

LETROZOLE VERSUS CLOMIPHENE CITRATE FOR OVULATION INDUCTION IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

By

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ABSTRACT

Background: Ovulation is the central event in the reproduction cycle. Anovulatory dysfunction is a common problem and is responsible for about 40% of female infertility. Polycystic ovarian syndrome (PCOS) with abnormalities in the metabolism of androgens and estrogen and in the control of androgen production remains one of its leading causes. Polycystic ovary syndrome (PCOS) is a common multisystem endocrine disorder in women, with long-term health consequences

Objectives: Comparing the efficacy of Letrozole and Clomiphene citrate, as a first line treatment for induction of ovulation in cases of polycystic ovary syndrome.

Patients and Methods: This study was randomized comparative study involving 100 Egyptian women having polycystic ovary syndrome attending Al-Azhar University Maternity hospital (Sayed Galal/ Infertility outpatient clinic, And 6th October Health Insurance Hospital). During the initial visit, anthropometric measurements and baseline investigations were performed. Patients were randomized to 5.0 mg Letrozole daily (50 Patients) or 100 mg Clomiphene citrate (50 Patients) from the third until the eighth day of menstruation. Serial transvaginal scans were performed to see the dominant follicles, endometrial thickness and number of follicles. Transvaginal scans were performed serially to look for evidence of ovulation.

Results: The difference between Letrozole and Clomiphene citrate for ovulation rate was 44 (88%) versus 30 (60%) respectively. Patients taking Letrozole exhibited a mean endometrial thickness (ET) at mid cycle of menses (Day 11-D14) of 9.2 mm (SD 2.37) versus 8.4 mm (SD 1.61) for patients taking Clomiphene citrate, and these differences were statistically significant. In terms of pregnancy rate, Letrozole facilitated pregnancy induction in 19 patients (38%) versus 8 patients (16%) for Clomiphene citrate, which was statistically significant. More dominant follicles exhibiting a mono-follicular morphology were observed in patients treated with Letrozole compared to patients treated with Clomiphene citrate, with a mono-follicular dominant follicle observed in 23 (46%) versus 14 (28%) patients respectively.

Conclusion: Letrozole provided a more efficient stimulation compared to Clomiphene citrate in terms of ovulation induction, thickening of the endometrial lining and achievement of a successful pregnancy.

Keywords: Polycystic Ovarian Syndrome; Ovulation Induction; Clomiphene Citrate; Letrozole.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most common endocrinopathy, affecting 6% of women at reproductive

age (Rotterdam ESHRE/ASRM (2014). The overall prevalence of PCOS among reproductive-age women in the United States (US) was 4% (Joham et al., 2015).

Clomiphene citrate has been the first-line and standard drug treatment for PCOS for the last 40 years. Early studies proved that up to 80% of anovulatory patients responded well to Clomiphene citrate as assessed by achievement of ovulation, with about half of those who were ovulatory achieving pregnancy. However, approximately 20% of patients required a high dose of Clomiphene citrate (200 mg daily taken for 5 days early in the cycle), which may be a result of anti-estrogenic activities on the endometrium and cervical mucus.

Letrozole was proposed as an alternative to Clomiphene citrate as a highly selective aromatase inhibitor that prevents androgen-to-estrogen conversion. This aromatase inhibitor has a short half-life (45 hours); thus it is rapidly eliminated from the body. No adverse effects on estrogen target tissues or down regulation of estrogen receptor (ER) are seen with Letrozole due to this short half-life, unlike Clomiphene citrate (*Behnoud et al., 2019*).

The aim of aromatase inhibitor was to avoid the peripheral anti-estrogenic effects of Clomiphene citrate, especially thinning of the endometrial lining (*Badawy et al., 2009-a*). Hence, a randomized comparative study was conducted to determine which regime, Clomiphene citrate or Letrozole, was the best ovulation induction agent in infertile women with PCOS.

PATIENTS AND METHODS

This study was conducted in Al-Azhar University Maternity hospital (Sayed Galal / Infertility outpatient clinic. and 6th October Health Insurance Hospital).

