ORIGINAL ARTICLE

Comparative Study between Letrozole versus Clomiphene Citrate in Treatment of Polycystic Ovaries (PCO)

Shaimaa A. Abdellatif, Ghada I. Soror, Shaimaa M. ELshaarawy *

Department of Obstetrics and Gynecology, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt

Abstract

Background: ***Polycystic Ovary Syndrome (PCOS) is probably the most common reason that influences females of childbearing age and regularly prompts barrenness.***

Aim: ***To compare Letrozole versus Clomiphene citrate in the treatment of Polycystic ovaries (PCOS).***

Patients and methods: ***This prospective clinical trial, involved 60 cases complaining of primary infertility diagnosed as PCOS and were selected from the Gynecology and Obstetrics clinics of Alzahraa University Hospital throughout the duration from January 2023 to August 2023.***

Results: ***Regarding endometrial thickness, in the Clomiphene citrate group, the mean endometrial thickness was 7.70±1.49 20% have 1 follicle not less than 18 mm on HCG administration day, 36.7% have 2 follicles, 26.7% have 3 follicles, 16.7% have 4 follicles. In Letrozole, the mean endometrial thickness was 9.37±7.14; 30% had 1 follicle not less than 18 mm on HCG administration day, 43.3% had 2 follicles, 26.7% had 3 follicles, and none had 4 follicles. There is a statistically insignificant distinction among the 2 groups regarding the number of follicles not less than 18 mm on HCG administration day. There is statistically significantly greater endometrial thickness in the Letrozole than in the Clomiphene citrate group. Regarding ovulation, the Letrozole group has a statistically significantly greater ovulation rate than the Clomiphene citrate group (83.3% vs 60%). Regarding pregnancy outcome, there was a statistically significant higher pregnancy rate in Letrozole than in the Clomiphene citrate group (33.3% vs 10%).***

Conclusion: ***The study compared Letrozole and Clomiphene citrate for treating polycystic ovaries, finding Letrozole significantly higher in ovulation, pregnancy rates, and endometrial thickness.***

Keywords: Clomiphene Citrate; PCOS; Letrozole

1. Introduction

Polycystic Ovary Syndrome is a major medical issue. Polycystic ovary syndrome is likely the main cause influencing females of reproductive age and often leads to barrenness.[1]

The research suggests that between five and ten percent of females between the ages of 18 and 44 are affected by Polycystic Ovary Syndrome, rendering it the most frequent endocrine disorder among women of reproductive age in the United States. Various treatments have been proposed for infertile females with Polycystic Ovary Syndrome. Nonetheless, the optimal administrative decision has not been proven fulfilled.[2]

Polycystic ovary syndrome is a disorder of the hypothalamus-pituitary–ovarian (HPO) axis that impacts approximately twenty percent of reproductive-age females globally. Polycystic ovary syndrome is characterized by anovulation, elevated androgen levels, and the presence of polycystic ovaries. A clinical diagnosis of PCOS requires the presence of two of the three features according to the Rotterdam criteria. Additional characteristics involve irregular gonadotropin secretion, namely elevated luteinizing hormone (LH), an increased LH: FSH (follicle-stimulating hormone) ratio, decreased sex hormone-binding globulin (SHBG), and chronic inflammation. Endometrial Cancer (EC) ranks among the most prevalent cancers in females, with approximately 142,000 cases and 42,000 fatalities globally. Type 1 endometrial cancer, the most prevalent lesion, is correlated to an excellent prognosis, whereas Type 2 endometrial cancer is frequently high-grade and has a tendency for recurrence.[3]

Accepted 19 January 2025.
Available online 31 January 2025

* Corresponding author at: Obstetrics and Gynecology, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt.
E-mail address: shaimaashaarawy77@gmail.com (S. M. ELshaarawy).

https://doi.org/10.58675/2682-339X.2875

This investigation aimed to compare Letrozole with Clomiphene citrate in the treatment of Polycystic ovaries (PCOS).

