

Role of Letrozole Versus Clomiphene Citrate in Induction of Ovulation in Patients with Polycystic Ovarian Syndrome

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Abstract

Objective: the aim of this work is to compare the effect of Letrozole versus Clomiphene citrate (CC) in induction of ovulation in Polycystic ovarian syndrome (PCOS) patients.

Patients and methods: The study was conducted in Al Maadi Military Hospital at the department of Obstetrics and Gynecology (out-patient infertility clinic). The study is a prospective randomized study consisting of 100 Egyptian patients diagnosed as having PCOS. Patients were divided into two groups with randomization sheet and allocation concealment: **Group (A):** includes 50 females taking Letrozole 5mg tab orally once daily started in day 3 to day 7 of menstrual cycle for 3 cycles. **Group (B):** includes 50 females taking Clomiphene Citrate 100mg tab orally once daily started day 3 to day 7 of menstrual cycle for 3cycles. Trans-vaginal ultrasound was done from day 9-11 of the cycle to document ovulation rate, endometrial thickness and number of follicles and from day 14 (mid cycle day) to evaluate the target size of the follicle (18-22mm) and to assess the need to HCG administration.

Results: Letrozole is significantly higher regarding endometrial thickness (Let 9.2mm Vs CC 8.0mm) and pregnancy rate (Let 48% Vs CC 28%), while Clomiphene Citrate (CC) is significantly higher regarding number of follicles (48%) as it produces multiple number of follicles compared to Letrozole (26%) which produces mono-follicle only. Both drugs are significantly similar regarding the ovulation rate. The study concluded that Letrozole can be used as first line therapy for induction of ovulation in polycystic ovary syndrome patients.

Conclusion: The pharmacodynamics of Letrozole (does not deplete ERs, short half-life, keeps intact hypothalamic pituitary axis) ensures improved endometrial thickness and cervical mucus and monofollicular ovulation. Therefore, these factors may lead to a higher pregnancy rate and greater likelihood of singleton pregnancy.

Keywords: Letrozole-Clomiphene Citrate-Induction of Ovulation - Polycystic Ovarian Syndrome.

Introduction

Ovulation dysfunction is one of the most common causes of reproductive failure in infertile couples. The prevalence of this disorder in infertile women is about 30 to 40%. Polycystic ovary syndrome is a common disease that is closely related to ovulation dysfunction and 7% of women of childbearing age are affected with it. It is heralded as one of the most common endocrine disorders occurring in women [1,2].

In 2003, a consensus panel established a controversial definition (the Rotterdam criteria) for PCOS, to include at least 2 of the following criteria: oligo-anovulation, hyperandrogenism (laboratory-confirmed or clinical symptoms), or polycystic ovaries on ultrasound [12 or more follicles measuring 2-9 mm in diameter or increased ovarian volume more than 10cm³] [3]. Using the Rotterdam criteria a clinical

diagnosis of PCOS is easily reached [4].

Clomiphene citrate (CC) has been the most widely used drug for the treatment of infertility since its introduction into clinical practices in the 1960s. It is a non-steroidal selective estrogen receptor modulator that has predominant anti-estrogenic action resulting in long-lasting estrogen receptor depletion [5]. Clomiphene citrate (CC) has a long half-life (2weeks), and this may have a negative effect on the cervical mucus and endometrium, leading to discrepancy between ovulation and conception rates [6]. It is known that Clomiphene citrate results in an ovulation rate 60-80% but a conception rate of only about 20% [7].

Clomiphene resistance together with side effects like multi-follicular development and cyst formation are areas of concern, the desire for an effective alternative persists [8]. Letrozole, on the other hand, acts by decreasing the conversion of andro-stenedione and testosterone to estrogen in the ovary. This decrease in circulating

estrogen increases gonadotropin secretion. Multiple developing follicles appear from day 7, but because letrozole does not deplete estrogen receptors, normal negative feedback occurs centrally as the dominant follicle grows and the estrogen level increases. This results in follicle-stimulating hormone suppression and atresia of smaller follicles, and midcycle mono-ovulation occurs in most patients and also does not possess the adverse antiestrogenic effect of Clomiphene specially thinning of the endometrial lining and is associated with higher pregnancy rate than CC treatment in patients with PCOS and has a short half-life (45 hours) thus it is rapidly eliminated from the body [9-11].