Inclusion criteria: were an age between 20 years and 35 years old, diagnosed with PCOS by the *Rotterdam criteria (2003)* and normal seminal fluid analysis (SFA *Roque et al., (2015)*). Patients were not illiterate and consented to participate in the study. Exclusion criteria were having medical problems such as renal disease, thyroid disorder, hyperprolactinemia, liver disease or having other causes of anovulatory infertility.

Power calculations were performed to determine the sample size. Sample size was calculated using PASS 11.0 and according to findings of study carried out by (*Elshabbahi et al., 2010*), Group sample sizes of 32 and 32 achieve 80% power to detect a difference of diameter of follicles more than 18 mm is 0.7 between the null hypothesis that both group means are 2.2 and the alternative hypothesis that the mean of group 2 is 1.5 with known group standard deviations of 1.2 and 0.8 and with a significance level (alpha) of 0.05000 using a two-sided Mann-Whitney test assuming that the actual distribution is uniform. The sample size will be increased 15% to compensate the loss to follow up in the studied patients. Finally sample will include 50 patients in Group L and 50 patients in group C.

Letrozole Group: Patients in this group were given Letrozole 5.0 mg daily from Day 3-Day 7 of menstruation. Baseline transvaginal ultrasound (TVS) on the second day of menstruation was performed, following spontaneous menses with serial TVS to document ovulation. If a dominant follicle (DF) was present (DF > 12 mm), a repeat TVS was performed every 2 days. Ovulation was diagnosed when the mature DF was approximately

18 to 22 mm followed by evidence of rupture approximately 3 to 4 days later. If a dominant follicle (DF) was absent (DF < 12 mm), a repeat TVS was performed every 3 – 4 days later. Endometrial thickness (ET) was measured at every follow-up. If there was absence of a dominant follicle (DF < 12 mm) up to Day 20, the patient was considered to be anovulatory.

Clomiphene Citrate Group: Patients were given Clomiphene Citrate 100 mg daily from Day 3-Day 7 of menses. Those patients who had spontaneous menstruation were received on the second day (baseline TVS) of their menstruation and baseline ultrasound (TVS) was performed to measure the number, size and location of the follicles on each ovary, as well as endometrial thickness (ET). TVS was repeated on the tenth day of menstruation, where the presence, number and size of the dominant follicles (DF) were evaluated. DFs were defined as follicles measuring at least 12 mm on the tenth day of menstruation. Serial transvaginal scans were performed to document the evidence of ovulation. If a dominant follicle (DF) was present (DF > 12 mm), a repeat TVS was performed every 2 days. Ovulation was diagnosed when the mature DF was approximately 18 to 22 mm followed by evidence of rupture approximately 3 to 4 days later. If a dominant follicle (DF) was absent (DF < 12 mm), a repeat TVS was performed every 3 – 4 days later. The absence of a dominant follicle (DF < 12 mm) by Day 20 was considered as failed induction or anovulation.

The investigator and the subject could choose to cease the study treatment or withdraw at any time, respectively.

All patients had a urine-based pregnancy test at 3 weeks after documented ovulation and continued amenorrhea. They were followed-up with until an ultrasound could document the viability of pregnancy. Primary outcome measures were ovulation rate, single follicle formation and endometrial thickness, while secondary outcome measures were pregnancy rate. The patients were given 5 cycles of treatment for the study.

Statistical Analysis:

Data entry and statistical analysis were performed using SPSS version 20. Means and standard deviations for numerical variables and frequency and proportion for categorical variables are reported. Two-tailed independent t-test was used to compare means and proportion was compared with the Chi-Square test or Fishers exact test. A P value of < 0.05 was considered significant. Multiple logistic regression analysis was performed to assess the association of Letrozole and Clomiphene citrate with the ovulation rate after controlling for confounders.

Simple logistic regression was used in univariate analysis as a screening in the selection of variables for further analysis. All variables with a P value less than 0.25 were selected for inclusion in multiple logistic regression analysis.

