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ORIGINAL ARTICLE

A Comparative Study Between Effect of Clomiphene Citrate and Letrozole on Endometrial Vascular Indices in Patients with Polycystic Ovarian Syndrome

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Abstract

Background: **Polycystic ovarian syndrome (PCOS) is one of the common causes of infertility in reproductive-age females. Clomiphene citrate and letrozole are commonly used to induce ovulation, although they are antiestrogenic.**

Aim and objectives: **To assess the role of clomiphene citrate and letrozole in helping ovulation and conception to occur and their impact on the receptivity of the endometrium of PCOS patients.**

Patients and methods: **In this study, there were two groups of anovulatory PCOS patients each group included 50 patients who attended Al-Hussein University Hospital outpatient infertility and Gynecology clinic during the period from March 2022 to September 2022. All studied cases were subjected to: Detailed history taking, Thorough general and pelvic examination and Transvaginal Ultrasonography (TVS).**

Result: **There was high variation between the two studied groups regarding endometrial vascular indices on day 21 of menstruation posttreatment.**

Conclusion: **Endometrial receptivity in letrozole group is superior to clomiphene citrate group in PCOS females throughout the implantation window, which can be linked to better conception rates and ongoing pregnancy rates. Certain issues, even though, were not addressed in this research and must be addressed in future research, such as cumulative outcomes of 6 cycles, rising doses in nonresponders and occurrence of miscarriage.**

Keywords: Clomiphene citrate, Letrozole, Polycystic ovary

1. Introduction

Polycystic Ovarian Syndrome (PCOS) is an endocrinal disorder in females of reproductive age and the primary reason for anovulatory infertility. Its occurrence ranges from 6 to 10% in the general population. Its diagnostic criteria are at least 2 of the following: Oligo or anovulation, Hyperandrogenism and PCO in ultrasound.[1]

Clomiphene citrate is a nonsteroidal selective estrogen receptor modulator with both estrogen agonist and antagonist characteristics that are used as first line of therapy for anovulation in infertile females. It binds to estrogen receptors, primarily in the hypothalamus, interrupting negative feedback of rising estrogen levels and resulting in continued follicle-stimulating hormone (FSH) production, which stimulates follicular growth and maturation.[2]

Clomiphene citrate is made up of 38% zuclomiphene and 62% enclomiphene. Zuclomiphene has mild estrogenic activity, with estrogenic agonist characteristics occurring when endogenous estrogen levels are very low, in addition to antiestrogenic activity, whereas enclomiphene is completely antiestrogenic.[3]

Clomiphene citrate is a safe and effective oral agent with good ovulatory rates; however, it has many drawbacks, including adverse antiestrogenic impacts on endometrium and cervical mucus, as well as low conception rates despite good ovulatory

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rates. Clomiphene citrate resistance was described as lack of ovulation after using the dose range of 100–150 mg/day for 5 days because, over 75% of ovulations happens within this dose range.[4]

Aromatase inhibitors for ovulation induction are taken orally and have minor side effects like very infrequent headaches and leg cramps. Letrozole, unlike Clomiphene citrate, has no antiestrogenic peripheral action and does not deplete estrogen receptors. Letrozole is cleared from body more quickly than Clomiphene citrate because of its shorter half-life.[5]

Endometrial thickness is described as maximum distance measured in the plane of uterine central longitudinal axis among echogenic interfaces of myometrium and endometrium. In context of assisted conception, there is a link relating endometrial thickness to the likelihood of conception. Very thin endometrium (less than 7 mm) appears to be recognized as a reliable indicator of suboptimal implantation potential.[6]

Furthermore, implantation needs a receptive endometrium with synchronous gland and stromal growth. Reduced uterine blood flow throughout the peri-implantation window can explain poor Clomiphene citrate therapy results.[7]

Prior research has shown that adequate blood supply to the subendometrial halo and endometrium outcomes in thicker endometrial wall, increasing chances of pregnancy.[8]

Primary objective: assessment of role of clomiphene citrate and letrozole in helping ovulation and conception to occur.

