COMPARATIVE STUDY BETWEEN CLOMIPHENE CITRATE AND LETROZOLE FOR OVULATION INDUCTION IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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Abstract

Purpose: Clomiphene citrate is the most commonly used ovulation induction agent in women with PCOS. During the past decade, fertility specialists tend to use letrozole to facilitate ovulation. This study was designed to compare the efficacy of letrozole with clomiphene citrate in infertile women with PCOS.

Methods: A prospective clinical trial have been applied on infertile women with PCOS after randomizing them into two groups: 87 women received clomiphene citrate and 79 women received letrozole. Ovulatory cycles have been monitored, ovarian follicles size and the endometrium lining thickness have been measured.

Results: Clomiphene citrate showed significantly greater improvement in endometrial thickness (p<0.05). Pregnancy and mono-ovulation rates (62% and 29%), as well as number of stimulated cycles (91%) were significantly higher in letrozole treated women. Number of multiple pregnancies with clomiphene citrate was significantly higher (30%, p<0.05). Furthermore, mean number of follicles after treatment with clomiphene citrate was significantly higher (p<0.0001).

Conclusion: Letrozole is preferable to clomiphene citrate regarding higher pregnancy rate as well as monofollicles that will decrease the risk of multiple pregnancies which is clearly observed with clomiphene citrate. A higher success of letrozole over clomiphene citrate thought to be related to the greater ovulation rate per cycle.

Keywords: PCOS, Clomiphene Citrate, Letrozole, Pregnancy Rate
INTRODUCTION

Polycystic ovary syndrome (PCOS), the commonest cause of anovulation in women, manifested by oligo- or anovulation [1,2] and hormonal abnormalities resulted from defects in the hypothalamic-pituitary axis that cause an elevation in luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH) levels while follicular-stimulating hormone (FSH) level may remain unchanged [3,4].

There are different guidelines for diagnosis of PCOS. The Rotterdam consensus is globally reliable across Europe, Asia and Australia. The Rotterdam Criteria require the presence of two of the followings: oligo/anovulation, hyperandrogenism or polycystic ovaries on ultrasound [5]. Excluding malignancies [6-13], PCOS is considered one of the major concerns of researchers to deal with.

Clomiphene citrate, act as estrogen receptor modulator, considered as the drug of choice for anovulatory infertility. During the early follicular phase, Clomiphene citrate will reverse the negative feedback mechanism through competing with estrogen for its receptors in the hypothalamus and pituitary glands. Thus, endogenous gonadotropin level increase and the dominant follicle is induced [14].

Letrozole, a specific aromatase inhibitor, acts by inhibiting estrogen synthesis via competitive reversible binding to the heme of its cytochrome P450 unit [15]. Efficacy of letrozole has been proven in ovulation inducing in women with anovulatory infertility and in women inadequately respond to clomiphene citrate [16].

The aim of this study was to compare the efficacy of Letrozole with clomiphene citrate in a group of women with PCOS and anovulatory infertility.

MATERIALS AND METHODS

This randomized clinical trial was performed from in the Um El Benin Center for Infertility Treatment and IVF / Medical City of Imam Al – Kadhimin/ Baghdad/ Iraq. After approval from the scientific committee in the center and...
take the consent of patients wishing to participate in the study, we enrolled (179) women in the reproductive age (18-39 years) who were unable to achieve pregnancy for at least 1 year and they were diagnosed with PCOS according to Rotterdam consensus meeting (2003), by achieving at least 2 out of 3 of Rotterdam criteria[5]. After taking clinical history and hysterosalpingography testing for patent fallopian tubes, as well as transvaginal ultrasonography to evaluate pelvic anatomy, women were randomized into two groups: **Group 1** include 94 women were given clomiphene citrate 50 mg tablet (Clomid®, Sanofi) twice daily from day 2 of the menstrual cycle for 5 days. **Group 2** include 85 women were given Letrozole 5 mg tablet (Femara®, Novartis) once daily from day 2 of the menstrual cycle for 5 days. Thirteen women (7 on clomiphene citrate and 6 on Letrozole) were lost in follow-up and the remaining 166 participants (clomiphene citrate, n = 87; Letrozole, n = 79) who passed the follow up successfully were analyzed. Figure 1 shows the flowchart of participants through the trial. Ovulatory cycles have been monitored by ultrasound examination to schedule other procedures. Transvaginal ultrasound examination was used to measure ovarian follicles size and the endometrium lining thickness.

