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Comparison between Two Methods of Ovulation Induction: Clomiphene alone and Clomiphene +Tamoxifen in PCOS Patients

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Background: Infertility affects about 10-15% of reproductive-age couples. About half the causes of infertility are female related and approximately 40% of the cases are caused by anovulation, mostly in PCO women.

Objective: This study was conducted to determine and compare the effects of two drug treatment regimens: higher dose of clomiphene and a combination of lower dose of clomiphene and tamoxifen in treating infertile women with PCO.

Materials and Methods: The study was a randomized clinical trial conducted on 100 infertile patients who referred to Yazd-Iran Infertility Clinic between the years 2001-2003. The patients were selected who had received at least 3 periods of clomiphene, but no pregnancy had occurred. They were randomly divided into two groups. In the first group, clomiphene was increased to 100 mg and the second group 20 mg of tamoxifen was added to 50 mg of clomiphene from day 5-9 of menstruation cycle. Infertility duration, duration of medicine used, PCT score, endometrial thickness, ovulation, and pregnancy rate were studied in both groups.

Results: Ovulation rate in clomiphene group was 54.9%; Tamoxifen + clomiphene group was 73.5% without significant differences in both groups. (PV = 0.053). Positive pregnancy rate in clomiphene group was 39.2%; clomiphene + tamoxifen group was 61.2% (P value < 0.05), which could be concluded that pregnancy rate was higher in clomiphene/tamoxifen group than in the clomiphene group. The presence of a dominant follicle in the two treatment groups in women between 18-24 was not significant, but in women between 25-39 years was significant (PV= 0.049) (Table III).

Conclusion: The recommendation is to add Tamoxifen to Clomiphene in 35-39 women with 20≤ BMI ≤26.99 before the use of gonadotropins treatment in PCOS with or without IUI, because these options have higher risk of multiple pregnancy and ovarian hyperstimulation syndrome.

Keywords: *Infertility, PCO, Clomiphene resistant, Tamoxifen, Clomiphene, IUI*

Introduction

Infertility is defined as a one-year unprotected intercourse which does not result in pregnancy (Jonathan 2002). 10 to 15 percent of couples face with this problem during their reproductive age (Hamilton *et al*., 1999). Half the causes of infertility are due to female infertility and infertility treatment are time consuming and expensive (Speroff 1999). Anovulation disorders cause 30 to 40 percent of infertility cases (Jonathan 2002). This problem can be seen in women as chronic anovulation (PCO) (Buckley and Goo 2000; Shoham *et al*., 1999). Treatments are "helping ovulation through anti-estrogenic (Borenstein *et al*., 2001; ESHRE 1999). Agents like clomiphene and tamoxifen". These drugs occupy the estrogenic receptors in hypotalamus which then cause the increase in gonadotropin secretion.

Previous studies reported 80% ovulation rate and 40% pregnancy rate after the prescription of clomiphene (50 mg oral) from day 5 to 9 of the menstruation cycle (Hull 1999). One reason for the low pregnancy rate was due to the effects of clomiphen on cervical mucus (Borenstein *et al*., 2001). In order to decrease the antiestrogenic

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Table I. Parameter's in two group

Group Parameter's	Clomiphene I			Clomiphene+Tamoxifen II			P .Value
	No.	Min.	SD	No.	Min.	SD	
Age	51	25.59	4.65	49	25.53	3.78	0.094
Infertility period	51	3.66	1.83	49	3.83	2.003	0.673
Times of previous treatment with Clomiphene	51	9.86	9.78	49	11.87	7.43	0.114

Table II. The respons to treatment in two groups

Group Response to treatment	Clomiphene I		Clomiphene+Tamoxifen I I		P .Value
	No.	Percent	No.	Percent	
Presence of dominant follicle	28	54.9	36	73.5	0.053
Positive pregnancy test	20	39.2	30	61.2	0.028

effect, 20 mg of tamoxifen was prescribed for 5-9 day of the menstrual cycle. Tamoxifen has a similar mechanism to clomiphene but has less negative effects on cervical mucus (Nicholas and Macklon 2000; Fox *et al*., 2000). Lack of response to the clomiphene treatment leads to more expensive and serious treatments like IUI and IVF (Tajima 1997; WU.C.H. 1997). The aim of the study was to investigate the effects of two drug treatment regimens: higher dose of clomiphene and a combination of lower dose of clomiphene and tamoxifen in treating infertile women with PCO.

