

## Short Letrozole Therapy Versus Extended (Long) Letrozole Therapy For Induction of Ovulation in Women With Polycystic Ovary Syndrome. Randomised study

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### Abstract

**Presentation:** Polycystic Ovary Syndrome is quite possibly the most well-known reasons for anovulatory fruitlessness, influencing 8-13% of conceptive matured ladies . It is by a long shot the most well-known reason for hyperandrogenic anovulatory fruitlessness and was depicted the greater part a century prior, the basic reason for this issue is as yet dubious . **Point:** to examine the viability of short(2.5mg day by day for 5 days) versus broadened course (2.5mg day by day for 10 days) of letrozole treatment for ovulation acceptance in ladies with polycystic ovary syndrome.**Subject &Method:** This examination directed on (40) patients with PCOS They were arbitrarily assigned in two gatherings. Gathering 1 (20 patients )got letrozole in adose of 5mg for 5 days while the gathering 2 (20 patients) got letrozole in adose of 2.5 mg for 10 days.**Result :** The all out number of follicles in the present moment letrozole was  $3\pm 1$  while it was  $4\pm 1$  in the long letrozole bunch. In our examination the endometrial thickness was  $8\pm 2$  in both short and long letrozole bunch .The pregnancy rate was 15% in short letrozole bunch while it was 25% in long letrozole bunch . **End:** The long letrozole treatment (2.5mg for 10 days) can create more develop follicles and in this manner a greater number of pregnancies than the short letrozole treatment (5mg for 5 days).

**Keywords:** PCOS, Letrozole.

### 1. Introduction

Polycystic ovary condition (PCOS) is a heterogeneous disorder and is thinking about the most well-known endocrine problem in ladies at regenerative age [1].

It was first portrayed in 1935 by Stein and Levanthal (1935) in the American Journal of Obstetrics and Gynecology. However, it stays a condition that is confounding to numerous patients and experts regarding its introduction, work-up, and the executives. There is a range of introducing objections and actual discoveries just as cover with different problems, like the metabolic disorder.

IT is the most widely recognized endocrine problem of conceptive matured ladies and influences roughly 4% to 12% overall populace studies(9) PCOS is related with 75% of all anovulatory messes causing fruitlessness, Diagnostic models of PCO PCOS Defined by ESHRE/ASRM (Rotterdam) 2003 as a disorder incorporates two out of the accompanying:

- a) Clinical and/or biochemical indications of hyperandrogenism
- b) Polycystic ovaries by ultra sound (presence of at least 12 follicles in every ovary estimating 2 to 9 mm in measurement or potentially expanded ovarian volume (10 cm<sup>3</sup>; determined utilizing the equation  $0.5 \times \text{length} \times \text{width} \times \text{thickness}$ ). The transvaginal approach ought to be used [12].

With prohibition of different conditions with comparable signs, for example, androgen-discharging tumors or Cushing's disorder and thyroid brokenness and hyperprolactinemia.

CC – obstruction alludes to the failure [10] to ovulate with 150 mg of cc for in any event 3 cycles, while CC-disappointment is characterized as inability to consider with CC regardless of fruitful ordinary ovulation for 6-9 cycles.

Elective strategies utilized for the ovulation enlistment in PCOS are CC in mix with metformin, CC in blend with dexamethasone, specific aromatase inhibitor, for example, letrozole and anastrozole, gonadotropins, laproscopic ovarian penetrating.

Aromatase (cytochrome P-450 [CYP]) catalyzes the rate-restricting advance (transformation of steroidal C-19 androgens to C-18 estrogens) in estrogen biosynthesis [14] Aromatization is the last advance in steroid biosynthesis; and, thusly, aromatase is an alluring objective for specific hindrance [7].

**Aromatase inhibitors:** The quest for intense and particular inhibitors of aromatase began with the original inhibitor aminoglutethimide. Be that as it may, aminoglutethimide needed selectivity for aromatase and hindered biosynthesis of cortisol, aldosterone, and thyroid chemical just as aromatase; additionally, aminoglutethimide was likewise found to incite hepatic proteins .

