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RESEARCH ARTICLE

LETROZOLE INDIFFERENT DOSAGES FOR OVULATION INDUCTION IN PATIENTS WITH POLYCYSTIC OVARIAN SYNDROME NOT RESPONDED TO CLOMIPHENE CITRATE

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ABSTRACT

Objective: To choose the suitable dose of letrozole (LTZ) for ovulation induction in anovulatory patients with polycystic ovarian syndrome (PCOS).
Design: Prospective randomized study.
Setting: OB/GYN department, Benha Teaching Hospital, Benha, Egypt.
Patient(s): 120 anovulatory infertile women with PCOSthatwerenot responded to clomiphene citrate(CC) stimulation for one cycle.
Intervention(s): The studied patients were randomly divided into 3 groups (A, B, C). LTZ was given in increasing dosage from group "A" to group "C".
Materials and Methods: In group "A": the dose of letrozolewas 2.5 mg / day, in group "B": it was 5 mg / day, and in group "C": it was 7.5 mg per day. The LTZ was given from day 2-6 of the menstrual cycle. Main outcome measures were: ovulation rate, number of mature follicles, endometrial thickness and pregnancy rate.
Results: On increasing the LTZ dosages between the three groups (A, B and C),only the mean number of dominant follicles and the numbers of ovulatory cycles were significantly increasing; (P=0.025) and (P=0.012), respectively. On the other hand, the relation was insignificant for mid-cycle endometrial thickness and the pregnancy rate; (*P*=0.542) and (*P*=0.765), respectively.The differences in the age, duration of infertility and body mass index (BMI) were not statistically significant between the three groups.
Conclusion: Letrozole is superior to CC in ovulation induction for patients with PCOS. Increasing the letrozole dosage will increase the number of mature follicles and ovulation rate, but has no effect on pregnancy rate.Until studies with large sample sizes are available, LTZ may be used as the first or second option for ovulation induction and to start with 2.5 mg per day and increase the dose gradually in the subsequent cycles if there is no adequate response.

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INTRODUCTION

Anovulation is responsible for about 20% of female infertility of which PCOS is a leading cause (Fisher *et al.,* 2002). Different treatment regimens have been used in PCOS patients, but none has had a significant outcome. The reason behind this diversity in treatment options is the multifactorial pathology of PCOS and its different manifestations as well as the role of genetics in its pathogenesis. So, it is difficult to use only one treatment option in PCOS.Clomiphene citrate (CC) leads to a 60%–85% ovulation rate and a 10%–20% pregnancy rate per cycle. Since 1962 CC has been the drug of choice for oral ovulation induction (Al-Fozan *et al.,* 2004).

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Clomiphene citrate has a long half-life (2 weeks), and may take up to two months to be cleared from circulation. This may have a negative effect on the cervical mucus and endometrium, leading to discrepancy between ovulation and conception rates. Also, CC may have a lot of side effects including hot flushes, breast discomfort, abdominal distension, nausea, vomiting, nervousness, sleeplessness, headache, mood swings, dizziness, hair loss and disturbed vision. The adverse effects may be cumulative (Fisher *et al.,* 2002). An aromatase inhibitor blocks the conversion of androgens to estrogens in the ovarian follicles, peripheral tissues, and in the brain. This result in two things: (a) Fall in circulating and local estrogens and (b) rise in intraovarian androgens. Fall in estrogen levels, releases the hypothalamopituitary axis from the negative feedback of estrogens. So, its effect is not by the inhibiting estradiol-receptor interaction, but rather by inhibition of estradiol synthesis. Thus, there is a surge in follicle stimulating hormone

(FSH) release, which results in follicular growth. Since, the feedback mechanism is intact; normal follicular growth, selection of dominant follicle, and atresia of smaller growing follicle occur; and thereby facilitating monofollicular growth and ovulation (Mitwally and Casper, 2005). The accumulated androgens in the ovary further increase follicular sensitivity to FSH by augmenting FSH receptors and stimulating insulin-like growth factor (IGF)-I; FSH and IGF-I act synergistically to promote follicular growth (Vendola *et al.,* 1999). Letrozole causes ovulation in 60%–80%; and pregnancy varied from 5 % - 41% (Begum *et al.,* 2009; Kamath *et al.,* 2010 and Bedaiwy *et al.,* 2011).

