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Ultrasonographic comparative study between letrazole and clomiphene citrate on endometrial receptivity during induced ovulation

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Abstract

Background: Infertility is a prevalent concern affecting numerous couples worldwide, often caused by anovulation or irregular ovulation. Induced ovulation using pharmacological agents, such as letrozole and clomiphene citrate, is a commonly employed approach to enhance fertility. However, the impact of these medications on endometrial receptivity, a critical factor for successful implantation and pregnancy, remains an area of ongoing research. The primary goal of this research was to compare endometrial receptivity during induced ovulation by letrazole or clomiphene citrate. **Methods:** This study was prospective comparative research where 120 PCO and infertility more than 1-year women were included and divided into 2 groups: Group A (Clomid induction group) (odd numbers); Clomid was administered in 100 mg/day for 5 days dose starting from day 3 to day 7. In this group, 130 women were followed and only 60 women were included, and 70 women were excluded because either data loss or failed ovulation. Group B (Letrozole induction group) (even numbers); Letrozole was given in the dose of 5 mg/day for 5 days starting from day 3 to day 7. In this group, 90 women were followed, and 60 women were included, and 30 women were excluded because either data loss or failed ovulation. **Results:** The results demonstrate significant differences in endometrial thickness among the two groups. On the 11th day of the cycle, Group B exhibited a significantly higher endometrial thickness (9.82 ± 0.21 mm) compared to Group A (7.00 ± 0.21 mm) ($T = -73.53$, $p < 0.0001$). Similarly, at the stage of mature follicle (follicle > 18mm), Group B showed a significantly greater endometrial thickness (10.22 ± 0.20 mm) compared to Group A (7.49 ± 0.20 mm) ($T = -73.49$, $p < 0.0001$). Furthermore, even 7 days after ovulation, Group B maintained a significantly thicker endometrium (10.65 ± 0.22 mm) compared to Group A (7.81 ± 0.20 mm) ($T = -74.33$, $p < 0.0001$). **Conclusions:** Letrozole induces a greater rise in endometrial thickness and conception rate than Clomiphene citrate in infertile PCOS women. Letrozole may enhance fertility by increasing endometrial receptivity relative to CC.

Keywords: Ultrasonographic, Letrazole, Clomiphene Citrate, Endometrial Receptivity, Induced Ovulation.

1. Introduction

Infertility is a major issue that affects countless couples throughout the globe. Anovulation or irregular ovulation, in which the process of releasing a mature egg from the ovary is disturbed, is one of the leading reasons of infertility. In such instances, pharmacological medications are routinely used to induce ovulation in order to increase fertility. Letrozole and clomiphene citrate are two major possibilities among the drugs used to induce ovulation [1].

Letrozole, a non-steroidal aromatase inhibitor, has gained attention as an alternative to clomiphene citrate due to its potential benefits, including improved ovulation rates and lower incidence of adverse effects. However, the impact of letrozole and clomiphene citrate on endometrial receptivity, a critical factor for successful implantation and pregnancy, remains a topic of interest and ongoing research [2].

Endometrial receptivity refers to the uterine lining's capacity to accept and sustain embryo implantation. It is a complicated process governed by hormonal, cellular, and molecular components, and any disruptions to this delicate equilibrium might endanger implantation success. Understanding the effects of letrozole and clomiphene citrate on endometrial receptivity is essential for directing treatment options and maximising results for women undergoing ovulation induction [3].

The influence of these drugs on ovulation rates, pregnancy rates, and other clinical outcomes has been studied extensively in the past. A full comparison of their effects on endometrial receptivity is, however, lacking. This research attempts to address this deficiency by doing an ultrasonographic comparison of endometrial receptivity during ovulation induction with letrozole and clomiphene citrate [4].

The ultrasonographic method permits noninvasive study of the endometrium, yielding useful information about its thickness, pattern, and vascularization. By adopting this technique, we may investigate and evaluate the effects of letrozole and clomiphene citrate on

endometrial receptivity measures, such as endometrial thickness, pattern, and sub-endometrial blood flow, and therefore acquire a better understanding of their disparate effects [5].