Second-age AIs incorporated the nonsteroidal inhibitor fadrozole and the steroidal inhibitor formestane (4-hydroxyandrostenedione). Fadrozole was better than aminoglutethimide regarding power, selectivity, and security, yet its selectivity was not finished and clinical preliminaries proposed that it was not any more successful than tamoxifen. To enhance fadrozole, Novartis incorporated a progression of new mixtures. Design action relationship examines were then performed to recognize the most intense AIs from a progression of benzyl-azole subsidiaries of fadrozole [13].

The third-age AIs Letrozole (Femara1) was the consequence of this construction movement way to deal with drug plan and accomplished the exploration objective of making an exceptionally strong and absolutely particular AIs.

**2. Aim of the work**

The point of this study, to think about the viability of short (5mg every day for 5 days) versus expanded course (2.5mg day by day for 10 days) of letrozole treatment for ovulation acceptance in ladies with polycystic ovary disorder.

**3. Subject and methods**

- Type of study : Prospective randomized comparative study .
- Site of study: Obstetrics and Gynecology department, Benha university .
- The study was approved by the Ethics Board of Benha university.
- Sample size: 40 infertile patients diagnosed as having PCO based on Rotterdam criteria (2003),

**Groups of the study: patients were randomly allocated in two groups :**

- Group 1: short letrozole therapy (20 patients).
- Group 2 : long letrozole therapy (20 patients).

**2.1. Inclusion criteria**

- Age: 18-35 years old.
- Infertility ≥ 2years.
- Diagnosis of PCOS according to Rotterdam Criteria.
- Nonsmoker or addict to any substance.
- married.

**2.2. Exclusion criteria**

- History of pelvic surgery or trauma.
- Women with infertility factors other than anovulation.
- Male factor of infertility.
- Smokers, alcohol addict.
- Other causes of hyperandrogenism.

**2.3. All participating patients had the following:**

**I-Full history**

- Personal history
- History of present illness
- Menstrual history
- Sexual history
- Past history
- Family history

**II-Complete examination**

- General examination
- Abdominal examination

- Local (Pelvic) examination

**III-Investigations**

- General (CBC, urinalysis, Random blood sugar) when needed.
- Specific: FSH, LH, Prolactin. Androgen, Estradiol, Estrone on day three of menstrual cycle.

**2.4. Methodology**

Patients of short letrozole treatment bunch (20 patients) got 5mg of letrozole (2 tablets of letrozole 2.5mg, Sandoz Pharmaceutical Company, Australia) day by day beginning from day 1 of unconstrained (or progesterone incited, utilizing Medroxyprogesterone acetic acid derivation 5 mg tab, one tab every day for 5 days)

Feminine seeping for 5 days (patients, up to 3 cycle).

Patients of long letrozole treatment group (20 patients) got 2.5mg of letrozole (one tab of letrozole 2.5mg, Sandoz Pharmaceutical Company, Australia) day by day beginning from day 1 of unconstrained (or progesterone initiated) feminine seeping for 10 days (patients, up to 3 cycles).

All patients of the two gatherings observed by trans-vaginal ultrasound for the mean follicular volume and thickness of the endometrium on day 10 of the cycles.

HCG infusion (5,000 IUIM) given when at any rate one follicle estimated ≥ 18mm.

Patients exhorted for intercourse 24-36h after HCG infusion.

Serum HCG decided fourteen days after HCG infusion without monthly cycle for determination of pregnancy followed by trans vaginal ultrasound for exhibit of the gestational sac.

**4. Results**

This study was conducted on forty patients attending the obstetrics and gynecology Department in Benha University Hospitals as a Prospective randomized comparative study.

General characteristics in both groups

There were no statistically significant differences between both groups regarding the age, weight, and height of patients. P values were 0.221, 0.575, and 0.637, respectively.

Table (1) General characteristics in both groups.