Though evidence from larger trials is still awaited, some encouragement may be taken from the success of preliminary results showing aromatase inhibitor Letrozole may be regarded as a possible replacement for the CC for the first-time treatment of anovulatory infertility and to determine which regime, Clomiphene citrate or Letrozole, was the best method for induction of ovulation as first line therapy [1]. The aim of this work is to compare the effect of Letrozole versus Clomiphene citrate (CC) in induction of ovulation in Polycystic ovarian syndrome (PCOS) patients.

Patients and Methods

This current study was conducted in Maadi Armed Forces Medical Compound (out-patient infertility clinic). The study is a prospective randomized study consisting of 100 Egyptian patients diagnosed as having PCOS.

The study was approved by the medical ethics committee of Maadi Armed Forces Medical Compound from **January 2016 till October 2016**. Informed consent was obtained from all the cases enrolled in the study.

Sample size determination

According to Holzer, et al. the parameter to be used is the ovulation rate. Group sample sizes of 50 in group one and 50 on group two achieve 81% power to detect a difference between the group proportions of 0.25 [12].

Patients were divided into two groups with randomized sheet

- Group (1): includes 50 females taking Letrozole 5mg tab orally once daily started in day 3 to day 7 of menstrual cycle for 3 cycles.
- Group (2): includes 50 females taking Clomiphene citrate 100 mg tab orally once daily started day 3 to day 7 of menstrual cycle for 3 cycles.

We used a randomization table generated via research randomizer program plus Annex (**randomization in clinical trials** at www.StatMed.com).

Inclusion criteria

- Age: 20-35 years old.
- Primary infertility.
- No conception for at least one year.
- Diagnosis of PCO as established by **Rotterdam criteria (2004)**:

(Requires the presence of two of three criteria).

- a) Oligomenorrhea and / or annovulation.
- b) Clinical (Hirsutism is defined as excessive terminal hair growth that taken on a male pattern distribution) and / or biochemical signs of hyper-androgenism (increase level of serum free testosterone).
- c) Polycystic ovaries diagnosed by Ultrasound (if there were 12 or

more follicles measuring 2-9mm in diameter or increased ovarian volume more than 10cm³).

- Bilateral patent tubes confirmed by HSG or laparoscopy.
- Normal husband's semen analysis according to **WHO criteria (2010)**.

Exclusion criteria

- Age < 20 and > 35 years old.
- Uterine pathology e.g. fibroid or ovarian cyst.
- Hyperprolactinemia, Hypo or Hyperthyroidism (endocrinological disorder).
- Impaired hepatic or renal function.
- History of hypersensitivity to study drugs.
- Endometriosis.
- Female with bilateral tubal blockage diagnosed by HSG or laparoscopy.
- Previous gynecological disorder.

All patients participated were subjected to the following

1. Written informed consent.
2. Detailed History including menstrual, obstetrical, medical, surgical history, history of drug intake and family history.
3. General examination: for acne and virilizing hair distribution, thyroid, breast and BMI.
4. Abdominal examination.
5. Investigation: Pelvic Ultrasound, Hormonal profile (Day 2 FSH, LH, Prolactin, TSH, testosterone and E2), HSG and husband semen analysis.
6. Folliculometry by transvaginal ultrasound (**MINDRAY DC-3**) starting from day 9 of the menstrual cycle then every other day.
7. HCG 10,000 IU, (CHORIOMON 5000 IU, IBSA) will be given when at least one follicle > or = 18mm.
8. Measurement of endometrial thickness on the day of HCG administration.
9. Patients were advised to have intercourse 36 hours after HCG injection.
10. Serum B-HSG will be measured after 2 weeks to diagnose pregnancy and is confirmed by trans-vaginal ultrasound after 4 weeks and half of the cycle or trans-abdominal ultrasound after 5 weeks and half of the cycle.

Drugs were given as following

- Group 1: Letrozole 5mg tab once daily from 3-7 day of menstrual cycle. (FEMARA, NOVARTIS) for 3 cycles.
- Group 2: Clomiphene citrate 100mg tab once daily from day 3-7 of menstrual cycle (CLOMID, SANOFI AVENTIS) for 3 cycles.

The main outcome

1. Number and size of mature follicles.
2. Ovulation rate.
3. Endometrial thickness on day of HCG administration.

The secondary outcome was: occurrence of clinical pregnancy.

Statistical methods

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013.

