The Egyptian Journal of Hospital Medicine (October 2023) Vol. 93, Page 7779-7782

Impact of Clomiphene Citrate, Tamoxifen and Letrozole in Women with Unexplained Infertility on Endometrial Thickness

Dina Y. Mansour[1], Amr M. El Helaly[1], Khaled H. Hassan[2]
[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, Egypt
[2]Department of Obstetrics and Gynecology, Qena General Hospital, Egypt
***Corresponding author:** Dina Yahia Mansour, **Mobile:** (+20) 01025375711, **E-mail:** Dinayahiamansour@hotmail.com

ABSTRACT
Background: Polycystic ovarian syndrome (PCOS), which is characterized by irregular menstrual cycles, is the most common diagnosis given to affected women. For these women, ovulation induction is the usual course of therapy.
Objective: To assess the impact of clomiphene citrate, letrozole, and tamoxifen on endometrial thickness in women with unexplained infertility.
Subjects and Methods: Female patients with unexplained infertility at Ain Shams University Maternity Hospital participated in the experiment. To stimulate ovulation, they were randomly assigned to receive letrozole, tamoxifen, or clomiphene citrate.
Results: The results indicate that there was a substantial statistical difference in basic endometrial thickness (ET) between the three groups, whereas there was not as much of a difference in pre-ovulatory ET.
Conclusion: Letrozole and tamoxifen (TMX) should be seen as optional therapies for women who are CC-resistant. In addition, letrozole showed fewer side effects than tamoxifen and performed better than TMX in terms of accelerating the rate of ovulation and pregnancy.
Keywords: Clomiphene Citrate, Endometrial Thickness, Letrozole, Ovulation Induction, Tamoxifen.

INTRODUCTION

Infertility is described as the inability of a couple to conceive after six months for women 35 and older and after twelve months for women under 35 who regularly engage in sexual activity without the use of contraception [(1)]. Inducing ovulation is a very successful therapy for such ladies. For a considerable amount of time, clomiphene citrate—a selective modulator of estrogen receptors—has been the drug of choice. It functions primarily on the hypothalamus, releasing the hypothalamus from negative feedback by acting antagonistically on estrogen receptors. This increases the release of gonadotrophin [(2)].

Letrozole, an aromatase inhibitor, is a substitute for clomiphene citrate in ovulation induction. It blocks the enzyme by preventing androgens from being aromatized to estrogen, relieving the hypothalamic-pituitary axis of estrogen's negative feedback [(3-5)].

This study aimed to assess the impact of clomiphene citrate, letrozole, and tamoxifen on endometrial thickness in women with unexplained infertility.

The first and second outcomes of this study were the number of mature follicles in each group, the endometrial thickness, unsuccessful induction, cycle cancellation, ovarian hyperstimulation syndrome, and mid-luteal serum progesterone and clinical pregnancy rate, respectively.

SUBJECTS AND METHODS

A double-blind randomized controlled trial was conducted at the Ain Shams University Maternity Hospital's outpatient infertility clinic. Female patients with unexplained infertility at Ain Shams University Maternity Hospital participated in the study. To stimulate ovulation, they were offered letrozole, tamoxifen, or clomiphene citrate.

The age range that was open to consideration was 20 to 35. Regarding examination of typical semen, The World Health Organization (WHO) has published revised lower reference limits for semen analysis [(6)]. A typical uterine cavity was seen on both HSG and transvaginal ultrasonography. Normal tubal patency was evaluated using chromotubation laparoscopy and/or HSG [(7)].

The following are the exclusion criteria: age greater than 35, low ovarian reserve as indicated by a serum FSH > 10 mIU/ml or a serum AMH < 1 ng/ml, body mass index of 35 kg/m^2 or higher, clomiphene citrate (CC), resistance to letrozole or tamoxifen, or a history of serious side effects from clomiphene citrate (CC) (blurring of vision, severe OHSS), predicted decreased endometrial receptivity (e.g., intrauterine abnormalities: adhesions or chronic endometritis).

Sampling Method and Randomization

Patients undergoing induction of ovulation with tamoxifen, letrozole, or clomiphene citrate were randomly allocated to one of three groups using a computer-generated sequence of 1: 1: 1. The groups were called the tamoxifen, letrozole, or clomiphene citrate group.

