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A Clomiphene Citrate and Letrozol Varsus Tamoxifen and Letrozole as an Infertility Treatment in Women with Polycystic Ovary Syndrome

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ABSTRACT

The polycystic ovary syndrome (PCOs) affects 5-10% of reproductive age women and it is the most common cause of unovulatory infertility. The aim of this clinical trial was to compare the combination therapy of letrozole and clomiphene with letrozole and tamoxifen as an infertility treatment in women with the polycystic ovary syndrome. In this study 9 infertile women between 18-40 years with the polycystic ovary syndrome who had no major medical disorders enrolled in this clinical trial. Patients were randomized in to 2 groups: one group was treated with Clomiphene Citrate (CC) 50 mg twice daily and letrozole 2.5 mg twice daily for 5 days (from day 3-7 of menstrual cycle) and group 2 took tamoxifen 10 mg twice daily and letrozole 2.5 mg twice daily for 5 days (from day 3-7 of menstrual cycle). Trans vaginal ultrasonography (TVS) was performed at the day 7 in order to determine number of follicles, size of follicles and Endometrial Thickness (ET). Pregnancy rate in the group of women who received tamoxifen and letrozole (Group B) was more than women who received CC and letrozole (Group A) (2.2% in group A vs. 17.8% in group B) that there is significant difference between two groups ($p = 0.01$). There is no significant association between two groups in incidence of OHSS, endometrial thickness and follicular size. It suggested co-administration of letrozole and tamoxifen was more effective due to low cost, low complication and greater access as an infertility treatment.

Key words: Letrozole, tamoxifen, clomiphene citrate, PCOS

INTRODUCTION

The Polycystic ovary syndrome (PCOs) is characterized by an ovulation, hyperandrogenism and polycystic ovaries on ultrasonography. The PCOs affects 5-10% of reproductive age women and it is the most common cause of unovulatory infertility (Broekmans *et al*., 2006). According to studies women with PCOs have abnormal function of hypothalamic-pituitary axis as well as another organ. Hypothalamus becomes hyperactive in PCOs and secrets gonadotropins releasing hormone (GnRH) more often than usual without identified reason that leads to excess production of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) (Ehrmann, 2005).

Clomiphene Citrate (CC), a selective estrogen-receptor modulator that antagonizes the negative feedback of estrogen at the hypothalamus with a consequent increase in ovarian stimulation by endogenous gonadotropin has become the most widely prescribed drug for ovulation induction to reverse an ovulation or oligoovulation (The Practice Committee of the American Society for Reproductive Medicine, 2013).

Increasing FSH stimulation on the ovary from pituitary by changing GnRH pulsatility secretion. Although CC has been used for decades it had drawbacks. Studies have shown poor efficacy (22% live birth rate after six cycles of CC), undesirable side effect including mood changes and hot flushes and failure to ovulate as clomiphene resistance (up to 25% of patients) (Legro *et al*., 2007).

Tamoxifen is a selective estrogen-receptor modulator. It behaves as an antagonist of the estrogen receptor in breast tissue via its active metabolite, 4-hydroxytamoxifen and acts as estrogen agonist in other tissues such as the endometrium (BIG 1-98 Collaborative Group *et al*., 2009). Tamoxifen has been used for treatment of breast cancer, gynecomastia and also infertility in women with an ovulatory disorders (Steiner *et al*., 2005). Letrozole is an oral non-steroidal aromatase inhibitor first used as the treatment of hormonally-responsive breast cancer after surgery. Letrozole also prescribed for ovarian stimulation since 2001 due to fewer side-effects (Tulandi *et al*., 2006). In some studies tamoxifen monotherapy compared with aromatase inhibitor monotherapy and results of these trials showed that letrozole as an aromatase inhibitor is more effective than tamoxifen (BIG 1-98 Collaborative Group *et al*., 2005; Goss *et al*., 2003; Ingle *et al*., 2009). Regarding the adverse effects of ovulation induction such as multiple gestations and Ovarian Hyper Stimulation Syndrome (OHSS), researchers are trying to find the treatment options which may have the best pregnancy rate with least adverse effects.

Present study related to combination therapy of letrozole and tamoxifen compared with letrozole and clomiphene, researcher's designed a double-blind controlled trial study as a hypothesis that letrozole and tamoxifen combination would be superior to letrozole and clomiphene as an infertility treatment.

