International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

International Journal of Pharmacology 11 (4): 377-381, 2015
ISSN 1811-7775

ansinet
Asian Network for Scientific Information

RESEARCH ARTICLE OPEN ACCESS

DOI: 10.3923/ijp.2015.377.381

Assessing an Optimal Regimen in Treatment of Infertility (Clomiphene Citrate, Tamoxifen and Vit. E Versus Estrogen, Letrozole and Tamoxifen): A Double Blind Control Trial

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ARTICLE INFO
Article History:
Received: January 07, 2015
Accepted: March 21, 2015

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ABSTRACT
An ovulation disorders cause 30 to 40% of infertility cases. There are several regimens to induce ovulation. Clomiphene Citrate (CC) has been the front-line therapy for ovulation induction, but failure to respond to CC occurs in up to 20% of cases, which may then require the use of other drugs for ovulation induction. The objective of this study is to compare the two drug regimens (Clomiphene Citrate, Tamoxifen and vitE versus estrogen, Letrozole and Tamoxifen) in infertile women with anovulatory cycles. This study is a double blind control trial which was done on 90 infertile women that referred to Dr.Rasekh clinic. Patients were divided into 2 groups blindly. Group A took Clomiphene Citrate, Tamoxifen and vitamin E. Group B took Letrozole, Tamoxifen and Estrogen. Efficacy of each regimen was compared with analyzing endometrial quality and thickening, follicular size pregnancy rate and incidence of OHSS. Results of this study demonstrate that mean of endometrial thickness is more in group B (10.020 vs. 7.360). Endometrial thickness has significant difference between group A and B (p-value<0.001). Mean of follicular size in group A is more than group B (15.630 vs. 14.264). Frequency of OHSS in group B is more than group A (6.7% vs. 0%) (p-value). 0.05) Odds ratio shows that frequency of pregnancy in group B is 9.5 fold more than group A. Comparing the frequency of pregnancy in two groups has significant difference, which shows the efficacy of group B is more than group A regimen.

Key words: Clomiphene citrate, letrozole, infertility, estrogen, vitamin E, ovulation

INTRODUCTION

Infertility is defined as a one-year unprotected intercourse which does not result in pregnancy. The 10-15% of couples encounter this problem during their reproductive age. Half the causes of infertility are due to female infertility. Infertility treatments are time consuming and expensive. An ovulation disorders cause 30-40% of infertility cases (Ghafourzadeh *et al*., 2004). CC was considered as the first choice in ovulation induction. As CC is an estrogen receptor modulator, it increases FSH stimulation to the ovary from pituitary by changing GnRH pulsatility secretion (Mitwally and Casper, 2001). After revealing some complications of CC such as Ovarian hyper stimulation syndrome (OHSS), failure of ovulation induction, multiple pregnancies and diminishing endometrial development and cervical mucus production (infertilityspecialist.com) it was replaced with other agents such as aromatase inhibitors mainly letrozole (Mitwally and Casper, 2001).

Letrozole suppresses estrogen synthesis thereby causing enhanced GnRH pulsatility and consequent FSH stimulation (infertilityspecialist.com). Letrozole doesn't have the complications of pervious drug. Besides pregnancy outcome has been reported higher in patients prescribed letrozole (Bao *et al*., 2009). Another substitute treatment for ovulation induction is Tamoxifen. It is a selective estrogen receptor

modulator and its mechanism is similar to CC whereas it acts as estrogen receptor agonist in the vagina and endometrium (Beall and DeCherney, 2012). On the other hand, α-tocopherol (vitamin E) is a lipid soluble vitamin used as Antioxidant (Murry *et al*., 2006), which affects ovulation by increasing capillary blood flow and protecting endothelium from oxidative damage (Chung *et al*., 1995; Shimpuku *et al*., 2000).

