Comparison of Letrazole and Clomiphene Citrate in Women with Polycystic Ovaries Undergoing Ovarian Stimulation

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Abstract

Objective: To evaluate the efficacy of letrozole in induction of ovulation in comparison to clomiphene citrate in patients with polycystic ovary syndrome and primary infertility patients.

Methodology: Seventy five women with polycystic ovarian syndrome and primary infertility at Basrah Maternity and Child Hospital, Infertility Center were randomized divided into 2 groups, the first group of 40 patients who received (100 -200 mg) clomiphene citrate daily and second group of 35 patients who received letrazole ( 2.5 -5 mg )daily. Both groups were followed by ultrasound until the dominant follicle reached a diameter > 18 mm, HCG 10.000 U/L was given and timed intercourse was advised.

Results: In comprising between the effect of both drugs on two groups it was observed that the number of mature follicles was significantly lower, but the endometrial thickness and ovulation were significantly higher in letrazole receiving group than in cc receiving group. No significantly difference in pregnancy rate between the two groups.

Conclusion: Letrazole may have a role as a first line treatment for unovulatory patients with polycystic ovary syndrome.
Introduction

Infertility is a unique medical condition, in that it is a disorder that often involves a couple, not an individual. An infertile couple is one that has been unable to conceive in one year of unprotected intercourse. It is subdivided to primary and secondary. Primary infertility applies to those who have never conceived, while secondary infertility designated to those who have conceive at some time in the past.

Polycystic ovary syndrome (PCOS) (Fig 1) is a common endocrine pathology in women in reproductive age. It is a heterogeneous disorder of unknown etiology affecting 5-10% of women between late adolescence and early menopause. It involves a group of women with obesity, excess hair growth and ovaries with multiple cysts. It is a disorder that affects the reproductive, endocrine and metabolic systems and it is the most common cause of an ovulatory infertility. It has eluded definitive description because of varied combination of clinical, biochemical and ultrasonographic features which may occur. The commonest association is of hyperandrogenism and chronic an ovulation; recognition of characteristic ovarian ultrasound features together with clinical symptoms of oligomenorrhea, hyperandrogenism, infertility or obesity is presently the preferred to diagnosis.
Figure 1. Ultrasonographic Picture of PCOS

Well recognized clinical presentation included menstrual cycle disturbances (oligo/amenorrhoea), obesity and hyperandrogenism manifesting as hirsutism, acne or androgen-dependent alopecia, however, as clinical features were noted to vary considerably between women, and indeed some women with polycystic ovaries do not appear to display any of the common symptoms. (5,8)

PCOS is characterized by ovulatory dysfunction. Menstrual Periods do not necessarily have to be absent. Many women with PCOS continue to ovulate, but do so either irregularly or with compromised progesterone production. Many women with PCOS are not obese, and many women with PCOS do not have excess hair growth, but to some extent virtually all women with PCOS have some degree of insulin resistance. Insulin resistance. The aim of the study is to compare between the use of letrazole and clomiphene citrate in women with polycystic ovaries undergoing ovarian
stimulation and to evaluate the pregnancy rate between the 2 groups.

**Patients and Methods**

This prospective clinical trial conducted in infertility center in Basrah Maternity and Child Hospital between Jan 2012 - Apr 2013.

Seventy five infertile women were selected from the women who were attending the infertility center with primary infertility (which defined as inability of a couples to obtain pregnancy after 1-2 years of unprotected intercourse).

All patients were diagnosed as having un- ovulation due to polycystic ovaries (PCOS).

PCOS were diagnosed when the USG findings of the ovaries were more than 10 follicles 2-8 mm in diameter scattered either around or through an echo-dense thickened central stroma were present plus one or more of the followings: oligomenorrhea, positive progesterone, withdrawal bleeding, hirsutism/acne, obesity, and raised LH/FSH ratio more than two or raised circulating androgen, normal thyroid stimulating hormone.

All Patients have documented patent tubes by either hysterosalpingiogram or laparoscopy, history of pelvic surgery with tubal blockage was excluded from the study, the male partners had to have a normal seminal analysis by WHO criteria

Inclusion criteria include age between 18-36 years, period of infertility is more than 2 years, serum prolactin level was normal, serum FSH < 12
u/L, normal thyroid function, and hirsutism was diagnosed when the Ferriman and Gallwey score > 8.\(^9\)

The patients were examined clinically, their weight, height, waist circumference, body mass index were estimated, transvaginal U/S examination was performed to exclude any pelvic pathology before treatment.