Materials and Methods

This was a randomized clinical trial study conducted on 100 PCO infertile patients who had normal hysterosalpangography and whose husbands had normal semen analysis according to WHO criteria. Since previous treatments with clomiphene (3 courses or more) had failed, they were referred to Yazd infertility clinic between 2001-2003, Patients were randomly divided into two groups: The first group received 100 mg (Table II) clomiphen from day 5-9 of the menstrual cycle. The second group received 50 mg (Table I) of clomiphen + 20 mg tamoxifen, from day 5-9 of the menstrual cycle.

The women in this research were between 18-39 years old with amenorrhea or oligomenrrhea and who often with hirsutism; and none of them suffered from cushing and adrenal hyperplasia (Buvat *et al.,* 2001). As confirmed by paraclinic test, sonography and pregnancy test.

Body Mass Index (BMI), the duration of infertility and duration of drug treatment were also measured. Response to treatment was the development of at least one dominant follicle (≥20 mm) and a positive pregnancy test. Data analysis was done by SPSS software. The statistical test were chi-square, fisher - exact test and T-test. P.Value was considered to be significant if < 0.05.

Results

According to age parameter, the average age of both groups did not have any significant difference (P.V= 0.094). Years of infertility and duration of drug administration did not result in any significant improvement in fertility rate (table I). The presence of a dominant follicle in second group who used Clomiphene + Tamoxifen was a little more (73.5%) than the first group (Clomiphene with higher dose) (54.5%) but this difference was not significant (Table II). The rate of positive pregnancy test, in second group was higher (61.3%) than first group (39.2%) and the difference between the two groups was significant (P< 0.05).

The presence of a dominant follicle in the two treatment groups among women aged between 18-24 was not significant, but in women aged between 25-39 was significant (PV= 0.049) (Table III). BMI affected the results of treatment with 20-

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Table III . Ovulation rate in Two groups

Clomiphene I		**Clomiphene+Tamoxifen** I I		**P .Value**
No.	Percent	No.	Percent	
17	63	16	76.2	0.327
11	45.8	19	73.1	0.049
17	47.2	21	75	0.025
11	78.6	13	72.2	1

Table IV. Positive pregnancy test in two groups

Group	**ClomipheneI**		**Clomiphene+Tamoxifen I I**		**P .Value**
Positive pregnancy test	No.	Percent	No.	Percent	
Age 18-24 years	12	44.4	14	66.7	0.125
Age 25-39 years	8	33.3	15	57.7	0.084
20≤BMI≤26.99	11	30.6	19	67.9	0.003
BMI ≥27	9	63.4	9	50	0.419

26.99 in second group than the first group. The patients with lower BMI had a better development of dominant follicle (P.Value < 0.05). In women with BMI ≥ 27 in both groups, no significant difference in dominant follicle was seen (P.Value ≅ 1).

Rate of positive pregnancy test was studied based on age and BMI parameters (Table IV).

Discussion

This study show that there was no significant difference in development of dominant follicle in both groups. The result of this study was similar to .Janicke and Estofans (Jonicke *et al*., 2000). They had reported 62.9% ovulation with clomiphen and 56.2% with Clomiphene + Tamoxifen But there were no significant differences. Researchers believe that Tamoxifen is as effective as Clomiphen in the development of a single dominant follicle. The results also support Robert and Jain's study who did not find any significant differences in the administration of the two drug regimens.

In Axelrod and Goldzieheve's study the results was different, so that, the ovulation rate with Clomiphene was higher than with Tamoxifen + Clomiphene (Goldziehev and Axelrod 1998).

In Clomiphene + Tamoxifen group positive pregnancy cases were more than the Clomiphene only group. Robert and Wach's (1999) study had the same result. In their study there was no significant difference on ovulation rate between two treatment groups. However Borestein and Shohan's study showed that the pregnancy rate increased by Tamoxifen significantly (Shoham 1999).

According to the results of this study, Tamoxifen + clomiphene increase the ovulation rate only in age group of 25 to 39 years old with 20≤BMI≤26.99 women. Thus age assumes to play a significant role in ovulation rate. In overweight women, adding tamoxifen to clomiphen did not increase ovulation, did not produce a single dominant follicle and did not yield a positive pregnancy test rate.

Thus the treatment choice is to administer a combination of Tamoxifen and Clomiphene for 35-39 year old women with 20≤BMI≤26.99 before administering gonadotropins treatment in PCOS with or without IUI.

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