Allocation and perception

Utilizing opaque, sealed envelopes sent to a nurse—a third party—who subsequently identified the women's research regions, which were their arms. Every woman was asked to remove one envelope. Based on the number inside their envelope—which was chosen at random by a computer—women were categorized into either group 1, group 2, or group 3.

Received: 23/05/2023
Accepted: 24/07/2023

Sample Size

Three groups comprising one hundred thirty-five women were employed in the study. Three groups of women were treated: forty-five on clomiphene citrate, forty-five on tamoxifen, and forty-five on orlistat.

Study procedures and interventions

The study statistician arbitrarily split the subjects into three groups: First group: starting on day two of the cycle and continuing through day six, 45 women using clomid® (sanofi Aventis, UK) for ovulation induction, were given 100 mg of the medicine daily for five days. The drug was supplied as 50 mg pills. Second group: 45 women were given 40 mg of tamoxifen (Nolvadex® Asrta Zeneca) every day for five days, starting on day two and ending on day six of the cycle, in order to promote ovulation. The drug was supplied in 20 mg tablet form. Third group: 5 mg of letrozole was administered daily for 5 days, from day 2 to day 6, of the cycle, to 45 women who were taking 2.5 mg tablets of the medicine (Letrozole; Femara 2.5 mg ®NOVARTIS) for ovulation induction.

For all selected women, the following was done:

Comprehensive medical history; baseline serum levels of FSH, LH, and E2; free testosterone, estradiol, TSH, free T3 and T4, prolactin, and HSG; semen analysis for their partners to rule out any infertility-related causes; and vaginal ultrasound folliculometry on the ninth day of the menstrual cycle with follow-up every other day until the largest follicle's mean diameter reaches 18 mm, human chorionic gonadotropin (HCG; Epifasi 5000 ®EPICO) injections of 10,000 IU were used to induce ovulation when the leading follicle reached a diameter of at least 18 mm. Protected sexual activity was advised in order to avoid high-order multiple conceptions, and injections of HCG were not given if three or more follicles measuring greater than 17 mm were found. It was advised to engage in unrestricted sexual activity the day after HCG injection. The endometrial thickness in millimeters on the day of trigger in the sagittal view was estimated using the maximum thickness between the highly reflective interface of the endometrial-myometrial junction and the mean endometrial thickness for the three cycles. Furthermore, the average number of follicles throughout the course of the three cycles was determined. Transvaginal ultrasonography was done every other day until day 20 of the cycle. The endometrial thickness was assessed at that point. If there was not a dominant follicle at that point in the cycle, it was terminated. Serum progesterone levels were measured after nine days of exposure to HCG triggers. If pregnancy appeared after two cycles, the mean value for the two cycles was computed; if not, just one reading was noted. Serum progesterone in the mid-luteal phase, endometrial thickness, and the number of developed follicles were measured throughout three cycles.

Ethical Consideration

Before this study could be conducted, the Ethical Committee of the Department of Obstetrics and Gynecology at Ain Shams University's College of Medicine provided its approval. Each participant provided her informed consent before to being included in the study and after being fully informed about its objectives and procedures. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Analysis

After being gathered, revised, coded, and entered, the data were uploaded to IBM SPSS, a statistical tool, version 20. The quantitative data, were expressed as means±standard deviations, and ranges while the qualitative data were given as percentages and frequency. Chi square test (X^2) is used to calculate the difference between two or more groups of qualitative variables. The independent samples t-test was developed to compare two independent groups of regularly distributed variables (parametric data). A P value of 0.05 was judged significant.

RESULTS

The next table shows that although there was no statistically significant difference in age or weight between the three groups, there was a statistically significant difference in the duration of infertility (**Table 1**).