One of the main goals of medical ovulation induction in all of the medication which were mentioned is to avoid complications such as multiple pregnancies and ovarian hyper stimulation syndrome (Sukcharoen, 2004). Similar aims follow through this clinical trial so we decide to add two other agents estrogen and Vitamin E in our regimens and compare the efficacy of administration of Clomiphene Citrate, Tamoxifen and vitamin E versus estrogen, Letrozole and Tamoxifen in order to recommend a novel regimen in ovulation induction.

MATERIALS AND METHODS

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

Study design: This study is a double blind control trial study ninety female patients participated in this study. Inclusion criteria of this study are the history of infertility for at least 12 months, body mass index (BMI) <28 and patients of anovulatory PCOS .Finally the diagnosis of PCOS was made based on the revised Rotterdam 2003 criteria (Al-Kataan *et al*., 2010). In all patients, a comprehensive infertility work-up perform that include husband semen analysis, pelvic ultrasonography and serum hormone assay (FSH, LH, TSH, T3, T4, Prolactin, DHEA-S, Estradiol, Progesterone and Testosterone) on the third to fifth day of the menstrual cycle, tubal patency test. Patients with abnormality in any of these tests, which may be responsible for reproductive failure are excluded from the study. All patients undergo laparoscopy and patients who has other factors in laparoscopic procedure, which may be responsible for infertility, are also excluded from the study. Sample size calculate using pregnancy rate as a primary outcome measure. Randomization of women is carried out using online software (http://www.randomization.com) to create a random number table. All patients randomize to receive one of the two drugs to be given over the next 3 months. Randomization codes (A, B) select; treatment and follow-up of subjects to ensure concealment of allocation. Infertility regimens A and B define as below:

- **Group A prescribe:** Clomiphene citrate (CC), Tamoxifen and vitamin E
- **Group B prescribe:** Tamoxifen, letrozole and estrogen

Protocol of regimen A: CC 50 mg, every 12 h, treatment administered from Day 3 to Day 7 (total of 5 days). Tamoxifen 10 mg daily, every 12 h, administered from Day3 to Day 7 (total of 5 days). Vitamin E 400 mg pearl tab, daily administered from Day 3 to the end of cycle.

Protocol of regimen B: Tamoxifen 10 mg and letrozole 2.5 mg daily, every 12 h, administered from Day 3 to Day 7 (total of 5days). Estradiol 2 mg from Day 3 to the end of cycle.

Patients undertake Trans Vaginal Ultrasonography (TVS) at the Day 7 in order to determine number of follicles, size of follicles and Endometrial Thickness (ET). Ultrasound TVS performed by a specialist (Dr.Rasekh). If the number of the follicles are more than 12 and the size is more than 25 mm the administered drugs should be stopped. If the follicle size is less than 18 mm, drugs should be continued for 5 other days. HCG prescribe 500-10,000 IU intramuscularly when one or more follicle ≥18 mm and ET ≥6 mm and endometrium should be lucent and triple layer 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 about 25 mm, the amount of HCG prescription reduce.

The women recommend to have intercourse in Day13-15 and 17. Duration of treatment in both groups is 3 months. Chemical pregnancy assesses by serum level of beta HCG measurement once the patient missed her period. Documentation of at least one gestational sac in USG confirm as clinical pregnancy. Both the groups without evidence of ovulation and with negative pregnancy tests ask to follow the respective schedule of treatment in subsequent cycles.

Statistical analysis: The mean number of follicles, endometrial thickness, ovulatory cycle rate, conception rate, and pregnancy outcome compare in both the groups. The sample divide into two groups using random allocated software. Statistical analysis and chi- square test are done using SPSS 19 software. Results express as mean and standard errors of mean. The p value of <0.05 is considered statistically significant.

RESULTS

Patients in each group was treated with specific regimen that mentioned above. Results of treatment in each group are compared based on frequency of pregnancy, abortion, OHSS and mean of endometrial thickness and follicular size.

Frequency of pregnancy in group A is 2.2% and in group B is 17.8%. Odds ratio show that frequency of pregnancy in group B is 9.5 fold more than group A. Frequency of pregnancy has significant difference between two groups (p value: 0.03). Frequency of abortion in group A is 0% and in group B is 2.2%. Frequency of abortion has no significant difference between two groups (p value >0.05).

