A randomized trial of letrozole versus clomiphene citrate in induction of ovulation in patients with polycystic ovary syndrome (PCOS)

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ABSTRACT

Objective: The aim of this study was to compare the effect of letrozole (2.5mg) and clomiphene citrate (150mg) on ovulation in patients with polycystic ovary syndrome.

Design: Prospective randomized trial.

Setting: University teaching hospital.

Materials and Methods: Sixty four consecutive patients with polycystic ovary syndrome were recruited. Thirty four patients (70 cycles) were given clomiphene citrate and thirty patients (64 cycles) were given letrozole. Both drugs were given orally on days 3-7 of menses. Letrazole, clomiphene citrate, ovulation induction, timed intercourse.

Main outcome measures: Number of follicles, endometrial thickness and pregnancy rates.

Results: The mean age, body mass index, and duration of infertility in both groups were similar. Ovulation occurred in 78% of the cycles (50 /64) in letrazole treated group and 73% of the cycles (51/70) in clomiphene citrate treaded group. The endometrial thickness was significantly higher in letrazole group, the number of mature follicles was significantly lower in the letrazole group. Pregnancy rate per cycle was 16% in the letrazole group and 13% in the clomiphene citrate group.

Conclusion: Aromatase inhibitor letrozole is as effective as clomiphene citrate in induction of ovulation in patients with polycystic ovarian syndrome, and may have a role as first line treatment for anovulatory patients with polycystic ovary syndrome.

Key words: letrozole, clomiphene citrate, polycystic ovary, ovulation, conception

Polycystic ovary syndrome is an extremely common disorder affecting 4% to 12% of women of reproductive age (1). For more than 4 decades, clomiphene citrate has been the main drug used in treatment of patients with polycystic ovary syndrome (2). Although clomiphene citrate is easy to use and results in ovulation in most patients with polycystic ovary syndrome, but pregnancy rates were disappointing. This has been attributed to its peripheral antiestrogenic effect on endometrium and cervical mucous (3). Recently, Mitwally and Casper published some data showing the success of the aromatase inhibitor (letrazole) in anovulatory women resistant to clomiphene citrate, women with unexplained infertility, and in addition with FSH to improve the ovarian response in poor responders (4, 5). The aim of this prospective randomized study is to determine whether letrozole can be used as an alternative to clomiphene citrate in induction of ovulation in patients with polycystic ovary syndrome.
Table 1. Characteristics of patients undergoing ovulation with letrozole and with clomiphene citrate

<table>
<thead>
<tr>
<th></th>
<th>Clomiphene citrate (70 cycles)</th>
<th>Letrozole (64 cycles)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.41±3.7</td>
<td>26.33±3.72</td>
<td>0.250</td>
</tr>
<tr>
<td>Mean infertility period (years)</td>
<td>3.12±1.66</td>
<td>2.87±1.8</td>
<td>0.565</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>32.16±4.18</td>
<td>31.26±4.2</td>
<td>0.394</td>
</tr>
</tbody>
</table>

Variables are given as mean ±SD
NS= not significant

MATERIAL AND METHODS

This prospective randomized trial was performed in Cairo university hospitals, Cairo, Egypt. Sixty four patients with polycystic ovary syndrome according to the Rotterdam revised criteria for polycystic ovary syndrome were included in the study (6), all patients had a history of oligomenorrhea or amenorrhea and ovaries with at least 12 subcapsular cysts 2-9mm in diameter and increased ovarian volume (>10 ml). Our inclusion criteria were age (18-37) years, period of infertility > 1 year, day 3 serum level of FSH < 12 IU/L, and serum prolactin level within normal limits in early follicular phase. Exclusion criteria were history of pelvic surgery or infertility factors other than anovulation.

The study protocol was approved by the hospital research ethics board. Study participants were counseled, and informed consent was taken before randomization. Patients were randomized to clomiphene citrate (n = 34) or letrozole (n = 30), a quasi-randomization method was used. Based on the attendance order, patients with odd numbers were prescribed letrozole and those with even numbers were given clomiphene citrate. Neither the patients nor the doctors were blinded in any of the groups. Letrozole (Femara; Novertis pharma AG, Basle, Switzerland) and Clomiphene citrate (Clomid; Aventis pharma S.AE, Global Napi pharmaceuticals, Cairo, Egypt) were given orally in doses of 2.5mg/day and 150mg/day respectively for five days beginning on day 3 of menstrual cycle. Transvaginal ultrasound (siemens, sonoline, prima) was performed on day 3 of the menstrual cycle before starting treatment, follicular development was monitored using transvaginal ultrasound from day 10 of the cycle.