		Short protocol(n= 20)	Long protocol(n= 20)	P value
Age (years)	Mean ±SD	29 ±4	31 ±3	0.221
	Range	22 – 35	25 – 35	
Weight (kg)	Mean ±SD	67 ±11	65 ±11	0.575
	Range	47 – 88	47- 88	
Height (cm)	Mean ±SD	157 ±9.3	158 ±10.6	0.637
	Range	140 – 170	140 - 180	

Independent t-test was used

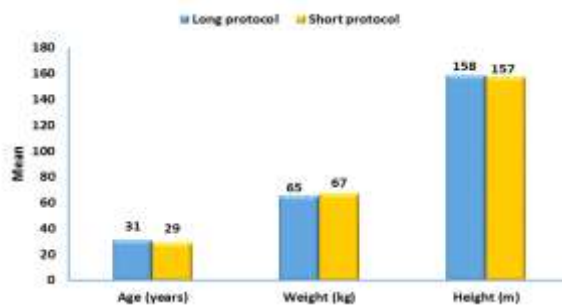


Fig. (1) General characteristics in both groups.

Type of infertility in both groups

Type of infertility showed a non-statistically significant difference between both groups. P-value was 0.519

Table (2) Type of infertility in both groups.

		Short protocol(n= 20)	Long protocol (n = 20)	P value
Type of infertility	1ry n (%)	7 (35.0)	9 (45)	0.519
	2ry n (%)	13 (65)	11 (55.0)	

Chi-square test was used.

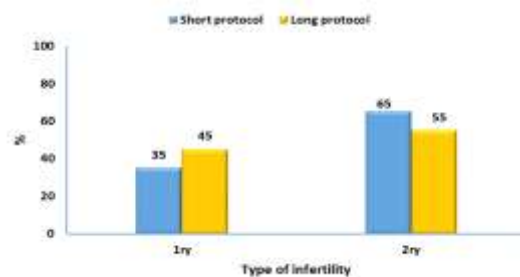


Fig. (2) Type of infertility in both groups

Infertility duration in both groups

Infertility duration showed a non-statistically significant difference between both groups. P-value was 0.675

Table (3) Infertility duration in both groups.

		Short protocol(n= 20)	Long protocol(n= 20)	P value
Infertility duration (years)	Mean ±SD	4 ±1	3 ±1	0.675
	Range	2 - 5	2 - 5	

Independent t-test was used

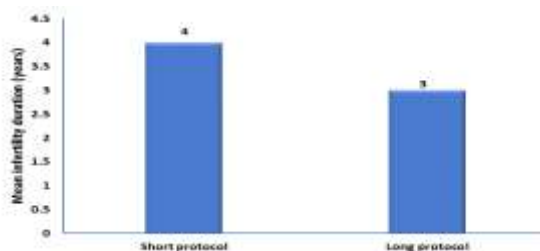


Fig (3) Infertility duration in both groups

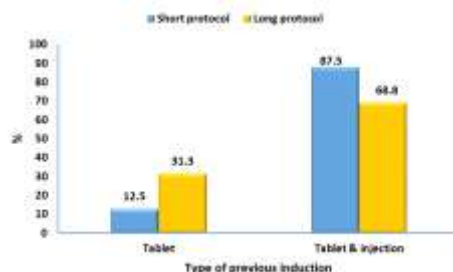
Previous induction & its types in both groups

Previous induction and its types showed non-statistically significant differences between both groups. P values were 1.0 and 0.394, respectively.

**Table (4)** Previous induction & its types in both groups.

		Short protocol (n = 20)	Long protocol (n = 20)	P value
<b>Previous induction</b>	<b>n (%)</b>	16 (80.0)	16 (80.0)	1.0
<b>Type of previous induction</b>	<b>Tablet</b>	2 (12.5)	5 (31.3)	0.394
	<b>Tablet &amp; injection</b>	14 (87.5)	11 (68.8)	

Fisher’s exact test was used



**Fig. (4)** Type of previous induction in both groups

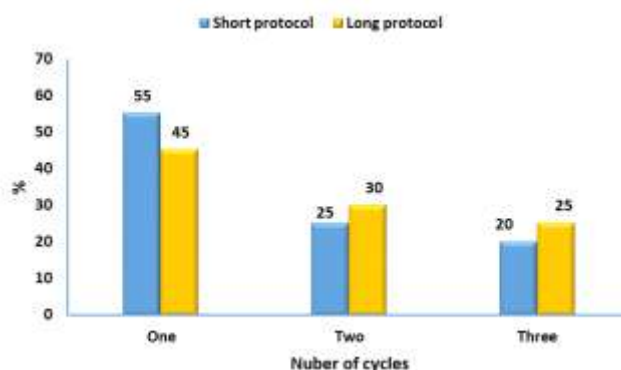
Number of cycles in both groups

The number of cycles showed a non-statistically significant difference between both groups. P-value was 0.844

