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Letrozole versus Tamoxifen in Treatment of Clomiphene Citrate Resistant Polycystic Ovarian Syndrome

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Abstract

Objective

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

Material and Methods

The study comprised a total of 60 infertile women (175 cycles) with CC-resistant PCOS selected from the clinics of the Department of Obstetrics and Gynecology of Tanta University Hospital. Patients were randomized to treatment with 2.5mg of letrozole daily (30 patients, 86 cycles) or 20mg of tamoxifen daily (30 patients, 89 cycles) for 5days from day 5 of menses and 10000 IU hCG when mature follicles becomes ≥18 mm in diameter.

Results

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

Conclusion

Both letrozole and TMX should be considered asoptional therapy for CC-resistant women. In addition, letrozole was super to TMX in achieving a higher pregnancy and ovulation induction rate, and lesser side effects than tamoxifen.

Keywords

Letrozole; Tamoxifen; Clomiphene resistance; Infertility; Oligomenorrhea; Polycystic ovarian syndrome; Ovulation induction

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common causes of an ovulatory infertility which affects 4-7% of women worlwide. It is by far the most common cause of hyperandrogenic an ovulatory infertility and was described more than half a century ago, the underlying cause of this disorder is still uncertain [1].

The therapeutic strategies for CC-resistant patients include the addition of corticosteroid such as: dexamethasone, [2] extended duration of clomiphen, [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 via hydroxylation steps to estrone and estradiolrespectively [6].

Before the onset of letrozole administration, early pregnancy should be ruled out, since information regarding possible teratogenic effects of this drug is limited [7].

Tamoxifen citrate (TMX) is a triphenylethylene derivative with a structure similar to CC. The suggested dose in ovulation-induction is 20-40mg daily, beginning on cycle day 3, for 5days. 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 with CC, and a meta-analysis has shown comparative rates of ovulation and pregnancy when compared with CC [8].

The goal of the current work was to determine the safety and efficacy of tamoxifen citrate (TMX) compared to letrozole, in achieving pregnancy in CC-resistant women with PCOS.

Materials and 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.

We recruited 60 CC-resistant patients ranging in age from 19 to 35years. All recruited patients filled the informed consent form.

Patients

This study was carried out on 60 CC-resistant patients seeking pregnancy, attending the outpatient clinic of Tanta University Hospital, and diagnosed according to Rotterdam criteria [8] as Polycystic Ovarian Syndrome and failed to ovulate after receiving 150mg of CC daily for 5days 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, East Hanover, NJ*) in a dose of 2.5mg/day given from day 5-9 of the menstrual cycle, for 3successive cycles.

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

The most imprtant inclusion criteria were: fulfillment of atleast two of Rotterdam criteria of PCOS, Negative history of medical problems that can affect fertility eg: diabetes mellitus, thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, normal hysterosalpingography and BMI between 20 and 30.

We excluded subjects having history of medical problems which affect fertility, history of recent hormonal therapy, presence of pelvic infections and/or having abnormal laboratory findings other than PCOS findings or if the husband has defective semen.

Methods

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

Hysterosalpingography was performed for each case for exclusion of tubal or uterine factor of 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 (18-24mm) 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) at a dose of 10000 IU was administered when at least one follicle with a mean diameter ≥18mm was observed using transvaginal ultrasound.

Serum F.S.H and L.H were measured in 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-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. For all tests, a P value >0.05 considered insignificant, $P < 0.05$ was significant, and $P < 0.001$ was highly significant.

Results

The mean age of studied groups was 26.91±3.21years. 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) as regards 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 9.20. Table [2] displays that the collective number of patients with follicles >18 mm 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 first cycle, 6.89% (2/29) during second and 7.41% (2/27) during third cycle with a cumulative pregnancy of five pregnancies in 90 cycles (5.56%).

In the tamoxifen group, the mean number of mature follicles >18 mm in diameter on the day of hCG administration, during the third month of tamoxifen therapy was 1.20. Table [3] shows that the accumulative number of patients with mature follicles (>18 mm) 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 first cycle, 3.33% (1/30) during second and 3.45% (1/29) during third cycle as shown in Table [2], with a cumulative pregnancy of two pregnancies in 90 cycles (2.22%).

	Letrozole = (n =30) Mean + S.E.	Tamoxifen (N =30) Mean + S.E.	P
Age	26.21±0.9	26.92±1.1	NS
Weight	71.35 kg	74.2 kg	NS
BMI	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

NT = not significant at 95%. Mean + S.E.

