ABSTRACT

To assess the efficacy of letrozole and clomiphene citrate (CC) in infertile women with polycystic ovarian syndrome for ovulation induction (PCOSs).

The study was prospectively registered with private clinical - Iraq. 90 infertile women with PCOS were assigned to receive either letrozole or CC for ovulation induction at progressive doses for a maximum of three cycles in this assessor blind randomized controlled experiment. With letrozole and clomiphene, respectively, means endometrial thickness was 9.87±2.32 mm and 9.38±2.04 mm (p = 0.750). Ovulation rate was 86.73 percent overall with letrozole and clomiphene, respectively, the percentages were 85.80 percent and 84.18 percent (p=0.750). Pregnancy was attained in 41.9 percent of women who took letrozole and 20.50 percent of women who took clomiphene (p=0.04). In the letrozole group, mono-follicular development was observed in 68.45% of ovulatory cycles compared to 44.83 percent in the clomiphene group (p=0.000). Letrozole (9.58 cycles) took considerably less time to obtain pregnant than CC (log rank p =0.0043) (11.057).

Letrozole is a preferable option for inducing ovulation in anovulatory women with PCOS because pregnancy rates are higher, time to conception is shorter, and the risk of multiple pregnancy is reduced due to increased mono-follicular development.

KEYWORDS: Infertility; PCOS; Clomiphene citrate; Letrozole; PCOS; Ovulation induction.

SYNOPSIS: For ovulation induction, letrozole is a better option than CC.

I. INTRODUCTION

Most prevalent cause of anovulatory infertility is polycystic ovarian syndrome (PCOS), which accounts for 70% of anovulation-related infertility cases. Since its debut into clinical practice in the 1960s, (CC) clomiphene citrate has been extensively used for treatment of infertility. Clomiphene citrate is reported to provide a 60–85 percent ovulation rate but only a 20 percent conception rate. Because (CC) clomiphene citrate has a lengthy half-life (2 weeks), it may have an adverse effect on cervical mucus and endometrium, resulting in a disparity in ovulation and conception rates [1].

One year of unprotected intercourse with conception considered infertility. Many cystic ovarian syndrome (PCOS) is the most common cause of anovulatory infertility, accounting for 70-80% of anovulation cases. The best candidates for ovulation induction are infertile anovulatory women. Clomiphene citrate has been around for a long time CC clomiphene citrate has long gold standard for ovulation induction in PCOS patients [2].

Despite a good ovulatory rate of up to 85 percent, pregnancy rates with clomiphene citrate have been poor at 35 percent to 40 percent. The peripheral anti-estrogenic activities and protracted periods of infertility have been attributed for the discrepancy between greater ovulation rates and conception rates.

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Clomiphene citrate CC has a two-week half-life. Endometrial growth is hampered later in the menstrual cycle as a result of this[3].

A molecule capable of promoting ovulation while avoiding the negative antiestrogen effects of CC has been sought. Recent research suggests that Letrozole, aromatase inhibitor, maybe have not the same negative antiestrogenic effects as clomiphene and is linked to higher conception rates in PCOS patients than Clomiphene citrate CC therapy. [4] Though larger trials are still needed, preliminary data suggest that the aromatase inhibitor Letrozole could be used instead of Clomiphene citrate CC for the first-time treatment of anovulatory infertility [6]. The purpose of this prospective randomized experiment was to compare outcomes [7,8,9,10].

II. MATERIALS AND METHODS

Participants & Setting: From March 2019 to October 2020, a trial was conducted among women who presented with anovulatory infertility owing to PCOS at a private clinic in Iraq. Women aged 20 to 37 years old with anovulatory infertility due to PCOS who met Rotterdam's criteria (Ref), which include any two of the following: I ovarian dysfunction (ii) androgenic excess identified by a raised modified ferraryman galley score or elevated serum testosterone then (iii) polycystic ovarian morphology by ultrasound. Polycystic ovarian syndrome threshold

Individual ovarian volume >10 ml and/or 12 follicles of 10 mm were used to define polycystic ovarian morphology. An investigation of the partner's sperm, a premenstrual endometrial biopsy, then a tubal patency exam were among the additional tests performed. Patients who failed any of foregoing tests were ruled out of the study. Those with thyroid issues and high prolactin levels, as well as those who had ovulation induction in the previous six months, were eliminated.

Block randomization was carried out in ten-block increments with a 1:1 allocation of participants in two groups. Random sequences were produced online then stored in the opaque sealed envelopes with sequential numbers. The statistician and the senior consultant who performed the transvaginal ultrasonography (TVS) for outcome evaluation were both blinded to the treatment allocation [11].