Frequency of OHSS in group A is 0% and in group B is 6.7%. Frequency of OHSS has no significant difference between two groups (p value >0.05).

Adjustment of HCG prescription is an important role in reducing the OHSS. Mean of endometrial thickness in group A is 7.360±3.0170 and in group B is 10.020±1.9020. Mean of endometrial thickness has significant difference between two

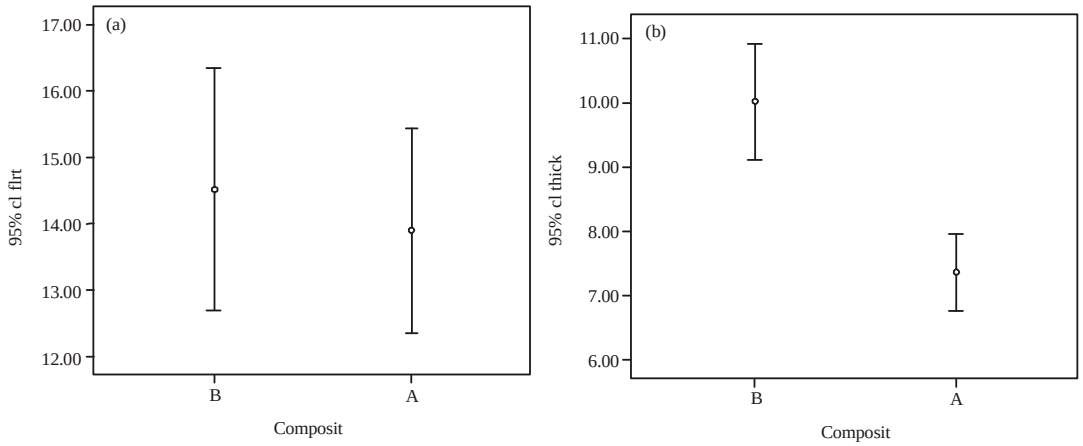

Fig. 1(a-b): Endometrial thickness flrt (follicular size)

Table 1: Mean of endometrial thickness in group A and B showing significant difference between two groups

Group	Mean± SD	df	T	p-value
A	7.360 ± 3.0170	85	4.880	0.001
B	10.020±1.902085	4.880	0.001	

Mean of follicular size in group A is15.630±3.90 and in group B is 14.264±5.432 that has no significant difference between both two groups (p value>0.05) (Table 2)

Table 2: Mean of Follicular size in group A and B had significant difference between two groups

Group	Mean± SD	df	T	p-value
A	15.630±3.90	85	-1.338	>0.05
B	14.264±5.432	85	-1.338	>0.05

Table 3: Frequency of OHSS, pregnancy and abortion in group A that had significant differences compared with group A

	p-value	Frequency
OHSS	>0.05	0%
Pregnancy	0.01	2.2%
Abortion	>0.05	0%

groups (p value: 0.001) (Table 1). Frequency of pregnancy in group A is 2.2% and in group B is 17.8%. Odds ratio show that frequency of pregnancy in group B is 9.5 fold more than group A. Frequency of pregnancy has significant difference between two groups (p value: 0.03). Frequency of abortion in group A is 0% and in group B is 2.2%. Frequency of abortion has no significant difference between two groups (p value> 0.05).

Frequency of OHSS in group A is 0% and in group B is 6.7%. Frequency of OHSS has no significant difference between two groups (p value> 0.05) (Table 3 and 4). The endometrial thickness shown in Fig. 1a-b.