This study aimed to compare endometrial receptivity during induced ovulation by letrazole or clomiphene citrate.

2. Methods

This study was a prospective comparative study where 120 women with PCO and infertility more than 1 year was included and divided into 2 groups: Group A (Clomid induction group) (odd numbers); Clomid was given in the dose of 100 mg/day for 5 days starting from day 3 to day 7. In this group, 130 women were followed and only 60 women were included, and 70 women were excluded because either data loss or failed ovulation. Group B (Letrozole induction group) (even numbers); Letrozole was given in the dose of 5 mg/day for 5 days starting from day 3 to day 7. In this group, 90 women were followed, and 60 women were included, and 30 women were excluded because either data loss or failed ovulation.

The study was conducted after receiving approval from the Benha University Faculty of Medicine's research ethics committee. All involved subjects gave their informed permission.

Inclusion criteria were age group of 18-35 years, The infertility persisted at least one year, PCOS diagnosis based on Rotterdam criteria provided that anovulation is one of the two required criteria, Normal pelvic ultrasound and Normal semen analysis.

Exclusion criteria were BMI > 35 kg/cm2, existence of additional infertility factors, >5 years infertility duration, Known poor response to either drug in previous cycles, history of pelvic surgery, endometriosis, pelvic inflammatory disease.

Study groups:

All patients were randomized into two groups: Group A (CC induction group) (odd numbers); CC were given in the dose of 100 mg/day for 5 days starting from day 3 to day 7. Group B (Letrozole induction group) (even numbers); Letrozole were given in the dose of 5 mg/day for 5 days starting from day 3 to day 7. Each subject received just one treatment cycle.

Both study groups will be subjected to detailed history taking, full clinical examination: Investigations: Routine laboratory investigations and Husband semen analysis.

Ultrasound: A transvaginal ultrasound evaluation will be done at first visit to diagnose PCO. Then induction of menses by progesterone and arrange to do transvaginal ultrasound at day 3 of the cycle in order to rule out pelvic pathology prior to therapy.

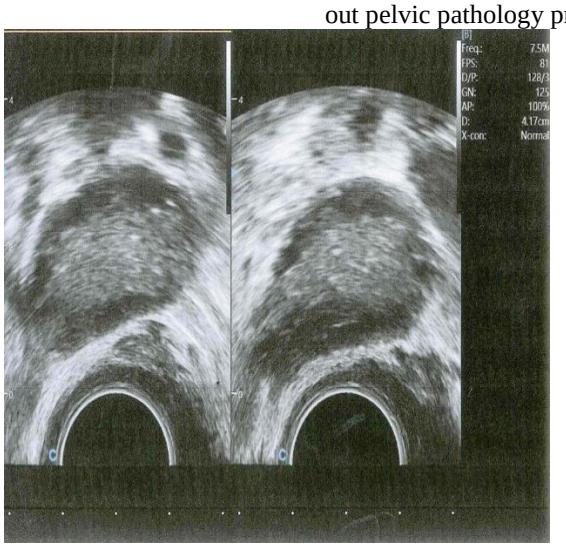

Fig. (1) Transvaginal ultrasound to diagnose PCO

The transvaginal ultrasound is the gold standard for diagnosing polycystic ovaries. Either one (unilateral polycystic ovary) or both ovaries may be affected.

Features include:

Elevated number of follicles per ovary (FNPO): more than or equal to 20 individual follicles are typically of comparable size, measuring 2-9 mm in diameter. Follicles peripheral distribution; This may give background ovarian growth, the appearance of a "string of pearls" (volume greater than 10 ml). Central stromal brightness +/- prominence (increased ovarian stromal area to total ovarian area (S/A) ratio). At day 10, 12, and 14 of the cycle, transvaginal ultrasonography monitoring

of follicular development was undertaken until at least one follicle with a follicular diameter equal to or greater than 18 mm or ovulation.

