

Comparison of Letrozole Versus Tamoxifen Effects in Clomiphene Citrate Resistant Women with Polycystic Ovarian Syndrome

Mohamed Nabih EL-Gharib *, Amal Elsayed Mahfouz, Manal Abdelraouf Farahat

- Department of Obstetrics and Gynecology, Faculty of Medicine, Tanta University, Tanta, Egypt

Abstract

Background: The objective of this prospective randomized study was to make a comparison between the effects of letrozole and tamoxifen (TMX) in ovulation induction in clomiphene (CC)-resistant women with polycystic ovarian syndrome (PCOS).

Methods: The study comprised a total of 60 infertile women (180 cycles) with CC-resistant PCOS selected from the clinics affiliated to the Department of Obstetrics and Gynecology of Tanta University. Patients were randomized to treatment with 2.5 mg of letrozole daily (30 patients, 90 cycles) or 20 mg of TMX daily (30 patients, 90 cycles) for 5 days from day 5 of menses and 10000 IU hCG when mature follicles become ≥ 18 mm in diameter. The chi-square and t-test were used for comparing two groups and $p < 0.05$ was considered significant.

Results: The total number of follicles (≥ 18 mm) in the letrozole group was more than TMX group. The endometrial thickness at the time of hCG administration was significantly higher ($p < 0.05$, at 95% CI) in the letrozole group than that of TMX group (10.2 ± 0.7 vs. 9.1 ± 0.2 mm). Ovulation occurred in 23.33% of cycles in the letrozole group and in 8.89% in the TMX group, whereas pregnancy occurred in 5.56% of the letrozole group and 2.22% of the TMX group.

Conclusion: Both letrozole and TMX should be considered as optional therapies for CC-resistant women. In addition, letrozole was superior to TMX in achieving a higher pregnancy and ovulation rate and also lesser side effects in comparison to tamoxifen.

Keywords: Clomiphene resistance, Infertility, Letrozole, Oligomenorrhea, Ovulation induction, Polycystic ovarian syndrome, Tamoxifen.

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* Corresponding Author:
Mohamed Nabih
EL-Gharib, Department of
Obstetrics and
Gynecology, Faculty of
Medicine, Tanta
University, Tanta, Egypt
E-mail:
mohgharib@hotmail.com

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common causes of anovulatory infertility which affects 4-7% of women worldwide. It is by far the most common cause of hyperandrogenic anovulatory infertility and was described more than half a century ago. The underlying cause of this disorder is still unknown (1). The therapeutic strategies for CC-resistant patients include the addition of corticosteroids such as dexamethasone (2), extended duration of clomiphene (3), the use of aromatase inhibitors (4), laparoscopic ovarian drilling or *in vitro* fertilization (5). Aromatase is a cytochrome P450 (CYP450)

hemoprotein-containing enzyme that catalyses the conversion of androstenedione and testosterone to estrone and estradiol, via hydroxylation steps respectively (6).

Before the administration of letrozole to infertile women, early pregnancy should be ruled out, since information regarding possible teratogenic effects of this drug is limited (7).

Tamoxifen citrate (TMX) is a triphenyl ethylene derivative with a structure similar to CC. The suggested dose is 20-40 mg daily in ovulation-induction, beginning on cycle day 3, and it continues for 5 days. It is less frequently used for ovulation-

induction as this indication is not licensed, although it is sometimes prescribed for women who experience side effects of CC administration, and a meta-analysis has shown the comparative rates of ovulation and pregnancy when compared with CC (8).

The goal of the current study was to determine the safety and efficacy of TMX compared to letrozole in achieving pregnancy in CC-resistant women with PCOS.

Methods

This prospective intervention study was performed during the period from January 2010 till August 2012 at the outpatient clinic of Tanta University Hospital. The study was approved by the institutional ethics committee of Tanta Faculty of Medicine.

In this research, 60 CC-resistant patients ranging in age from 19 to 35 years were recruited. All of them filled the informed consent form.