Multiple logistic regression was chosen as the dependent variable of the binary outcome. Level of significance was 5% and results had 95% confidence intervals. The independent variables were

a mix of numerical and categorical variables. Background and forward stepwise procedure was used for variable selection. Interactions between pairs of variables from all variables in the main

effect model were checked. Findings in the final model were presented as an adjusted odds ratio (OR), its 95% confidence interval (CI) and corresponding P value.

RESULTS

There were no significant differences noted with regard to socio-demographics, anthropometrics and duration of infertility between the studied groups, suggesting

that they were homogeneously distributed. The data were normally distributed (Table 1).

Table (1): Distribution of study population according to age, BMI and duration of infertility

Parameters	Group (L) Letrozole (n=50)			Group (C) Clomiphene citrate (n=50)			P value
	Range	Mean	SD	Range	Mean	SD	
Age (years)	20-33	24.12	3.24	20-35	24.61	4.15	> 0.05
Weight (kg)	49.5:93	68.34	18.71	46:95	69.51	19.12	> 0.05
Height (meter)	1.51:1.74	1.63	0.105	1.48:1.77	1.66	0.101	> 0.05
BMI (kg/m ²)	19.68 35.84	26.98	4.54	18.86- 33.75	25.0	4.31	< 0.03
Period of Infertility (years)	2-13	5.54	2.74	2-15	5.94	3.41	0.071

PCOS patients were randomized to the Letrozole group were approximately 1.5 times more likely to ovulate compared to the Clomiphene citrate group after

controlling for other variables such as age, duration of infertility, type of infertility, baseline FSH and LH levels and BMI (Table 2).

Table (2): Biochemical data of study population

Parameters	Group (L) Letrozole (n=50)			Group (C) Clomiphene citrate (n=50)			P value
	Range	Mean	SD	Range	Mean	SD	
FSH (mIU/mL)	3.21- 9.42	6.67	1.85	3.38-9.56	7.10	1.85	0.337 (NS)
LH (mIU/L)	9.42- 19.4	14.92	4.21	9.43- 19.30	14.45	3.87	0.129 (NS)
LH/FSH	0.79- 5.38	2.01	1.23	0.70-5.82	2.13	1.21	0.669 (NS)

Ovulation was significantly more frequent in the Letrozole group than Clomiphene citrate group, which was statistically significant with p value of < 0.002 (Table 3).

Table (3): Ovulatory response to letrozole and Clomiphene citrate

Parameters	Group L Letrozoe (n = 50)		Group C CC=50		P
	n.	%	n.	%	
Ovulation	44	88	30	60	< 0.002

Endometrial thickness (ET) measurement is a predictor for successful implantation following ovulation induction, mean ET in the Letrozole group was thicker than in the Clomiphene citrate group at mid-cycle of menses (Day 11- Day 14) (Table 4).

Table (4):The number of follicles ≥ 18 mm in diameter and endometrial thickness in each group on day of hCG administration

Parameters	Group L (letrozole) "n=50"	Group C (CC) "n=50"
No. of follicles ≥ 18 mm Range Mean S.D.	1.0-5.0 2.2 1.18	1.0.3.0 1.5 0.77
F P	35.13 0.00001**(S)	
Endometrial Thickness (mm) Range Mean S.D.	6.0-14.0 8.86 2.37	4.0 – 9.0 5.56 1.61
F P	78.7 0.0001**(S)	

** Highly significant

The number of successful ovulatory cycles and pregnancy rate was notably higher in the Letrozole treatment group compared to the Clomiphene citrate group (Table 5).