Table (1): Comparison between the letrozole and tamoxifen groups

		T.V.S On Day 10	**T.V.S On Day 12**	**T.V.S On Day 14 (day of hCG injection)**	**Number of patients with follicles >18**	**Number of Pregnancies**
First cycle	Diameter of follicle	6-8 mm	9-9 mm	9-19mm	6	1
	Mean diameter of follicle	7mm	9mm	18mm		
	Mean number of mature follicles			1.02		
Second Cycle	Diameter of follicle	5-7mm	8-9	10-20	7	2
	Mean diameter of follicle	6mm	8mm	18mm		
	Mean number of mature follicles			1.12		
Third cycle	Diameter of follicle	6-9mm	9-10	12-20	8	2
	Mean diameter of follicle	8mm	9mm	18mm		
	Mean number of mature follicles			1.20		

T.V.S. = transvaginal ultrasonography

Table (2): Folliculometry in the three cycles of letrozole group

		T.V.S On Day 10	T.V.S On Day 12	T.V.S On Day 14 (day of hCG injection)	Number of patients with follicles >18	Number of Pregnancies
First cycle	Diameter of follicle	6-8	9-9	9-19	2	0
	Mean diameter of follicle	7mm	9mm	18mm		
	Mean number of mature follicles			8.70		
Second Cycle	Diameter of follicle	7-9	9-9	10-19	3	1
	Mean diameter of follicle	8mm	9mm	18mm		
	Mean number of mature follicles			8.92		
Third cycle	Diameter of follicle	6-9mm	9-11mm	12-19mm	3	1
	Mean diameter of follicle	8mm	10mm	18mm		
	Mean number of mature follicles			9.20		

T.V.S. = transvaginal ultrasonography

Table (3): Folliculometry in the three cycles of tamoxifen group

About pregnancy rate, we did not find any statistical significant difference 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 that in the tamoxifen group.

		Ovulation Rate		Total
		+VE	-VE	
Letrozole Group	N	21	69	90
	%	23.33	76.67	100
Tamoxifen Group	N	8	82	90
	%	8.89	91.11	100
Total	N	29	151	180
	%	16.11	83.89	100
Chi-Square	5.92			
P-value	0.015			

Table (4): Incidence of ovulation in letrozole and tamoxifen groups

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.

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 reported during the study.

Discussion

Clomiphene citrate remains the first-line of treatment for PCOS-related an ovulatory infertility. 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, and drawbacks of this approach include its high cost, the potentially life threatening ovarian hyperstimulation syndrome and the significant risk of high order multiple gestations [9,10].

Both approaches are expensive and not without risks. In the past few years, the usefulness of letrozole for ovulation induction was investigated. Several studies found that the effectiveness of letrozole was comparable to that of combined CC and gonadotropin, and of gonadotropin alone for the induction of ovulation [11,12].

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

Aromatase inhibitors suppress estrogen production in both the ovaries and the brain, by inhibiting aromatization which releases the hypothalamic/pituitary axis of estrogenic negative feedback therapy by increasing gonadotropin secretion and resulting in stimulation of ovarian follicles. The selective nonsteroidal aromatase inhibitors have a relatively short half-life, approximately 40 hours [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 substrate to estrogen. There is evident that intraovarian androgens stimulate early follicular growth in primates [14].

The aromatase inhibitor letrozole induces ovulation in women with PCOS without having antiestrogenic effects on the endometrium. Furthermore, letrozole has a short half-life (45 hours), therefore rapidly eliminated from the body [10,15].

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

Tamoxifen is a triphenylethylene derivative with a structure similar to CC. The suggested dose in ovulation induction is 20-40mg 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 who referred to Yazd, Iran Infertility and Bahman Clinic between the years 2001-2003. Although they received clomiphene, no pregnancy occurred; patients were divided into two groups. In the first group, 100mg clomiphene and the second group 50mg Clomiphene + 20mg Tamoxifen were received in 5-9 menstruation days. Duration of medication used, endometrial thickness, ovulation, and pregnancy rate were studied in both groups. The authors 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 [18].

Steiner and associates did a meta-analysis to compare the effectiveness of tamoxifen to clomiphene for achievement of pregnancy. They concluded that clomiphene citrate and tamoxifen are equally effective. Although data regarding pregnancy rates and outcome are limited, there does 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 and coworkers conducted a study to evaluate the role of tamoxifen in women with an ovulatory infertility and find out the optimum dose needed 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 80mg 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 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 reported during the study.

We conclude that both letrozole and TMX should be considered as an optional therapy for CC-resistant women. In addition, letrozole was super to TMX in achieving a higher pregnancy and ovulation induction rate, and lesser side effects than tamoxifen.

Disclosure

We have no conflict of interests to declare.

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