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ORIGINAL ARTICLE

Extended Letrozole Regimen for Treatment of Clomiphene Resistant Polycystic Ovarian Patient

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Abstract

Background: **About 1 in 15 women are affected by polycystic ovarian syndrome (PCOS), a complex endocrine condition with a variety of causes. Excessive androgen secretion or activity is the primary endocrine disturbance, and aberrant insulin activity is seen in a large proportion of women.**

Aim and objectives: **To contrast the efficacy of a prolonged letrozole treatment for treating clomiphene-resistant PCOS to that of a short letrozole therapy and a placebo.**

Patients and methods: **This prospective, interventional, research was done at Qena University Hospital, Obstetrics and Gynecology Department. All cases were subdivided into three groups: group (A): 40 patients took short letrozole, Short letrozole group. Group (B): 40 patients took the long letrozole, Long letrozole group. Group(C): 40 patients took placebo, Placebo group. The research lasted anywhere from 6 to 12 months.**

Result: **There is a significant distinction among the groups regarding endometrial thickness with hCG trigger injection. Ovulation incidence was substantially greater in group B contrasted with group A contrasted with group C. Pregnancy incidence was substantially higher in group B contrasted with group A contrasted with group C.**

Conclusion: **More and larger mature follicles, Elevated endometrial thickness, and the number of pregnancies can be achieved with prolonged letrozole medication contrasted with shorter letrozole medication.**

Keywords: Clomiphene, Letrozole regimen, Polycystic ovary syndrome (PCOS)

1. Introduction

One in fifteen women suffer from polycystic ovarian syndrome (PCOS), a complex endocrine condition. Excess androgen secretion or activity is the primary endocrine disturbance, and aberrant insulin activity is seen in a sizable minority of females. PCOS is characterized by a wide range of symptoms and health problems, involving but not limited to menstruation disruption, infertility, hirsutism, acne, obesity, and metabolic syndrome.[1]

The higher likelihood of type 2 diabetes mellitus in cases with this illness is well-documented, whereas a greater likelihood of cardiovascular disease is still up for dispute. After ruling out other illnesses that cause similar symptoms, hyperandrogenism, persistent anovulation, and polycystic ovaries are used to diagnose PCOS.[2]

In cases with euestrogenic anovulation, clomiphene citrate (CC) is the drug of preference for ovulation stimulation. Due to the high likelihood of ovulation (60−85 %), anovulatory cases given a CC have a 10−20 % pregnancy rate/cycle.[3]

CC's antiestrogenic impacts on the cervical mucus and endometrium may contribute to the gap among ovulation and conception rates. Aromatase inhibitors (AIs) are one such alternative drug that has been utilized to stimulate ovulation.[4]

Treatment with 150 mg of clomiphene every day for 5 days each cycle, for as a minimum 3 cycles, does not induce ovulation, or ovulation occurs but the endometrium is extremely thin (≤5 mm) when hCG or during the luteinizing hormone (LH) surge would ordinarily be delivered, indicating clomiphene resistance.[5,6]

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Over 20 years have passed since the first articles were published on the application of AI letrozole for inducing ovulation.[7] CC was contrasted to letrozole in 2 early randomized trials of cases with PCOS.[3]

While the estradiol levels were lower in the letrozole group, the ovulation percentage, the number of live births and the thickness of the uterine lining were all comparable.[8] The letrozole group had a lesser number of mature follicles, but they also had a thicker endometrium, greater ovulation rates, and a greater pregnancy incidence.[9]

2. Patients and methods

Prospective interventional research was conducted at Department of Obstetrics & Gynecology, Faculty of Medicine - Al-Azhar University between December 2021 and December 2022 at Qena University's infertility clinic inside the Department of Gynecology and Obstetrics within the Faculty of Medicine.