Secondary objective: assessment of effect of clomiphene citrate and letrozole on the receptivity of the endometrium of PCOS patients.

2. Patients and techniques

The research included 100 studied cases divided into two groups of anovulatory PCOS patients each group included 50 patients who attended Al-Hussein University Hospital outpatient infertility and Gynecology clinic during the period from March 2022 to September 2022.

Inclusion criteria: PCO syndrome studied cases had the following criteria: All patients were between the age of 25 and 35, were not on a specific diet or exercise program, and were suffering from infertility because of PCOS, either primary and secondary.

N.B: Based on Androgen Excess and PCOS Society, existence of following criteria were needed for diagnosis of PCOS: Hirsutism, Hyperandrogenemia, ovarian Dysfunction and other androgen excess related disorders like: (nonclassic congenital adrenal hyperplasia, androgen-secreting neoplasms, androgenic/anabolic drug use and abuse, Hyperandrogenic-Insulin Resistance-Acanthosis Nigricans syndrome and thyroid dysfunction).

Exclusion Criteria: patients under the age of 25 or over 35 years old, females planning to begin diet or a specific physical activity program, concurrent medical illness like cardiovascular, neoplastic, hepatic disorder, tubal, Uterine, Male factor of infertility, endocrinological disorders such as diabetes, hyperprolactinemia, Cushing's syndrome, nonclassic congenital adrenal hyperplasia and studied cases who were out.

All patients were subjected to the following: Consent: All cases received both verbal and written informed consent after ethical committee explained details of research to them. Detailed history taking: Name, age, marital status, obstetric history, menstrual history, past history, family history, history of drug intake, contraceptive methods, history of systemic diseases, previous investigations and treatment. Thorough general and pelvic examination: Anthropometric measurements [such as height, weight, BMI & waist hip ratio] were taken on every patient. Routine laboratory investigations included: Complete blood picture, blood chemistry (liver and kidney function, HbA1C) and hormonal profile.

How to detect Anovulation: by the exclusion of progesterone hormone level rises after ovulation from a baseline of 1.5 ng/ml to 3 ng/ml 1 day after ovulation and levels continue to rise and peak by a week after ovulation measuring 10–20 ng/ml). The standardized method for hirsutism scoring was the Ferriman Gallwey score: Ferriman–Gallwey score is a technique for assessing female hirsutism. D. Ferriman and J.D. Gallwey first published the technique in the Journal of Clinical Endocrinology in 1961 (Ferriman and Gallwey, 1961).

The modified technique reduced the original technique's 11 body areas to 9: upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, upper arms and forearms. (Thighs and legs were removed in modified technique).

Hair growth in each of the 9 sites varies from 0 (no terminal hair growth) to 4 (extensive hair growth). As a result, studied case's score can range between 0 and 36 when we use the modified technique. The quantity of hair expected for each ethnic group should be taken into account. A score of 8 and greater, e.g., is considered an indicator of androgen excess in Caucasian females.

These studied cases were evaluated for endometrial receptivity parameters like endometrial thickness, uterine artery vascular indices: resistance index, pulsatility index, endometrial and

subendometrial vascularity and spiral arteries Doppler research before therapy.

The first group of patients received clomiphene citrate 100 mg once every day for 5 days starting from cycle day 2. The second group received letrozole 5 mg once every day for 5 days starting from cycle day 2. Then they were reassessed by transvaginal ultrasound (TVS) on day 14 and 21 to identify any change. Serum progesterone was measured on day 21 of spontaneous and progesterone-induced menses where Ovulation was detected by level greater than 3 ng/ml on day 21 of cycle. N.B: we measured serum progesterone on day 21 of progesterone-induced cycle in studied cases with amenorrhea and in studied cases with a history of having a 28 days cycle, however, in those patients with regular cycles serum progesterone was measured 1 week before the duration of predictable menses e.g., day 28 of a 35-day cycle.