MATERIALS AND METHODS

Approval: This study has been approved by research and ethics committee of Jahrom University of Medical Science and patients participated in the study after a satisfactory consent.

Study design: This study is a double blind control trial study. From 90 infertile women 18-40 years old age with the polycystic ovary syndrome who had no major medical disorders and who were not taking confounding medications such as primarily sex steroids and other infertility drugs. Enrollment began in February 2011 and was completed in January 2014. Participants were infertile women who referred to gynecology clinic. We used modified Rotterdam criteria to diagnose the polycystic ovary syndrome (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Accordingly, all participating women had a comprehensive infertility work-up include male partner semen analysis, pelvic ultrasonography and serum hormone assay (FSH, LH, TSH, T3, T4, Prolactin, DHEA-S, Estradiol, Progesterone and Testosterone) on the 3-5 day of the menstrual cycle, tubal patency test. Patients who had abnormality in any of these tests and who had factors in laparoscopic procedure, which may be responsible for infertility were excluded from the study. Patients were randomly divided to two groups (A and B) according to a computer-generated randomization list in to one of the regimen. Each group received one of the two combination drugs group over the 3 months. Infertility regimens A and B include:

- Group A prescribe Clomiphene Citrate (CC) 50 mg twice daily and letrozole 2.5 mg twice daily for 5 days (from day 3-7 of menstrual cycle)
- Group B prescribe tamoxifen 10 mg twice daily and letrozole 2.5 mg twice daily for 5 days (from day 3-7 of menstrual cycle)

Transvaginal ultrasonography (TVS) was performed at the day 7 in order to determine number and size of follicles and Endometrial Thickness (ET). The TVS performed by an expert specialist. If the number of the follicles is more than 12 and the size more than 25 mm the administered drugs stopped. If the follicle size is less than 18 mm, drugs should be continued for 5 other days. The HCG prescribe 5000-10,000 IU intramuscularly when one or more follicle $\geq$18 mm and Endometrial Thickening (ET) $\geq$6 mm with lucent and triple layer pattern in endometrium in TVS.

The amount of HCG depends on the number and size of follicles. If the number of follicles is about 10 and the size of follicles more than 25 mm, the amount of HCG prescription reduce.

Patients were advised to have intercourse in day 13-15 and 17 of menstrual cycle. During the treatment and after that if any patient missed her menstruation, pregnancy test was performed by serum level of beta HCG measurement. Clinical pregnancy confirmed by USG with documentation of at least one gestational sac.

Statistical analysis: The mean number of follicles, endometrial thickness, ovulatory cycle rate, conception rate and pregnancy outcome compare in both groups. With the use of Pearson's chi-square test at a two-sided significance level of 0.05. All analysis was performed by using SPSS software version 19.

RESULTS

Ninety Patients with the polycystic ovary syndrome referred to Dr. Rasekh clinic. They were randomly assigned to a treatment group. The two groups (Each group consisted of 45 patients) were well matched at baseline. The average age was 26.6±4.44 years old in group A and it is 27.55±5.68 in group B.

Table 1: Comparison of pregnancy rate, mean endometrial thickness, incidence of OHSS, abortion rate, mean follicular size in both group A and B

Results	Group A	Group B	p-value
Pregnancy rate	3.2%	19.8%	p<0.05
Mean endometrial thickness	7.350±1.90	10.020±3.01	p>0.05
OHSS rate	4.2%	2.2%	p>0.05
Abortion rate	2.2%	0	p>0.05
Follicular size mean	14.264±5.432	16.630±3.90	p>0.05

OHSS: Ovarian hyper stimulation syndrome

Frequency of pregnancy, abortion, Ovarian Hyper Stimulation Syndrome (OHSS), mean of endometrial thickness and follicular number and size are compared in both groups (Table 1). Pregnancy rate in the group of women who received tamoxifen and letrozole (group B) was more than the group of women who received CC and letrozole (group A) (3.2% in group A vs. 19.8% in group B).

There is significant difference between the two groups (p = 0.01). Frequency of abortion in group A was 2.4% and in group B was 0%. No significant difference is identified between two groups (p = 0.31).

Frequency of OHSS in group A was 4.2 % (OHSS) and in group B was 2.2%.

Frequency of OHSS had no significant difference between two groups (p>0.05).