Inclusion criteria: Cases between the ages of 20 and 35 who had been diagnosed with PCOS-related primary infertility using the Rotterdam consensus criteria (women are said to have PCOS) if they exhibit a minimum of two of the symptoms listed below 1: anovulation or oligo-. 2: Evidence of hyperandrogenism in clinical and/or biochemical tests. 3: PCOS. Cases reported a previous inability to conceive when using clomiphene (by 'clomiphene resistance', we define inability to ovulate while taking 150 mg of CC once every day for 5 days during every cycle for a minimum 3 separate cycles (Practice Committee of the American Society for Reproductive Medicine, 2006)). Women with BMI between 18 and 30; patent tubes and a healthy uterus as determined by hystero-salpingography; serum prolactin levels between 5 and 20 ng/ml; and normal results from the husband's semen sample.

Exclusion criteria: individuals either below the age of 20 or above the age of 35 cases with infertility stemming from the tubal, peritoneal, or uterine, to diagnose male factor infertility in any case, Hyperprolactinemia and thyroid dysfunction are 2 more disorders that share symptoms with androgen-secreting tumors and Cushing's syndrome. Larger-than-6-centimeter ovarian cysts, a history of genital-system surgery, liver and kidney failure, and ovulation suppression factors include diabetes mellitus and the use of medicines such nonsteroidal anti-inflammatory drugs, hormones, or chemotherapy.

This study base on a study carried out by Khodary and colleagues was used to calculate the sample size by considering the following assumptions: −95 % two-sided confidence level, with a power of 80 % and α error of 5 %. The final maximum sample size taken from the output was 78. Thus, the sample size was increased to 80 patients to assume any dropout cases during follow-up.[10]

$$\left(\frac{Z_{a/2}+Z_B}{P_1-P_2}\right)^2 (p_1q_1+p_2q_2)$$

(Khodary et al. 2023)

n = sample size.

$Z_{a/2}$ (The critical value that divides the central 95 % of the Z distribution).

Z_B (The critical value that divides the central 20 % of the Z distribution).

p_1 = Accuracy prevalence in TCD group.

p_2 = Accuracy prevalence in FL group.

Ethical consideration: the investigation was given the go light by the Ethical Committee of Qena faculty of the medicine. Cases gave their signed consent forms.

All cases were separated into three groups: 40 cases were assigned to group (A), where they received 5 mg of letrozole everyday beginning on day 1 of menstruation for a total of 5 days. Group (B) received letrozole 2.5 mg daily beginning on day 1 of menstruation and continuing for 10 days. This group consisted of 40 individuals. Group(C): contained 40 cases who were given placebo folic acid 5 mg pills daily beginning on day 1 of menstruation for a total of 10 days, alongside the long letrozole group. This is the placebo group.

Complete case histories were taken, and cases underwent examinations (involving a general, abdominal, and bimanual pelvic examination), diagnostic tests, and follow-up.

2.1. Statistical analysis

All data was entered into SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) for tabulation and statistical analysis.

The Shapiro-Wilk test was utilized to examine the data for a normal distribution. The qualitative information was shown as a breakdown of frequencies and percentages. The indicated distinctions among qualitative variables were computed utilizing the χ^2 test and the Fisher exact test. For parametric data, we used the mean ± SD (Standard Deviation), while for nonparametric data, we utilized the median and range. Quantitative variables among the two groups were determined utilizing the Independent *T* test for parametric variables and the Mann–Whitney test for nonparametric variables.

If there were more than two groups for contrast and the variables were normally distributed, a one-

way ANOVA test supplemented with the LSD test was performed.

All tests for statistical significance were two-tailed tests. If the *P*-value is less than or equal to 0.05, the distinction is considered significant; if it is less than 0.001, the difference is considered extremely significant.

3. Results

Table 1.

This table shows: there is no significant distinction among the 3 researched groups regarding age, BMI, and residence Table 2.

This table revealed that there is no substantial distinction among the three researched groups concerning Infertility duration, menstrual cycle length, and Infertility types Table 3.

This table reveals that there is a noticeable distinction among the three groups concerning total number of follicles Table 4.