Human chorionic gonadotropin (Pregnyl ;N.V. Organon, Oss, Holland) at dose of 10.000 IU was used to trigger ovulation when at least one follicle exceeding 18mm was noted. Endometrial thickness was assessed according to the method described by Goren and Casper (7), the endometrial thickness was measured at the greatest diameter perpendicular to the midsagittal plane in the fundal region, including both layers of the endometrial cavity, the image was oriented so that the endometrial canal and the cervical canal were visualized in the same plane to ensure measurement through the center of the endometrium. Pregnancy was diagnosed by β-subunit HCG performed 2 weeks from timed intercourse, and ultrasound was performed 2 - 4 weeks after a positive pregnancy test to confirm clinical pregnancy.

Statistical methods

Data were statistically described in terms of mean ± standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi square ($\chi^2$) test was performed. Yates correction was used in stead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago,
Table 2. Induction of ovulation with letrozole and clomiphene citrate

<table>
<thead>
<tr>
<th></th>
<th>Clomiphene citrate (70 cycles)</th>
<th>Letrozole (64 cycles)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of HCG administration</td>
<td>12.73±0.93</td>
<td>13.06±0.89</td>
<td>0.072</td>
</tr>
<tr>
<td>Endometrial thickness(mm)</td>
<td>6.43±1.85</td>
<td>9.44±1.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ovulation rate per cycle</td>
<td>(51/70)(72.85%)</td>
<td>(50/64)(78.12%)</td>
<td>0.613</td>
</tr>
<tr>
<td>Number of follicles more than 18mm on the day of HCG administration</td>
<td>2.49±1.21</td>
<td>1.3±0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pregnancy rate per cycle</td>
<td>(9/70)(12.85%)</td>
<td>(10/64)(15.62%)</td>
<td>0.833</td>
</tr>
</tbody>
</table>

Pregnancy rate per cycle and ovulation rate are expressed as N (%), all other values are given as mean ±SD
HCG : human chorionic gonadotrophin

RESULTS

The mean age, body mass index, and duration of infertility in both groups were similar (Table 1). The duration to reach dominant was 13.06±0.89 days in the letrozole group and 12.73±0.93 days in the clomiphene citrate group. Ovulation occurred in 78.12% of the cycles (50 /64) in letrozole treated group and 72.85% of the cycles (51/70) in clomiphene citrate treated group. The endometrial thickness was significantly higher in letrozole group. In the clomiphene citrate group the endometrial thickness on the day of HCG administration was more than 5 mm in 60 cycles and less than 5mm in 10 cycles, pregnancy did not occur in any of these ten cycles, the endometrial thickness was more than 5 mm in all cycles with letrozole. The number of mature follicles was significantly lower in the letrozole group. Pregnancy rate per cycle was 15.62% in the letrozole group and 12.85 % in the clomiphene citrate group (Table 2). One case of twin pregnancy occurred in clomiphene citrate group. One case of abortion occurred in each group, ectopic pregnancy did not occur in any group.

DISCUSSION

Clomiphene citrate is the most commonly prescribed medication for ovulation induction in patients with polycystic ovary syndrome (2). Clomiphene citrate initiates or augments ovulation by binding to estrogen receptors throughout the body due to structural similarity to estrogen, clomiphene citrate binding to estrogen receptors occurs for prolonged periods i.e. weeks rather than hours as with natural estrogen. This extended binding ultimately depletes estrogen receptors concentrations by interfering with the normal process estrogen receptors replenishment (8). Depletion of hypothalamic receptors prevent correct interpretation of circulating estrogen levels, estrogen concentration was falsely perceived as low leading to reduced estrogen negative feedback on GnRH production and subsequent increased gonadotropin (FSH and LH). The rise of FSH promotes the growth of ovarian follicles and ovulation in anovulatory women (9). Ovulation is restored in 70 % – 80 % but will lead to pregnancy in only about 30 % - 40 % (10). Peripheral antiestrogenic effect of clomiphene citrate on the endometrium and cervix are frequently suggested as the possible explanation of such discrepancy, in addition the accumulation of the isomers of clomiphene citrate (zu-clomiphene) in the body due to its long half life (several days to weeks) add to persistence of this antiestrogenic effect (11). While depression of cervical mucous, occur in about 15% of patients, may be overcome by intrauterine insemination, suppression of the endometrial proliferation, unrelated to dose or duration of treatment but apparently idiopathic (12). Prolonged endometrial estrogen receptor depletion results in significant thinning of the endometrium. Compared with natural cycles, this endometrial thinning has been observed in 15% to 50% on clomiphene citrate (13). Gonen and Casper reported no pregnancies occurring in cycles with
endometrial thickness < 6mm at midcycle and a significantly higher rate of biochemical pregnancy when the endometrial thickness was 6-8 mm (7).