Seven days following ovulation, the endometrial thickness was measured by ultrasonography. Seven days following ovulation, a comparison of endometrial thickness between the clomid and letrozole groups will be performed.

Sample size:

OpenEpi program was used to calculate the least sample size at 0.05 level of significance and power 0.8, it was 60 in each group. Total sample size was 120. The study included healthy women with PCOS undergoing induction of ovulation.

Statistical analysis:

SPSS v26 was used to do statistical analysis (IBM Inc., Armonk, NY, USA). Using the Shapiro-Wilks test and histograms, the normality of the data distribution was determined. As mean and standard deviation, quantitative parametric data were given (SD). Non-parametric quantitative data are provided as the median and interquartile range (IQR). Using the Chi-square test, qualitative data were expressed as frequency and percentage (%) and examined. A two-tailed P value less than or equal to 0.05 was deemed statistically significant.

3. Results

The mean age was 22.85 years in Group A ranged between 18 to 28 years and mean BMI was 24.75 while Infertility duration was 1.72 years in average. Type of infertility was Primary infertility in 46 (76.7%) of cases in group A. The mean age was 23.28 years in Group B ranged between 19 to 34 years and mean BMI was 24.57 while Infertility duration was 1.93 years in average. Type of infertility was Primary infertility in 45 (75%) of cases in group A. No statistically substantial change was seen among both groups regarding Age, BMI or Infertility duration.

Table (1) Comparison between both groups regarding cases main properties

		Group A	Group B	T	P value
Age		22.85 ± 2.92	23.28 ± 3.29	-0.76	0.45
BMI		24.75 ± 4.27	24.57 ± 4.29	0.24	0.82
Type of infertility	Primary	46 (76.7%)	45 (75%)	0.046	0.831
	Secondary	14 (23.3%)	15 (25%)		
Infertility duration		1.72 ± 0.76	1.93 ± 0.97	-1.36	0.18

Regarding ultrasonic parameters in Group A. Endometrial thickness at day 11 of cycle was 7.00 mm and became 7.49 mm at mature follicle (follicle >18mm). After 7 days of ovulation, Endometrial thickness became 7.81 mm in average.

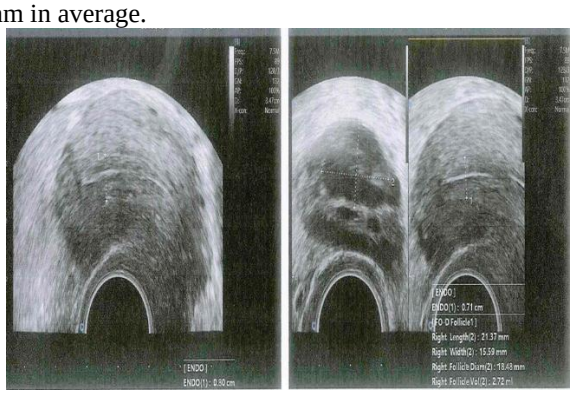

Fig. (2) Transvaginal ultrasound in Group A at induction by clomiphene citrate

Transvaginal ultrasound of endometrium at time of mature follicle after induction by clomiphene citrate 100 mg from day 3 to day 5

Regarding ultrasonic parameters in Group B, Endometrial thickness at day 11 of cycle was 9.82 mm and became 10.22 mm at mature follicle (follicle >18mm). After 7 days of ovulation, Endometrial thickness became 10.65 mm in average.

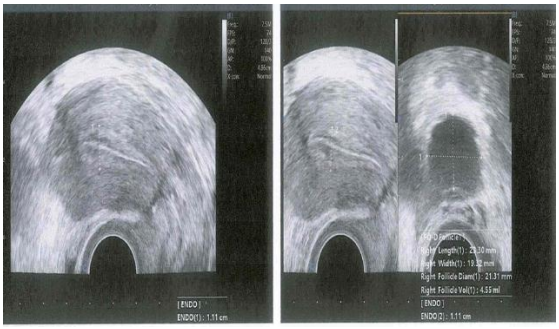

Fig.(3) Transvaginal ultrasound in group B at induction by letrozole

Transvaginal ultrasound of endometrium at time of mature follicle after induction by letrozole 5mg from day 3 to day 5.