**Table (5)** Number of cycles in both groups.

		Short protocol (n = 20)	Long protocol(n= 20)	P value
<b>Number of cycles</b>	<b>One</b>	11 (55.0)	9 (45.0)	0.844
	<b>Two</b>	5 (25.0)	6 (30.0)	
	<b>Three</b>	4 (20.0)	5 (25.0)	

Fisher’s exact test was used



**Fig. (5)** Number of cycles in both groups

Ultrasound criteria of PCOs in both groups

Ultrasound criteria of PCOs showed a non-statistically significant difference between both groups. P-value was 0.490

**Table (6)** Ultrasound criteria of PCOs in both groups

		Short protocol(n = 20)	Long protocol (n = 20)	P value
<b>US criteria of PCOs</b>	<b>n (%)</b>	15 (75.0)	13 (65.0)	0.490

Chi-square test was used

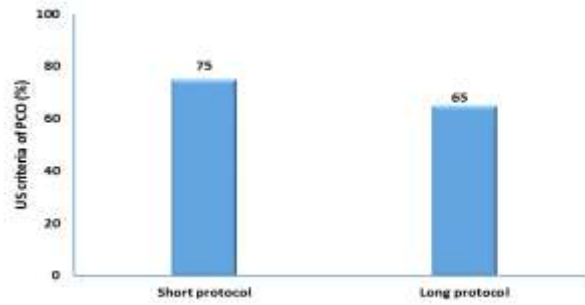


Fig. (6) Ultrasound criteria of PCOs in both groups.

Hyperandrogenism in both groups

Hyperandrogenism showed a non-statistically significant difference between both groups. P-value was 0.525

Table (7) Hyperandrogenism in both groups

		Short protocol (n = 20)	Long protocol (n= 20)	P value
Hyperandrogenism	n (%)	12 (60.0)	10 (50.0)	0.525

Chi-square test was used

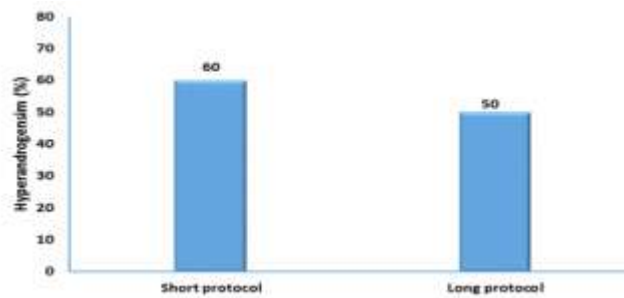


Fig. (7) Hyperandrogenism in both groups

Ovulation in both groups

Ovulation status showed a non-statistically significant difference between both groups. P-value was 1.0

Table (8) Oligo-ovulation in both groups

		Short protocol (n = 20)	Long protocol (n = 20)	P value
Ovulation	Anovulation	9 (45.0)	7 (35.0)	0.519
	Oligo-ovulation	11 (55.0)	13 (65.0)	

Chi-square test was used

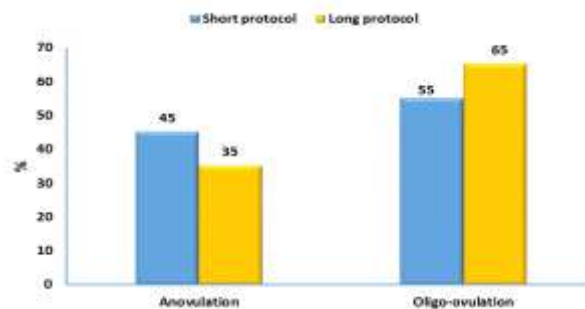


Fig. (8) Ovulation in both groups.