Table (5):The number of recorded pregnancies in group Letrozole and Clomiphene citrate

Parameters	Group L (Letrozole) "n=50"		Group C (CC) "n=50"	
	n.	%	n.	%
Pregnancy	19	38	8	16
P	0.02*			
Total number of cycles	152		156	
% of pregnancy cycle	7.2		3.2	
P	0.03*			

DISCUSSION

Clomiphene citrate is an anti-estrogen with a 60% ovulation rate and a 16% pregnancy rate. This is due to the anti-estrogen effect of Clomiphene citrate, resulting in long-lasting estrogen receptor (ER) depletion. Clomiphene citrate accumulates in the body due to its long half-life (2 weeks), causing adverse effects on the quality and quantity of cervical mucus. In addition, it affects endometrial development, causing implantation failure and significant thinning of the endometrium. These undesirable effects of Clomiphene citrate on the endometrium may explain the relatively poor pregnancy rate associated with Clomiphene citrate despite the high rate of ovulation (*Begum et al., 2009*).

Letrozole is a type IIa third-generation highly selective cytochrome P-450-linked aromatase inhibitor that prevents androgen-to-estrogen conversion. Letrozole has the same mechanism as Clomiphene citrate in initiating gonadotropin release through the withdrawal of negative feedback on the pituitary by reducing blood estrogen levels. 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 intra-ovarian 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. A single dominant follicle and mono-ovulation should occur in most cases (*Franik et al., 2018*). In the endometrium, estrogen receptors may be upregulated, resulting in rapid endometrial growth once estrogen secretion is restored following clearance of Letrozole (*Mejia et al., 2019*).

Ovulation was significantly more frequent in the Letrozole group 44 (88%) than Clomiphene citrate group 30 (60%), which was statistically significant with p value of 0.03. Other studies showed similar ovulation rates of 82.4% and 63.2% for Letrozole and Clomiphene citrate, respectively. Previously published studies reported ovulation rates for Letrozole and Clomiphene citrate of 82.4% and 63.2%, respectively. Another study found that among women taking Letrozole, 62.5% had achieved ovulatory cycling as compared to 37.5% of women taking Clomiphene citrate, which was not different significantly (*Begum et al., 2009*). However, our study correlates with previously reported data that Letrozole increases the percentage of women achieving ovulatory stimulation. Another study comparing Letrozole and combined metformin-Clomiphene citrate treatment showed no difference in rates of ovulation and pregnancy (*Abu Hashim et al., 2010*).

Ultrasound variability is an important confounding factor, particularly if follicle size is the main deciding factor of ovulation induction. This becomes especially true when ultrasonography 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.

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. In our study, mean ET in the Letrozole group was thicker than in the Clomiphene citrate group at mid-cycle of menses (Day 11-Day 14), with ET values of 9.2 mm and 8.4 mm respectively. This difference was statistically significant. These findings were consistent with other studies reporting that most patients taking Letrozole had a thicker endometrium and conceived more frequently as compared to those taking Clomiphene citrate (*Sharief and Nafee, 2015*). Similar findings showed that Letrozole had an overall greater beneficial effect on the endometrium (*Banerjee Ray et al., 2012* and *Franik et al., 2018*).

Surprisingly, *Badawy et al., (2009-a)* 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.

Historically, the overall successful pregnancy rates after ovulation induction range from as low as 9% to as high as 25% *Teede et al., (2018)*. These controversies may stem from differences in the treatment groups, diagnostic criteria, techniques used, age of the cohort, cause of infertility and the number of treatment cycles. In our study,

consistent with the number of successful ovulatory cycles, pregnancy rate was notably higher in the Letrozole treatment group compared to the Clomiphene citrate group with 19 (38%) and 8 (16.0%) pregnancies, respectively; and this was significantly significant. The pregnancy rate observed in our study was consistent with other reported studies such as that by *Nahid and Sirous (2012)*. In which a pregnancy rate of 25% was observed for PCOS patients treated with 2.5 mg Letrozole. Additionally, *Sharief and Nafee (2015)*. Also found a pregnancy rate of 21.6% after treatment with 2.5 mg Letrozole and 9.1% after treatment with 100 mg Clomiphene citrate, which was statistically significantly different. There are a few studies that showed significantly higher pregnancy rates with Letrozole than with Clomiphene citrate (*Badawy et al., 2009-b, Kar 2012* and *Legro et al., 2014*).