This table revealed that there is no substantial distinction among the three researched groups concerning follicle stimulating hormone (FSH), LH, progesterone, E2, and antimullerian hormone (AMH) levels were determined on day 2 of the menstrual cycle Table 5.

This table reveals that there is a noticeable distinction among the groups concerning mid-luteal progesterone, and E2 at hCG Table 6, Figs. 1 and 2.

This table reveals that there is a noticeable distinction among the groups concerning endometrial thickness at hCG Table 7, Fig. 3.

This table reveals that the rate of ovulation was significantly larger in group B contrasted with group A compared with group C. Pregnancy rate was

Table 1. Demographic data of the 3 researched groups.

	Group A ($N = 40$)	Group B ($N = 40$)	Group C ($N = 40$)	F/χ^2	*P*
Age (y)					
Mean ± SD	27.58 ± 6.42	28.4 ± 5.94	28.36 ± 6.21	0.712	0.493
Range	23–35	22–34	20–35		
BMI (kg/m^2)					
Mean ± SD	27.54 ± 2.86	28.42 ± 1.67	27.61 ± 2.58	1.63	0.201
Range	21–30	24–31	22–30		
Residence					
Rural	26 (65 %)	16 (40 %)	18 (45 %)	5.6	0.061
Urban	14 (35 %)	24 (60 %)	22 (55 %)		

Table 2. Clinical characteristics distribution among the researched groups.

	Group A ($N = 40$)	Group B ($N = 40$)	Group C ($N = 40$)	F/χ^2	*P*
Infertility duration (years)					
Mean ± SD	7.41 ± 1.97	7.26 ± 2.23	7.39 ± 2.16	0.059	0.943
Range	4–16	3–13	4–15		
Menstrual cycle length (days)					
Mean ± SD	30.51 ± 4.33	31.19 ± 4.79	31.24 ± 4.68	0.077	0.926
Range	27–34	28–35	28–35		
Types of infertility					
Primary infertility	28 (70 %)	26 (65 %)	24 (60 %)	0.879	0.644
Secondary infertility	12 (30 %)	14 (35 %)	16 (40 %)		

Table 3. Follicles characteristics distribution between the studied groups measured by serial transvaginal ultrasound on days 10, 12, and 14 of the cycle.

	Group A ($N = 40$)	Group B ($N = 40$)	Group C ($N = 40$)	F/χ^2	*P*
Number of follicles					
Mean ± SD	4.36 ± 0.792	6.47 ± 0.752	4.19 ± 0.816	104	<0.001
Range	3–6	4–8	3–5		
Follicles size					
Follicles <14	14 (35 %)	12 (30 %)	15 (37.5 %)		
Follicles 14–17	8 (20 %)	6 (15 %)	12 (30 %)	4.8	0.309
Follicles ≥18	18 (45 %)	22 (55 %)	13 (32.5 %)		

Table 4. Laboratory data of basal hormones on Day 2 of the menstrual cycle amongst the studied groups.

	Group A ($N = 40$)	Group B ($N = 40$)	Group C ($N = 40$)	F	*P*
LH (IU/ml)					
Mean ± SD	11.85 ± 1.76	12.13 ± 2.28	11.74 ± 1.83	0.417	0.662
Range	7.68–14.24	8.21–15.6	7.15–15.29		
FSH (IU/ml)					
Mean ± SD	5.28 ± 1.47	5.16 ± 1.81	4.97 ± 2.14	0.293	0.747
Range	1.89–8.4	1.72–8.68	1.5–8.34		
Progesterone (ng/ml)					
Mean ± SD	0.356 ± 0.157	0.390 ± 0.184	0.367 ± 0.172	0.410	0.665
Range	0.17–0.83	0.21–0.785	0.19–0.806		
E2 (pg/ml)					
Mean ± SD	39.47 ± 8.85	42.88 ± 6.11	40.26 ± 8.32	2.1	0.131
Range	21.3–76.5	28.7–82.3	25.4–82.9		
AMH (ng/ml)					
Mean ± SD	4.19 ± 2.74	4.08 ± 2.1	4.12 ± 2.31	0.022	0.979
Range	1.2–8.35	1.1–7.96	1.2–8.15		

AMH, antimullerian hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone.