This study was carried out on 60 CC-resistant patients seeking pregnancy and they were diagnosed with PCOS according to Rotterdam criteria (8). Moreover, the patients failed to ovulate after receiving 150 mg of CC daily for 5 days per cycle, for at least three cycles and were arranged at random, by sealed envelopes, into 2 groups, each group contains 30 patients:

Group (A) received letrozole (Femara; Novartis) with a dose of 2.5 mg/day given from day 5-9 of the menstrual cycle, for 3 successive cycles.

Group (B) received TMX with a dose of 20 mg/day given from day 5-9 of the menstrual cycle, for 3 successive cycles.

The most important inclusion criteria were fulfillment of at least two of Rotterdam criteria of PCOS, negative history of medical problems that can affect fertility such as diabetes mellitus, thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, normal hysterosalpingography and BMI between 20 and 30.

The excluded subjects were the ones having history of medical problems which affect fertility, history of recent hormonal therapy, having pelvic infections and/or having abnormal laboratory findings other than PCOS findings. Moreover, the patients whose husbands had defective semen were excluded as well.

All women subjected to history taking, physical examination, counseling and signing a written consent were taken from each case.

Hysterosalpingography was performed for each

case for exclusion of tubal or uterine factor infertility.

Serial ultrasound monitoring was conducted for each case for detection of ovulation throughout the course of therapy starting from day 10 of menstrual cycle depending on follicular size (18-24 mm) from which human chorionic gonadotropin (hCG) was administered. Untrasound was also used to measure endometrial thickness at the time of hCG administration.

Human chorionic gonadotrophin (hCG) with a dose of 10 000 IU was administered when at least one follicle with a mean diameter ≥ 18 mm was observed using transvaginal ultrasound.

Serum FSH and LH levels were measured on the second day of menstrual cycle.

Semen analysis was done for the husband of every case involved in the study.

Statistical methods: The data were transferred to IBM cards using an IBM personal computer and analyzed with the Statistical Program for Social Sciences V11.0 (SPSS Inc, Chicago, IL)

Descriptive statistics comprised the mean and standard deviation (SD). Analytical statistics comprised the student's t-test to make comparisons between independent quantitative means, and the chi-square test to make comparisons between the different groups with regard to qualitative data. The chosen level of significance was $p < 0.05$ in all studies.

Results

The mean age of studied groups was 26.91 ± 3.21 years. Approximately, 30% of patients had oligomenorrhea and 70% had evidence of hyperandrogenism as hirsutism and acne. There were no significant differences between cases of both groups (letrozole and tamoxifen) regarding age, period of infertility and BMI (kg/m^2) as depicted in table 1.

In the letrozole group, the mean number of mature follicles > 18 mm in diameter on the day of hCG administration, during the third month of letrozole therapy was 1.20. Table 2 displays the collective number of patients with follicles > 18 mm which was 21; the mean endometrial thickness on the day of ovulation was 7.85 ± 1.46 mm. In addition, the cumulative ovulation occurred in 23.30% of the studied cycles. The pregnancy rate was 3.33% (1/30) during the first cycle, 6.89% (2/29) during the second and 7.41% (2/27) during the third cycle with a cumulative of five pregnancies in 90 cycles (5.56%).

In the tamoxifen group, the mean number of ma-

Table 1. Comparison between the letrozole and tamoxifen groups in CC resistant PCOS women

Parameters	Letrozole (n=30) Mean±SEM	Tamoxifen (n=30) Mean±SEM	p-value
Age (year)	26.21±0.9	26.92±1.1	NS
Weight (kg)	71.35	74.2	NS
BMI (kg/m ²)	27.7±4.12	28.4±3.84	NS
Basal FSH (mIU/ml)	4.42±0.83	4.46±1.13	NS
Basal LH (mIU/ml)	9.76±1.65	9.83±2.19	NS
Duration of infertility in years	3.2±2.7	3.0±2.1	NS

NS: Not Significant at 95%

Table 2. Folliculometry in three cycles of letrozole group in CC resistant PCOS women