Generally, conception should result within five treatment cycles. Beyond that, pregnancy rate is lower because the cohort of women remaining represents the harder to obtain pregnant cases.

Pregnancy rate may be altered by other confounding factors; for example, approximately 10% of women in our study were more than 35 years old. This factor lowered the number of pregnancies and made the study sample a relatively less fertile group.

Current studies have shown that Letrozole is generally safe for use in pregnancy (*Kar 2012*). Known complications of Clomiphene citrate use include multi-fetal pregnancy and pregnancy wastage. A major complication associated with the use of Clomiphene

citrate is the occurrence of ovarian hyperstimulation syndrome (OHSS). All complications of this therapy are essentially related to the degree of ovarian stimulation that occurs during ovarian induction *Sharief and Nafee (2015)*. In this study, two subjects had multiple pregnancies with Clomiphene citrate and no subjects had OHSS.

CONCLUSION

In this study, Letrozole was noted to be better at ovulation induction as the ovulation rate was 88 % and 60% respectively which was statistically significant. The mean ET in the Letrozole group was statistically significantly thicker than in the Clomiphene citrate group at mid-cycle of menses (Day 11-Day 14) The Letrozole group had a significantly higher pregnancy rate. Letrozole treatment was prone to production of mono-follicles and hence led to reduced incidences of the adverse pregnancy outcome of multiple fetuses as compared to treatment with Clomiphene citrate. Overall, this study demonstrated that Letrozole was superior to Clomiphene citrate as an inducer of ovulation cycles.

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المقارنة بين عقار اللتروزول وعقار سترات الكلوميفين فى الحث على التبويض فى مريضات متلازمة تكيس المبيضين

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خلفية البحث: إن التبويض هو الحدث الرئيسى فى الدورة الشهرية، إن اضطرابات التبويض مشكلة شائعة ومسؤولة عن حوالى 40% من أسباب العقم عند السيدات. إن مرض متلازمة تكيس المبيضين مع اضطرابات فى هرمونات الذكورة وهرمون الإستروجين وفى إنتاج هرمونات الذكورة يظل أحد الأسباب الشائعة. حيث يعد مرض متلازمة تكيس المبيضين من أشهر أسباب الاباضية على الاطلاق وهو يؤثر على السيدات فى فترة الخصوبة.

الهدف من البحث: المقارنة بين كفاءة عقار اللتروزول وعقار سترات الكلوميفين فى الحث على التبويض فى مريضات متلازمة تكيس المبيضين.

المريضات وطرق البحث: تم اختيار 100 سيدة من المريضات المترددات على العيادة الخارجية (عيادة العقم) بمستشفى التوليد وأمراض النساء(سيد جلال) جامعة الأزهر و مستشفى 6 أكتوبر للتأمين الصحى. وتم تشخيص الحالات كمريضات لمتلازمة تكيس المبيضين. وقد تم تقسيم السيدات الى مجموعتين: المجموعة 1: تشمل هذه المجموعة (50) سيدة تم تشخيصهن من قبل كمريضات متلازمة تكيس المبيضين تم اعطائهن دواء اللتروزول 5 ملليجرام يوميا من اليوم الثالث الى اليوم السابع للدورة. المجموعة 2: تشمل هذه المجموعة (50) سيدة تم تشخيصهن من قبل كمريضات متلازمة تكيس المبيضين تم اعطائهن دواء سترات الكلوميفين 100 ملليجرام يوميا من اليوم الثالث الى اليوم السابع للدورة.

نتائج البحث: أظهرت نتائج المجموعة الأولى التى تم إعطائها (اللتروزول) إستجابة جيدة من حيث نمو وعدد البويضات وسمك بطانة الرحم وحدث حمل بفارق ذو جدوى احصائية مقارنة بالحالات فى المجموعة الثانية التى تم إعطائها سترات الكلوميفين.

الإستنتاج: عقار اللتروزول فعال لعلاج العقم فى حالات اللاباضية.