Intervention: Subjects at group one were given letrozole to induce ovulation, while those in group two were given Clomiphene Citrate (CC) till birth or for a couple extra pregnancies. After spontaneous or progesterone-induced bleeding. For six days, letrozole was administered at a dose of 2.5 mg once per day (from day 2 to 6) and then increased by 7.5 mg if ovulation does not occur, every time up to a maximum of 150 mg in the next cycle. Clomiphene Citrate (CC) was given at a dose of 50 mg once day for 5 days, then increased by 50 mg per cycle until reaching a maximum of 150 mg if ovulation did not occur. Between days 12 and 18, a consultant performed serial TVS on alternate days using a diagnostic ultrasonic probe with a frequency of 6.5 MHz, picture from the fundus. When the dominant follicle reaches a certain size, >18 mm, Chorionic Gonadotrophin (HCG) is a hormone produced by the human body. (hCG) 4000 IU was administered intramuscularly as an ovulation trigger. Intercourse should be planned between 24 and 36 hours following the hCG injection. TVS 48 hours later verified ovulation with or without day 21 serum progesterone Hormone. [12].

Outcome: The major result of your study was to compare the ET in two groups. Secondary results included ovulation rate, mono-follicular development, analysis of pregnancy rate, and time to pregnancy. The presence of a free fluid in the Douglas pouches and collapsed follicles on TVS were used to identify ovulation, as well as a serum progesterone Harmon value of less than 3 ng/ml on day 21. The presence of urine hCG (human chorionic gonadotropin) is a hormone produced by the human ovary (hCG) and/or the presence of a gestation sac by ultrasonography were used to determine pregnancy[13].

Sample Size Calculation: The sample size was calculated using the difference between the mean ET with CC and letrozole on the day of hCG injection [16]. With 85 percent power then alfa (Type 1 error) set at 0.07, a sample size of 94 (47 in each arm) was aimed should be able to distinguish a 16 percent variation in ET between two groups.

Statistical Analysis: All of the analyses were carried out with the help of the Statistical Package for Social Science (SPSS). The statistical package for social sciences (SPSS) software was used to conduct all of
the analyses (version 21.0). The analysis was conducted with the intent to treat (ITT) and per procedure (PP) in mind, and both analysis’ results were announced. The ITT analysis included all randomized individuals. Regardless matter whether they were successful or not, the trial medication. Only those who completed the study after randomization were included in the per protocol analysis. In the ITT analysis, People who were unable to be contacted due to a lack defeat of follow up were presumed not to have ovulated or conceived. The distribution of continuous data was examined for normality [14].

For regularly distributed data, the Academic test was employed, while for data that is not typically distributed, the Mann Whitney U test was utilized. The chi-square test was performed to examine the differences between two groups for categorical variables at a 0.05 significance threshold on all sides. The Kaplan Meier plot was used to compare the length of time weeks of start of pregnancy after ovulation induction and To establish significance, the log rank test was utilized.

III. RESULTS

Total, 230 patients were approached for enrollment. 94 patients were randomized, and 85 patients finished the research, a total of 215 cycles of ovulation induction were performed in 90 patients, including 95 cycles in the letrozole group and 120 cycles in the CC arm (Figure 1). Both groupings' baseline characteristics were similar. (Table 1)[15].

Outcomes: In the letrozole group, the average endometrial thickness was 9.87±2.33 mm, comparable to 9.38±2.04 mm in the CC group. However, the difference (ITT p=0.760, Per Protocol p= 0.750) was not clinically meaningful. Ovulation occurred in 87.02 percent of letrozole-induced cycles versus 84.18 percent of CC-induced cycles (p= 0.750).

Mono-follicular development was observed in 68.45 percent of Letrozole-induced cycles against 44.83 percent of CC-induced cycles, and a difference was very significant (P.<0.000). Pregnancy rates were 41.9 percent in the letrozole group and 20.50 percent in the clomiphene group, with a statistically significant difference (p =0.04) between the two groups (Table 2). Ovulation, monofollicular development, and pregnancy rates were all analyzed according to procedure, statistical significance was not lost. (Table three) We also looked at the elapsed time since ovulation was induced to conception and discovered that it was considerably narrower with letrozole (log rank P=0.043) than with Clomiphene citrate CC (11.05) weeks (Table NO2)

In the group of letrozole, 68.22% of patients conceived at 2.5 mg, while the rest conceived with higher doses. In CC clomiphene citrate group, 78.7% of individuals conceived after taking 50 mg, while the rest came up with after taking larger drug doses[16].