	TVS			Number of patients with follicles >18	Number of pregnancies
	day 10	day 12	day 14 *		
First cycle					
Diameter of follicle (mm)	6-8	9-9	9-19	6	1
Mean diameter of follicle (mm)	7	9	18		
Mean number of mature follicles	--	--	1.02	--	
Second cycle					
Diameter of follicle (mm)	5-7	8-9	10-20	7	2
Mean diameter of follicle (mm)	6	8	18		
Mean number of mature follicles	--	--	1.12	--	
Third cycle					
Diameter of follicle (mm)	6-9	9-10	12-20	8	2
Mean diameter of follicle (mm)	8	9	18		
Mean number of mature follicles	--	--	1.20	--	

TVS: Transvaginal Ultrasonography
* Day of hCG injection

ture follicles >18 mm in diameter on the day of hCG administration, during the third month of tamoxifen therapy was 9.20. Table 3 shows the accumulative number of patients with mature follicles >18 mm which was 8; the mean endometrial thickness on the day of ovulation was 8.14±1.17 mm.

In this group, cumulative ovulation occurred in 8.89% of the studied cycles. The pregnancy rate was 0.0% during the first cycle, 3.33% (1/30) during the second and 3.45% (1/29) during the third cycle as shown in table 2, with a cumulative of two pregnancies in 90 cycles (2.22%).

About pregnancy rate, no statistically significant difference was found between letrozole and tamoxifen groups. Concerning the success rate of ovulation induction, table 4 shows that ovulation rate was significantly higher in the letrozole group than the tamoxifen group.

Concerning the side effects, no patients required discontinuation of letrozole therapy. The most

frequent side effects (which occurred in 10% of patients) were gastrointestinal side effects in the form of nausea, vomiting, diarrhea, vague abdominal pain and bloating. Fortunately, the gastrointestinal distress was transient and disappeared gradually. As regards tamoxifen, no side effects reported during the study.

Discussion

The present study compared the reproductive outcomes of women with CC-resistant PCOS after administration of the letrozole as an aromatase inhibitor and tamoxifen. In the present study, the ovulation rate with letrozole (23.33%) was higher than with tamoxifen (8.89%) as depicted in tables 2 and 3.

Clomiphene citrate remains the first-line treatment for PCOS-related anovulatory infertility (9). Failure to respond to clomiphene citrate occurs in up to 20% of cases which may require the use of injectable gonadotrophins as a second-line treat-

Table 3. Folliculometry in three cycles of tamoxifen group in CC resistant PCOS women

	TVS			Number of patients with follicles >18	Number of pregnancies
	day 10	day 12	day 14 *		
First cycle					
Diameter of follicle	6-8	9-9	9-19	2	0
Mean diameter of follicle (mm)	7	9	18	--	--
Mean number of mature follicles	--	--	8.70	--	--
Second cycle					
Diameter of follicle	7-9	9-9	10-19	3	1
Mean diameter of follicle (mm)	8	9	18	--	--
Mean number of mature follicles	--	--	8.92	--	--
Third cycle					
Diameter of follicle (mm)	6-9	9-11	12-19	3	1
Mean diameter of follicle (mm)	8	10	18	--	--
Mean number of mature follicles	--	--	9.20	--	--

TVS: Transvaginal Ultrasonography

* Day of hCG injection

Table 4. Frequency of ovulation incidence in letrozole and tamoxifen groups in cc resistant PCOS women

	Ovulation Rate		Total
	+VE	-VE	
Letrozole group, n(%)	21 (23.33)	69 (76.67)	90 (100)
Tamoxifen group, n(%)	8 (8.89)	82 (91.11)	90 (100)
Total	29 (16.11)	151 (83.89)	
Chi-square	5.92		
P-value	0.015		

Notice that ovulation rate was higher in letrozole group than that in tamoxifen group. The Pearson chi-square, uncorrected for continuity is 6.95 and $p=0.0084$

ment. The drawbacks of this approach include its high cost, the potentially life threatening ovarian hyperstimulation syndrome and the significant risk of high order multiple gestations (10).

Both approaches are expensive and risky. In the past few years, the usefulness of letrozole for ovulation induction was investigated (11). Several studies found that the effectiveness of letrozole was comparable to that of combined CC and gonadotropin and gonadotropin alone for the induction of ovulation (12).