2. Patients and methods

This prospective clinical trial involved 60 cases complaining of primary infertility diagnosed as PCOS. The cases were selected from the Gynecology and Obstetrics clinics of Alzahraa University Hospital throughout the duration from January 2023 to August 2023.

Sample Size: This research has been based on an investigation conducted by El Omda et al.[4] The sample size has been calculated utilizing Epi Info STATCALC based on the following assumptions: - A two-sided confidence level of ninety-five percent accompanied with a power of eighty percent. An error of five percent in the calculated odds ratio is 1.115. The ultimate maximum sample size derived from the Epi-Info output was 53. Consequently, the sample size has been increased to sixty cases to account for potential dropout cases throughout monitoring. Inclusion criteria: females aged 18-35 diagnosed with primary infertility attributed to polycystic ovary syndrome (PCOS). According to the Rotterdam criteria, females with a Body Mass Index (BMI) between 18 and 30, a normal uterus, patent tubes as confirmed by hysterosalpingography, normal blood prolactin levels (5-20 nomograms per milliliters), and a normal semen analysis of the partner are considered.

Exclusion criteria: Pathology of the uterus and adnexa, such as leiomyomas. Ovarian cysts exceeding five centimeters, hyperthyroidism or hypothyroidism, and a history of genital tract operation, along with impaired renal or hepatic function, hyperprolactinemia, diabetes mellitus, and medications that may disrupt ovulation, particularly the chronic administration of nonsteroidal anti-inflammatory drugs, hormonal agents, or chemotherapeutic agents. Methods

Patient were subdivided into Group A: Thirty cases received Letrozole, administered at 2.5 milligrams twice for five days, starting from the second day of their menstrual cycle. Group B: Thirty cases have been treated with clomiphene citrate, given at a dosage of fifty milligrams twice a day for five days, also starting on the second day of the menstrual cycle. All cases underwent full history taking. General assessment: Vital signs (temperature, blood pressure, respiration rate, heart rate), signs of (pallor, cyanosis, jaundice, and lymphadenopathy), and body mass index. Laboratory Investigation: Analysis of semen, serum FSH and LH, thyroid function tests, serum prolactin, and pelvic ultrasound will be conducted. A breast examination has been conducted for galactorrhea. The uterus has been determined to be devoid of disease, while polycystic ovary syndrome has been diagnosed utilizing biochemical and clinical evidence of hyperandrogenism, polycystic ovaries, ovulatory dysfunction, or adult anti-Müllerian hormone levels.[5] These cases have been monitored for three cycles using transvaginal ultrasound folliculometry to document ovulation. Folliculometry was conducted on days eleven, thirteen, and Fifteen of the cycle to assess the size and number of progressing follicles, performed via vaginal ultrasound. US EDAN DOS PLUS 60. The number of follicles was measured between 18-22 millies, and endometrial thickness was measured. An intramuscular injection of HCG (10,000 IU) has been administered to induce ovulation upon detection of a mature follicle measuring 18-22 millimeters. An ultrasound has been conducted forty-eight hours post-HCG administration to confirm ovulation. Cases have been instructed to engage in intercourse 24 to 36 hours following the HCG injection. Serum βHCG levels have been evaluated if menstruation has been delayed by one week for diagnosis of pregnancy chemically, followed by TVS to identify the gestational sac at four weeks of gestation and fetal pulsation. After two months of treatment, laboratory investigations, including serum FSH, LH, prolactin levels, and pelvic ultrasound, have been performed to assess the efficiency of letrozole and clomiphene citrate in polycystic ovaries.

Data Analysis

The gathered information has been processed, coded, and analyzed utilizing the SPSS program (Version 25) for Windows. Descriptive statistics have been calculated to include medians, standard deviations, ranges, means, and percentages. Independent t-tests have been conducted for continuous parameters to compare the means of normally distributed data, whilst Mann–Whitney U tests have been utilized for median comparisons of non-normally distributed data, and chi-square tests have been utilized for categorical data.