**Statistical analysis**

Statistical analysis was performed using Microsoft Excel 2007. Data are expressed as means ± standard deviation (SD) and as number and percentage. Paired Student’s t test used to compare means while chi-square test used to compare percentage between the groups. A p-value of <0.05 was considered statistically significant.

**RESULTS**

Table 1 shown that women enrolled in both groups were statistically non-significantly different in term of age, duration and types of infertility and endometrial thickness at baseline (p>0.05).

As shown in table 2, both letrozole and clomiphene citrate showed significant improvement in endometrial thickness (6.71 ± 1.69 vs. 7.66 ± 1.41, p<0.001 for letrozole) and (6.67 ± 1.86 vs. 8.08 ± 1.28, p<0.0001 for clomiphene citrate). However clomiphene citrate showed significantly greater improvement in endometrial thickness than letrozole (8.08 ± 1.28 vs. 7.66 ± 1.41, p<0.05).

<table>
<thead>
<tr>
<th>Table 1: Characteristics of the patients at baseline</th>
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<td>Characteristics</td>
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The clinical pregnancy rate was significantly higher in letrozole treated group compared to clomiphene citrate treated group (62% vs. 38% respectively, p<0.01). As well as mono-ovulation showed significantly higher rates in letrozole group compared with clomiphene citrate (29% vs. 5.75% respectively, p=0.0001).

Number of stimulated cycles (Resulted in follicles ≥ 16mm) was significantly higher in letrozole treated women than in clomiphene citrate treated women (91% vs. 78% respectively, p<0.05).

Number of multiple pregnancies in clomiphene citrate group was significantly higher than letrozole group (10 cases, 30% vs. 6 cases, 12% respectively, p<0.05).

Ten patients (20%) on letrozole treatment and six patients (18%) on clomiphene citrate treatment experienced miscarriage; there was no significant difference between two groups (p>0.05). Furthermore, the mean number of follicles after treatment with clomiphene citrate was significantly higher compared to letrozole (3.07 ± 1.23 vs. 1.97 ± 0.83 respectively, <0.0001).

There was no significant difference between clomiphene citrate and letrozole immature follicles size after treatment (18.82 ± 3.91 vs. 19.71 ± 3.103 respectively, p>0.05). As well as the live birth rate between the two groups was statistically non-significant difference (p>0.05).

**Table 2. Comparison the outcome of Clomiphene citrate and Letrozole**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Clomiphene (n=87)</th>
<th>Letrozole (n=79)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of stimulated cycles (Resulted in follicles ≥ 16mm), no (%)</td>
<td>68 (78%)</td>
<td>72 (91%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Endometrial thickness after treatment (mm), mean ± SD</td>
<td>8.08 ± 1.28 **</td>
<td>7.66 ± 1.41 *</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Number of mature follicles after treatment, mean ± SD</td>
<td>3.07 ± 1.23</td>
<td>1.97 ± 0.83</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mature follicles size after treatment, mean ± SD</td>
<td>18.82 ± 3.91</td>
<td>19.71 ± 3.103</td>
<td>NS</td>
</tr>
</tbody>
</table>
Mono-ovulation rate (per ovulatory cycles), no(%) | 5 (5.75%) | 23 (29%) | 0.0001
---|---|---|---
Pregnancy rate, no (%) | 33 (38%) | 49 (62%) | <0.01
Live birth rate, no (%) | 27 (81%) | 39 (80%) | NS
Rate of Miscarriage (in recent pregnancy), no (%) | 6 (18%) | 10 (20%) | NS
Number of multiple pregnancy, no (%) | 10 (30%) | 6 (12%) | <0.05

NS: Non-significant difference.
*: significant difference before and after treatment, P < 0.001
**: significant difference before and after treatment, P < 0.0001

DISCUSSION

In many fertility guidelines, clomiphene citrate is recommended as the first-line treatment for women with anovulation or PCOS [17-21]. However, other guidelines recommend both clomiphene citrate and letrozole as first-line treatments [22-24]. Recent studies found that letrozole be superior on clomiphene citrate in many respects [25-27].

Previous studies showed that percentage of stimulated cycles responded to letrozole was higher than those responded to clomiphene citrate. While, mean number of mature follicles (≥ 18 mm) developed in clomiphene citrate treated group was high compared with letrozole treated group, these results are compatible with the present study [28-31]. Nevertheless, as others found, the dominant follicle size produced was comparable in both groups (>18 mm)[31-33].