The patients were randomized divided into two groups. The first group which was 40 had received clomiphene citrate (cc) for six months with a dose between 100-200 mg for five days beginning on day three of menstrual cycle. The second group which was 35 were received aromatase inhibitor (letrazole) 2.5-5 mg daily for 5 days starting from the third day of a spontaneous or progesterone induced menstrual bleeding.

Follicular development was monitored using transvaginal U/S from day 10 onward. When at least one mature follicle (with a mean diameter > 18 mm) was observed, 10.000 IU of HCG were given subcutaneously to trigger ovulation, the second transvaginal U/S was done after 48 hrs of injection of (HCG) to observe the release of ova. Ovulation was ascertained by observing the rupture of follicle by transvaginal U/S and day 21 serum progesterone.

A progesterone level > 10 mg/ml was considered as ovulatory. The main outcome measure was rate of ovulation and detection of pregnancy by BHCG level obtained 2 weeks after timed intercourse and U/S was performed 2-4 weeks after missed period by the presence of cardiac activity.
The work has approved by the ethical committee at the College of Medicine, University of Basrah, Iraq. T-test was carried out. P value <0.5 was considered significant.

Result

A total 75 women with polycystic ovary syndrome were enrolled into the study, of these 40 patients received clomiphene and 35 patients received letrozole.

The demographic characteristics and endocrine status of the two studied groups were shown in Table (1). There were no statistically significant difference between the two groups.

Table 1. Demographic characteristic of patients with primary infertility in both groups receive clomiphene and letrozole for ovulation induction.

<table>
<thead>
<tr>
<th></th>
<th>Clomiphene Citrate N:40</th>
<th>Letrozole N:35</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.3 ± 2.1</td>
<td>26.1 ± 1.3</td>
<td>N.S</td>
</tr>
<tr>
<td>Mean infertility period</td>
<td>2.3 ± 0.4</td>
<td>2.4 ± 0.6</td>
<td>N.S</td>
</tr>
<tr>
<td>Body mass index (Kg/m²)</td>
<td>27.8 ± 1.7</td>
<td>28.1 ± 1.91</td>
<td>N.S</td>
</tr>
<tr>
<td>Basal hormonal on day 3 of cycle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>6.82 ± 1.22</td>
<td>7.23 ± 2.1</td>
<td>N.S</td>
</tr>
<tr>
<td>LH</td>
<td>6.39 ± 2.12</td>
<td>5.92 ± 3.1</td>
<td>N.S</td>
</tr>
<tr>
<td>E2</td>
<td>62.25 ± 18.1</td>
<td>63.42 ± 1.5</td>
<td>N.S</td>
</tr>
<tr>
<td>TSH</td>
<td>2.85 ± 1.35</td>
<td>3.1 ± 2.1</td>
<td>N.S</td>
</tr>
<tr>
<td>Prolactin</td>
<td>24.86 ± 8.37</td>
<td>25.38 ± 7.1</td>
<td>N.S</td>
</tr>
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</table>
Table (2) showed the response of the women in the two groups to ovarian stimulation. The number of mature follicles was significantly lower in women who received letrozole. But the endometrial thickness and ovulation were significantly higher in letrozole receiving group.

Pregnancy rate is of no significant difference between the two groups. The day on which HCG given did not differ between the two groups. One twin pregnancy occurred in the cc receiving group.

Table 2. Response to ovarian stimulation in patients with clomiphene versus letrazole therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clomiphene No. 40 Mean ± SD</th>
<th>Letrazole No. 35 Mean ± SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular development by day 14 (mm)</td>
<td>22.3 ± 1.0</td>
<td>21.5 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>No. of follicles &gt; 18 mm on day of HCG administration</td>
<td>2.4 ± 1.1</td>
<td>1.3 ± 0.31</td>
<td>0.0001</td>
</tr>
<tr>
<td>Serum E2 on day of HCG (PG/ml)</td>
<td>415 ± 1.3</td>
<td>325 ± 1.25</td>
<td>N.S</td>
</tr>
<tr>
<td>Endometrial thickness (mm) at 14 day</td>
<td>52 ± 1.2</td>
<td>84 ± 1.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Day of HCG administration</td>
<td>12.9 ± 1.6</td>
<td>12.8 ± 1.8</td>
<td>N.S</td>
</tr>
<tr>
<td>Ovulation</td>
<td>25 (62.5%)</td>
<td>29</td>
<td>0.01</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>7</td>
<td>10</td>
<td>N.S</td>
</tr>
</tbody>
</table>
Discussion

Fertility and child bearing is a complex process and ovulation is the first step to be identified for the conquest of infertility. Ovulation is the result of well-synchronized balance between the central nervous system-hypothalamus-pituitary axes and ovary.