Administrative considerations

An Official permission has been acquired from hospital of Alzahraa university and the study has been from January 2023to August 2023.An official permission has been acquired from the Institutional Research. Approval from ethical committee in the faculty of medicine (Institutional Research Board IRB).

3. Results

Regarding age distribution, the mean age in Clomiphene citrate group was 26.03±1.45 years, the mean age in Letrozole was 26.17±1.51 years, and the mean BMI in Clomiphene citrate group was 23.8±1.75, the mean age in Letrozole was 24.19±1.67. A statistically insignificant distinction

has been observed among the 2 groups ag regard the age and body mass index (Table 1).

Table 1. BMI Demographic data distribution of the examined population.

	Mean	SD	Mean	SD	t	P-value
AGE (YEARS)	26.03	1.45	26.17	1.51	-0.349	0.729 (NS)
BMI (KG/M²)	23.80	1.75	24.19	1.67	-0.891	0.377 (NS)

NS= non-significant (p value > 0.05), S= Significant (p value < 0.05), HS= highly significant (p value ≤0.001).

Regarding TSH, T4, T3, in Clomiphene citrate group the mean TSH was 2.28±1.05, the mean T4 was 1.26±0.29, the mean T3 was 3.25±0.44. In Letrozole the mean TSH was 1.84±1.1, the mean T4 was 1.43±0.26, the mean T3 was 3.15±0.58. A statistically insignificant distinction has been observed among the 2 groups as regard the TSH and T3 but T4 was significantly greater in Letrozole than Clomiphene citrate group, Regarding LH, FSH, PL, in Clomiphene citrate group the mean LH was 13.8±4.22, the mean FSH was 8.13±4.62, the mean PL was 9.07±4.8. In Letrozole the mean LH was 13.57±4.22, the mean FSH was 7.5±4.43, the mean PL was 7.8±4.0.

A statistically insignificant distinction has been observed among the 2 groups as regard the LH, FSH and PL levels. Regarding semen analysis, in Clomiphene citrate group the mean Semen count was 19.77±2.82, the mean Semen volume was 27.33±6.00, 40% has impaired forward motility. In Letrozole the mean Semen count was 20.5±3.05, the mean Semen volume was 29.00±6.50, 40% has impaired forward motility. A statistically insignificant distinction has been observed among the 2 groups as regard the semen analysis (Table 2).

Table 2. Laboratory data of the examined group.

	Mean	SD	Mean	SD	t	P-value
TSH (MIU/L)	2.28	1.05	1.84	1.10	1.585	0.118 (NS)
T4 (NG/ML)	1.26	0.29	1.43	0.26	-2.408	0.019 (S)
T3 (NG/ML)	3.25	0.44	3.15	0.58	0.728	0.469 (NS)
LH (IU/ML)	13.80	4.22	13.57	4.62	0.204	0.839 (NS)
FSH (IU/L)	8.13	3.79	7.50	4.43	0.595	0.554 (NS)
PL (NG/ML)	9.07	4.80	7.80	4.00	1.11	0.272 (NS)
SEMEN (MILLION/ML)	19.77	2.82	20.50	3.05	-0.966	0.338 (NS)
SEMEN VOLUME (MM)	27.33	6.00	29.00	6.50	-1.033	0.306 (NS)
FORWARD MOTILITY	N	%	N	%	X2	P-value
IMPAIRED	18	60%	18	60%	0.000	1.000 (NS)
NORMAL	12	40%	12	40%		

Regarding the HCG administration day, in Clomiphene citrate group 26.7% were in day 11, 23.3% were in day 12, 20% were in day 13, 16.7% were in day 14 and 13.3% were in day 15. In Letrozole the mean Semen count was 23.3% were in day 11, 16.7% were in day 12, 23.3% were in day 13, 26.7% were in day 8 and10% were in day 15. A statistically insignificant distinction has been observed among the 2 groups as regard the HCG administration day. (Table 3).