A high statistically substantial change was present among both groups concerning Endometrial thickness at 11 days of cycle, at mature follicle (follicle >18mm) and 7 days after ovulation.

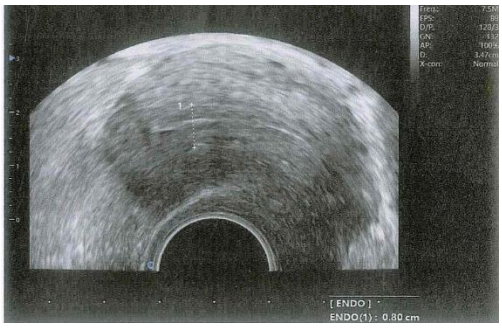

Fig. (4) Transvaginal ultrasound in group A 7 days after ovulation

Transvaginal ultrasound of endometrium 7 days after ovulation in patient induced by clomiphene citrate.

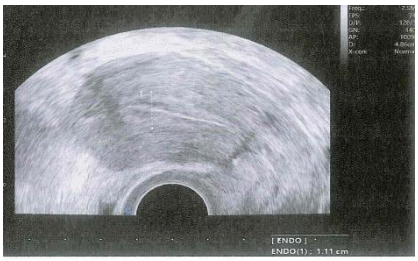

Fig. (5) Transvaginal ultrasound in group B 7 days after ovulation

Transvaginal ultrasound of endometrium 7 days after ovulation in patient induced by litrazol.

Table (2) Comparison between both groups regarding cases main properties

	Group A	Group B	T	P value
Endometrial thickness 11 day of cycle (mm)	7.00 ± 0.21	9.82 ± 0.21	-73.53	<0.0001
Endometrial thickness at mature follicle (follicle>18mm)(mm)	7.49 ± 0.20	10.22 ± 0.20	-73.49	<0.0001
Endometrial thickness 7 days after ovulation (mm)	7.81 ± 0.20	10.65 ± 0.22	-74.33	<0.0001

4. Discussion

PCOS is a prevalent endocrine condition and a common reason for infertility, depressive symptoms, and unhappiness with life. PCOS is expected to afflict 20 to 33% of women of reproductive age, with 50% of PCOS sufferers being obese [6].

In this study, regarding ultrasonographic parameters in Group A. Endometrial thickness at day 11 of cycle was 7.00 mm and became 7.49 mm at mature follicle (follicle >18mm).

After 7 days of ovulation, endometrial thickness became 7.81 mm in average. Regarding ultrasonographic parameters in Group B, Endometrial thickness at day 11 of the cycle was 9.82 mm and became 10.22 mm at mature follicle (follicle >18mm). After 7 days of ovulation, endometrial thickness became 10.65 mm in average. A high statistically substantial change was observed among both groups concerning Endometrial thickness at 11 days of the cycle, at mature follicle (follicle >18mm) and 7 days after ovulation.

This agreed with Choavaratana et al who found that endometrial thickness was significantly decreased after three consecutive stimulation cycles in the CC compared with letrozole group. The decrease remained significant after adjustment for other potential factors [7]. Some randomized studies reported a similar finding in a single cycle treatment. Moreover, according to the study by Sattar et al.; in group A (CC), endometrial thickness was substantially less than in group B (letrozole) [8].

Definition of thin endometrium varies from less than 5 to 8 mm. The recommended follicular phase endometrial thickness, which is positively associated with pregnancy outcome, is 7 mm [9]. Past research found no pregnancy occurred when endometrial thickness was less than 6 mm [10]. In Hock et al study, an equivalent number of participants had endometrial thickness less than 7 mm in the CC and letrozole groups 12 mm [11]. Although endometrial thickness is one of the most important determinants of a successful pregnancy, it may not be the only important factor to consider [7].