Table 5. Laboratory parameters after treatment between the three studied groups (E2 at hCG injection and mid-luteal Progesterone).

	Group A ($N = 40$)	Group B ($N = 40$)	Group C ($N = 40$)	F	*P*
E2 (pg/ml) (at hCG)					
Mean ± SD	328.3 ± 64.9	352.6 ± 73.22	309.3 ± 58.4	4.35	0.015
Range	279–514	295–586	265–478		
Post Hoc	**A*B $P = 0.120$**	**A*C $P = 0.173$**	**B*C $P = 0.005$**		
Progesterone (ng/ml) (mid-luteal)					
Mean ± SD	9.35 ± 0.872	10.26 ± 1.16	8.82 ± 1.57	14	<0.001
Range	5.2–16.4	5.8–18.3	4.8–16.5		
Post Hoc	**A*B $P = 0.001$**	**A*C $P = 0.066$**	**B*C $P = 0.001$**		

Table 6. Endometrial thickness between the three studied groups.

	Group A (N = 40)	Group B (N = 40)	Group C (N = 40)	F	*P*
Endometrial thickness (mm)					
Pretreatment					
Mean ± SD	4.82 ± 0.542	4.61 ± 0.617	4.7 ± 0.574	1.33	0.269
Range	2–7	2–7	2–8		
At hCG					
Mean ± SD	10.58 ± 0.741	11.29 ± 0.755	9.41 ± 1.56	30	<0.001
Range	6–13	7–14	6–12		
Post Hoc	A*B P < 0.001	A*C P < 0.001	B*C P < 0.001		

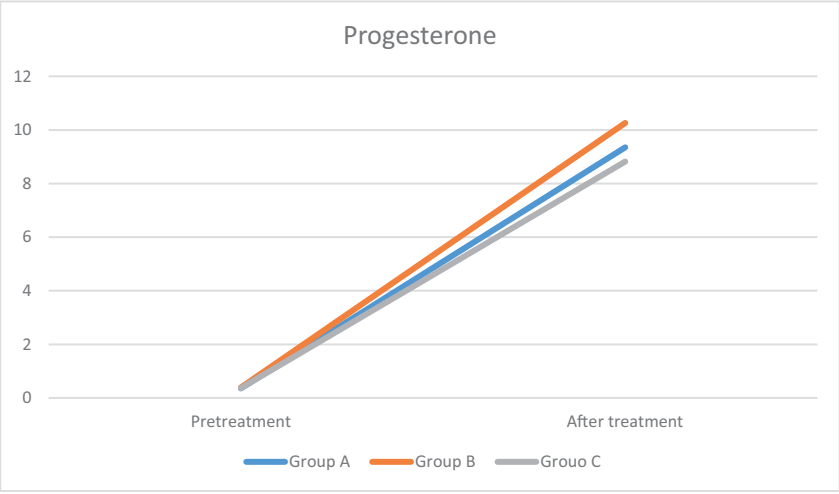


Fig. 1. This figure reveals that there is a noticeable distinction among the groups concerning midluteal progesterone.

