Journal of Advances in Medicine and Medical Research

33(19): 31-39, 2021; Article no.JAMMR.71992
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Extended Letrozole Versus Recombinant FSH in Ovulation Induction in Cases of Clomiphene Citrate Resistant Polycystic Ovary

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i1931076
Editor(s):
(1) Dr. Rameshwari Thakur, Muzaffarnagar Medical College, India.
Reviewers:
(1) Aida Petca, Carol Davila University of Medicine and Pharmacy, Romania.
(2) Ranjit Aich, Nanaji Deshmukh Veterinary Science University, College of Veterinary Science and Animal Husbandry, India.
Complete Peer review History: https://www.sdiarticle4.com/review-history/71992

Original Research Article

Received 01 June 2021
Accepted 09 August 2021
Published 06 September 2021

ABSTRACT

Background: Clomiphene citrate (CC) is still the traditional therapy used for inducing ovulation in polycystic ovary syndrome (PCOS). Clomiphene resistance, which refers to persistence of anovulation after standard CC therapy, occurs in 15%–20% of patients. We aimed to compare between extended letrozole versus recombinant FSH in ovulation induction in cases of clomiphene resistant polycystic ovary
Methods: Seventy women with PCOS were included then patients were equally randomized to receive one of the two drugs to be given over the next 3 months. In current study Group A: letrozole group 2.5 mg two tablets once daily for 10 days from day 2 of menses. Group B: Recombinant FSH 75 i.u s.c daily from day 2 for 5 days then monitoring dose according to folliculometry.
Results: There was non-significant difference between two groups as regard FSH and LH but as regard Serum E2 (pg/mL) at day 5 of HCG administration there was significant higher in FSH recombinant group. There was insignificant difference between two groups as regard Ovulating, Number of follicles >18. There was insignificant difference between two groups as regard Size of

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dominant follicle, endometrial thickness at hCG (mm). OHSS, discontinuation due to OHSS, clinical pregnancy, multiple pregnancy and abortion was higher in FSH recombinant group but differences didn't reach significance.

Conclusions: There was non-significant difference between two groups in relation to ovulation, Number of follicles, Size of dominant follicle, Endometrial thickness at day of HCG injection however it was reported that OHSS, discontinuation due to OHSS, positive pregnancy test, was higher in FSH recombinant group but differences didn't reach significance level.

Keywords: Extended letrozole; recombinant FSH; ovulation induction; clomiphene citrate resistant; polycystic ovary.

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies, affecting 5–10% of women at reproductive age. PCOS is a heterogeneous disorder characterized by several clinical and metabolic abnormalities [1].

The need to establish universally accepted diagnostic criteria led to the Rotterdam consensus meeting in 2003, concluding that diagnosis of PCOS should be based on at least two of three major criteria, including oligo/anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries as identified by ultrasonography, also excluding other androgen excess disorders [2].

The primary etiology of PCOS is still largely unknown; but it is believed to be a multifactorial disorder involving genetic and environmental factors [3]. There are plethora of health implications that have been associated with the diagnosis of PCOS, many of these constituting lifelong complications such as cardiovascular disease and Type II diabetes. Insulin resistance plays a central role in the pathophysiology of the syndrome, and can be found in 60–80% of all women with PCOS and in 95% of obese women with PCOS [4].

PCOS is the most common cause of anovulation. Out of all couples seeking treatment for infertility, 30% of cases are due to anovulation, and It is estimated that 90% of anovulation cases are actually caused by PCOS [5].

The treatment of infertility in PCOS includes lifestyle changes (diet and exercise), pharmacological therapies (oral agents such as clomiphene citrate, letrozole or metformin or injectable agents such as gonadotrophins), surgical therapy (laparoscopic ovarian surgery) or IVF [6].

Current guidelines on PCOS either are limited in breadth, do not follow rigorous best practice in development, have not involved consumers or are outdated [5,7].

Aromatase inhibitors (AIs), such as letrozole or anastrozole, have been introduced for treatment of PCOS women with CC-resistant anovulation. It has been postulated that blocking estrogen production by inhibiting aromatization in the ovary would release the hypothalamic-pituitary axis from estrogenic negative feedback. As a result, FSH secretion increases, stimulating the development of ovarian follicles. Preliminary studies have reported that aromatase inhibitors were useful for inducing ovulation and in superovulation [8].