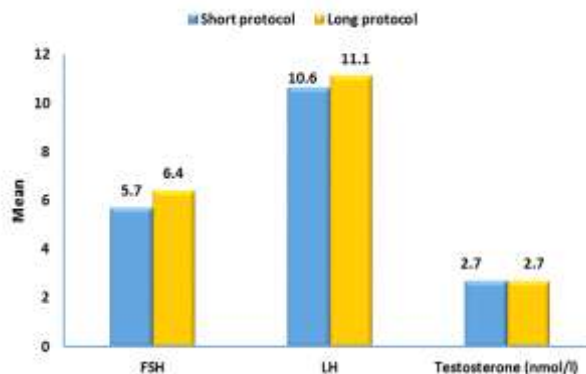
Levels of FSH, LH, and testosterone in both groups

Levels of FSH, LH, and testosterone showed non-statistically significant differences between both groups. P values were 0.257, 0.667, and 0.946, respectively.

**Table (9)** Levels of FSH, LH, and testosterone in both groups.

		Short protocol (n = 20)	Long protocol (n = 20)	P value
FSH	Mean ±SD	5.7 ±1.7	6.4 ±2.1	0.257
	Range	3.5 - 9	3.4 - 9.5	
LH	Mean ±SD	10.6 ±4.4	11.1 ±4	0.667
	Range	4.5 - 19	6 - 19	
Testosterone (nmol/l)	Mean ±SD	2.7 ±0.7	2.7 ±0.7	0.946
	Range	1.5 - 3.8	1.5 - 3.7	

Independent t-test was used



**Fig. (9)** Levels of FSH, LH, and testosterone in both groups.

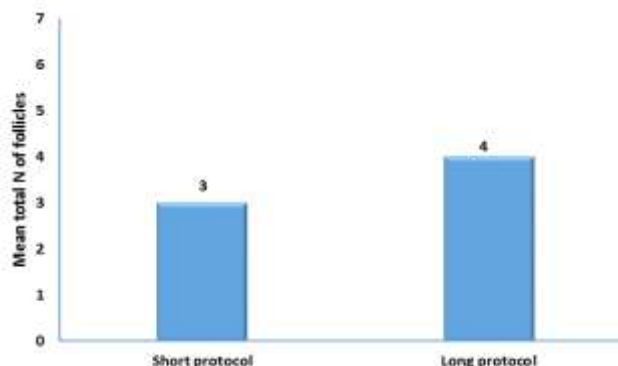
Total number of follicles in both groups

The mean total number of follicles was precycle of ovulation induction significantly higher in the long protocol group (4) than the short protocol group (3). P-value was <0.001.

**Table (10)** Total number of follicles in both groups.

		Short protocol (n = 20)	Long protocol (n = 20)	P value
Total N of follicles	Mean ±SD	3 ±1	4 ±1	<0.001
	Range	2 - 3	3 - 5	

Independent t-test was used



**Fig. (10)** Total number of follicles in both groups.

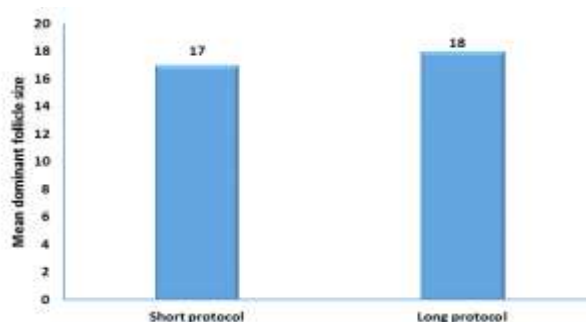
Dominant follicle size in both groups

Mean dominant follicle size was larger in the long protocol group (18 mm) than the short protocol group (17 mm), with no statistical significance. P-value was 0.476.

**Table (11)** Dominant follicle size in both groups.

		Short protocol (n = 20)	Long protocol (n = 20)	P value
Dominant follicle size (mm)	Mean ±SD	17 ±4	18 ±4	0.476
	Range	12 - 25	12 - 25	

Independent t-test was used



**Fig. (11)** Dominant follicle size in both groups

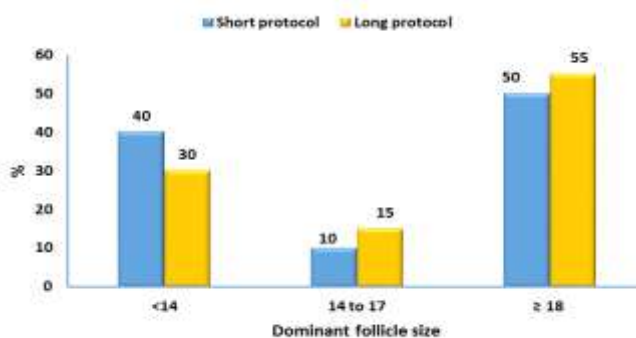
Dominant follicle size categories in both groups