Table (1): Comparison between CC group, tamox group and letrozole group regarding age, duration of infertility and obesity

		CC group	Tamox group	Letrozole group	One Way ANOVA test/X^2	
		No.= 45	No.= 45	No.= 45	F/X^2	P-value
Age	Mean ± SD Range	28.04 ± 4.59 20 – 38	28.36 ± 4.84 20 – 38	28.76 ± 4.57 20 – 38	0.263•	0.769
Duration of infertility	Mean ± SD Range	3.46 ± 1.15 2 – 5	4.13 ± 1.21 3 – 7	3.95 ± 1.41 2 – 6	3.389•	0.037
Obesity	No Yes	28 (62.2%) 17 (37.8%)	33 (73.3%) 12 (26.7%)	31 (68.9%) 14 (31.1%)	1.297*	0.523

Semen analysis, uterine cavity, and tubes were normal for all the cases of this study (Table 2).

Table (2): Distribution of the studied cases according to semen analysis, uterine cavity and tubes

		CC group		Tamox group		Letrozole group	
		No.	**%**	**No.**	**%**	**No.**	**%**
Semen analysis	Normal	45	100.0%	45	100.0%	45	100.0%
Uterine cavity	Normal	45	100.0%	45	100.0%	45	100.0%
Tubes	Patent	45	100.0%	45	100.0%	45	100.0%

While there was no statistically significant difference between the three groups in terms of basic ET, there was a highly significant difference in terms of preovulatory ET (**Table 3)**.

Table (3): Comparison between CC group, tamox group and letrozole group regarding basic ET and preovulatory ET

		CC group	Tamox group	Letrozole group	One Way ANOVA test	
		No.= 45	**No.= 45**	**No.= 45**	**F**	**P-value**
Basic ET	Mean ± SD Range	2.90 ± 1.02 1 – 4.8	2.68 ± 0.75 1 – 3.7	2.61 ± 0.68 1 – 3.7	1.474	0.233
Preovulatory ET	Mean ± SD Range	6.91 ± 2.13 4 – 10	10.96 ± 2.23 7.5 – 15.9	11.60 ± 2.38 8.1 – 16.2	57.410	< 0.001

There was a statistically significant difference in the clinical pregnancy rate between the three groups; however, no significant difference was seen in the number of follicles or the mid-luteal serum progesterone (**Table 4**).

Table (4): Comparison between CC group, tamox group and letrozole group regarding No. of follicles, Clinical pregnancy rate and Mid-luteal serum progesterone

		CC group	Tamox group	Letrozole group	One Way ANOVA test/X^2	
		No.= 45	**No.= 45**	**No.= 45**	**F/X^2**	**P**
No of follicles	Mean ± SD Range	1.98 ± 0.93 0.5 – 3	1.31 ± 0.64 0.4 – 2.5	1.14 ± 0.56 0.3 – 2.5	16.600	< 0.001
Clinical pregnancy rate	No Yes	34 (75.6%) 11 (24.4%)	30 (66.7%) 15 (33.3%)	27 (60.0%) 18 (40.0%)	2.495	0.287
Mid-luteal serum progesterone	Mean ± SD Range	25.07 ± 4.81 17 – 34	30.22 ± 4.98 20 – 38	29.44 ± 4.86 20 – 38	14.568	< 0.001

DISCUSSION

TMX functions as a selective modulator of estrogen receptors. TMX improves endometrial thickness and cervical mucus by acting as an agonist on the estrogen receptor in the endometrium and vaginal mucosa, with a short half-life of 5-7 days [8].

Our results are in line with **Elshamy and Khalafallah** [9] study, which found no appreciable variations in the prevalence of obesity among the three categories. They did not discover any appreciable variations in the duration of infertility, which sets their results apart from ours. Additionally, our results are corroborated by their observation that there was no statistically significant variation in basic endometrial thickness among the three groups.

The results of this study show that there was a statistically significant difference in preovulatory endometrial thickness between the tamoxifen and letrozole groups on one side and the clomiphene citrate group (CC) on the other. These groups are letrozole group 2 and TMX group 3.

While groups 2 and 3 had higher clinical pregnancy rates than group 1, the difference did not achieve statistical significance. Group 1 had a significantly larger mean number of mature follicles than the other two groups. Furthermore, compared to group 1, groups 2 and 3 showed significantly increased mid-luteal serum progesterone levels.

This research found that the mean number of follicles in the TMX group was 1.31 ± 0.64 follicles, ranging between 0.4 and 2.5 follicles, and that the clinical pregnancy rate was 33.3%. The mid-luteal serum progesterone had a mean of 30.22 ± 4.98 ng/mL and ranged from 20 to 38 ng/mL.