Throughout the 6 months' time of the study, we asked patients to measure serum B-hCG once a month in studied cases with amenorrhea and 1 week after missed period in studied cases having menses.

Transvaginal Ultrasonography: TVS scans were done with the use of an ultrasonic scanner (GE Logiq F6) equipped with 7.5 MHz vaginal probe.

Protocol of treatment: Both groups of the PCOS studied cases were treated with clomiphene citrate and letrozole as mentioned before. All patients were taught to follow their usual diet and physical activity.

In these PCOS patients we performed two dimensional and Doppler Ultrasonography before and after treatment using serial ultrasonographic assessments by the same experienced operator to evaluate: Uterine artery Doppler: resistance index and pulsatility index, endometrial thickness, endometrial, and Subendometrial vascularity indices: spiral arteries Doppler study.

In both study groups, scans were done before and during therapy on day 14 (periovulatory phase) and day 21 (midluteal phase) after onset of either spontaneous and induced menses to evaluate the correlation, if there is any, between uterine impacts of (clomiphene citrate and letrozole) administration and outcomes.

Ultrasonographic and Doppler assessments: To minimize any external impacts on blood flow, patients rested for 15 min before the TVS examination and completely emptied their bladders just prior to the TVS examination. Scans were taken in both study groups before and during therapy. They were taken before therapy on day fourteen and day 21 after the onset of progesterone-induced menstruation. The color Doppler system was used to study uterine arteries, while the power Doppler system was used to assess endometrial and subendometrial flows.

Uterine artery Doppler: blood flow impedance (resistance index) on both sides was determined for each studied case. The pulsatility index was calculated and expressed as blood flow impedance (resistance index). The machine determined these 2 parameters electronically.

Following the assessment of endometrium itself in current research, the subendometrial region was considered to be in one mm of originally defined myometrial–endometrial junction, spiral arteries Doppler study was done.

2.1. Statistical analysis of data

Data was fed into a computer and analyzed with IBM SPSS software package version twenty. IBM Corporation, Armonk, New York Numbers and percentages were used to define qualitative data. Kolmogorov-Smirnov exam was used to confirm distribution's normality. Range, mean, standard deviation, median, and interquartile range were used to define quantitative data. Significance of got findings was determined at a 5% level.

3. Results

There was no variation among two studied groups regarding age or period of infertility Table 1.

This table finds that there was no variation among the two studied groups regarding ovulation Table 2.

This table finds that there was great variation among the two studied groups as regard endometrial vascular indices on day 14 of menstruation posttreatment Table 3.

This table finds that there was great variation among the two studied groups as regard endometrial vascular indices on day 21 of menstruation posttreatment.

4. Discussion

Receptive endometrium is required for implantation of embryos and ultimately success of pregnancy. Steroid hormones, growth factors, cytokines as well as a rich blood supply control the growth of receptive endometrium, which is needed for optimal implantation Hu and colleagues.[9]

Doppler ultrasonography research revealed a decrease in uterine and endometrial arterial resistance, particularly throughout the midluteal phase. Research's goal is to compare effects of Clomiphene citrate and Letrozole throughout ovulation induction.

Table 1. Comparing the two studied groups based on demographic data.

Demographic data	Studied cases		Test of Significance	*P*
	Clomiphene (n = fifty)	Letrozole (n = fifty)		
Age				
Range.	26–37	25–38	t = 1.078	0.284
Mean ± SD.	31.66 ± 3.19	32.38 ± 3.48		
Period of infertility (years)				
Range.	3–7	3–7	t = 0.996	0.322
Mean ± SD.	4.84 ± 1.09	5.06 ± 1.11		

t: Student *t*-test.
P: *P* value comparison among studied groups.
*: significant at *P* less than or equal to 0.05.