Incidence of OHSS is 7.3% in mild and moderate type and 4.2% in sever types but total incidence of OHSS is variable up to 33% (Berek, 2007). In this study only one patient in group A has the criteria of mild OHSS. In TVS ultrasonography only large follicles about 30-40 mm are detected in both groups without any sign and symptoms of OHSS such as Low abdominal distension, Progressive increase in abdominal circumference measure at the level of the umbilicus, Nausea

Table 4: Frequency of OHSS, pregnancy and abortion in group A that had significant differences compared with group B

	p-value	Frequency
OHSS	>0.05	6.7%
pregnancy	0.01	17.8%
Abortion	>0.05	2.2%

and vomiting preventing intake of food and fluids, dyspnea and respiratory distress due to an elevated diaphragm and hydrothorax, diarrhea, quick weight gain and ovaries enlarged up to >12 cm (Ovarian Hyperstimulation Syndrome (OHSS) Guidelines).

DISCUSSION

The present results show that group B regimen is more efficient than group A regimen. Researchers have compared ovulation induction drugs with each other and assessed their efficacy but none of them focused on combination of these drugs as a novel regimen. Al-Kataan *et al.* (2010) showed that PCOS produce significant reduction in serum antioxidant vitamins (A, C and E) when compared with control (Al-Kataan *et al.*, 2010). Tarin *et al.* (1998) in their study indicated the enhancing effect of vitamins C and E on ovulation rate. So these results are not completely in agreement with our findings about the efficacy of adding Vitamin E in our regimens (Tarin *et al.*, 1998).

Roy *et al.* (2012) in their prospective study about comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome, concluded that letrozole caused better endometrial response and pregnancy rate (Roy *et al.*, 2012), also Bao *et al.* (2009) have concluded the same results and believe that letrozole may be an appropriate choice for anovulation disorders due to expression of integrin αvβ3 and HOXA10 (Bao *et al.*, 2009) Most of studies indicate that Letrozole has better ovulation and pregnancy rate comparing CC in patients with PCOS. (Begum *et al.*, 2009; Zeinalzadeh *et al.*, 2010; Roy *et al.*, 2012; Wallace *et al.*, 2011; Nahid and Sirous, 2012) also the patient who was treated with letrozole had higher rate of

mature follicles (Zeinalzadeh *et al*., 2010). Clomiphene citrate caused endometrial thinning more often than letrozole. Also the side effects reported by patients in the group receiving clomiphene citrate were higher while in the group receiving letrozole no complication was reported (Ibrahim *et al*., 2012). These are in consistent with our results since we use letrozole as one of the other drugs in regimen B. Wang *et al*. (2008) used tamoxifen and gonadotropins in their study, showed lower miscarriages in pregnant women and noted that as promising choice in patients with thin endometrium. But side effects during treatment with clomiphene were more pronounced than Tamoxifen therapy (Gerhard and Runnebaum, 1979; Reynolds *et al*., 2010; Steiner *et al*., 2005). These are in agreement with our findings as focusing on combination therapy and use of tamoxifen and letrozole as the effective agents.

On the contrary, Fariba Seyedoshohadaei and her colleagues compared letrozole, CC and Tamoxifen with each other and showed that CC was more successful due to higher pregnancy rate and also Badawy *et al*. (2009) showed in their study comparing CC and tamoxifen for ovulation induction in women with PCOS indicated that CC is more successful than tamoxifen for ovulation induction in women with PCOS. These findings don't support our results. Some of the studies show no significant difference between the drugs neither in the duration of the luteal phases nor in the pregnancy rate (Seyedoshohadaei *et al*., 2012; Badawy *et al*., 2009).

Also estradiol administration can develop endometrial thickness in follicular phase (Yagel *et al*., 1992). In our study estradiol is one of the effective agent in the optimal regimen in group B.

Suginami *et al*. (1993) used CC and tamoxifen as combination therapy, showed that this combination was more efficient than cc alone. This result is consistent with our administrating method in combing drugs to recommend a better regimen in ovulation induction.

CONCLUSION

As many controversies exist in the field of ovulation induction we decide to recommend an optimal regimen for treatment of infertility for the first time. We compare two regimens A and B in our study and we understand that regimen B has more efficacy than regimen A due to fewer complications (better pregnancy out comes).

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