RESEARCH ARTICLE

Tamoxifen vs. Letrozole as Ovarian Stimulants in Infertile Iraqi Women

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ABSTRACT

Background: Infertility is defined as the inability to become pregnant after one year of non-contraceptive sexual activity. Letrozole, a potent, non-steroidal selective, reversible aromatase inhibitor, is considered an established treatment for ovulation induction. Tamoxifen citrate (TMX) is a triphenylethylene derivative with a structure similar to CC that has been considered for ovulation dysfunction treatment. If the female has good quality of follicles in her ovaries and no other reasons for infertility, treatment with these medications can result in conception.

Objectives: This study aimed to compare the effectiveness of tamoxifen and letrozole in ovulation induction outcomes in infertile Iraqi women.

Patients and Methods: This prospective randomized study was carried out from November 2020 to March 2021 on 88 infertile women, selected randomly from the infertile center in Alkut Hospital for Maternity and Childhood.

The patients were divided into two groups viz. the first group (48 patients) received letrozole 2.5 mg twice daily from day 3 of the cycle for 5 days for three cycles, and the second group (40 patients) received tamoxifen 20 mg twice daily from day 2 for 5 days for three cycles.

Results: The current study shows a statistically significant difference between both groups regarding the endometrial thickness, which was significantly higher in the tamoxifen group than the letrozole group. No significant difference was reported between both groups as regarding pregnancy rate, rate of miscarriage, Mean number of mature follicles ≥ 18 mm, and follicular diameter.

Conclusion: Both letrozole and TMX were effective ovulation induction agents, TMX was superior to letrozole in achieving a higher Endometrial thickness.

Keywords: Tamoxifen, Letrozole, Ovarian stimulants, Infertility, Iraqi women

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INTRODUCTION

Infertility is described as a disorder characterized by the failure to achieve a clinical pregnancy after 12 months of regular; unprotected sexual intercourse or by an impairment of a person's reproductive capability; either as an individual or with his or her partner, according to the most recent international glossary on infertility and fertility care. According to the WHO's most recent definition, It is a condition that causes disability in the form of functional impairment.[1] The leading cause of infertility is divided into three groups according to the World Health Organization (WHO).[2]

Group I Disorders: Hypogonadotropic hypogonadism, which accounts for 10% of all anovulation, is caused by hypothalamic failure. Adenoma interference, Kallmann Syndrome, panhypopituitarism of apoplexy, and infection are only a few examples. Hypothalamic failure can also be caused by head trauma, Sheehan Syndrome (postpartum hemorrhage), or head trauma.[3]

Group II Disorders: 85% of anovulatory patients are caused by HPO axis dysfunction; Ovulatory dysfunction (hypothalamus, pituitary, ovarian) in the United States, the most prevalent cause of female infertility. Issues can emerge at any phase in the process (hypothalamus, pituitary, and ovarian) and cause ovulation failure.[4] Polycystic ovarian syndrome (PCOS) is an endocrinopathy that is the root cause of anovulatory infertility in more than 90% of instances.[5] PCOS affect women between the ages of 18 and 44, about 2 to 20% of this age group are affected by this condition. It is one cause of impaired fertility,[6] and characterized by a wide variety of endocrine and metabolic disorders, resulting in a heterogeneous image of anovulation with associated infertility, hyperandrogenism, obesity, insulin resistance and other metabolic disturbances.[7] The majority of PCOS females have increased LH levels and low or normal FSH levels.[8]

Group III Disorders: Ovarian insufficiency or failure suggests that oocytes have been depleted prematurely due to genetic,

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iatrogenic, or acquired reasons. The loss of ovarian function before the age of 40 years is known as primary ovarian insufficiency (POI), and it is a common cause of female infertility.[9]