Descriptive statistics were done for quantitative data as minimum & maximum of the range as well as mean±SD (standard deviation)

for quantitative normally distributed data, while it was done for qualitative data as number and percentage.

Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with normally distributed data. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions. The level of significance was taken at P value < 0.050 is significant, otherwise is non-significant.

Results

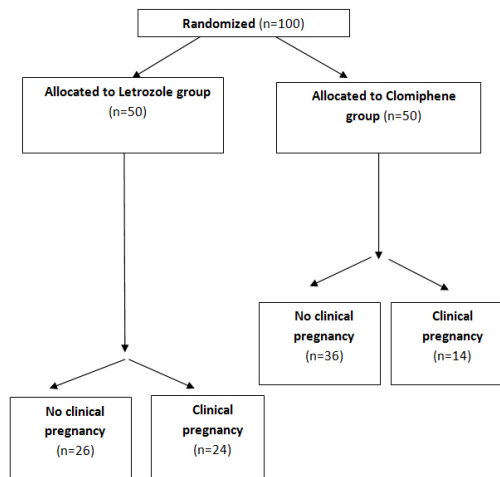


Figure 1: Study CONSORT

Table 1: Demographic characteristics among the studied groups

Variables		Letrozole (N=50)	Clomiphene (N=50)	^P
Age (years)	Mean±SD	27.0±3.5	28.0±3.3	28.0±3.3
	Range	20.0–35.0	21.0–35.0	
BMI (kg/m ²)	Mean±SD	29.1±1.3	29.3±1.1	0.428
	Range	25.9–31.9	26.1–31.7	
Duration of infertility (years)	Mean±SD	4.0±0.8	4.1±0.7	0.341
	Range	2.0–5.0	3.0–6.0	

^Independent t-test

No significant difference between Letrozole and Clomiphene groups regarding **demographic characteristics**.

Table 2: Basal hormonal profile on day-3 among the studied groups

Variables		Letrozole (N=50)	Clomiphene (N=50)	^P
FSH (mIU/mL)	Mean±SD	10.1±1.0	10.2±1.3	0.482
	Range	8.1–12.0	7.0–13.0	

LH (mIU/mL)	Mean±SD	18.1±3.8	19.5±3.7	0.073
	Range	15.0–27.0	15.0–26.0	
Prolactin (ng/mL)	Mean±SD	20.7±3.4	20.6±3.4	0.837
	Range	15.0–26.0	15.0–27.0	
E2 (pg/mL)	Mean±SD	45.4±9.5	45.7±9.1	0.889
	Range	30.0–60.0	30.9–69.0	
Testosterone (pg/mL)	Mean±SD	44.6±21.8	43.1±17.3	0.706
	Range	9.4–103.0	5.5–76.3	
TSH (μIU/mL)	Mean±SD	2.1±0.5	2.0±0.3	0.210
	Range	1.3–3.0	1.3–2.7	

^Independent t-test

No significant difference between Letrozole and Clomiphene groups regarding **basal hormonal profile on day-3**.

Table 3: Endometrial thickness (mm) among the studied groups

Measures	Letrozole (N=50)	Clomiphene (N=50)	^P
Mean±SD	9.2±0.6	8.1±0.6	<0.001*
Range	8.0–10.0	7.0–9.0	
Value of using Letrozole over Clomiphene			
Items	Mean±SE	95% CI	
Thickness increase	1.1±0.1	0.9–1.4	

^Independent t-test, *Significant, CI: Confidence interval

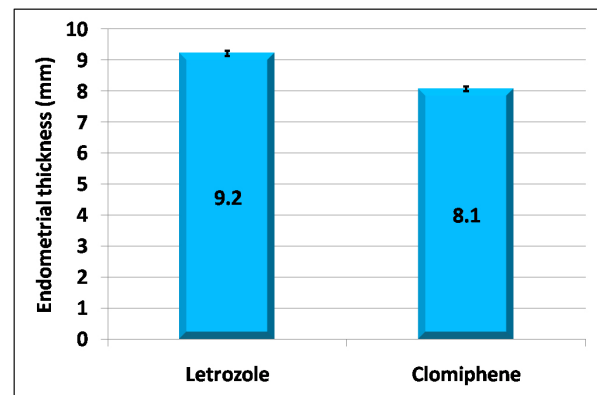


Figure 2: Endometrial thickness among the studied groups Table (3) and figure (2) show that: **Endometrial thickness** was significantly higher among Letrozole group than among Clomiphene group.

