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ORIGINAL ARTICLE

A Comparative Study of the Effects of Clomiphene Citrate, Tamoxifen, and Letrozole on Endometrial Thickness During Ovulation Induction

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Abstract

Background: **Infertility is described as married couple's incapability to conceive in 1 year despite regular marital life. This issue affects ten-fifteen percent of married couples worldwide.**

Aim: **Research's goal is to compare the effects of three drugs used to induce ovulation: clomiphene citrate, tamoxifen, & letrozole.**

Regarding: **Impact on endometrial blood flow. Impact on endometrial thickness in females with anovulatory infertility.**

Subject and methods: **The study had been carried out in Al Hussin Maternity Hospital and Military Production Specialized Hospital. Studied cases were drawn from our studied case infertility clinic.**

Results: **Endometrial thickness, endometrial PI, and endometrial RI differ significantly among the 3 groups ($P < 0.001$).**

Conclusion: **Letrozole and TMX both had significantly greater endometrial thickness than CC. Letrozole significantly increased the number of follicles compared to other TMX & CC groups. So letrozole and TMX can induce and even offer better results than CC and each one may be used as the first line for therapy of anovulatory infertility.**

Keywords: Clomiphene citrate, Endometrial thickness, Induction of ovulation, Tamoxifen & letrozole

1. Introduction

Infertility is defined as a married couple's inability to conceive in 1 year despite regular marital life. This is an issue that affects ten-fifteen percent of married couples worldwide.[1]

Anovulation accounts for approximately twenty-twenty-five percent of the reasons for infertility because ovulation is a critical event in reproduction. Anovulation can be affected by issues with the ovary, pituitary gland, or hypothalamus. World Health Organization (WHO) has classified these reasons into 3 major categories according to the site of lesion and gonadotropin production: WHO type 1 (hypogonadotropic hypogonadism): affected by any lesion impacting pituitary or hypothalamus and impacting gonadotropin production. WHO type 2 (normogonadotropic hypogonadism): the common reason for anovulation, affected by polycystic ovarian syndrome (PCO). WHO type 3 (hypergonadotropic hypogonadism): This is a typical sign of ovarian failure.[2]

Polycystic Ovarian Syndrome (PCO) was an endocrinal disorder in females of reproductive years old and is the primary reason for anovulatory infertility. Its prevalence range from six-ten% in the general population. Its diagnostic criteria are at least two of the following (Rotterdam criteria): 1- oligo or anovulation 2- hyperandrogenism (laboratory-confirmed or by clinical symptoms) 3- polycystic ovaries on ultrasound.[2]

CC is a non-steroidal selective oestrogen receptor modulator that acts as both an oestrogen agonist and antagonist. It binds to oestrogen receptors,

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primarily in hypothalamus, interrupting negative feedback of rising oestrogen levels and resulting in continued FSH production, which stimulates follicular growth and maturation.[3]

It may also improve folliculogenesis by involving a direct action on ovary without the intervention of the hypothalamo-pitutary system.[4]

It performs like agonist on oestrogen receptors in the endometrium and vaginal mucosa, and its half-life is short (5–7 days), resulting in improved cervical mucus, increased endometrial thickness, and possibly improved endometrial blood flow.[4]

Badawy and Gibreal,[5] study shows that CC is superior to tamoxifen for ovulation induction as first-line therapy. In **Dhaliwal *et al.*,**[5] and **Pant *et al.*,**[6] studies show that tamoxifen is superior to CC. In **Kar *et al.*,**[7] and **Roy *et al.*,**[8] studies show that letrozole is superior to CC. These studies were done to detect the effect of these drugs on ovulation induction in anovulatory women and their relation to pregnancy rate and the results were not the same. **Selim and Borg**,[9] and **Wang *et al.*,**[10] studies show that endometrial blood flow and thickness during ovulation induction may have a role in improving pregnancy results. So this study was held to detect if these drugs have positive or negative impacts on endometrial blood flow and thickness during ovulation induction, which may affect the pregnancy rate.

Research's goal is to compare the effects of three drugs used to induce ovulation: clomiphene citrate, tamoxifen, and letrozole, Regarding: Impact on endometrial blood flow. Impact on endometrial thickness in females with anovulatory infertility.

2. Patients and methods

The study had been carried out in Al Hussin Maternity Hospital and Military Production Specialized Hospital. Studied cases had been recruited from an out Patient Infertility clinic.