Letrozole is type II aromatase inhibitor(non-steroidal), that works by blocking the active site of the CYP19A1 enzyme and consequently the electron transfer chain. This competitive inhibition prevents androgens from converting to estrogens.[10] One proposed mechanism is the production of suppressed estrogen resulting in decreased negative feedback on the hypothalamus and increased FSH secretion.[11] Tamoxifen is a selective estrogen receptor modulator (SERM) that works as both an ovarian stimulator and an estrogen enhancer in the lower genital tract.[12] Acts primarily by binding estrogen receptors to the hypothalamus; resulting in a reported decrease in endogenous estrogen levels, eventually leading to increased gonadotropin secretion and consequent ovulation induction.[13]

AIM OF THE STUDY

The study was designed to compare the effectiveness of tamoxifen and letrozole in ovulation induction outcomes in infertile Iraqi women**.**

PATIENTS AND METHODS

Study Population

A prospective comparative study was conducted on eighty-eight patients were recruited from Al-Kut Fertility center from November 2020 to March 2021. The patients were selected according to the following criteria:

Inclusion Criteria

- Women with polycystic ovary syndrome(PCOS).
- With isolated anovulation (non PCOS) with infertility.
- Normal tubes & uterus by HSG.

Exclusion Criteria

The exclusion criteria included

- Patients have medical diseases affecting fertility like thyroid diseases, hyperprolactinemia, DM, congenital adrenal hyperplasia.
- Male factor.
- Age above 45.
- Any uterus or tubal abnormalities that affect fertility or any pelvic inflammatory condition.

The patients were assigned to two groups: the first letrozole group (48 patients) and the second tamoxifen group (40 patients).

Study Protocol

Letrozole group received dose for ovulation induction 2.5 mg twice daily from day 3 of the menstrual cycle for 5 days for three cycles, and Tamoxifen group received dose for ovulation induction 20 mg twice daily on days 2, 3, 4, 5 and 6 of cycle for three cycles. Treatment has been stopped if they become pregnant or fail to the concept after three months. All the selected patients underwent hormonal assessment and BMI was calculated at baseline data. Ultrasound examinations are done at day 12 of the menstrual cycle to monitor dominant follicle measurements, endometrial thickness, and follicular number. Secondary outcome measures include pregnancy rate, miscarriage rate and occurrence of adverse events.

Statistical Analysis

The data were analyzed with Statistical Package for Social Sciences (SPSS)-27, a statistical tool that was readily available (SPSS-version 27). Frequency, percentage, mean, standard deviation, and range are used in statistics (minimum-maximum values). Measurements were employed to present the data. Students' t-test for difference between two independent means was used to assess the significance of differences between various means (quantitative data). When available, the significance of differences in percentages (qualitative data) was examined using the Pearson Chi-square (χ2-test) with Yate's correction or the Fisher Exact test. When the p-value was equal to or less than 0.05, statistical significance was evaluated.

RESULTS

A total of 88 infertile women seeking pregnancy were enrolled in this study. They were randomly assigned to 2 treatment groups (40 patients TMX group, 48 patients letrozole group). The mean age of TMX group was 30.7 ± 5.7 years, The mean age of letrozole group was 28.3 ± 7.1 years, Table 1 shows that there was no statistically significant difference in the patients' characteristics (age, BMI and duration of infertility) between both studied groups, $p > 0.05$

As regarding primary outcome measure, TMX showed significantly higher endometrial thickness (8.11 ± 1.10 mm versus 7.52 ± 1.52 mm) in first cycle and (8.48 ± 1.11 mm versus 7.63 ± 1.59 mm) in the second cycle compared to letrozole group while in third cycle, tamoxifen showed higher endometrial thickness but not significant (8.33 ± 1.56 mm versus 7.49 ± 1.25 mm) compared to letrazole group (Table 2).