Clomiphene citrate which is the most commonly prescribed medication initiates ovulation by blocking the negative feedback on endogenous estrogen at the level of hypothalamus-pituitary promoting on increase in the pulsatile release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in an ovulatory POCS patients. (10)

For many years the first treatment of choice for ovulation induction in POCS was clomiphene citrate, (11) but up to 58% of such patients are resistant to it and do not ovulate. (12) The pregnancy rate per cycle remain relatively low. (12) It has also been demonstrated that clomiphene citrate has an antagonistic effect on the endometrium and may reduce endometrial thickness. (13) Clomiphene citrate may block estrogen receptors in the cervix, producing a negative effect on the quality and quantity of cervical mucus. (14) Therefore there is a discrepancy between the ovulation and conception rates associated with clomiphene citrate use. (15)

Although not all patients behave in a similar manner, 50% of women on clomiphene citrate develop a thin endometrium < 8 mm with a tendency toward a non-trileminar pattern at mid-cycle, by additional supplemental estrogen the phenomena cannot be
improved, suggesting that it is a result of estrogen receptor depletion.\(^{(15)}\)

Inappropriate development of endometrium is associated with a low implantation rate and early pregnancy loss caused by luteal phase defect.\(^{(14)}\)

Some patients (20% - 28%) do not respond to clomiphene citrate in spite of high dose, as the anti estrogenic effect is dose dependent, a daily dose of clomiphene citrate > 150 mg not recommended.\(^{(15)}\)

To produce a good ovulation after clomiphene citrate regimen is induction with gonadotropins, which increase both the cost and risk associated with treatment.\(^{(16)}\)

Letrazole an aromatase inhibitor has the same role as clomiphene citrate in initiating gonadotropin release by withdrawing negative feedback to the pituitary by reducing the blood estrogen level by blocking the conversion of androgen to estrogen. So the initial release of FSH may be more than with clomiphene citrate.\(^{(17)}\)

Multiple developing follicles appear on day 7 but because letrazo ledose not deplete oestrogen receptors unlike clomiphene citrate,\(^{(18)}\) normal negative feedback occur centrally as the dominant follicle grows and oestrogen levels increase.\(^{(17)}\)

This result in FSH suppression and atresia of smaller follicles, and mid cycle mono-ovulation occurs in most patients.\(^{(17)}\) Single follicle is the major advantage of using aromatase inhibitors for ovulation induction particularly desirable in patients with PCOS who are often hyper-responsive to gonadotropins.\(^{(19)}\)

Sammour et al.\(^{(20)}\) found in their double-blind randomized trial comparing the use of an aromatase inhibitor with clomiphene
citrate for stimulation in 49 women with infertility that increased endometrial thickness compared with those receiving clomiphene citrate because 3 folds increased in the pregnancy rate was observed in patients who received aromatase inhibitor in comparing with clomiphene citrate treatment (16.7%) versus (5.6%) respectively.

In women in PCOS who did not have an adequate response to clomiphene citrate, ovulation occurred in 75% of the letrazole treatment cycles and clinical pregnancy was achieved in 17% of the cycles.\(^{(12)}\)

In the present study the day of HCG administration did not differ in those treated with clomiphene citrate compared with letrazole. Although the ovulation and number of is significantly lower in letrazole group in comparing with clomiphene citrate group, but the rate of clinical pregnancy was significantly lower in letrazole group in comparing with clomiphene citrate group; But the number of patients studied was small, so the result of this study suggest that letrazole may have a role as a first-line treatment for an ovulatory patients.

In conclusion, letrazole may have role as first line in certain group of patient with infertility. Letrazole had short duration of administration, non invasive, less costly in regard to parental drugs of ovulation. Need further studies to evaluate the side effects and the outcome of the drug on the pregnancy in future.
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