

Comparison Between Two Methods of Ovulation Induction: Clomiphene Alone and Clomiphene +Tamoxifen in PCOS Patients

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Abstract

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 Albatool Infertility Clinic between the years (Jan. 2009-Dec.2009). 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, 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).

Conclusion: 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).

The recommendation is to add Tamoxifen to Clomiphene in 35-39 women with $20 \leq \text{BMI} \leq 26.99$ before the use of gonadotropins treatment in PCOS with or without IUI (intra uterine insemination), because these options have higher risk of multiple pregnancy and ovarian hyperstimulation syndrome.

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

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Introduction

Infertility is defined as a one-year unprotected intercourse which does not result in pregnancy [12]. 10 to 15 percent of couples face with this problem during their reproductive age [9]. Half the causes of

infertility are due to female infertility and infertility treatment are time consuming and expensive [14]. Anovulation disorders cause 30 to 40 percent of infertility cases [12]. This problem can be seen in women as chronic anovulation (PCO) [1]. Treatments are "helping ovulation through anti-estrogenic

[1]. Agents like clomiphene and tamoxifen”. These drugs occupy the estrogenic receptors in hypothalamus 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 [10]. One reason for the low pregnancy rate was due to the effects of clomiphene on cervical mucus [1]. In order to decrease the antiestrogenic 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 [16]. Lack of response to the clomiphene treatment leads to more expensive and serious treatments like IUI and IVF(invitro fertilization) [20]. 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 hysterosalpingography 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 Albatool infertility clinic between Jan 2009-Dec.2009, Patients were randomly divided into two groups: The first group received 100 mg (Table II) clomiphene from day 5-9 of the menstrual cycle. The second group received 50 mg (Table I) of clomiphene + 20 mg tamoxifen, from day 5-9 of the menstrual cycle.

Table (1): parameter’s in two group.

Group parameter’s	ClomipheneI			Clomiphene+TamoxifenII			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 (2): The respons to treatment in two group.

Group respons to treatment	ClomipheneI		Clomiphene+TamoxifenII		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

The women in this research were between 18-39 years old with amenorrhea or oligomenorrhea and who often with hirsutism; and none of them suffered from cushing and adrenal hyperplasia [3]. 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 .

Table (3):Ovulation rate in two groups:

Group	Clomiphene Group 1		Clomiphene+Tamoxifen Group 2		P.Value
	No.	Percent	No.	Percent	
Ovulation Rates in 2 groups					
Age 18-24	17	63%	16	76%	0.327
Age 25-39	11	45%	19	73%	0.049
20-26 BMI	17	47%	21	75%	0.025
BMI above 27	11	78%	13	72%	1

Table (4): Rate of positive pregnancy test was studied based on age and BMI parameters test in two group.

Group	ClomipheneI		Clomiphene+TamoxifenII		P.Value
	No.	Percent	No.	percent	
positive pregnancy test					
Age 18-24years	12	44.4	14	66.7	0.125
Age 25-39years	8	33.3	15	57.7	0.048
20≤BMI≤26.99	11	30.6	19	67.9	0.003
BMI≥27	9	63.4	9	50	0.419

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 1). 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 2). 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 3). BMI affected the results of treatment with 20-26.99 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).

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 [13]. They had reported 62.9% ovulation with clomiphene and 56.2% with Clomiphene + Tamoxifen But there were no significant differences. Researchers believe that Tamoxifen is as effective as Clomiphene 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 [8].

In Clomiphene + Tamoxifen group positive pregnancy cases were more than the Clomiphene only group. [17] 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 [18].

Recomendation

According to the results of this study, Tamoxifen + clomiphene increase the ovulation rate only in age group of 25 to 39 years old with $20 \leq \text{BMI} \leq 26.99$ women. Thus age assumes to play a significant role in ovulation rate. In overweight women, adding tamoxifen to clomiphene 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 $20 \leq \text{BMI} \leq 26.99$ before administering gonadotropins treatment in PCOS.

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