Table 3. The HCG administration day of the examined population.

	N	%	N	%	X2	P-value
DAY 11	8	26.7%	7	23.3%	1.312	0.859 (NS)
DAY 12	7	23.3%	5	16.7%		
DAY 13	6	20%	7	23.3%		
DAY 14	5	16.7%	8	26.7%		
DAY 15	4	13.3%	3	10%		

Regarding endometrial thickness, in Clomiphene citrate group the mean endometrial thickness was ,7.70±1.49 20% have 1 follicle not less than eighteen millimeters on HCG administration day, 36.7% have 2 follicles, 26.7% have 3 follicles, 16.7% have 4 follicles. In Letrozole the mean endometrial thickness was 9.37±7.14, 30% have 1 follicle not less than eighteen millimeters on HCG administration day, 43.3% have 2 follicles, 26.7% have 3 follicles, and none has 4 follicles. A statistically insignificant distinction has been observed among the 2 groups as regard the no. of follicles not less than eighteen millimeters on HCG administration day. There is statistically significant greater endometrial thickness in Letrozole than Clomiphene citrate group. (Table 4).

Table 4. Endometrial thickness and No. of follicles not less than eighteen millimeters on HCG administration day of examined population.

	Mean	SD	Mean	SD	t	P-value
ENDOMETRIAL THICKNESS (MM)	7.70	2.47	9.37	3.24	2.245	0.029 (S)
NO. OF FOLLICLES ≥ 18 MM ON DAY OF HCG ADMINISTRATION	N	%	N	%	X2	P-value
1 FOLLICLES	6	20%	9	30%	5.767	0.124
2 FOLLICLES	11	36.7%	13	43.3%		(NS)
3 FOLLICLES	8	26.7%	8	26.7%		
4 FOLLICLES	5	16.7%	0	0%		

Regarding ovulation, in Letrozole group has statistically significant higher ovulation rate than Clomiphene citrate group (83.3% vs 60%) (Table 5).

Table 5. Ovulation outcome of the examined population.

	N	%	N	%	X2	P-value
NO OVULATION	12	40%	5	16.7%	4.022	0.04 (S)
OVULATION	18	60%	25	83.3%		

Regarding pregnancy outcome, a statistically significant higher pregnancy rate has been observed in Letrozole than Clomiphene citrate group (33.3% vs 10%). (Table 6).

Table 6. Pregnancy outcome of the examined population

	N	%	N	%	X2	P-value
NO PREGNANCY	27	90%	20	66.7%	4.812	0.028 (S)
PREGNANCY	3	10%	10	33.3%		

4. Discussion

Polycystic ovary syndrome is a frequent endocrinologic and reproductive disorder found in six to ten percent of the female population.[6]

In our study, regarding age distribution, the mean age in Clomiphene citrate group was 26.03±1.45 years, the mean age in Letrozole was 26.17±1.51 years, and the mean BMI in Clomiphene citrate group was 23.8±1.75, the mean age in Letrozole was 24.19±1.67. A statistically insignificant distinction has been observed among the 2 groups regarding the BMI and age.

Agreeing with our results, Emara et al.[7] conducted a study to assess the efficiency of letrozole therapy compared to clomiphene citrate therapy for ovulation induction in cases with polycystic ovarian syndrome. The research involved one hundred infertile cases who have been randomly assigned to receive either Letrozole or extended clomiphene treatment. They reported that the mean age in the Clomiphene citrate group was 25.90 ±2.46 years, the mean age in Letrozole was 24.90±2.92 years, and the mean BMI in the Clomiphene citrate group was 26.58 ± 2.97, the mean age in Letrozole was 26.34±3.04. A statistically insignificant distinction has been observed between the two groups in terms of BMI and age.