In PCOS, serum FSH is too low, hence exogenous gonadotropins are administered to increase its levels and stimulate follicular growth. Due to the presence of multiple follicles in PCOS, conventional doses of gonadotropins are associated with high rates OHSS and multiple pregnancies. However, low-dose gonadotropin therapy has been proven to be effective in inducing mono-follicular ovulation [9]. Various types of gonadotrophin have been developed: urinary–derived products, available in purified (FSH–P), and highly purified (FSH- HP) form, and human menopausal gonadotrophin, also available in highly purified form (HP- HMG). Finally, recombinant FSH (rFSH) was developed artificially to obtain even higher purity [10].

The aim of this study is to compare between extended letrozole versus recombinant FSH in ovulation induction in cases of clomiphene resistant polycystic ovary.

2. PATIENTS AND METHODS

This prospective randomized clinical trial conducted on 70 women with PCOS among those attending the gynecology outpatient clinic in Tanta University Hospitals.

The inclusion criteria include patients that are 20 – 25 years old, having anovulatory infertility due

to PCO, have a history of failed ovulation induction using clomiphene citrate for previous 3 consecutive cycles and their diagnosis of PCOS was made on the basis of revised Rotterdam 2003 criteria. *(Rotterdam and Group, 2004)*: Oligo or Anovulation, Hyperandroginism and Polycystic ovary on ultrasound.

The exclusion criteria included some other causes of infertility (Tubal factor, uterine factor, abnormal semen parameters), ages above 35 years old and BMI >30 kg/cm2. Some chronic diseases like thyroid dysfunction, DM and hypertension were excluded. As well as neoplastic diseases such as pituitary tumors, adrenal tumors, Cushing syndrome and androgen-secreting tumors and hyperprolactinemia.

All patients were randomized to receive one of the two over the next 3 months.

- **Group A (35 Patients):** Subjects who administered letrozole 2.5 mg two tablets once daily for 10 days from day 2 of menses.
- **Group B (35 Patients):** Subjects who administered recombinant FSH 75 i.u s.c daily from day 2 for 5 days then monitoring dose according to folliculometry.

Both study groups were subjected to detailed history taking. As well as clinical examination; general examination, such as vital signs, systemic examination and local examination; assessment of tenderness or signs of infections.

All patients underwent investigations to investigate comprehensive infertility work-up including tubal patency test, pelvic ultrasonography, husband semen analysis, serum hormone measurements on the 2nd to 5th day of the cycle.

Withdrawal bleeding was achieved using 10 mg levonorgesterel tablets for 10 days before stimulation or spontaneous cycle.

Subjects were monitored by transvaginal ultrasound for the mean follicular size and thickness of the endometrium on day 8 then according to follicular size every other day till mature follicle, HCG injection will be given when at least on follicle ≥18 ml, serum E2 (pg/mL), SerumP (ng/mL) on day 21–23 and serum P (ng/mL) was measured on day 21–23 of the cycle by RIA using antibody coated-tube method.

The primary outcome measures were number of growing and mature follicles, serum E2 (pg/mL), serum P (ng/mL), and endometrial thickness (mm).

Secondary outcome measures were the occurrence of positive pregnancy Test.

2.1 Statistical Analysis

The collected data was coded, revised, cleaned, tabulated, and analyzed through Statistical Package for Social Science (SPSS) version 26 software using appropriate statistics. The descriptive statistics including percentages (%), arithmetic mean (X) and standard deviation (SD) were calculated for various qualitative and quantitative data to describe the study population. The analytic statistical tests comprised Chi squared, fisher's exact, and independent T test with P value ≤ 0.05 was considered statistically significant. The tests used were Chi-square test, Fisher's Exact correction, student t-test, Mann Whitney test.

3. RESULTS

There was insignificant difference between two groups as regard age, BMI p-value 0.786, 0.878 respectively Table 1.

There was insignificant difference between two groups as regard duration and type of infertility p-value 0.941, 0.811 respectively Table 2.