Table 2. Comparing the two studied groups based on posttreatment Ovulation.

	Studied cases		χ^2	*P*
	Clomiphene (n = 50) No. (%)	Letrozole (n = 50) No. (%)		
Ovulation				
No	24 (48.0)	21 (42.0)	0.364	0.546
Yes	26 (52.0)	29 (58.0)		
Follicle diameter				
<18 mm	24 (48.0)	21 (42.0)	0.364	0.546
≥18 mm	26 (52.0)	29 (58.0)		

χ^2, Chi-square test; MC, Monte Carlo.
P: *P* value comparison among studied groups.

We discovered no variation among the two studied groups in terms of age and period of infertility ($P > 0.05$) in this research.

In a study to assess ultrasonographic markers of endometrial receptivity of letrozole and clomiphene citrate in unexplained infertile females, ElKattan,[10] found that age and parity in both groups of studied cases were similar ($P > 0.05$).

Wallace and colleagues,[11] found that there were no variations in age, BMI and cycle date when biopsy was taken or when hormone levels were measured among females taking and not taking clomiphene citrate and letrozole.

Table 3. Comparing the two studied groups based on endometrial vascular indices posttreatment on day 14.

	Studied cases		T	*P*
	Clomiphene (n = 50)	Letrozole (n = 50)		
Endometrial				
Thickness (mm)				
Range.	5.1–8.8	7.4–12.7	12.288	<0.001*
Mean ± SD.	7.16 ± 1.2	10.34 ± 1.38		
PI				
Range.	1.29–1.93	1.13–1.64	6.369	<0.001*
Mean ± SD.	1.62 ± 0.19	1.4 ± 0.16		
RI				
Range.	0.68–0.77	0.58–0.68	14.697	<0.001*
Mean ± SD.	0.72 ± 0.03	0.63 ± 0.03		
Uterine artery				
PI				
Range.	1.41–2.12	1.27–2.08	2.710	0.015*
Mean ± SD.	1.75 ± 0.23	1.62 ± 0.23		
RI				
Range.	0.48–0.84	0.4–0.81	1.448	0.151
Mean ± SD.	0.71 ± 0.1	0.68 ± 0.09		
Subendometrial				
PI				
Range.	0.55–1.33	0.46–1.17	3.028	0.003*
Mean ± SD.	0.86 ± 0.22	0.74 ± 0.17		
RI				
Range.	0.46–0.66	0.39–0.62	3.994	<0.001*
Mean ± SD.	0.53 ± 0.05	0.49 ± 0.06		

t: Student *t*-test.
P: *P* value comparison among studied groups.
*: significant at *P* less than or equal to 0.05.

Table 4. Comparing the two studied groups based on endometrial vascular indices posttreatment on day 21.

	Studied cases		*t*	*P*
	Clomiphene (n = 50)	Letrozole (n = 50)		
Endometrial				
Thickness (mm)				
Range.	4.5–8.8	7.1–12.4	12.160	<0.001*
Mean ± SD.	6.88 ± 1.27	10.15 ± 1.42		
PI				
Range.	1.31–2.03	1.17–1.7	6.524	<0.001*
Mean ± SD.	1.68 ± 0.2	1.44 ± 0.17		
RI				
Range.	0.68–0.84	0.59–0.76	11.473	<0.001*
Mean ± SD.	0.76 ± 0.04	0.67 ± 0.04		
Uterine artery				
PI				
Range.	1.44–2.27	1.33–2.14	2.613	0.010*
Mean ± SD.	1.84 ± 0.24	1.72 ± 0.24		
RI				
Range.	0.51–0.91	0.42–0.86	1.655	0.101
Mean ± SD.	0.77 ± 0.11	0.73 ± 0.1		
Subendometrial				
PI				
Range.	0.57–1.37	0.48–1.21	3.143	0.002*
Mean ± SD.	0.89 ± 0.22	0.76 ± 0.17		
RI				
Range.	0.47–0.69	0.41–0.66	3.747	<0.001*
Mean ± SD.	0.56 ± 0.06	0.52 ± 0.06		

t: Student *t*-test.
P: *P* value comparison among studied groups.
*: significant at *P* less than or equal to 0.05.