In our study regarding TSH, T4, T3, in Clomiphene citrate group the mean TSH was 2.28±1.05, the mean T4 was 1.26±0.29, the mean T3 was 3.25±0.44. In Letrozole the mean TSH was 1.84±1.1, the mean T4 was 1.43±0.26, the mean T3 was 3.15±0.58. A statistically insignificant distinction has been observed among the 2 groups as regard the TSH and T3 but T4 was significantly greater in Letrozole than Clomiphene citrate group.

In accordance with our results, Sakar et al.[8] conducted a study to compare the clinical findings of ovulation induction (OI) through timed intercourse with Letrozole (LTZ) and clomiphene citrate (CC). Three hundred twenty-three cases with polycystic ovary syndrome received ovulation induction with letrozole or clomiphene citrate. The cases have been divided into 2 groups: the clomiphene citrate group (number=148) and the letrozole group (number=175). They observed no statistically insignificant distinction among the 2 groups regarding TSH. (P-value equals 0.422).

In our investigation regarding LH, FSH, PL, in Clomiphene citrate group the mean LH was 13.8±4.22, the mean FSH was 8.13±4.62, the mean PL was 9.07±4.8. In Letrozole the mean LH was 13.57±4.22, the mean FSH was 7.5±4.43, the mean PL was 7.8±4.0. A statistically insignificant distinction has been observed among the 2 groups as regard the LH, FSH and PL levels.

Inconsistent with our results, Al-Shoraky Mohamed et al.[9] reported a statistically insignificant distinction among the 2 groups regarding the LH and FSH.

In our study regarding semen analysis, in the Clomiphene citrate group, the mean Semen count was

19.77±2.82, the mean Semen volume was 27.33±6.00, 40% has impaired forward motility. In Letrozole, the mean Semen count was 20.5±3.05, the mean Semen volume was 29.00±6.50, and 40% had impaired forward motility. A statistically insignificant distinction has been observed among the 2 groups as regards the semen analysis.

In our studies, regarding HCG administration day, in the Clomiphene citrate group, 26.7% were on day 11, 23.3% were on day 12, 20% were on day 13, 16.7% were on day 14, and 13.3% were on day 15. In the Letrozole group, the HCG administration day was 23.3% were on day 11, 16.7% were on day 12, 23.3% were on day 13, 26.7% were on day 8, and 10% were on day 15. A statistically insignificant distinction has been observed among the 2 groups regarding the day of HCG administration. In supporting our results, MOBUSHER et al.[10] revealed that A statistically significant distinction had been observed among the two groups on the HCG injection day.

In our findings, regarding endometrial thickness, in the Clomiphene citrate group, the mean endometrial thickness was 7.70±1.49 20% have 1 follicle not less than eighteen millimeters on HCG administration day, 36.7% have 2

follicles, 26.7% have 3 follicles, 16.7% have 4 follicles.

In the Letrozole group, the mean endometrial thickness was 9.37±7.14; 30% had 1 follicle not less than eighteen millimeters on HCG administration day, 43.3% had 2 follicles, 26.7% had 3 follicles, none had 4 follicles. A statistically insignificant distinction has been observed among the 2 groups regarding the number of follicles not less than eighteen millimeters on HCG administration day. There was statistically significantly greater endometrial thickness in the Letrozole than in the Clomiphene citrate group.

Also, in Najafi et al.[11] in their study, there were 220 patients; 110(50%) of each of the two groups were classified into 2 groups. Cases who received Letrozole (group A) and cases who received clomiphene citrate (group B). They reported that in the Clomiphene citrate group, Endometrium thickness follicles; Average ±SD was 8.3 ± 2.6, the number of follicles was 1.3 ± 0.4, and the size of follicles was 18.8 ± 1.5. While in the Letrozole group, the Endometrium thickness of follicles; Average ±SD was 11.8 ± 2.7, the number of follicles was 1.4 ± 0.6, and the size of follicles was 19.3 ± 1.6, indicating that the endometrial thickness was significantly higher in the letrozole group than in the CC group. A non-significant difference has been observed among the 2 groups in terms of follicle number and follicle size.