Table 1. Comparison between the two studied groups according to demographic data

	Letrozole (n = 35)	Recombinant FSH (n = 35)	t	p
Age (years)				
Min. – Max.	22.0 – 34.0	23.0 – 36.0	0.273	0.786
Mean ± SD.	27.94 ± 3.05	27.91 ± 3.47		
***BMI(kg/m^2)**				
Min. – Max.	24.0 – 30.0	24.0 – 30.0	0.154	0.878
Mean ± SD*	26.66 ± 1.57	26.71 ± 1.53		

***SD**: Standard deviation, BMI: body mass index*

Table 2. Comparison between the two studied groups according to duration of infertility and type of infertility

	Letrozole (n = 35)		Recombinant FSH (n = 35)		Test of Sig.	p
	No.	%	No.	%		
Duration of infertility						
Min. – Max.	2.0 – 5.0		3.0 – 6.0		t=0.075	0.941
Mean ± SD.	3.53 ± 0.81		3.69 ± 0.806			
Type of infertility						
Primary	18	51.4	17	48.6	χ^2=0.057	0.811
Secondary	17	48.6	18	51.4		

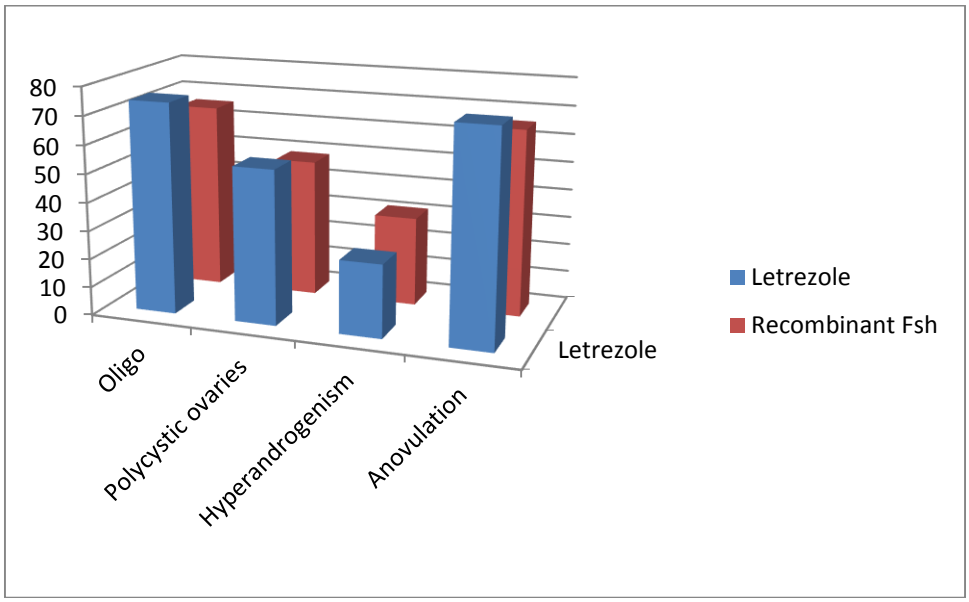

Fig. 1. Comparison between the two studied groups according to clinical presentation

There was non-significant difference between two groups as regard clinical presentation [Fig. 1]

There was insignificant difference between two groups regarding FSH, LH p-value 0.991, 0.816 respectively. While it showed that Serum E2 (pg/mL) at day 5 of HCG administration was significant higher in FSH recombinant group Table 3.

This following table shows that there was insignificant difference between two groups as regard s. Progesterone at day 21 (ng/mL) p-value 0.221 Table 4.

Table 3. Comparison between the two studied groups according to hormonal profile

	Letrozole (n = 35)	Recombinant FSH (n = 35)	t	P
FSH				
Min. – Max.	6.0 – 9.80	7.0 – 10.80	0.011	0.991
Mean ± SD.	7.53 ± 1.07	7.73 ± 0.91		
LH				
Min. – Max.	3.50 – 7.0	4.00 – 7.50	0.234	0 .816
Mean ± SD.	5.86 ± 1.11	5.97 ± 0.97		
Serum E2 (pg/mL) at day of HCG administration				
Min. – Max.	232.0 – 389.0	250.0 – 589.0	5.903*	<0.001*
Mean ± SD.	292.09 ± 54.58	389.23 ± 80.62		

Table 4. Comparison between the two studied groups according to Progesterone concentration at day 21 (ng/mL)