Study design: research included ninety infertile females who had already been diagnosed with anovulatory infertility and met inclusion criteria. This research adhered to the rules of the Al Azhar University Obstetrics and Gynecology Ethics Committee. All females participating in this research who had anovulatory infertility had their research procedures explained to them, and informed written consent had been acquired.

Inclusion Criteria for patients in the study: years old: eighteen—thirty-five, body mass index: eighteen - thirty kg/m^2, studied cases with normogonadotropic hypogonadism (WHO type 2), normal uterus and studied case fallopian tubes showed by hystrosalpingography, history and clinical data suggestive of PCO e.g. obesity, hirsutism, oligomenorrhea …. etc, normal semen analysis of husband and Normal serum Prolactin.

Exclusion Criteria for patients in research: Hyperprolactinemia, thyroid dysfunction, active liver diseases, etc, local diseases like endometriosis, ovarian tumors, hydro- or pyosalpinx, etc, history of chronic cardiovascular disease, and known allergy to any of medications used in the induction of ovulation.

This research includes 90 infertile females who have already been diagnosed with anovulatory infertility. All patients had been randomly divided by computer allocation method into 3 groups.

Group A: This group included 30 studied cases who were using clomiphene citrate to induce ovulation. From day three to day seven of the cycle, studied cases take one hundred mg of the drug daily for five days. Because each tablet of the drug contains 50 mg, studied cases take a dose in form of two tablets after breakfast for 1 cycle.

Group B: This group included 30 studied cases who were using letrozole to induce ovulation. Studied case Patients take 5 drugs daily for five days, beginning on day 3 and ending on day seven of the cycle. Because each tablet of the drug contains 2.5 mg, studied cases take a dose in the form of two tablets after breakfast for one cycle.

Group C; this group consists of 30 studied cases who are undergoing tamoxifen-induced ovulation induction. Studied cases take 60 mg of the drug daily for five days, beginning on day three and ending on day 7 of the cycle. Because each tablet of the drug contains 20 mg, studied cases take three tablets after breakfast for one cycle.

Operational design: All females taking part in the research have explained the process. Before beginning research, all studied cases provided written consent and were counseled on the risks and benefits of research.

2.1. Methods

Complete history taking: Personal history: name, years old, marital status, address menstrual history: years old of menarche, menstrual disturbance, dysmenorrhea, and related symptoms. Current history: of chronic diseases, duration of infertility, symptoms, and signs suggestive of endocrine disorders and medication, HTN, DM, family history of similar condition or diabetes, history of allergy to any medication, surgical history of operation, laparoscopic interference, laser therapy of hirsutism.

Examination: General examination: Assessment of vital signs, measurement weight, height and

determination of acne. **Abdominal and local clinical examination:** Scar from the previous operation, mass, tenderness or rigidity, and any clinically detectable pathology in the abdomen or pelvis. **Bimanual pelvic examination of** both the adenexa and the uterus is examined for any abnormalities of the female genitalia.

Investigations: Hormonal profile on day two-five of the cycle: FSH, LH, E2, Prolactin, TSH, free T3 and T4. Hysterosalpingography was to confirm tubal patency and to rule out the malefactor, sperm analysis was performed. Endometrial thickness in mm was measured in sagittal view like maximum thickness among greatly reflective interfaces of the endometrial-myometrial junction on day ten of the cycle, then every other day until the mean diameter of the biggest follicle reached 18 mm. If no dominant follicle appeared at day fourteen or fifteen of the cycle, transvaginal ultrasound was continued till day twenty and on this day endometrial thickness was measured.

Midluteal (day 21of cycle) serum progesterone was done for patients to reveal the presence or absence of ovulation, and to evaluate the presumed role of color Doppler, if any, in assessment of ovulation manifested by a better ovulation rate.

Primary outcome: Endometrial thickness.

Secondary outcome: Endometrial blood flow, improvement and number of the follicles (Ovulation) and pregnancy rate (biochemical).

Ethical Consideration: The research protocol had been submitted to the Institutional Research Board of Al Azhar University's faculty of medicine for approval. Each research participant had given verbal consent after being informed. Confidentiality and personal privacy were respected at all stages of the research.

Statistical analysis: Data from the history, basic clinical examination, laboratory investigations, and result measures were coded, entered, and analyzed in Microsoft Excel software. After that, data was imported into Statistical Package for Social Sciences (SPSS version 21.0) software for analysis. Depending on type of data, the following examination was used to examine for significance: change and association of qualitative variable by Chi-square test (X^2). The *t*-test is used to compare quantitative independent groups. The *P* value for significant outcomes was set at <0.05 and < 0.001 for highly significant outcomes.