Furthermore, the study done by El Kateeb and Mahran, involved 200 PCOS infertile women who were described regarding the Rotterdam criteria and were split into 2 groups CC and letrozole; significantly greater endometrial thickness was seen in the letrozole group 10.1 ± 0.22 mm compared to CC group 8. 2 ± 0.69 mm [12].

The study done by Anwar et al., is based on 150 PCO patient between two groups CC and letrozole showing significantly thinner endometrium in the CC group 6.9 ± 1.2 mm compared with Letrozole group 9.6 ± 1.6 mm [13]. In addition, Zakaria et al. demonstrated a substantially critical change in endometrial thickness among the CC and letrazole groups, with CC producing considerably thinner endometrium than letrazole [14]. Hussain et al., 150 anovulatory patients were split into two2 groups in this research (CC and letrozole) [15]. Number of follicles was greater in the CC group than in the letrozole group, ovulation rate was considerably greater in the letrozole group (78.7%) compared to CC group (53.3%), pregnancy rate was greater in the letrozole group (25.3%) compared to CC group (16%), and mean endometrial thickness was greater in the letrozole group (9.2mm) compared to CC group (8.2mm).

In research by Roy et al., 204 anovulatory women were separated into two groups (CC and letrozole). The results indicated that the number of follicles was greater in CC than letrozole group, the ovulation rate was almost identical in CC group and letrozole group (67.9 percent and 66.6 percent, respectively), the pregnancy rate was substantially greater in letrozole group (43.8% vs. 26.4%), and the mean endometrial thickness was substantially greater in the letrozole group (9.1mm vs. 6.3 mm) [16].

Al-Obaidi et al., revealed that in the letrozole group, the dominant follicle mean size was greater than in the control group. In the letrozole group, this was linked with a much thicker endometrial wall [17]. Khakwani et al., reported that, Women who were administered letrazole had considerably thicker endometriums than those who received placebo (8.1±1.5 mm vs. 6.8±1.9 mm) [18]. According to research from Turkey, letrazole dramatically reduced endometrial thickness compared to CC [2].

The results of Selim et al., research indicate that PCO infertile women experience no substantial differences in the mature ovarian follicles number (diameter > 18mm) and ovulation rate, although there was a considerable rise in conception rates among those who took letrozole compared to those who received CC [19]. In situations of CC resistance or failure with a thin endometrium, this research also suggests a much greater ovulation rate and conception rate with letrozole than with CC treatment. It has been observed that the usage of letrozole leads in a superior endometrial response (9.9 + 1.8 mm) in comparison to the endometrial response gained utilizing CC (7.7 + 1.6mm) in terms of endometrial thickness.

Lan Shi et al., reported that, the endometrial thickness was significantly different among CC and letrazol. In individuals with PCOS, the use of letrozole to promote ovulation had a greater impact on endometrial thickness than CC [20].

Comparing letrozole and clomiphene in 172 women with unexplained infertility, Harira., found that letrozole was considerably more beneficial than clomiphene in reducing endometrial thickness [21]. In contrary, A

comprehensive review and meta-analysis demonstrated no substantial changes among CC and letrozole therapy for unexplained infertility in endometrial thickness [22].

Moreover, the study done by Elshamy et al., involved 103 anovulatory women, who were split into 2 groups CC and letrozole; The average endometrial thickness was almost identical between the two groups. CC 7.6 mm and letrozole 7.65 mm [23].

Comparing the CC and letrozole groups, the mean endometrial thickness was comparable in the study done by Dehbashi [24]. Despite sufficient ovulation, Jang and Jee found that CC resulted in endometrial thickness of 6.5 mm or less [25].

5. Conclusion

Letrozole increase the endometrial thickness and rate of pregnancy more than Clomiphene citrate in the infertile PCOS women induced ovulation. Letrozole may enhance fertility by increasing endometrial receptivity relative to CC.

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