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Extended Letrozole Therapy for Ovulation Induction in clomiphene resistant Women with Polycystic Ovary Syndrome

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Abstract

Objective: This study aimed to evaluate the efficacy of short and extended long course of letrozole therapy for ovulation induction in clomiphene resistant women with polycystic ovary syndrome.

Patients: One hundred infertile women were selected from the patients attending the outpatient clinic of Manshiet El-Bakry general hospital. All patients were diagnosed as having anovulation due to polycystic ovary syndrome (PCOS).

Interventions: Patients were randomly allocated to treatment with either long letrozole group took 2.5 mg of letrozole daily starting day 1 of spontaneous or progesterone inducing menstrual bleeding for 10 days (50 patients, up to 3 cycles) or short letrozole group took 5 mg of letrozole daily starting day 1 of spontaneous or progesterone inducing menstrual bleeding for 5 days (50 patients, up to 3 cycles).

Results: The number of ovulating patients was greater in the long letrozole group (74% vs. 56%), but without statistical differences. The total number of follicles during stimulation was insignificantly greater in the long letrozole group (8.2 vs. 8.17). The numbers of follicles ≥18 mm were significantly greater in the long letrozole group. Pregnancy occurred in 7 in the short group (14%) and 12 of (24%) in the long letrozole group, and the difference was statistically insignificant.

Conclusion: The long letrozole protocol (10 days) can produce more mature follicles and subsequently more pregnancies than the short letrozole therapy (5 days).

Key Words: Extended Letrozole, Ovulation induction, clomiphene resistance, PCOS.

Introduction

The polycystic ovary syndrome accounts for approximately 80% of women with anovulatory infertility [(1)]. Various factors influence ovarian function and fertility is adversely affected by an individual being overweight, the degree of hyperandrogenism and having elevated serum concentrations of LH [(2)]. Polycystic ovary syndrome (PCOS) is the most common cause of infrequent periods (oligomenorrhea) and absence of periods (amenorrhea), affecting about 4-8% of women worldwide in their fertile years [(3)].

Aromatase inhibitors:

Aromatase inhibitors have been proposed as an alternative treatment to Clomiphene Citrate (CC) therapy as the discrepancy between ovulation and pregnancy rates with CC has been attributed to its anti-estrogenic action and estrogen receptor depletion. Inhibition of the aromatase enzyme decreases the aromatization of androgens to estrogens that in turn releases the hypothalamic–pituitary axis from negative feedback of estrogen. There are reports of good pregnancy rates with a lower incidence of multiple pregnancies [(4)]. Aromatase inhibitors (AIs) are a newer class of drugs that were introduced for ovulation induction in 2001 by [(5)]. Over the last ten years data from many clinical trials have been collected and there is evidence that the AI letrozole might be as effective as CC, but the outcome data vary. AIs are like CC administered orally, but due to their short half-life elimination time of 48 hours there are fewer adverse effects on estrogen target tissues such as endometrium and cervix compared to CC [(6)]. The aim of this prospective randomized study was to evaluate the efficacy of short and long course of letrozole therapy in induction of ovulation in clomiphene resistant women with PCOS.

Patients and methods

Patients:

One hundred infertile women were selected from the patients attending the outpatient clinic of Manshiet El-Bakry General Hospital. Written consent was obtained from patients. All patients were diagnosed as having anovulation due to polycystic ovary syndrome (PCOS). The diagnosis of PCOS based on the revised 2003 consensus on diagnostic criteria

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and long-term health risks related to polycystic ovary syndrome [7].

Patients randomly allocated using a computer-generated random table into two treatment groups: short letrozole group (50 patients) and long letrozole group (50 patients).

Patients in the short letrozole group took 5 mg of letrozole daily starting day 1 of spontaneous or progesterone inducing menstrual bleeding (using 10 Medroxyprogesterone acetate was prescribed 10 mg/day for 5 days to induce withdrawal bleeding in the amenorrheic patients) for 5 days (50 patients, up to 3 cycles), and patients in the long letrozole group took 2.5 mg of letrozole daily starting day 1 of spontaneous or progesterone inducing menstrual bleeding for 10 days (50 patients, up to 3 cycles). All patients were monitored by transvaginal ultrasound for the mean follicular volume and thickness of the endometrium on days 10, 12, and 14 of the cycle.

The hCG injection (5,000 IU IM) was given when at least one follicle measured ≥18 mm. Patients were advised for intercourse 24–36 h after hCG injection. Serum hCG was determined 2 weeks after hCG injection in the absence of menstruation for diagnosis of pregnancy, followed by transvaginal ultrasound for demonstration of the gestational sac.

The primary outcome measures were number of growing and mature follicles, secondary outcome measures were the occurrence of pregnancy and miscarriage.

Statistical Analysis

Sample size calculation, using StatCalc 3.02 computer package (Acastat software, Leesburg, VA). Data obtained were statistically analyzed using the SPSS computer package (SPSS, Chicago, IL). Results were expressed as mean and standard error of the mean and were compared by Student t test. Proportions were analyzed using the $\chi 2$ test. The differences were considered to be statistically significant with $P<0.05$.

Results

The study comprised one hundred patients in total. There were no statistical significant differences between the two groups regarding age, duration of infertility, body weight, height, body mass index (BMI), (Table 1). Table 2 shows that the number of ovulating patients was greater in the long letrozole group (74% vs. 56%), but without statistical differences. The total numbers of follicles in short therapy group was 8.17 and 8.2 in long therapy group, number of follicle was insignificant between two groups p-value 0.951. Regarding the cases with follicles' size **>14 mm<18mm**, there was insignificant difference between two groups regarding follicles **>14 mm<18mm**, P-value> 0.05.