	Letrozole (n = 35)	Recombinant FSH (n = 35)	t	P
s.Progesterone at day 21 (ng/mL)				
Min. – Max.	7.25 – 14.83	7.54 – 15.26	1.238	0.221
Mean ± SD.	10.86 ± 2.92	11.76 ± 3.17		
Median (IQR)	10.7 (9.1 – 11.9)	11.6 (10.7 – 13.9)		

Table 5. Comparison between the two studied groups according to ovulation and duration of infertility

	Letrozole (n = 35)		Recombinant FSH (n = 35)		Test of Sig.	p
	No.	%	No.	%		
Number of follicles >18						
Min. – Max.	0.0 – 6.0		0.0 – 7.0		U=	0.440
Mean ± SD.	3.65 ± 1.99		4.00 ± 1.97		547.50	
Median (IQR)	4.0 (2.0 – 5.0)		4.0 (3.0 – 6.0)			
Ovulation						
No	15	42.9	11	31.4%	χ^2=	0.322
Yes	20	57.1	24	68.6%	0.979	

This table shows that there was non-significant difference between two groups as regard Ovulating, Number of follicles >18p-value 0.322, 0.440 respectively Table 5.

This table shows that there was insignificant difference between two groups as regard Size of dominant follicle, endometrial thickness at hCG (mm) p-value 0.151, 0.926 respectively Table 6.

Follicle with mean diameter 14 mm and Follicle with mean diameter 18 mm and Uterus showing triple line endometrial pattern measuring 9mm. (Figs. 2 - 4).

This table shows that OHSS, discontinuation due to OHSS, +ve pregnancy test was higher in FSH recombinant group but differences didn't reach significance Table 7.

4. DISCUSSION

Aromatase is the key enzyme that converts testosterone to estradiol (E2) . The concept of using aromatase inhibitors (AIs) as a new method of controlled ovarian stimulation has been extensively investigated by several research groups in the past few years .AIs have less antiestrogenic effects on the endometrium, which can be advantageous to keeping the endometrium in optimal condition for maintaining pregnancy [11].

Table 6. Comparison between the two studied groups according to size of dominant follicle and endometrial thickness at HCG (mm)

	Letrozole (n = 35)	Recombinant FSH (n = 35)	Test of Sig.	p
Size of dominant follicle				
Min. – Max.	8.0 – 24.0	10.0 – 26.0	U= 491.0	0.151
Mean ± SD.	16.74 ± 5.90	18.80 ± 5.94		
Median (IQR)	18.0 (11.50 – 20.0)	19.0 (15.0 – 21.0)		
Endometrial thickness at hCG (mm)				
Min. – Max.	7.50 – 10.20	7.80 – 10.0	t=0.093	0.926
Mean ± SD.	8.57 ± 0.64	8.56 ± 0.65		
Median (IQR)	8.70 (7.95 – 9.0)	8.70 (7.95 – 9.0)		