Letrozole is a third generation non steroidal aromatase inhibitor licensed for treatment of breast cancer. Letrozole exerts its function through binding to the hemomoiety of the aromatase enzyme, which is a member of the cytochrome P450 hemoprotein containing enzyme complex superfamily that catalyze the rate limiting step in the production of estrogen, that is, the conversion of androstendione and testosterone via three hydroxylation steps to estrone and estradiol respectively (14).

Letrozole has the proposed mechanisms of ovarian stimulation by letrazole are a central effect on releasing the pituitary-hypothalamic axis from estrogenic negative feedback, therefore increases gonadotropin secretion and resulting ovarian follicular development. This indicates that letrazole lead to the same action of clomiphene citrate without depletion of estrogen receptors, or antiestrogenic effect on cervical mucous or endometrium.

In women with polycystic ovary syndrome, there is relative aromatase deficiency in the ovary, resulting in increase in the ovarian androgen production (15) which is converted to estrogen by aromatization in the brain, leading to relative oversuppression of FSH. Letrozole suppress the estrogen production in both the ovaries and the brain therefore resulting in increase in FSH release and subsequent follicle stimulation and ovulation. In addition to the central effect on the pituitary-hypothalamic axis letrazole acts locally on the ovaries, preventing the conversion of intraovarian androgens into estrogens, leading to temporary accumulation of androgens and enhancing follicle stimulating hormone receptor gene expression leading to an increase in the sensitivity of the ovarian follicles to gonadotropins stimulation (16).

The present study reveals that the induction of ovulation with letrazole is associated with limited number of mature follicles compared to clomiphene citrate, because letrazole doesn't deplete estrogen receptors and have short half (45 hours), unlike clomiphene citrate, normal negative feedback occurs centrally as the dominant follicle grows and estrogen levels increase, this results in FSH suppression and atresia of small follicles, and midcycle mono-ovulation occurs in most patients (17). The result of the present study highlights the main advantage of letrazole in induction of ovulation in patients with polycystic ovary syndrome which is mono-ovulation, patients with polycystic ovary syndrome are often hyper-responders to gonadotropins and at higher risk for ovarian hyperstimulation syndrome.

One case of twin pregnancy occurred in clomiphene citrate group and all the pregnancies in the letrazole group were singleton, this is attributed to mono-ovulation which occurred in 70% of patients in letrazole group. Mitwally et al reported that the use of aromatase inhibitor letrazole is associated with significantly lower multiple pregnancy rates compared with other methods of ovarian stimulation, they explained this results by the fact that letrazole induce limited number of mature follicles compared to other methods of induction of ovulation (18).

Higher endometrial thickness was reported on the day of HCG administration with the letrazole group compared with clomiphene citrate, in addition all cycles in the letrazole group had endometrial thickness more than 5 mm while in clomiphene citrate group the endometrial thickness was less than 5 mm in ten cycles. This indicates the adverse effect of clomiphene citrate on the endometrial growth that is thought to be due to depletion of the endometrial receptors, and indicates that letrazole has no adverse effect on endometrium (19). These results agrees with the results of Mitwally and Casper and Atay et al (4) (20). On the other hand another study revealed that there is no significant difference in endometrial thickness (21).

Although the pregnancy rate per cycle was higher in the letrazole group (15.62%) than in clomiphene citrate group (12.85%), that difference is not statistically significant. In a prospective randomized study the pregnancy rate per cycle was nearly similar between two groups of patients with polycystic ovary syndrome treated with letrazole or clomiphene citrate (22). In contrast to our finding, other randomized study comparing the use of letrazole or clomiphene citrate in patients with polycystic ovary syndrome, pregnancy rate per cycle was significantly higher in patients in...
letrazole group (21% versus 9.1%) (20).

In summary, this prospective randomized study has demonstrated the advantages of use of letrazole in patients with polycystic ovary syndrome, which is mono ovulation and absence of antiestrogenic effect on endometrium, and higher pregnancy rate per cycle. These properties make letrazole a viable alternative to clomiphene citrate in patients with polycystic ovary syndrome.

REFERENCES


Received on August 13, 2007; revised and accepted on September 2, 2007