Aromatase inhibitors suppress estrogen production in both ovaries and the brain by inhibiting aromatization which releases the hypothalamic/pituitary axis of estrogenic negative feedback that increases gonadotropin secretion, resulting in stimulation of ovarian follicles. The selective non-steroidal aromatase inhibitors have a relatively short half-life, approximately 40 hr (13).

Aromatase inhibitors also act locally in the ovary to increase follicular sensitivity to FSH. This may result from accumulation of intraovarian androgens because they block the conversion of androgen substrates to estrogen. There is evidence that intraovarian androgens stimulate early follicular growth in primates (14).

Letrozole as an aromatase inhibitor induces ovulation in women with PCOS without having anti-estrogenic effects on the endometrium (10). Furthermore, letrozole has a short half-life (45 hr), therefore, it is rapidly eliminated from the body (15).

In study of Holzer et al., they found that letrozole gave an ovulation rate of 70-84% and a pregnancy rate of 20-27% per cycle in PCOS women resistant to CC (16). Both single doses and split dose regimens achieved similar clinical pregnancy rates (10). More follicle development and a higher clinical pregnancy rate were reported in the longer letrozole regimen (2.5 mg daily for 10 days) when compared with the standard regimen (5 mg daily for 5 days) (4).

Tamoxifen is a triphenylethylene derivative with a structure similar to CC. The suggested dose in ovulation induction is 20-40 mg daily, beginning on cycle day 3 for 5 days. A meta-analysis including four RCTs comparing tamoxifen and CC showed similar ovulation rates (17).

Karimi et al. conducted a clinical trial on 100 infertile patients referred to two Iranian infertile clinics between the years 2001-2003. The patients were divided into two groups. In the first group,

100 mg clomiphene and the second group 50 mg clomiphene+20 mg tamoxifen were given for days 5-9 of menstrual cycle. Duration of medication, endometrial thickness, ovulation and pregnancy rate were studied in both groups. The ovulation rate in the clomiphene group was 54.9% and tamoxifen plus clomiphene group was 73.5% without significant differences between two groups. Positive pregnancy rate in the clomiphene group was 39.2% and clomiphene+tamoxifen group was 61.2%. They concluded that pregnancy rate was more in the clomiphene and tamoxifen regime in comparison with the clomiphene group (18).

Steiner et al. did a meta-analysis to compare the effectiveness of tamoxifen vs. clomiphene for achievement of pregnancy. They concluded that clomiphene citrate and tamoxifen are equally effective. Although data regarding pregnancy rates and outcome were limited, there did not appear to be a significant benefit of one medication over the other (19).

Tamoxifen may be a better choice in some patients who fail to either ovulate or conceive with clomiphene due to its favorable effect on the cervical mucus and endometrium. Dhaliwal et al. conducted a study to evaluate the role of tamoxifen in women with anovulatory infertility and found the optimum dose for achieving the best outcome. They reported that 20 out of 70 women conceived, giving a pregnancy rate of 28.5% with a dose of 80 mg tamoxifen/day given from day 5-9 of the menstrual cycle. They concluded that tamoxifen is a good alternative to clomiphene in women with PCOS and clomiphene-resistant cases (20).

Concerning pregnancy rate, it was 5.56% in the letrozole group, compared with 2.2% in the tamoxifen group. No statistically significant difference was found between both groups. The relative low pregnancy rate in our results may be attributed to the fact that we used a relatively small dose of the drugs.

Concerning the side effects, no patients required discontinuation of the letrozole therapy. The most frequent side effects (which occurred in 10% of patients) were the gastrointestinal side effects in the form of nausea, vomiting, diarrhea, vague abdominal pain and bloating. Fortunately, the gastrointestinal distress was transient and disappeared gradually. As regards tamoxifen, no side effects were reported during the study.

Conclusion

We concluded that both letrozole and TMX should be considered as optional therapies for CC-resistant women. In addition, letrozole was superior to TMX in achieving a higher pregnancy and ovulation induction rate and lesser side effects in comparison to TMX.

Conflict of Interest

We have no conflict of interests to declare.

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