In our investigation, regarding ovulation, in Letrozole group has statistically significant higher ovulation rate than Clomiphene citrate group (83.3% vs 60%).

In consistent with our results, Sahu et al.[12] who found that in letrozole group, the ovulation rate was better in comparison to clomiphene citrate group.

In our findings, there was a statistically significant higher pregnancy rate in Letrozole than in the Clomiphene citrate group (33.3% vs 10%)

In accordance with our results, Sahu et al.[12] who found that in letrozole group, the rate of pregnancy was better in comparison to clomiphene citrate group.

4. Conclusion

In our investigation, we compared Letrozole versus Clomiphene citrate in the management of polycystic ovaries. Accordingly, we found that regarding ovulation, the Letrozole group has a statistically significantly higher ovulation rate than the Clomiphene citrate group (83.3% vs 60%). Also, there was a statistically significant higher pregnancy rate in Letrozole than Clomiphene citrate group (10% vs 33.3%). Endometrial thickness in letrozole is better than in clomiphene citrate.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

Funding

No Funds : Yes

Conflicts of interest

There are no conflicts of interest.

References

1. Meier RK. Polycystic Ovary Syndrome. Nurs Clin North Am. 2018 Sep;53(3):407-420.
2. Guang HJ, Li F, Shi J. Letrozole for patients with polycystic ovary syndrome: A retrospective study. Medicine (Baltimore). 2018 Nov;97(44):e13038.
3. Prakash A, Nourianpour M, Senok A, Atiomo W. Polycystic Ovary Syndrome and Endometrial Cancer: A Scoping Review of the Literature on Gut Microbiota. Cells. 2022 Sep 28;11(19):3038.
4. El Omda F, Abd El Fattah A, Hashish M, Khalil M. A randomized trial of combined letrozole with metformin versus clomiphene citrate with metformin in polycystic ovary (PCOS) patients. The Egyptian Journal of Hospital Medicine. 2018 Jul 1;72(4):4382-8.
5. Christ JP, Cedars MI. Current Guidelines for Diagnosing PCOS. Diagnostics (Basel). 2023 Mar 15;13(6):1113. doi: 10.3390/diagnostics13061113.
6. Zehravi M, Maqbool M, Ara I. Polycystic ovary syndrome and reproductive health of women: a curious association. Int J Adolesc Med Health. 2021 Apr 21;33(6):333-337
7. Emara MA, Mohamed DI, Hassanein MA, Fathey AA. Letrozole therapy versus extended clomiphene citrate therapy for induction of ovulation in resistant patients with polycystic ovarian syndrome in low resource communities. The Egyptian Journal of Hospital Medicine. 2020 Oct 1;81(7):2456-61.
8. Sakar MN, Oglak SC. Letrozole is superior to clomiphene citrate in ovulation induction in patients with polycystic ovary syndrome. Pak J Med Sci. 2020 Nov-Dec;36(7):1460-1465.
9. Al-Shoraky Mohamed S, El-Din Hussien H, Ahmed El-Desouky ES. Letrozole versus clomiphene citrate for ovulation induction in women with polycystic ovary syndrome. AlAzhar Medical Journal. 2020 Jan 1;49(1):209-18
10. MOBUSHER I. Comparison of the efficacy of letrozole and clomiphene citrate for ovulation induction in infertile women with polycystic ovary syndrome. Age (years). 2014;24(2.33):24-29.
11. Najafi PZ, Noghabi SP, Afzali N, Mohammadzadeh S. Comparing the effect of clomiphene citrate and letrozole on ovulation induction in infertile women with polycystic ovary syndrome. J Pak Med Assoc. 2020 Feb;70(2):268-271.
12. Sahu M, Rout NR. Comparative study of clomiphene citrate versus letrozole as first-line ovulation induction drug in infertile polycystic ovary syndrome women. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2020 Jul 1;9(7):294853.