Table 4: Follicular development among the studied groups

Response	Letrozole (N=50)	Clomiphene (N=50)	#Ps
Monofollicular	37 (74.0%)	26 (52.0%)	0.023*
Multifollicular	13 (26.0%)	24 (48.0%)	

#Chi square test, *Significant, CI: Confidence interval

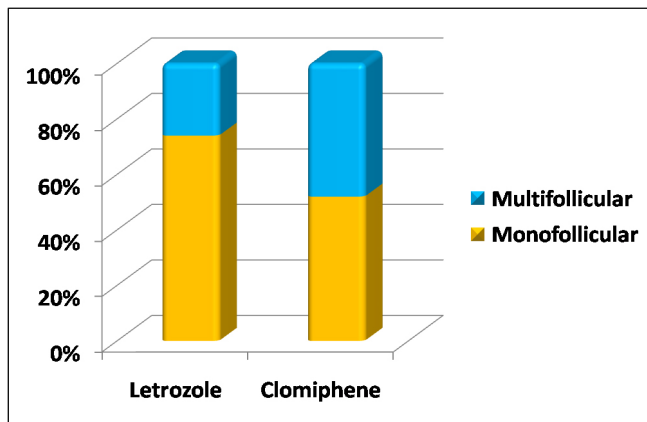


Figure 3: Follicular development among the studied groups Table (4) and figure (3) show that: Monofollicular was significantly more frequent among letrozole group than in letrozole group.

Table 5: Ovulation rate among the studied groups

Response	Letrozole (N=50)	Clomiphene (N=50)	#P
Occurred	32 (64.0%)	31 (62.0%)	0.836
Not	18 (36.0%)	19 (38.0%)	
Value of using Letrozole over Clomiphene			
Items		Value	95% CI
Rate in study group		64.0%	53.8%-74.1%
Rate in control group		62.0%	51.9%-72.2%
Rate elevation		2.0%	-18.5%-22.3%
Efficacy		4.4%	-31.7%-68.3%
Relative Rate		1.0	0.7-1.7
Number needed to treat		46.6	4.2-100.0

#Chi square test, *Significant, CI: Confidence interval Table (5) shows that: No significant difference between Letrozole and Clomiphene groups regarding **ovulation rate**.

Table 6: Clinical pregnancy among the studied groups

Response	Letrozole (N=50)	Clomiphene (N=50)	#P
Occurred	24 (48.0%)	14 (28.0%)	0.038*
Not	26 (52.0%)	36 (72.0%)	
Value of using Letrozole over Clomiphene			
Items		Value	95% CI
Rate in study group		48.0%	37.5%-57.5%
Rate in control group		62.0%	18.5%-38.5%
Rate elevation		2.0%	-1.0%-38.9%
Efficacy		4.4%	-2.2%-120.5%
Relative Rate		1.0	1.0-2.2
Number needed to treat		46.6	2.4-100.0

#Chi square test, *Significant, CI: Confidence interval

Table (6) shows that: **Clinical pregnancy** was significantly more frequent among Letrozole group than among Clomiphene group.

Discussion

Polycystic ovary syndrome (PCOS) is a common heterogeneous endocrine disorder characterized by irregular menses, hyperandrogenism, and polycystic ovaries. The prevalence of PCOS varies depending on which criteria are used to make the diagnosis, but is as high as 15%-20% when the European Society for Human Reproduction and Embryology/ American Society for Reproductive Medicine criteria are used [2]. Clomiphene citrate is considered first-line therapy for ovulation induction for women with PCOS and infertility [13].

The discrepancy between ovulation and pregnancy rates may be partly explained by the peripheral anti-estrogenic effects of clomiphene citrate on quality of cervical mucus and the endometrium, which may inhibit sperm penetration and affect implantation [14]. Gonadotropins and gonadotropin-releasing hormone (GnRH) analogs are accepted alternatives to CC; however, they increase risk of multiples, are associated with ovarian hyperstimulation syndrome, are available only as injectable formulations, and are expensive [13].

Letrozole is a third generation aromatase inhibitor that acts by preventing negative feedback inhibition of the hypothalamopituitary axis by estrogen, thus increasing FSH level and also increasing the follicular sensitivity to FSH [14]. It is postulated that aromatase inhibitors may have superior ovulation induction properties in terms of follicular growth and endometrium development, which is important for embryo implantation [15].