Follicle size <14 mm was higher in short protocol (40.0%) than long protocol (30.0%), follicle size of 14 to 17mm was higher in long protocol (15.0%) than short protocol (10.0%), and follicle size of ≥ 18 mm was higher in long protocol (55.0%) than short protocol (50.0%), with no statistical significance (P value = 0.766)

**Table (12)** Dominant follicle size categories in both groups.

		Short protocol (n = 20)	Long protocol (n = 20)	P value
Dominant follicle size	<14	n (%) 8 (40.0)	6 (30.0)	0.766
	14 to 17	n (%) 2 (10.0)	3 (15.0)	
	≥ 18	n (%) 10 (50.0)	11 (55.0)	

Chi-square test was used



**Fig. (12)** Dominant follicle size categories in both groups.

Endometrial thickness at the time of HCG administration size in both groups

Endometrial thickness at the time of HCG administration showed a non-statistically significant difference between both groups. P-value was 0.713

**Table (13)** Endometrial thickness at the time of HCG administration size in both groups.

		Short protocol (n = 20)	Long protocol (n = 20)	P value
Endometrial thickness at time of HCG (mm)	Mean ±SD	8 ±2	8 ±2	0.713
	Range	5 - 11	5 - 11	

Independent t-test was used

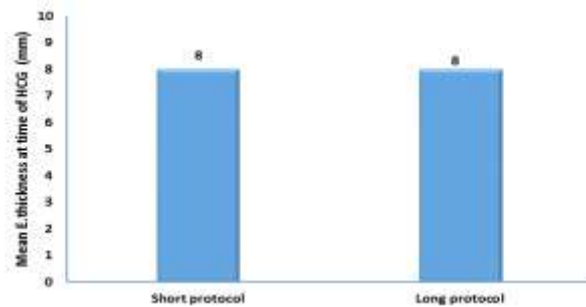


Fig. (13) Endometrial thickness at time of HCG administration size in both groups.

The occurrence of ovulation in both groups

Ovulation occurrence was higher in the long protocol group (65.0%) than the short protocol group (60.0%), with no statistical significance. P-value was 0.744

Table (14) Occurrence of ovulation in both groups.

		Short protocol(n = 20)	Long protocol (n= 20)	P value
<b>Ovulation occurrence</b>	<b>n (%)</b>	12 (60.0)	13 (65.0)	0.744

Chi-square test was used

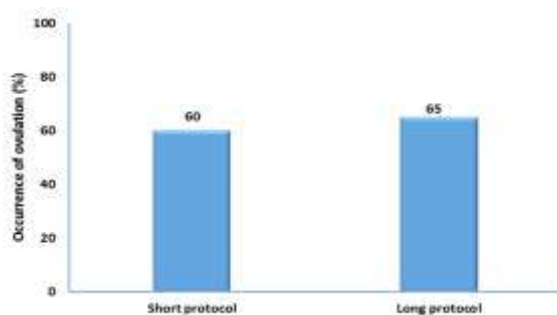


Fig. (14) Occurrence of ovulation in both groups.

The occurrence of pregnancy & miscarriage in both groups

The occurrence of pregnancy was higher in the long protocol group (25.0%) than the short protocol group (15.0%), with no statistical significance. P-value was 0.695

Table (15) Occurrence of pregnancy & miscarriage in both groups

		Short protocol (n = 20)	Long protocol (n = 20)	P value
<b>Occurrence of pregnancy</b>	<b>n (%)</b>	3 (15.0)	5 (25.0)	0.695
<b>Miscarriage*</b>	<b>n (%)</b>	0 (0.0)	1 (20.0)	-

Fisher’s exact test was used

\* Percentage was calculated based on total pregnancies

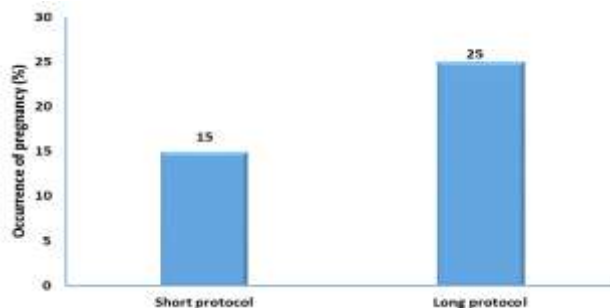


Fig. (15) Occurrence of pregnancy in both groups.