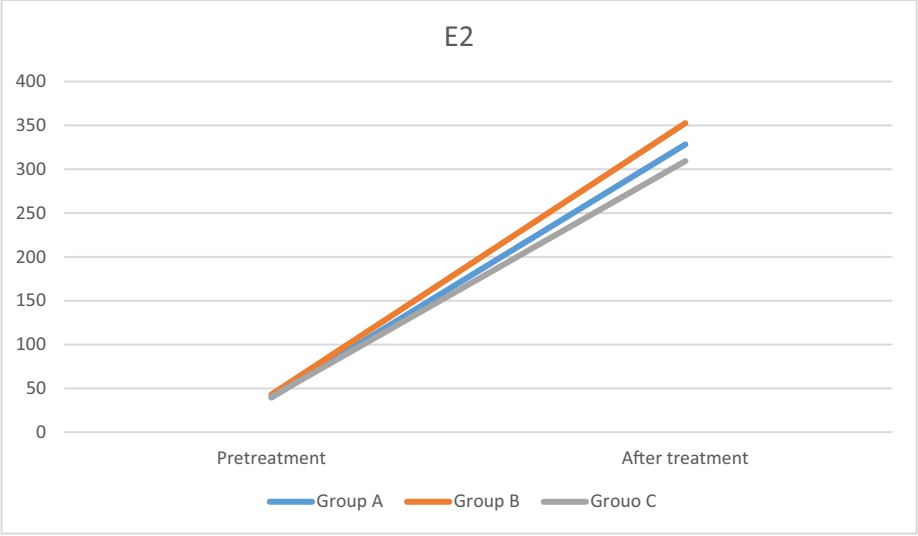


Fig. 2. This figure reveals that there is a noticeable distinction among the groups concerning E2 at hCG triggering.

Table 7. Ovulation occurred and pregnancy rate after treatment distribution among cases groups.

	Group A ($N = 40$) N (%)	Group B ($N = 40$) N (%)	Group B ($N = 40$) N (%)	P
Ovulation rate				
Yes	23 (57.5)	25 (62.5	14 (35)	0.032
No	17 (42.5)	15 (37.5	26 (65)	
Pregnancy rate				
Yes	6 (15 %)	13 (32.5)	4 (10 %)	0.027
No	34 (85 %)	27 (68.5)	36 (90 %)	