3. Results

Our research contained 90 infertile females who had already been diagnosed with anovulatory infertility and meet inclusion criteria. Research followed ethical committee rules of Obstetrics and Gynecology, Al Azhar University., 30 took Tamoxifen and 30 took Letrozole Table 1.

Based on the table above we found Mean ± SD for age in group one 28.5 ± 4.75 and 26.5 ± 4.25 for group two 28 ± 4.5 for group three. We also found no variation among the 3 groups concerning Weight and BMI Tables 2 and 3.

Table 1. Demographic data.

Age (years)	CLOMIPHENE group *n*, thirty (percent)	TAMOXIFEN group *n*, thirty (percent)	LETROZOLE group *n*, thirty (percent)	Test of sig	*P* value
Mean ± SD.	28.5 ± 4.75	26.5 ± 4.25	28 ± 4.5		
Median (IQR)	29 (23–30)	27 (25–31)	28 (25–31)	F = 1.201	0.218
Range (Min-Max)	19 (19–38)	17 (18–35)	18 (19–37)		
Weight (kg)	CLOMIPHENE group n, thirty (percent)	TAMOXIFEN group n, thirty (percent)	LETROZOLE group n, thirty (percent)	Test of sig	*P* value
Mean ± SD.	101.6 ± 22	99.2 ± 24	109.05 ± 24.25		
Median (IQR)	85 (78–100)	85 (70–104.7)	93 (79.3–107.3)	F = 1.123	0.307
Range (Min-Max)	7 (23–30)	8 (23–31)	5 (24–29)		
BMI	CLOMIPHENE group n, thirty (percent)	TAMOXIFEN group n, thirty (percent)	LETROZOLE group n, thirty (percent)	Test of sig	*P* value
Mean ± SD.	26.5 ± 1.75	27 ± 2	26.5 ± 1.25		
Median (IQR)	27 (26–28)	26 (25–27.75)	27 (26–28)	F = 1.265	0.160
Range (Min-Max)	88 (57.7–145.5)	96 (51.2–147.2)	97 (60.9–157.2)		

Table 2. Showing endometrial thickness distribution among the study sample.

Endometrial thickness	CLOMIPHENE group *n*, thirty (%)	TAMOXIFEN group *n*, thirty (%)	LETROZOLE group *n*, thirty (%)	Test of sig	*P* value
Mean ± SD.	5.95 ± 1.675	8.6 ± 2.05	9.55 ± 1.575		
Median (IQR)	7 (5.918–7.4)	10 (8.5–10.5)	9 (8.5–10.8)	F = 0.192	<0.001
Range (Min-Max)	6.7 (2.6–9.3)	8.4 (4.5–12.7)	6.3 (6.4–12.7)		

Table 3. Showing Ovulation percentage distribution among the study sample.

Ovulation Percentage	CLOMIPHENE group *n*, thirty (percent)		TAMOXIFEN group *n*, thirty (percent)		LETROZOLE group *n*, thirty (percent)			
Ovulation	positive	negative	positive	negative	positive	negative	Test of sig	*P* value
N (%)	31 (62)	19 (38)	36 (72)	14 (28)	34 (68)	16 (32)	$X^2 = 26.7$	<0.001