In our randomized control study a hundred female patients were randomly selected diagnosed as having infertility due to PCO according to Rotterdam criteria at Al Maadi Military Hospital, Department of Obst & Gynecology. They were divided into two groups (A&B). Group A (50 patients) were given Letrozole 5mg from the 3rd day of the menstrual cycle for five days. Group B (50 patients) were given Clomiphene Citrate from the 3rd day for five days.

Age, duration of infertility, BMI were statistically similar in both groups. (Table 1). Also all basal hormonal profile on day 3 of the cycle including FSH, LH, PROLACTIN, E2, Testosterone and TSH levels were statistically non-significant in both groups. The results of the present study revealed that both types of treatment were effective in treatment of PCOS patients regarding ovulation rate where there was no statistical significant difference between CC group (62.0%) and Letrozole group (64.0%). This was in agreement with that found that similar ovulation rate for both Letrozole and clomiphene citrate [9]. Ovulation was significantly higher in the Letrozole group (78.7%) than clomiphene citrate group (53.3%) in the study of Nik et al. [16]. This may be explained by the fact that ultrasound variability is an important confounding factor, particularly if follicle size is the main deciding factor for ovulation induction. This becomes especially true when ultra-sonography reveals a collapsed follicle that has already ovulated. Measuring such a follicle can result in a misclassification bias where the diameter of the follicle is assigned to an incorrect category and hence, underestimates the true value.

In the present study multi-follicular development was statistically significantly higher in cc group (CC 48.0%, Let 26.0%), this is in agreement with Holzer et al. and Zeinalzadeh et al. [17-19]. Clomiphene citrate blocks estrogen receptors (ERs) to mimic estrogen deficiency in the pituitary, while Letrozole creates an estrogen deficiency by blocking the conversion of androgen to estrogen. Hence, the initial release of FSH may be increased in patients treated with Letrozole than in those treated with Clomiphene citrate. In the ovary, aromatase inhibitors increase follicular sensitivity to FSH by the accumulation of intraovarian androgens. As the dominant follicle grows and estrogen levels rise, normal negative feedback occurs centrally, resulting in suppression of FSH secretion and atresia of the smaller growing follicles.

Endometrial thickness (ET) measurement is a predictor for successful implantation following ovulation induction, with many studies reporting more success with a thickness of 9 - 10 mm [16]. In our study, mean ET in the Letrozole group was thicker than in the Clomiphene citrate group at midcycle of menses (Day 11-Day 14), with ET values of 9.2 mm and 8.0 mm respectively. This difference was statistically highly significant (p value < 0.001). These findings were consistent with other studies reporting that most patients taking Letrozole had a thicker endometrium compared to those taking Clomiphene citrate [6,16]. Surprisingly, another study revealed that the endometrium was statistically significantly thicker in the Clomiphene citrate group, possibly due to an increase in the number of growing follicles and thus a higher level of estrogen and progesterone, although endometrial thickness in both study groups was >5 or 6 mm [10].

In our study pregnancy rate per cycle was significantly higher with Letrozole group (48.0%) vs. Clomiphene citrate group (28.0%). This is in agreement with another study that found a pregnancy rate of 21.6% after treatment with 2.5 mg Letrozole and 9.1% after treatment with 100 mg Clomiphene citrate [20]. In a study by Hendawy et al. pregnancy rate in Letrozole group was higher than Clomiphene citrate group [21]. Kar in a study showed that Letrozole has excellent pregnancy rates compared to Clomiphene citrate. This may be explained by the fact that the anti-estrogenic effect of clomiphene citrate results in long lasting estrogen receptor depletion and its accumulation in the body due its long half-life (2 weeks), causing adverse effects on the quality and quantity of cervical mucus [22]. In addition endometrial development causing implantation failure and significant thinning of the endometrial. These undesirable effects of clomiphene citrate on the endometrium may explain the relatively poor pregnancy associated with clomiphene citrate despite the high rate of ovulation.

Conclusion

The pharmacodynamics of Letrozole (does not deplete ERs, short half-life, keeps intact hypothalamic pituitary axis) ensures improved endometrial thickness and cervical mucus and monofollicular ovulation. Therefore, these factors may lead to a higher pregnancy rate and greater likelihood of singleton pregnancy.

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