## 5. Discussion

PCOS is a typical endocrine issue, It is related with constant anovulation, and causes barrenness in 4%–6% of ladies in the regenerative age group. Despite the wide acknowledgment of clomiphene citrate as a first-line drug for ovulation enlistment in ladies with PCOS, a significant extent of ladies don't react to this treatment [3].

Different administrations were proposed for barren ladies with PCOS (15,17,18). In any case, the ideal administration alternative has not been tended to fulfilled. Albeit different medicines including weight decrease, clomiphene citrate, metformin, gonadotropins, and ovary searing have been accounted for to treat such condition, the viability actually has deficient proof to help [8,11].

Past investigation had proposed that letrozole, a third-age aromatase inhibitor, can be utilized for ovulation acceptance, and it is related with a higher possibility of simple pregnancy and a lower hazard of various pregnancy than clomiphene citrate.

The current investigation was done at Benha University Hospital out-patient center of obstetric & gynecology to analyze between short (5mg day by day for 5 days) versus broadened course (2.5mg day by day for 10 days) of letrozole treatment for ovulation enlistment in ladies with polycystic ovary condition.

This planned similar examination included 40 fruitless ladies who were analyzed as having PCOS. The remembered ladies for this examination were separated into two gatherings. Gathering I was initiated to ovulate by short course. Gathering II was initiated to ovulate by broadened course.

In the current investigation, the outcomes were as following:

- Age dissemination among bunch I (short letrozole bunch) was 22y to 35y ( $29 \pm 4$ ) and among bunch II (long letrozole bunch) was 25y to 35y ( $31 \pm 3$ ).
- Number of Oligo-ovulating patients was more noteworthy in the long letrozole bunch contrasted with short letrozole bunch (65% versus 55%), separately.
- Number of patients with Hyper-androgenism among group I (short letrozole) was 60% and bunch II (long letrozole) was 60%.
- Percentage of patients with positive US information was 75% in short letrozole bunch and 75% in long letrozole bunch.
- The mean worth  $\pm$  SD for complete number of follicles after incitement was altogether more prominent in the long letrozole bunch ( $4 \pm 1$ ) versus ( $3 \pm 1$ ) in short letrozole group;  $P < 0.001$
- This outcome come in concur with the consequence of study done by Yadav, (16)) that was done to assess the viability - on richness result by present moment letrozole versus broadened letrozole routine in clomiphene citrate safe PCOS ladies, directed on 105 ladies with clomiphene safe PCOS, Group 1 (55

patients) got short letrozole routine, bunch 2 ( 50 patients) got long letrozole routine