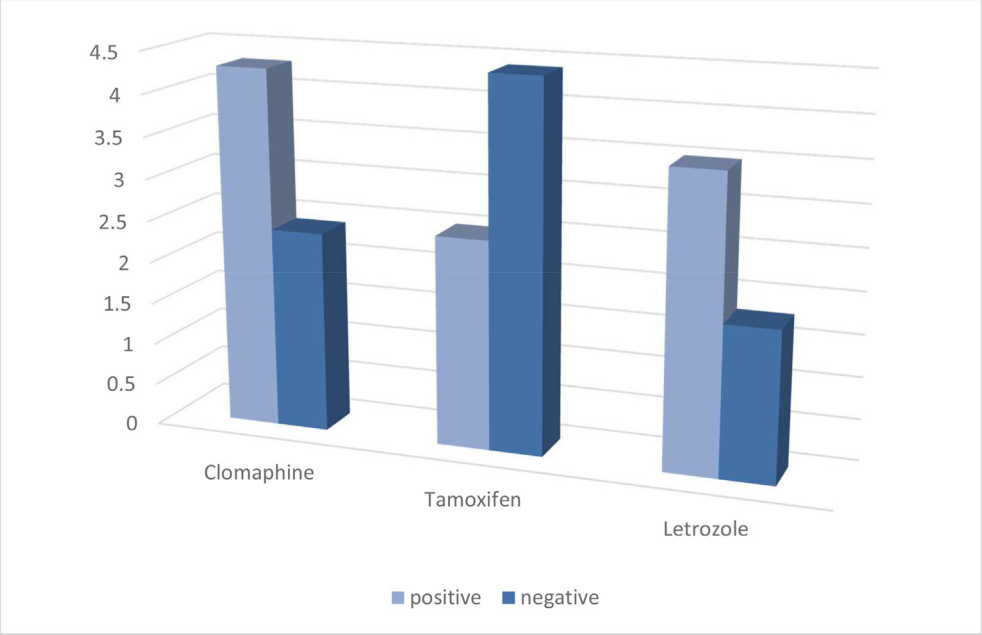

Fig. 1. Boxplot showing follicle diameter among the study population.

According to the table, there is variation among the 3 groups Fig. 1.

There is variation among the 3 groups.

4. Discussion

Research carried out in Al Hussin Maternity Hospital and Military Production Specialized Hospital. Studied cases recruited from an out Patient Infertility clinic. This research included 150 infertile females who had already been diagnosed with anovulatory infertility and met inclusion criteria. The research adhered to ethical committee rules of the Department of Obstetrics and Gynecology at Al Azhar University. All females with anovulatory infertility in this research were explained research processes, and informed written consent was acquired. All studied cases were haphazardly separated by method into three groups **Group A**: This group contained 30 studied cases who were using clomiphene citrate to induce ovulation. From day three to day seven of the cycle studied cases took one hundred mg of the drug daily for five days. Because each tablet of the drug contains 50 mg, studied cases took a dose in the form of two tablets after breakfast for one cycle. **Group B**: This group contained 30 studied cases who were using letrozole to induce ovulation. From day three to day seven of the cycle studied cases took five mg of drug daily for five days. Because each tablet of the drug contains 2.5 mg, studied cases took a dose in the form of two tablets after breakfast for one cycle. **Group C**; This group contained 30 women who were using tamoxifen to induce ovulation. From day three to day seven of the cycle, the studied cases took 60 mg of the drug daily for five days. Because each tablet of the drug contains 20 mg, studied cases took three tablets after breakfast for one cycle.

-we found Mean ± SD for age in group one 28.5 ± 4.75 and 26.5 ± 4.25 for group two 28 ± 4.5 for group three. We also found no variation among the three groups concerning Weight and BMI.

In a study by **Fariba *et al.*,**[11] they showed 150 unovulatory infertile females with the isolated nonpolycystic ovarian syndrome were randomly assigned to one of three groups. For five days, Group A obtained clomiphene fifty mg to a maximum of 150 mg, Group B received tamoxifen ten mg to a maximum of thirty mg, and Group C obtained letrozole 2.5 mg to a maximum of 7.5 mg

till ovulation was induced. If ovulation did not happen after five days of therapy, the drug was continued for another seven days. Therapy was discontinued if they became pregnant or if the studied case did not ovulate with a maximum dose for seven days (therapy resistance) or failed to conceive after 6 months in spite of ovulation (failure of therapy). Following were the primary result measures: number of mature follicles, endometrial thickness, pregnancy rate, multiple pregnancy rate, live birth, and miscarriage. They found Mean ± SD for age in group one 24.72 (±4.66) and 25.44 (±4.18) for group two 26.94 (±4.59) for group three.

The study by **Zakaria *et al.*,**[12] was performed at El Entag El Harby Hospital. In December 2017 and June 2018, studied cases were recruited from Infertility Outpatient Clinic. This research enrolled 150 infertile females with anovulatory infertility who met inclusion criteria. This research adhered to ethical committee rules of Al Azhar University's Department of Obstetrics and Gynecology. All females with anovulatory infertility in the research were explained research processes, and informed written consents were procured. Studied cases were split into 3 groups of fifty in the latest research: Group 1 (CC), Group 2 (letrozole), and Group 3. (TMX). To begin with, groups in the research were equal in terms of birth date, BMI, type, and period of infertility. They found Mean ± SD for age in group one 27.5 ± 4.1 and 27.2 ± 3.9 for group two 27.5 ± 4.1 for group three. There was no variation in studied cases' features (birth date and BMI) between the three studied groups, P value > 0.05.