IV. DISCUSSION

The primary target aim of our research saw if letrozole, as a major trigger of ovulation medication, has greater endometrial growth than CC, which would result in a difference in ET. When comparing patients induced with letrozole (9.87±2.33 mm) to those induced with CC, the letrozole group had a higher mean ET (9.86 ±2.322 m)

9.38 mm x 2.06 mm The change, however, was not statistically important. Similar findings were observed by Xi et al. In four trials, ET was shown showed the letrozole group to be significantly higher than in the CC group. 12; 16, 18; 12; 16; 18; 12; 16; 18; 12; Two investigations, on the other hand, found that CC resulted in significantly increased ET. (4),

V. CONCLUSION

Letrozole treatment of infertile PCOS women more successful in obtaining pregnancy than Clomiphene Citrate (CC) medication, and conception is Letrozole therapy allows you to achieve more sooner. Due to the study’s overall solid and repeatable design, the data provided by this trial is trustworthy and generalizable, despite a few flaws.

DECLARATIONN OF THE PATIENT: CONSENT

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The authors guarantee that they collected every all relevant patient permission forms. By completing the form, the patients has granted their approval for their photographs and other clinical data to be published in the journals. A patients have been advised their identifiers and initials will not be published.

### TABLE 1 PATIENTS’ BASELINE FEATURES

<table>
<thead>
<tr>
<th></th>
<th>Letrozole (n=45)</th>
<th>Clomiphene citrate (n=45)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28.0±3.66</td>
<td>28.0±3.98</td>
<td>0.235</td>
</tr>
<tr>
<td>BMI (kg/m²)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23.90±3.57</td>
<td>23.20±3.65</td>
<td>0.277</td>
</tr>
<tr>
<td>Duration of infertility (years)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.9±2.3</td>
<td>3.5±2.5</td>
<td>0.344</td>
</tr>
<tr>
<td>mFGS</td>
<td>5 (3-5)</td>
<td>3 (1.6-3.5)</td>
<td>0.075</td>
</tr>
<tr>
<td>Primary infertility&lt;sup&gt;c&lt;/sup&gt;</td>
<td>29/45 (64.4)</td>
<td>31/46 (68.8)</td>
<td>0.658</td>
</tr>
<tr>
<td>Secondary infertility Phenotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenotype A</td>
<td>28/45(64.2%)</td>
<td>27 (60.0%)</td>
<td>0.929</td>
</tr>
<tr>
<td>Phenotype B</td>
<td>13/45 (27.6%)</td>
<td>12/45 (28.5%)</td>
<td></td>
</tr>
<tr>
<td>Phenotype C</td>
<td>2/45 (5.4%)</td>
<td>3 (7.4%)</td>
<td></td>
</tr>
<tr>
<td>Phenotype D</td>
<td>2/45 (5.1%)</td>
<td>3 (7.5%)</td>
<td></td>
</tr>
</tbody>
</table>

a. Numerical data in the form of mean and standard deviation  

b. FGS; modified ferriman gallwey score presented as median (Interquartile Range)  

c. Categorical data information in the form of n (percent)  

d. Phenotype A: AE+OD+PCOM, Phenotype B: AE+OD, Phenotype C: AE+PCOM, Phenotype D: OD+PCOM

AE stands for androgen excess, OD stands for ovarian dysfunction, and PCOM is for polycystic ovarian morphology.

### TABLE 2 PER PROTOCOL STUDY OF LETROZOLE VS. CLOMIPHENE CITRATE CC OUTCOMES

<table>
<thead>
<tr>
<th></th>
<th>Letrozole (n=41)</th>
<th>Clomiphene citrate CC (n=39)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET (mm)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.87±2.33</td>
<td>9.38±2.04</td>
<td>0.750</td>
</tr>
<tr>
<td>Number of ovulatory cycles divided by the total number of treatment cycles equals the cumulative Ovulation rate (percent)</td>
<td>82/95 (85.80 %)</td>
<td>94/110 (85.57 %)</td>
<td>0.750</td>
</tr>
<tr>
<td>Monofollicular development</td>
<td>63/83 (68.45 %)</td>
<td>41/94 (43.78 %)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>19/41 (41.9%)</td>
<td>9/39 (20.50%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

AEendometrial thicknesses in millimeters are reported as mean sd deviation.

B. Per ovulatory cycle, monofollicular development occurs.

C. Pregnancy rate for person n(%)