Importantly, unlike clomiphene citrate, letrozole is devoid of any anti estrogenic peripheral action. Letrozole is also cleared from the circulation more rapidly due to a shorter half-life (48 hours). The side effects, while similar to those of clomiphene, are far milder and less frequent(Al-Fozan *et al.,* 2004).There are different studies with different results comparing different regimens and dosages for letrozole in ovulation induction (Mitwally and Casper, 2001 and Al-Fozan *et al.,* 2004). The aim of this study was to compare the effect of letrozole in different dosages on ovulation induction in PCOS patients that were not responded to clomiphene citrate.

Materials and Methods

This study was done in Benha teaching hospital between the periods 2009 and 2011. The selected patients were infertile, anovulatory and had PCOS. Anovulation was diagnosed by transvaginal ultrasound through fertility screening cycles. Diagnosis of PCOS was made on the basis of revised Rotterdam 2003 criteria. Presence of two out of three criteria (oligo and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries) was chosen as a diagnostic of PCOS. The selected patients had normal thyroid-stimulating hormone and prolactin levels and normal recent hysterosalpingograms and spermograms.All the patients were not responding to clomiphene citrate stimulation for five days (100 mg /day, from cycle day two).

Thirty patients with previous diagnostic laparoscopy with no abnormality have been included in the study, and all have shown the typical laparoscopic appearance of PCO; thick, white glistening capsule, enlarged ovaries and no sign of ovulation.

Before starting LTZ, those 120 selected patients had been instructed not to receive any ovulatorydrugs for a period equal to the length of two menstrual cycles.

All the patients were randomly divided into three groups, 40 patients each.Great effort was done to equally divide the patients; regarding age, BMI, duration of the infertility, primary and secondary infertility and previous diagnostic laparoscopy.Transvaginal ultrasound was done on cycle day two before starting treatment and those patients with ovarian cysts more than 14 mm were excluded.

First group (A) received letrozole in a dose of 2.5 mg daily. Second group (B) received 5 mg letrozole daily, and the third group (C) received 7.5 mg letrozole daily. In the three groups, treatments were administered for 5 days, from day 2 to day 6, of a spontaneous cycle or withdrawal bleeding after a 5-day course of 30 mg/day dydrogesterone.Serial transvaginal ultrasound (TVS) was done starting from day ^{8th} to day 20thof the menstrual cycle and sometimes itwas extended little more. In each patient, the number of follicles and endometrial thickness in each cycle were documented. Ultrasound in all patients was demonstrated by single observer (me, the corresponding author). Injection of human chorionic gonadotropin (HCG) 10,000 IU intramuscularly was given to the patients when a dominant follicle ≥18 mm. Endometrial thickness on the day of HCG administration was recorded.Each woman was asked to have intercourses on the same day of HCG injection and one and half days and two and half days after the time of injection. On subsequent TVS, usually one day after the last intercourse, collapsed or disappeared follicle (s), or intrafollicular bleeding usually with the presence of fluid in Douglas pouch denote ovulation. Pregnancy test was done once the patient missed her period or two weeks after HCG injection.The mean number of follicles, endometrial thickness, and pregnancies were compared between the three groups. Statistical analysis was done using SPSS software. Student's t-test and Chi-square were used when appropriate. Results were expressed as mean and standard errors of mean. The *P* value of <0.05 was considered statistically significant.

RESULTS

The mean numbers of dominant follicles in the three groups (A, B and C) were 1.16±0.25, 1.32±0.16 and 1.75±0.15 respectively (*P*=0.025). Numbers of ovulatory cycleswere 4 (10%), 7 (17.5%) and 12 (30%), respectively (*P*=0.012). The mean mid-cycle endometrial thickness on triggering day was 6.1±5.4 mm, 8.1± 4.8 mm and 7.8 ± 5.1mm, respectively (*P*=0.542). 1 patient, 3 patients and 2 patients from the three groups respectively became pregnant (*P*=0.765) (Table 2). The age, duration of infertility and BMI were not statistically different between the three groups (Table1).