Research by **Anwar *et al.*,**[13] expected to compare the impacts of ovulation induction agents clomiphene citrate, tamoxifen, and letrozol on endometrial thickness and blood flow like non-invasive endometrial receptivity parameters in females with polycystic ovaries, found Mean ± SD for age in group one 27.5 ± 4.1 and 27.2 ± 3.9 for group two 27.5 ± 4.1 for group three.

Our results reported that There is variation among the 3 groups Regarding Endometrial thickness, Endometrial PI as well as Endometrial RI ($P < 0.001$).

In agreement with us **Zakaria *et al.*,**[12] purpose of research is to compare effects of the following three drugs throughout ovulation induction: 1- Clomiphene citrate, 2- Tamoxifen, and 3- Letrozole. It was found that there was a great variation in endometrial thickness and Doppler indices (PI and RI) as measured by *trans*-vaginal U/S in 3 tested groups, $P < 0.001$.

In agreement with us **Roy *et al.*,**[8] there are 204 anovulatory patients in 2 groups (CC and letrozole). Outcomes showed that the CC group had more follicles than the letrozole group, that ovulation rates were almost identical in the CC and letrozole groups that the pregnancy rate was greater in the letrozole group 43.8% than CC 26.4%, and that mean endometrial thickness was greater in letrozole group 9.1 mm than CC group 6.3 mm.

In agreeing with us **Hussain *et al.*,**[14] 150 anovulatory studied cases were split into 2 groups (CC and letrozole) the number of follicles was greater in the CC group than letrozole group, ovulation rate was significantly greater in the letrozole group 78.7% than CC group 53.3%, the pregnancy rate was greater in letrozole group 25.3% than CC group 16%, and mean endometrial thickness was greater in letrozole group 9.2 mm than CC group 8.4 mm.

In agreement with us **Selim and Borg,**[9] contained two hundred anovulatory PCOS studied cases, separated into 2 groups (CC and letrozole). outcomes were ovulation rate which was somewhat greater in the letrozole group 70.6% than CC group 64.6%, the pregnancy rate was somewhat greater in the letrozole group 28.4% than CC group 20.2%, mean endometrial thickness was greater in letrozole group 9.9 mm than CC group 7.7 mm, mean endometrial blood flow (PI and RI) was lower in letrozole group (1.27, 0.75) than CC group (1.67, 0.87).

In agreement with us **Badawy and Gibreal,**[5] this study includes 371 anovulatory PCOS studied cases, split into two groups (CC and TMX). Outcomes were the number of stimulated follicles are bigger in CC group than TMX, endometrial thickness was (CC 9.3 mm and TMX 10.2 mm), ovulation rate CC 64% and TMX 51.6%, Pregnancy rate CC 18.7% and TMX 10.8%.

In contrast to the research **of Fariba *et al.*,**[11] the purpose of the research was to compare the efficacy of clomiphene, tamoxifen, and letrozole in inducing ovulation in isolated non-PCOS unovulatory studied cases. Endometrial thickness was greater with tamoxifen on fourteen cycles, but not significant (8.03 ± 3.13 mm in group B vs. 7.7 ± 4.15 mm in group A and 6.07 ± 2.76 mm in group C).

Research revealed that there is significant variation among the three groups regarding ovulation percentage.

In contrast with us Zakaria *et al.*,[12] there was no variation in Ovulation and follicle diameter between 3 groups studied, $P > 0.05$.

In agreeing with us Anwar *et al.*,[13] 150 cases meeting the selection criteria were randomized into three groups: the first group received one hundred mg of clomiphene citrate, the second group received five mg of letrozole, and the third group received forty mg tamoxifen. In 3 groups, transvaginal ultrasound and Doppler were used to measure

endometrial thickness and endometrial blood flow as well as pulsatility index and resistance index on day of maximum follicular growth or day twenty in the absence of dominant follicle. Rates of ovulation (at least 1 follicle with diameter of eighteen m or greater) in 3 groups were as follows: Group 1 had a rate of thirty-three (sixty-six percent), Group 2 had a rate of thirty-six (seventy-two percent), and Group 3 had a rate of thirty-four (sixty-eight percent). A *P*-value greater than 0.05 was not significant.

4.1. Conclusion

Endometrial thickness was greater in both letrozole and TMX than in CC. The number of follicles was greater with letrozole than with other TMX and CC groups which are significantly different. So letrozole and TMX can induce and even offer better results than CC and each one can be used as the first line for the treatment of anovulatory infertility.

Consent for publication

I verify that all authors have agreed to submit the manuscript.

Availability of data and material

Available.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article.

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Conflict of interest

The authors declared that there were NO conflicts of Interest.

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