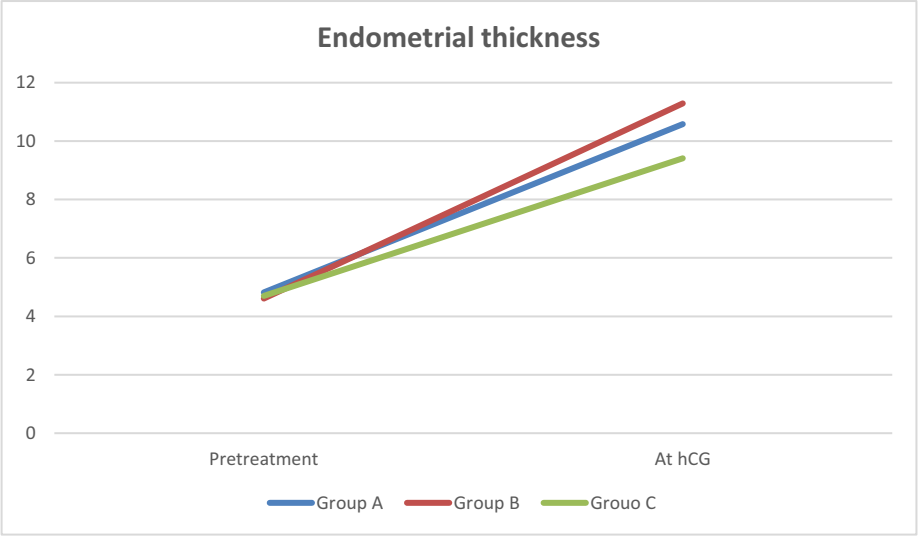
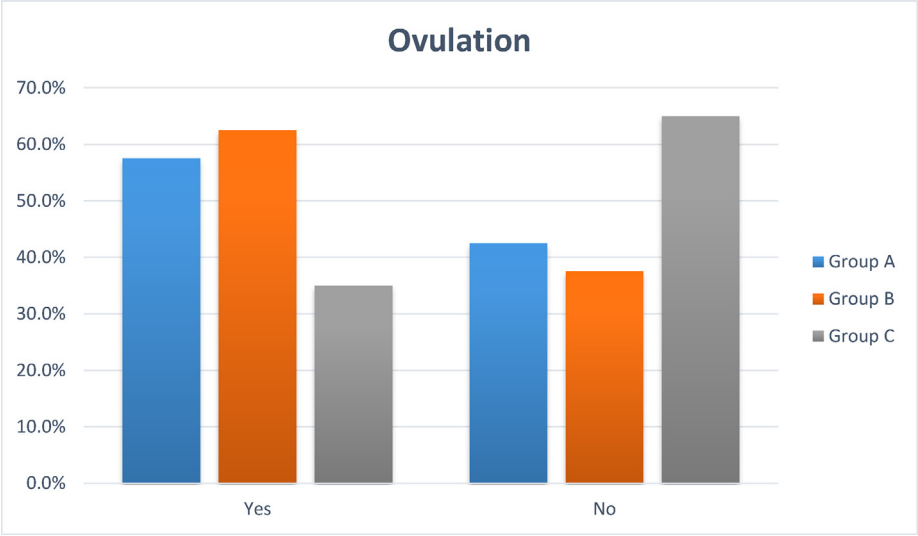
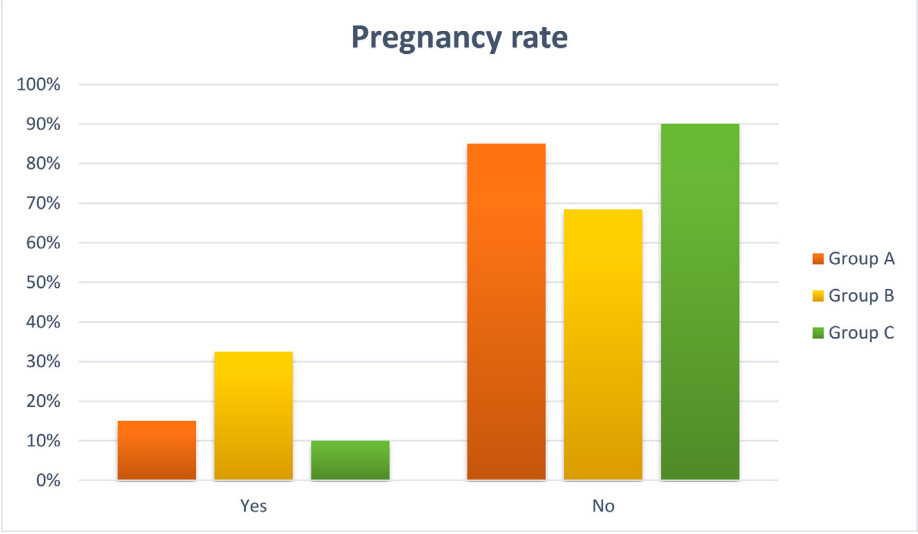


Fig. 3. Endometrial thickness amongst the three studied groups.

Table 8. Miscarriage rate after treatment distribution among cases groups.

	Group A ($N = 6$) N (%)	Group B ($N = 13$) N (%)	Group B ($N = 4$) N (%)	P
Yes	1 (16.7 %)	2 (15.4 %)	1 (25 %)	0.905
No	5 (83.3 %)	11 (84.6 %)	3 (75 %)	





substantially greater in group B in contrast to group A compared with group C Table 8.

This table demonstrate that there is no noticeable variations among the groups concerning miscarriage rate.

4. Discussion

The main findings of this research were: none of the three groups differ substantially from one another in terms of age, BMI, or country of origin.