The cases with Follicles size **≥ 18 mm**, there was significant differences between two groups regarding follicles **≥ 18 mm** as in long therapy group there was more follicles with size **≥ 18 mm, P-value< 0.05.**

Pregnancy occurred in 7 in the short group (14%) and 12 of (24%) in the long letrozole group, and the difference was statistically insignificant.

Table (1) Patients' characteristics

	Short letrozole group (n = 50)	**Long letrozole group (n = 50)**	**P value**
Age (years)	24.97 ± 4.26	24.87 ± 4.22	>0.05
Period of Infertility (Years)	2.67 ± 0.80	2.77 ± 0.86	>0.05
Height (cm)	166.63 ± 4.45	165.82 ± 5.13	>0.05
Weight (kg)	77.37 ± 6.48	78.53 ± 7.30	>0.05
Clinical presentation			
Oligo/anovulation			
Oligo	37 74%	37 74	>0.05
Anovulation	13 26%	13 26%	
Testosterone (nmol/L)	1.37 ± 0.82	1.47 ± 0.71	>0.05
Positive US Criteria	37(74%)	42(84%)	>0.05
BMI (kg/m2)	27.86 ± 1.91	28.59 ± 2.56	>0.05
FSH (mIU/mL)	5.16 ± 1.61	6.0 ± 1.14	>0.05
LH (mIU/L)	9.88 ± 1.14	9.45 ± 2.33	>0.05

Note: Significant difference as $P<0.05$.

Table 2. Outcome in short letrozole and long letrozole groups

	Short letrozole group (n = 50)	Long letrozole group (n = 50)	t	P value
Number of ovulating patients	28 (56%)	37 (74%)	χ^2=1.832	0.176
Total number of follicles	8.17 ± 2.04	8.20 ± 2.19	0.061	0.951
Number of cases with follicles >14<18 mm	38(76%)	40(80%)	χ^2=2,425	P> 0.05
Number of cases with follicles ≥18 mm	27(54%)	33(66%)	χ^2=17.7	P< 0.05
Pregnancy/cycle	7 (14%)	12 (24%)	χ^2=1.002	0.317

∗Significant difference as P< 0.05.

Discussion

Inability of Clomiphene Citrate (CC) to induce ovulation, CC resistance, is unexpected and for most an unexplainable event. Traditional alternatives to CC include AIs, gonadotropins, and laparoscopic ovarian drilling. Mitwally and Casper [(5)]. performed the first trial in a group of PCOS women who had failed to respond to CC. Twelve women with PCOS received letrozole 2.5 mg daily from days 3 to 7 of menses. Ovulation occurred in nine patients (75%), and pregnancy was achieved in three cycles (25%), two of which were singleton clinical pregnancies and one a chemical pregnancy. Thereafter, many reports released confirming the efficacy of AIs [(8-12)].

There have been several mechanisms proposed for AI success. It was put forward that it would be possible to block estrogenic negative feedback, without depletion of estrogen receptors by administration of an AI in the early part of the menstrual cycle. Inhibition of aromatization would block estrogen production from all sources and would release the hypothalamic-pituitary axis from estrogenic negative feedback. The resultant increase in gonadotropin secretion would stimulate growth of ovarian follicles. Withdrawal of estrogen centrally also increases activins, which are produced by a wide variety of tissues, including the pituitary gland [(13)], and stimulate synthesis of FSH [(14)]. Because AIs do not deplete estrogen receptors, normal central feedback mechanisms remain intact. As the dominant follicle grows and estrogen levels rise, normal negative feedback occurs centrally, resulting in suppression of FSH and atresia of the smaller growing follicles. A single dominant follicle, and mono-ovulation, should occur in most cases. This might be of advantage in cases of PCOS, thereby avoiding the risk of ovarian hyperstimulation syndrome. Nonetheless, this monofollicular growth might come at the cost of lower ovulation and pregnancy rates. Therefore, letrozole could be used in conjunction with FSH injections to increase the number of preovulatory follicles that develop and improve the outcome of treatment. Addition of FSH, however, will remarkably increase the cost of therapy and recommence the risk of ovarian hyperstimulation syndrome[(15)].

In the present study, we tested a novel protocol of extended letrozole therapy to keep the in vivo production of FSH continuous for a longer duration. This allowed a greater cohort of small follicles, recruited in the early part of the cycle, to reach maturity (≥18 mm). Pregnancy rate was more in the extended letrozole group. The rationale behind using this extended regimen was based on our understanding of the physiology of follicular growth. Decremented follicular-phase FSH levels (referred to as the FSH window) appear to be crucial for selection of a single dominant follicle from the recruited cohort [(16)]. As FSH levels fall, all but the dominant follicle (with its increased sensitivity to FSH) lose the stimulus to further development and become atretic [(17)]. The concept of extending the FSH window by administering exogenous FSH or extending the duration of letrozole therapy in the midfollicular phase would maintain FSH levels above the threshold, allowing multifollicular development to occur. There were no extra costs for the extended therapy, because we used the same ten tablets over 10 days rather than 5 days.

This new 10-day letrozole protocol proved to be more effective than the standard 5-day protocol, with more mature follicles and more pregnancies. The extended therapy caused no increase in the number of twin pregnancies than usual or in ovarian hyperstimulation syndrome.

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