We divided the 124 anovulatory patients into two groups (letrozole and CC). The CC group had more follicles than the letrozole group, and the letrozole group's mean endometrial thickness was 8.3 mm, higher than that of the CC group's 7.2 mm. The letrozole group had higher pregnancy rates (33% vs. 28%) while the CC group had higher ovulation rates (69.5% vs. 40%). In addition, 200 anovulatory people were divided into two groups, CC and TMX, and participated in the **Pant's** study. The results of the study indicated that the rate of ovulation was 65% and the rate of pregnancy was 63% [10]. Furthermore, in line with our results, **El-Gharib *et al.*** [11] study found that letrozole outperformed TMX in achieving a higher clinical pregnancy rate, 5.56% versus 2.22% respectively. In the experiment, 60 infertile women with PCOS, that was resistant to CC, were divided into two groups: TMX and letrozole.

But according to another study by **Diamond *et al.*** [12], which included 746 infertile women, CC, letrozole, and gonadotrope were the three groups given ovarian stimulation; the results indicate that CC has a greater clinical pregnancy rate than letrozole.

CONCLUSION

For female patients who are CC-resistant, letrozole and TMX need to be considered as elective treatments. Furthermore, letrozole outperformed TMX in terms of speeding the rate of ovulation and pregnancy and had less adverse effects than tamoxifen.

- **Financial support and sponsorship:** Nil.
- **Conflict of Interest:** Nil.

REFERENCES

1. **Barbieri R (2019):** Female infertility. In: Yen and Jaffe's Reproductive Endocrinology. Philadelphia, Content Repository Only. pp. 556-581. https://search.worldcat.org/title/yen-jaffes-reproductive-endocrinology-physiology-pathophysiology-and-clinical-management/oclc/1025333557
2. **Farquhar C, Bhattacharya S, Repping S *et al.* (2019):** Female subfertility. Nature Reviews Disease Primers, 5(1): 1-21.
3. **Franik S, Kremer J, Nelen W *et al.* (2014):** Aromatase inhibitors for subfertile women with polycystic ovary syndrome. Cochrane Database of systemic Review, (2): CD010287. doi: 10.1002/14651858.CD010287.
4. **Sanchez-Spitman A, Swen J, Dezentje V *et al.* (2019):** Clinical pharmacokinetics and pharmacogenetics of tamoxifen and endoxifen. Expert Review of Clinical Pharmacology, 12(6): 523-536.
5. **Cooper T, Noonan E, von Eckardstein S (2010):** World Health Organization reference values for human semen characteristics. Hum Reprod Update, 16: 231-45.
6. **Ecochard R, Boehringer H, Rabilloud M *et al.* (2001):** Chronological aspects of ultrasonic, hormonal, and other indirect indices of ovulation. BJOG., 108:822-29.
7. **Lim C, Hasafa Z, Bhattacharya S *et al.* (2011):** Should a hysterosalpingogram be a first-line investigation to diagnose female tubal subfertility in the modern subfertility workup? Hum Reprod., 26: 967-71.
8. **Gadipudi A, Dasari P, Sagili H (2017):** Tamoxifen for ovulation induction in infertile PCOS women who did not conceive with 3 or more cycles of clomiphene citrate: A prospective clinical study. Fertil Sci Res., 4: 22-29
9. **Elshamy E, Khalafallah M (2018):** Impact of clomiphene citrate, tamoxifen and letrozole to induce ovulation in anovulatory women with polycystic ovary syndrome on endometrial thickness and clinical pregnancy rates, a two center cohort study. Obstet Gynecol Int J., 9(4): 260-264.
10. **Pant P (2013):** Comparison of efficacy of tamoxifen and clomiphene citrate for induction of ovulation. Medica Innovatica, 2(1): 68–71.
11. **El-Gharib M, Mahfouz A, Farahat M (2015):** Comparison of letrozole versus tamoxifen effects in clomiphen citrate resistant women with polycystic ovarian syndrome. J Reprod Infertil., 16(1): 30-35.
12. **Diamond M, Legro R, Coutifaris C (2015):** Letrozole, gonadotropin, or clomiphene for unexplained infertility. N Engl J Med., 373:1230-1240.