Sixty infertile, PCO and CC-resistant cases were allocated random to one of two groups in the research by Morad and colleagues group I (short letrozole therapy) obtained two point 5 mg twice/day from the second day of cycle for 5 days and repeated for three cycles (classical regimen), while group II (long letrozole therapy) obtained two point 5 mg once/day from the second day of cycle for 10 days and repeated for three cycles (prolonged regimen). There were no substantial variations in any of the analyzed demographic features of the cases across the researched groups.[11]

Similarly, Badawy and colleagues demonstrated that cases were then randomly assigned utilizing a computer-generated random table to 1 of 2 treatment groups: the short letrozole group (110 cases, 225 cycles) or the long letrozole group (108 cases, 219 cycles). Considering age, body weight, height, and BMI, neither group varied substantially from the other statistically.[12]

The current research revealed that there are no notable distinctions among the 3 analyzed groups in terms of Infertility duration, menstrual cycle length, or Infertility type.

In agreement with the findings of the research by Hassanein and colleagues as reported, cases were given either a long or short course of letrozole medication based on a random assignment. The long letrozole group took two point 5 mg of letrozole every day beginning day one of spontaneous or progesterone-causing flow of menstrual blood for 10 days (50 cases, with a maximum of three cycles). The short letrozole group took 5 mg of letrozole everyday beginning day one of spontaneous or progesterone-causing flow of menstrual blood for 5 days (50 cases, with a maximum of three cycles). The duration of infertility did not vary statistically considerably amongst the two groups.[13]

In addition, the duration of infertility did not vary statistically considerably between the two groups in the research conducted by Badawy et al.[12]

The current research showed a substantial variation in the total number of follicles among the three groups.

This was in accordance with the results of El-Aziz et al., who discovered that the total number of follicles following stimulation was substantially higher in the long letrozole group (6.48 ± 0.68) vs. (4 ± 0.91) in short letrozole group; ($P = 0.001$.[14]

Another research conducted by Ramezanzadeh and colleagues demonstrated that there was no notable distinction among the 2 groups with regard to the number of intermediate (0.83 ± 0.75 vs. 0.62 ± 0.76) and mature follicles (1.13 ± 1.11 vs. 1.22 ± 1.03).[15]

Considering basal FSH, LH, progesterone, E2, and AMH, there is not a significant distinction among the groups in the present research. Following treatment, there is significant distinction among the groups in terms of progesterone and E2. There is a significant disparity in endometrial thickness at hCG among the groups.

In contrast, in the investigation done by Morad and colleagues, the average thickness of the endometrium at human chorionic gonadotrophin (HCG) injection was 8.4 ± 1.76 mm for group I and 8.83 ± 1.45 mm for group II, with no substantial distinction amongst the two groups ($P = 0.076$). The distinction between these investigations and ours may be attributable to sample size differences.[11]

The current research revealed that the ovulation incidence in group B was substantially greater than in groups A and C.

This was in accordance with our results, Morad and colleagues stated that following treatment, 56.7 % of group I cases and 63.3 % of group II cases ovulated, with no substantial distinction amongst the two groups ($P = 0.598$).[11]

According to previous research conducted by El-Aziz et al., the percentage of women in group II who ovulated following treatment was higher than in group I (63.3 % vs. 56.7 %, respectively).[14]

Our findings revealed that the pregnancy incidence in group B was substantially greater than in groups A and C. There is no substantial disparity in miscarriage rates among the groups.

Our findings were corroborated by the findings of El-Aziz et al., who stated that pregnancy took place in 4 out of 30 cases (13.3 %) in the short letrozole group and in 6 out of 30 cases (20 %) in the long letrozole group. In the long letrozole group, there was one twin pregnancy (16.67 % of pregnancies). The contrast among the two groups based on post-treatment pregnancies favored the protracted group with a P-value greater than 0.05.[15]

In their research, Badawy and colleagues found that pregnancy took place in 28 of 225 cycles (12.4 %) in the short letrozole group and 38 of 219 cycles (17.4 %) in the extended letrozole group, with the distinction being statistically substantial.[12]

4.1. Conclusion

The extended letrozole therapy can generate more and larger mature follicles, a thicker endometrium and consequently more pregnancies than the shorter letrozole therapy.

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.

Conflicts of interest

The authors declared that there were no conflicts of interest.

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