Mean of endometrial thickness in group A was 7.35±1.90 and in group B was 10.02±3.01. There was no significant difference between two groups' mean of endometrial thickness (p>0.05).

Mean of follicular size in group A was 14.264±5.432 and it was 16.630±3.90 in group B. A 20% of total women's follicular size in group A had more than 18 mm and 35.6% of women's follicular size in group B had more than 18 mm. There was no significant difference between two groups in follicular size (p>0.05).

DISCUSSION

The main purpose of this clinical trial is to compare combination therapy of letrozole and clomiphene with letrozole and tamoxifen (TMX) as an infertility treatment in women with the polycystic ovary syndrome. The result of our research is letrozole and tamoxifen more effective than letrozole and clomiphene as an infertility treatment. Incidence of OHSS, mean of endometrial thickness, mean of follicular size did not differ significantly between two treatment groups (Table 1). Although researchers have compared the effect of various treatments in infertile women, there is no trial to compare this type of combination therapy. In spite of failure to respond to clomiphene citrate as an infertility treatment, it remains the first-line of treatment for PCOS related an ovulatory infertility (Legro *et al*., 2007). This resistance cases may require the use of injectable gonadotropins as a second line and drawbacks of this approach include its high cost, the potentially life threatening ovarian hyper stimulation syndrome and the significant risk of high order multiple gestations (Mitwally and Casper, 2003). In recent years, the usefulness of letrozole for ovulation induction was investigated. A number of studies found that the effect of letrozole was comparable to that of combined CC and gonadotropins and of gonadotropins alone and CC alone for the induction of ovulation (Ganesh *et al*., 2009; Nejad *et al*., 2008). Also some studies have demonstrated that some patients do not respond to letrozole as an infertility treatment.

The aromatase inhibitor letrozole induces ovulation in women with PCOS without having anti estrogenic effects on the endometrium. Also, letrozole has a short half-life (45 h), so rapidly eliminated from the body (Mitwally and Casper, 2003; Kilic-Okman *et al*., 2003). In a study, it has concluded that letrozole gave a pregnancy rate of 20-27% per cycle in PCOS women resistant to CC. More follicles developed and higher clinical pregnancy rates were reported in the longer letrozole (Mitwally and Casper, 2003; Holzer *et al*., 2006; Badawy *et al*., 2008). Tamoxifen is a triphenylethylene derivative with a structure similar to CC. A meta-analysis including four RCTs comparing tamoxifen and CC showed similar ovulation rates. Boostanfar *et al*. (2001) and Karimi *et al*. (2002) conducted a clinical trial on 100 infertile women. They found that ovulation rate in the clomiphene group were 54.9%, tamoxifen plus clomiphene group was 73.5% without significant differences in both groups. Positive pregnancy rate in the clomiphene group was 39.2%, clomiphene+tamoxifen group was 61.2%, concluded that pregnancy rate was more in the clomiphene and tamoxifen regime in comparison with the clomiphene group (2002) Steiner and associates compared the effectiveness of tamoxifen to clomiphene for achievement of pregnancy. They concluded that clomiphene citrate and tamoxifen are equally effective (Wang *et al*., 2008). Some studies indicated tamoxifen is a good alternative to clomiphene in women with PCOS and clomiphene-resistant cases (Gerhard and Runnebaum, 1979; El-Gharib *et al*., 2014). The EL-Gharib MN conducted in a study letrozole therapy has side effects which occurred in 10% of patients. The most important were the gastrointestinal side effects in the form of nausea, vomiting, diarrhea, vague abdominal pain and bloating. As regards no side effects reported with tamoxifen therapy during the study. They concluded that both letrozole and TMX should be considered as an optional therapy for CC-resistant women (Rasekhjahromi *et al*., 2015). The purpose of this study is combination therapy of letrozole and TMX compare with combination therapy of letrozole and CC due to some reports that indicated resistance to letrozole therapy or tamoxifen therapy or clomiphene therapy alone as an infertility treatment in PCOS related infertile women. While other studies have indicated the more effectiveness of letrozole and tamoxifen.

CONCLUSION

The result of this study indicated that co-administration of letrozole and TMX has higher pregnancy rate than letrozole

and clomiphene. Another advantage of this combination therapy, low costs, low complication and greater access to these drugs as an infertility treatment.

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