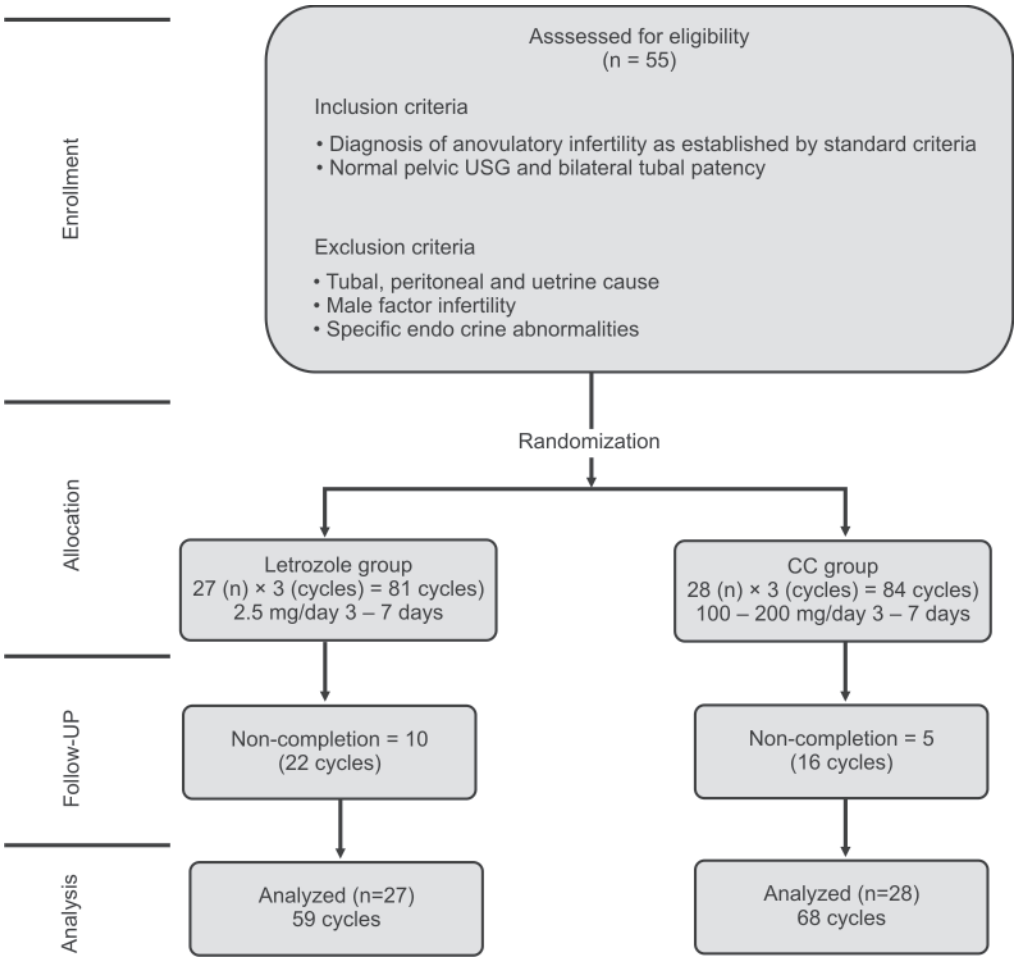

Fig. 1: Progress through the phases of randomized study

Pregnancy rates were slightly higher with letrozole (11.9 %) than with CC (8 %) though not statistically significant. Similar rates have been reported with letrozole and CC in other studies.[1,12] Mitwally et al[13] studied pregnancy rates in 167 cycles with letrozole 2.5 mg/ day and 994 cycles with CC 50-100 mg/ day. The pregnancy rate was 19.8% with letrozole and 8 % with CC. They observed that pregnancies achieved after letrozole use were not associated with increased risk for miscarriages; with the rates of miscarriage from positive pregnancy test being 12.1% with letrozole and 18.8 % with CC. Davar et al[14] noted miscarriage rates of 25 % with letrozole and 66.6 % with CC. Selvaraj et al[15] reported miscarriage rates of 25 % with letrozole and 66.7 % with CC. In our study, the abortion rate with letrozole (57.1 %) was significantly higher than CC (16.7 %). A possible reason could be the small sample size.

No adverse events were noted in both treatment groups. No congenital malformations were seen in babies born from women who conceived during this study. In a study by Tulandi et al[16] congenital malformations and chromosomal abnormalities were found in 2.4% newborns in letrozole and 4.8% in CC group. They concluded that there was no difference in the overall rates of major and minor congenital malformations among newborns from mothers who conceived after letrozole or CC treatments.

A number of studies support the necessity of treatment options for ovulation induction. Letrozole has a low incidence of adverse effects and good ovulation induction rates.[1-15] Gonadotropins are expensive[17,18] and there is scope for reduction in injection dose when combined with ovulation inducing drugs.[6,17-19] Letrozole has been seen to be effective for ovulation induction inpatients who fail to respond adequately to CC.[1]

Table 1: Demographic features of the letrozole and CC treated groups

Variable	*Letrozole*	*Clomiphene citrate*	*P value*
No. of patients	27	28	
No. of cycles treated	59	68	
Mean age in years (range)	26.7 (21-32)	26.6 (21-37)	0.89
Cause of infertility (n)			
• Polycystic ovary syndrome	17	22	0.32
• Hormonal imbalance	9	6	
Mean duration of infertility in years	4.9	3.8	0.19
No. of patients with post-treatment for infertility			
• Clomiphene citrate 50-150 mg	22	20	
• Letrozole 2.5 mg	2	0	
• Human menopausal gonadotropin 75-150 IU	3	2	
• Metformin 500 mg	4	4	

Table 2: Efficacy outcome of the letrozole and CC groups

Variable	*Letrozole*	*Clomiphene citrate*	*P value*
Total no. of ovulations (% of cycles)	46/59 (77.9)	55/68 (80.9)	0.27
No. of spontaneous ovulations (% of cycles)	2/46 (4.4)	0	0.20
Endometrial thickness in mm	9	8.8	0.29
No. of patients with endometrial thickness < 7 mm (%)	6/59 (10.2)	12/68 (17.7)	0.34
Pregnancy rate per cycle (%)	7/59 (11.9)	6/68 (8.8)	0.64

We demonstrated that letrozole is as effective as CC in anovulatory infertility. Letrozole is a good alternative to CC is effective inpatients with failure on CC and should be considered before switching to gonadotropin.

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