Table 1. Characteristic clinical variables in the studied groups based on mean±SD values

Variables	Letrozole dosage			P value
	Group A 2.5mg	Group B 5mg	Group C 7.5mg	
Age *	24.8±4.5	26.6±4.6	25.5±4.3	0.405
BMI *	30.0±6.7	29.5±7.1	30.3±6.9	0.583
Mean infertility duration (years)	3.0±2.2	2.9±2.1	4.1±2.7	0.897

* Note: no significant difference between treatment t-test.

Table 2. Comparison of different variables in letrozole groups based on mean±SD values

Variables	Letrozole dosage			P value
	Group A 2.5mg	Group B 5mg	Group C 7.5mg	
No of follicle ≥18mm on triggering day	1.16±0.25	1.32±0.16	1.75±0.15	**0.025**
No of ovulatory cycles	4/40(10)	7/40(17.5)	12/40(30)	**0.012**
Endometrial thickness on the triggering day	6.1±5.4	8.1±4.8	7.8±5.1	0.542
No. of pregnancy	1(2.5%)	3(7.5%)	2(5%)	0.765

DISCUSSION

There is still debate about the optimal protocol to use LTZ in ovarian stimulation. The dosage of LTZ, therefore, differs between studies. The majority of researchers have used 2.5-5.0 mg LTZ daily based on the dosage used for the treatment of patients with breast cancer (Bajetta *et al*., 1999).

In this research, andunlike CC, there was a response to LTZ stimulation from the first trial. With increasing the LTZ dosages from 2.5 mg to 7.5 mg per day, the ovulation rate and the number of mature follicles were significantly increasing (P = 0.012) and (P = 0.025), respectively. However the pregnancy rate remained low between 2.5 – 7.5% (P =0.765) and was highest with RTZ dosage 5mg per day. In the literatures, the results are variable and there is a wide range in the pregnancy ratesfrom 5.6% (Kamath *et al*., 2010), as is the pregnancy rate in this research, to 40.6% (Begum *et al*., 2009). Begum and his group in 2009 have stated that the ovulation induction by LTZ is superior to CC in terms of follicular growth and endometrial response (Begum *et al*., 2009).In another study, 7.5 mg LTZ for 5 days was significantly advantageous if compared to 150 mg CC for 5 days as regard ovulation and pregnancy rates (Al-Fozan *et al*., 2004). In a study done by Rahmani *et al*. (2012), the percentage of pregnancy was increasing from 15.9% to 61.36% with increasing the letrozole dosage from 2.5 mg to 7.5 mg daily. In a study done by Kamath *et al*. (2010), the ovulation rate was 33.3% on using 2.5 mg LTZ administered from cycle days 2-6 compared to 0.00% in placebo group.The variability of the results in ovulation and pregnancy rates may be attributed to the choice of cases, methods for detection of ovulation and to the small number of different studied PCOS patients in most of the published researchers. This may affect the reliability of the statistics and makes comparison inaccurate.

In this study, there was no improvement in the endometrial thickness in spite of the significant improvement in the number of mature follicles. This may denote that the endometrial thickness is not directly related to oestrogen concentration and/or other factors may be responsible and modulating (positively or negatively) the effect of oestrogen on the endometrium or it may be receptors concerns. High pregnancy rate and low multiple gestation has encouraged some authors to recommend usage of 2.5 mg letrozole for induction of ovulation as a first-line drug (Bajetta *et al*., 1999). Although letrozole is more expensive than clomid, it is cheaper than gonadotropins and it is more cost effective (Rahmani *et al*., 2012).

Conclusion

Letrozole is superior to CC in ovulation induction in patients with PCOS. However, it is costlier than CC. In addition, some may consider the monofollicular growth in LTZ regimen is undesirable advantage; this may be attributed to the couple personalities, educational levels and the cultural and traditional believes. Until studies with large sample sizes are availablewithdifferent races in addition to unification of the protocol of regimen, methods of ovulation detection and stabilization of the bioactivity of the drugs; LTZmay be usedas a first or a second line treatment option. In the meantime, it may be advisable to start treatment with 2.5 mg letrozole daily and increase the dose gradually in the subsequent cycles if the is no adequate response.

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