Cheung and colleagues,[12] found that there were no variations between the two groups in terms of age of females, type and period of infertility.

Our results found that there was high variation between the two studied groups regarding endometrial vascular indices on day 14 of menstruation posttreatment.

ElKattan,[10] showed that the Letrozole group had the upper hand regarding endometrial thickness and volume in comparison to the clomiphene citrate group. In terms of Doppler research, there was no variation in uterine artery Doppler indices among clomiphene citrate and Letrozole groups. Spiral artery Doppler indices differed significantly among clomiphene citrate and Letrozole groups.

Al-Obaidi and colleagues,[13] found that when compared with clomiphene citrate group, letrozole group has significantly lower resistance index and pulsatility index.

Median and Asim,[14] found that studied subendometrial arteries PI and RI in the Letrozole group were better than those in clomiphene group on day of triggering, but variation was not significant on mid-luteal day.

Anwar and colleagues,[15] The researchers looked at effects of clomiphene citrate, letrozole, and tamoxifen on endometrial thickness and endometrial blood flow as noninvasive parameters in the evaluation of endometrial receptivity and discovered that clomiphene citrate group had thinner endometrium than the other two groups ($P < 0.001$).

In our study, we found that there was high variation between the two studied groups regarding endometrial vascular indices on day 21 of menstruation posttreatment.

Wang and colleagues,[16] found that on day of hCG administration, a ratio of multilayered endometrial pattern was better in letrozole group compared with clomiphene citrate group ($P < 0.05$). Endometrial thickness, volume, VI, FI, and VFI were better in letrozole group compared with clomiphene citrate group on the day of hCG administration and 7–9 days after ovulation ($P < 0.05$).

A study done by El Kateeb and Mahran,[17] shows agreement with our study, this trial contained 200 infertile females with PCOS who were described based on the Revised Rotterdam criteria and were separated into two groups letrozole and clomiphene citrate; endometrial thickness was significantly better in letrozole group 10.1 ± 022 mm than the clomiphene citrate group 8.2 ± 0.69 mm ($P = 0.01$).

Baruah and colleagues,[18] found that when compared with clomiphene citrate group, both RI and PI in letrozole group had lower blood flow impedance ($P < 0.05$).

Wang and colleagues,[19] found that ET, EV, VI, FI, and VFI were better in letrozole group, and integrinavb3 and VEGF concentrations in the uterine fluid were better in letrozole group than in clomiphene citrate group and natural cycle group ($P < 0.05$).

This outcome was similar to the outcome shown by Palomba and colleagues,[20] endometrial thicknesses and patterns were found to be impaired in PCOS females taking clomiphene citrate. These findings imply that endometrial receptivity parameters may have been worse in clomiphene citrate studied cases, resulting in lower implantation and pregnancy rates.

In this study, we concluded that Letrozole ovulation induction improves endometrial receptivity more than clomiphene citrate throughout the implantation window in PCOS females, which may be linked to better conception rates and ongoing pregnancy rates. Certain issues, even though, were not discussed in this research and should be addressed in future research, such as cumulative outcomes of 6 cycles, raising dose in nonresponders, and occurrence of miscarriage.

4.1. Conclusion

Endometrial receptivity in letrozole group is superior to clomiphene citrate group in PCOS females throughout the implantation window which can be linked to better conception rates and ongoing pregnancy rates. Certain issues, even though, were not discussed in this research and should be discussed in future research, such as cumulative outcomes of 6 cycles, raising dose in nonresponders, and occurrence of miscarriage.

Disclosure

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

Authorship

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Conflicts of interest

The authors declared that there were no conflicts of interest.

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