Less number of mature follicles in letrozole group supports the high mono-ovulation rate recorded in our study (29%), which is consistent with previous studies who were found that the mono-follicular cycles were greater in letrozole compared to clomiphene citrate treated women [33-37].

In the ovary, aromatase inhibitors increase androgens production thus increases follicular sensitivity to FSH. As estrogen level increases and the dominant follicle grows, repression of FSH secretion as a result of centrally negative feedback occurs, resulting in shrinkage of the smaller follicles. Thus resulting in single dominant follicle and mono-ovulation [36,37]. Polyzos et al. in his study elucidates that according to the hypoestrogenic state produced by letrozole not last late in the follicular phase of the menstrual cycle due to its short half-life, resulting a higher probability of mono-follicular occurrence [38]. Meanwhile, Robert et al. stated that aromatase inhibition does not antagonize estrogen receptors in the brain, and the initiation of follicle growth accompanied by increasing
concentrations of both estradiol and inhibin results in a normal negative feedback loop that limits FSH response, thereby avoiding the risk of high multiple ovulation and ovarian hyper stimulation syndrome[39].

However, this limitation in the number of mature follicles in letrozole group contribute to reduce the risk of multiple pregnancy. Amigos study demonstrated that the use of letrozole for ovarian stimulation can reduce the rates of multiples from that observed with clomiphene citrate treatment[40]. That is in consistent with present study, low rate of multiple pregnancy (12%) was observed in women treated with letrozole versus (30%) in women treated with clomiphene citrate, this is may be associated with risk for development of ovarian hyperstimulation syndrome as a response to ovulation induction by clomiphene citrate that reported by Pourali et al. and others[41-43]. Casper in his work demonstrated that mono-ovulation is the major advantage of aromatase inhibitors for ovulation induction in women with PCOS[44], whereas multiple pregnancy may increase the incidence of maternal and neonatal complications that has been well documented by previous studies[45,46].

Regarding endometrial thickness there’s conflicting findings, present study agrees with Suhaila et al. and Amer et al. studies which recoded an improvement in mid-cycle endometrial thickness after treatment with both letrozole and clomiphene citrate although the latter was superior in such increment [28,47]. On the contrary others found that greater endometrial thickness in letrozole group in comparison to clomiphene citrate group[29,35,48-51], while Kar et al. and Shahrzad et al. showed that there was no significant difference in terms of endometrial thickness between the two groups [52,53]. The superiority of clomiphene citrate on letrozole concerning endometrial thickness may return to the high level of estrogen released with each follicle produced which is actively correlated with the development and growth of endometrium as demonstrated by Badawy et al. [31]. Although some studies demonstrated that endometrial thickness measurement is a predictor of endometrial capability for follicle implantation [54,55], others don’t support this view, many studies observed no relationship between the endometrial thickness, morphology and pregnancy outcomes and even thin endometrium does not necessarily affect the possibility of implantation, which can support our findings [56-58].

Pregnancy rate recorded in our study was higher in letrozole group (62%) compared to clomiphene citrate group (38%), this agrees with Pourali et al. Amer et al. and Legro et al. studies [41,47,59]. Legro et al. believed that the
higher pregnancy rate with letrozole could be partly due to lower estradiol level and higher progesterone levelin
mid-luteal phase which may be related to sustained aromatase inhibition into the luteal phase [59,60].

Live birth rate as well as miscarriage rate recorded in the present study were comparable in both groups as reported
by others [41,47,61].

CONCLUSION

Present study agrees with those found letrozole superior on clomiphene citrate. Letrozole is preferable regarding
pregnancy rate and monofollicles production that will decrease the risk of multiple pregnancy and its consequences.

We believe no relationship between the endometrial thickness, and pregnancy outcomes. A higher success of
letrozole over clomiphene citrate thought to be related to the greater ovulation rate per cycle.

DECLARATIONS

Acknowledgement

Authors would like to thank Mustansiriya University (www.uomustansiriyah.edu.iq), Baghdad - Iraq for its support
in the present work and special thanks to Imam Al – Kadhimin Medical City for their help in providing the practical
platform of this study.

Conflicting Interest

The authors declare no conflict of interest.

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platform of this study.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims
relating to the content of this article will be borne by the authors.

Hadeel Delman Najim was responsible for statistical work and tabulating, Zahraa Abdulghani Albasry was
responsible for writing, Wrood Salim Alkhafajy was responsible for patients’ data collection.

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