The mean ± SD of follicular diameter in the three cycles for both groups: the first cycle, in TMX group was 18.44 ± 2.72 mm,

Table 1: Patients' characteristics in both study groups

		Tamoxifen	*Letrozole*	*p-value*
Age (years)	Mean ± SD (Range)	30.7 ± 5.7 (18–42)	28.3 ± 7.1 (17–42)	0.100
BMI (Kg/m^2)	Mean ± SD (Range)	27.43 ± 4.82 (19.57–46.74)	29.27 ± 6.01 (18.90–43.57)	0.123
Duration of infertility (years)	Mean ± SD (Range)	5.0 ± 2.5 (1-11)	5.2 ± 3.7 (1–16)	0.758

#Significant difference among two independent means using Students-t-test.

in letrazole group was 18.59 ± 3.12 mm. In the second cycle, the TMX group becomes 19.58 ± 3.51 mm, and the letrozole group becomes 18.91 ± 3.19 mm. The third cycle was 17.94 ± 3.92 mm (TMX group) and 18.81 ± 2.09 mm (letrozole group). The follicular diameter was comparable in both groups, no significant difference between TMX and letrozole groups as shown in Table 3.

TMX group showed 30 patients conceived (pregnancy rate of 75%) and 2 patients had a miscarriage (5%). In letrozole group, 29 women conceived (60.4%), and only 2 patients had a miscarriage (4.2%). TMX higher pregnancy rate than letrozole (75% versus 60.4%), with no statistically significant difference (Table 4).

DISCUSSION

Anovulation disorders cause about 30% of infertility and are characterized by irregular periods (oligomenorrhoea) or the lack of menstruation (amenorrhoea).[14] Problems with the ovary, pituitary, or hypothalamus can cause anovulation. The most frequent endocrine disorder in women of reproductive age and the major cause of anovulatory infertility is polycystic ovarian syndrome (PCO).[15] In the present study, Follicular diameter is almost convergent no statistically significant difference between both groups. Agree with Abd El Monaem *et al.* that 150 infertile women who were diagnosed as anovulatory infertility patients were divided into three groups: Group 1 (CC), Group 2 (letrozole), Group 3 (TMX). It shows no statistically significant difference regarding follicle diameter in the three studied groups. In the present study, endometrial thickness was significantly higher with the use of TMX. The Eman A. Kishk study reported that tamoxifen showed significantly higher endometrial thickness (8.2 mm versus 7.08 mm) than the letrozole group.[16] According to Abu Hashim *et al.*, there was no significant increase in endometrial thickness in the letrozole group on the day of hCG injection.[17] Unlike the current study, Seyedoshohadaei *et al.* reported higher endometrial thickness with letrozole than tamoxifen, although there was no statistically significant difference.[18] The present study has shown that TMX higher rate of pregnancy than letrozole (75% versus 60.4%), with no statistically significant difference. Both TMX and letrozole have a comparable rate of miscarriage (5% *vs.* 4.2%) Results shown in Figures 1 to 3.

Table 2: Comparison of endometrial thickness of 3 cycles between the two study groups by Students-t-test

	Tamoxifen	*Letrozole*	*p-value*
Endometrial thickness after treatment:			
First	8.11 ± 1.10 (5–10)	7.52 ± 1.52 (5–10)	0.047#
Second	8.48 ± 1.11 (6–10)	7.63 ± 1.59 (5–10)	0.017#
Third	8.33 ± 1.56 (5–10.5)	7.49 ± 1.25 (6–10)	0.067

-Data were presented as Mean ± SD (Range)

#Significant difference among two independent means using Students-t-test.

Table 3: Comparison of follicular diameter of 3 cycles between the two study groups by Students' t-test

	Tamoxifen	*Letrozole*	*P-value*
Follicular diameter			
First	18.44 ± 2.72 (11–23)	18.59 ± 3.12 (8–25)	0.815
Second	19.58 ± 3.51 (9–24)	18.91 ± 3.19 (12–26)	0.427
Third	17.94 ± 3.92 (12–24)	18.81 ± 2.09 (14–22)	0.364

#Significant difference between two independent means using Students-t-test.