- Their outcomes - in this point – were that the absolute number of follicles during incitement was altogether more noteworthy in the long letrozole bunch ( $6.8 \pm 0.3$  versus  $3.5 \pm 0.5$ )
- The consequences of our examination were in concur with the aftereffects of the investigation by Al Fadhli (2) which showed that the ovulation rate and pregnancy rate was 1.9 and 18% separately in the gathering who got letrozole in a portion of 20 mg while it was lower i.e . 1.7 and 15% in the gathering who got letrozole in a portion of 12.5mg. On contrasting the two gatherings in the short letrozole bunch the pregnancy rate was 12.5% and the unnatural birth cycle rate was 16.7 % while in the all-encompassing letrozole bunch it was 18.3% and 11.1% separately These outcomes were reliable to the investigation directed by Badawy and Alaa Mosbah [4] in which the pregnancy rate was 12.4% and the premature delivery rate was 18.4 % in the short letrozole bunch while it was 17.4% and 17.9% in the long letrozole bunch individually
- These outcomes likewise come concur with the consequences of study done by Badawy (4) that was done to assess the result of long letrozole treatment for enlistment of ovulation in patients with clomiphene-safe polycystic ovary disorder (PCOS) on 218 patients with clomiphene-safe PCOS and patients were arbitrarily assigned to treatment with either long letrozole treatment (n = 108) or short letrozole treatment (n = 110). Their outcomes in this point were the absolute quantities of follicles during incitement was essentially more prominent in the long letrozole bunch ( $6.7 \pm 0.3$  versus  $3.9 \pm 0.4$ ).
- Another examination was conveyed by Fouda (6) on 136 ladies who reacted ineffectively to GnRH agonist long convention in their first IVF cycle and were randomized into two equivalent gatherings utilizing PC produced list and were treated in the second IVF cycle by either expanded letrozole routine (5 mg/day during the initial 5 days of cycle and 2.5 mg/day during the resulting 3 days) joined with hPFSH-GnRHant convention or short letrozole routine (2.5 mg/day from cycle day 3-7) joined with hPFSH-GnRHant convention. The examination was done to think about the viability and cost-adequacy of broadened high portion letrozole routine/hPFSH-gonadotropin delivering chemical opponent (GnRHant) convention with short low portion letrozole routine/hPFSH-GnRHant convention in helpless responders going through IVF-ET. The study showed that there were no huge contrasts between the two gatherings concerning number of oocytes recovered in expanded letrozole bunch and in short letrozole bunch ( $5.39 \pm 2.08$  versus  $5.20 \pm 1.88$ ), separately.
- Another examination was finished by Ramezanzadeh (5) to think about the impacts of either a 5 or 7.5 mg

every day portion of Letrozole in PCOS ladies going through ovulation acceptance. 67 PCOS patients with barrenness were haphazardly isolated into two gatherings and treated with either 5 mg/day (30 patients, bunch 1) or 7.5 mg/day (37 patients, bunch 2) Letrozole, for 5 days beginning from day 3 of the monthly cycle. The outcome showed no huge contrast in the quantity of intermediate ( $0.83 \pm 0.75$  versus  $0.62 \pm 0.76$ ) and develop follicles ( $1.13 \pm 1.11$  versus  $1.22 \pm 1.03$ ) on days 12–14 between bunch 1 and 2, individually.

- In the current examination, the mean size (mm) of greatest follicles was more prominent ( $18 \pm 4$ ) in the long letrozole bunch when contrasted with short letrozole bunch ( $17 \pm 4$ ), without measurable contrasts ( $P=0.476$ ).
- In the current investigation, the quantity of patients with follicles estimating  $\geq 18$  mm and between 14–17mm was more prominent in the long letrozole bunch ( $P=0.766$ ). These outcomes came in similar with the consequences of Badawy (4)
- In the current examination, The mean of endometrial thickness at the hour of hCG organization  $\pm$  SD in bunch I was  $8 \pm 2$  mm and  $8 \pm 2$  among bunch II. There was no critical contrast in the endometrial thickness at the hour of hCG organization between the two gatherings ( $P=0.713$ ).
- That came concur with Badawy (4) and Ramezanzadeh (5).
- In the current examination, level of ovulation occurred after treatment, bunch II (long letrozole bunch) was more noteworthy than Group I (short letrozole bunch) (65% versus 60%, individually).

In the current examination, the mean size (mm) of greatest follicles was more prominent ( $18 \pm 4$ ) in the long letrozole bunch when contrasted with short letrozole bunch ( $17 \pm 4$ ), without measurable contrasts ( $P=0.476$ ).

In the current investigation, the quantity of patients with follicles estimating  $\geq 18$  mm and between 14–17mm was more prominent in the long letrozole bunch ( $P=0.766$ ). These outcomes came in similar with the consequences of Badawy [4].

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That came concur with Badawy [4] and Ramezanzadeh [5].

In the current examination, level of ovulation occurred after treatment, bunch II (long letrozole bunch) was more noteworthy than Group I (short letrozole bunch) (65% versus 60%, individually).

## 6. Conclusion

The long letrozole treatment (2.5mg for 10 days) can deliver more develop follicles and thusly a greater

number of pregnancies than the short letrozole treatment (5mg for 5 days).

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