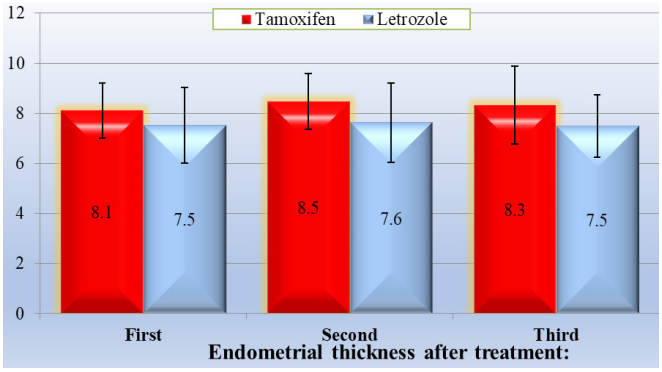

Figure 1: Comparison of endometrial thickness of 3 cycles between the two study groups by Students-t-test

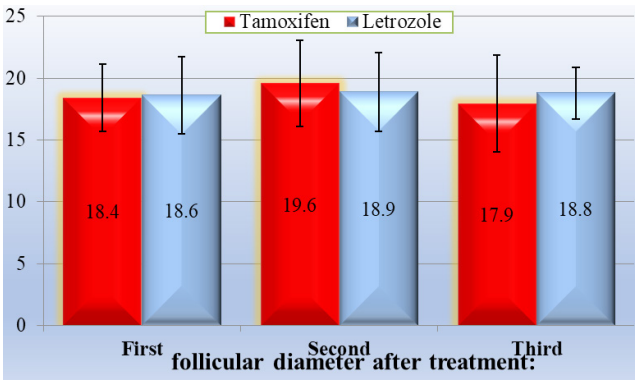

Figure 2: Comparison of the follicular diameter of 3 cycles between the two study groups by Students' t-test

Table 4: Comparsion among the studied groups regarding their clinical pregnancy rate and rate of miscarriage

		Tamoxifen		*Letrozole*		
		No	*%*	*No*	*%*	*p value*
Pregnancy rate	Positive	30	75.0	29	60.4	0.147
	Negative	10	25.0	19	39.6	
Rate of miscarriage	Positive	2	5.0	2	4.2	0.852
	Negative	38	95.0	46	95.8	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

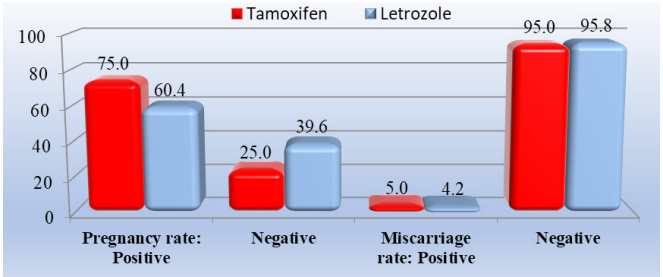

Figure 3: Comparsion between the studied groups regarding their clinical pregnancy rate and rate of miscarriage

Hassan ZB comparative study between CC and TMX for induction of ovulation hypothesizes TMX estrogenic impact on the endometrium and cervical mucus would lead to higher pregnancy rate.[19] The clinical effects of ovulation induction with letrozole and clomiphene citrate were compared in a study by Sakar *et al.* The letrozole group had a clinical pregnancy rate of 52%.[20] No significant difference in The rate of miscarriage in both groups this agree with Eman A. Kishk in which Spontaneous abortion rate (3.3% and 5% for letrazole and tamoxifen, respectively),[16] in the present study (4% and 5% for letrazole and tamoxifen, respectively).

CONCLUSION

Both letrozole and TMX were effective ovulation induction agents. There was no significant difference between both agents in Follicular diameter, Number of mature follicles, rate of miscarriage. TMX was superior to letrozole in achieving a higher Endometrial thickness. There was a high pregnancy rate, high in TMX group compared to lertozole group, and both drugs had few tolerable side effects.

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