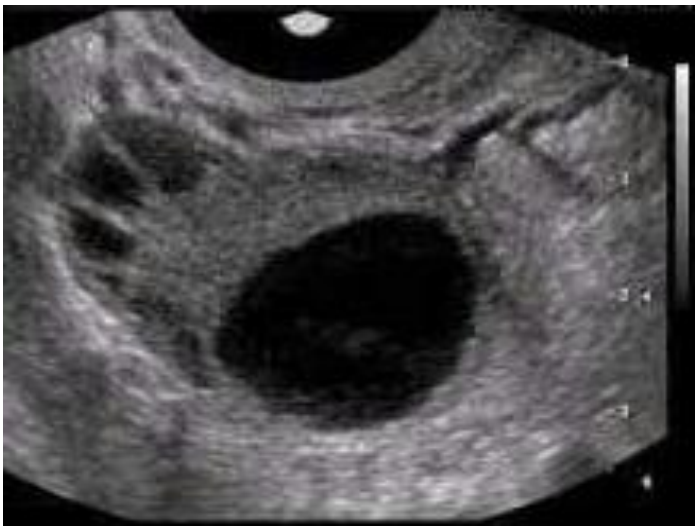

Fig. 2. Follicle with mean diameter 14 mm

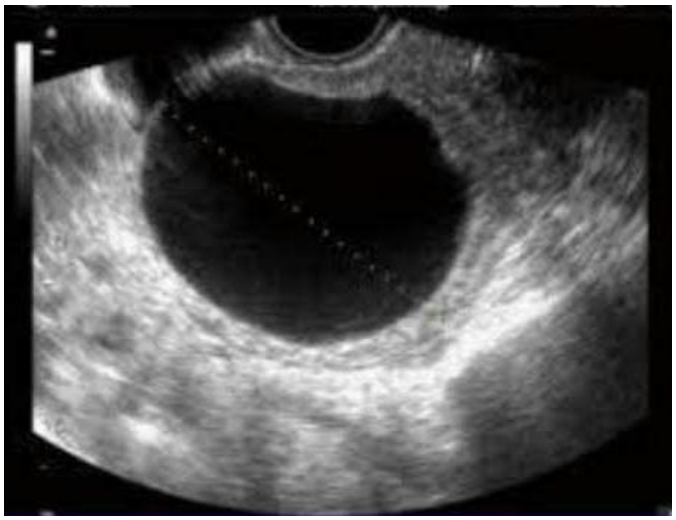

Fig. 3. Follicle with mean diameter 18 mm

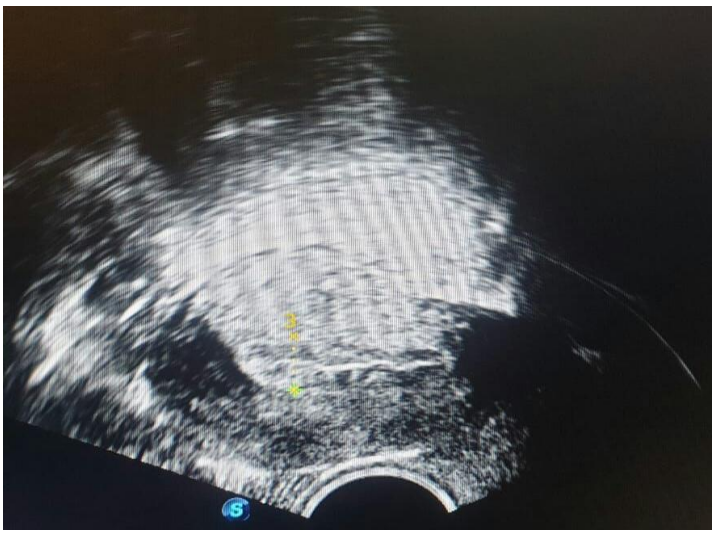

Fig. 4. Uterus showing triple line endometrial pattern measuring 9mm

Table 7. Comparison between the two studied groups according to different parameters after triggering

	Letrozole (n = 35)		Recombinant FSH (n = 35)		χ^2	p
	No.	%	No.	%		
OHSS	3	8.6	5	14.7	0.633	FEp=0.477
Discounted due to OHSS	3	8.6	5	14.7	0.633	FEp=0.477
+ve pregnancy test	8	22.9	9	26.5	0.121	0.728

Additionally, AIs have become an excellent alternative to clomiphene citrate treatment as ovulation inductors for the treatment of infertility, particularly in assisted reproduction programs. Letrozole, a highly selective AI, has been found to be efficacious in inducing ovulation in infertile women, especially those with an inadequate response to clomiphene citrate .Treatment with recombinant follicle-stimulating hormone (rFSH) leads to recruitment of more follicles. The application of rFSH can significantly and positively affect endometrial thickness, embryo development and pregnancy rates [12].

In this study we found that there was insignificant difference between two groups as regard FSH,LH p-value 0.991, 0.816 respectively but as regard Serum E2 (pg/mL)at day of HCG administration there was significant higher in FSH recombinant group.

This consistent with Shi S et al as showed that the serum E_2 concentration in HMG group was significantly higher than that in the letrozole group, the difference was statistically significant [13].

Wang HY et al also showed that the base serum hormone levels (luteinizing hormone: p = 0.342, FSH: p = 0.278, E2: p = 0.336) were not significantly different among the groups either [12].

In current study we found there was insignificant difference between two groups as regard Ovulating, Number of follicles >18p-value 0.322, 0.440 respectively.

Ganesh A et al. conducted a large randomized, single-blind clinical trial comparing the effects of letrozole, CC with recombinant FSH, and recombinant FSH alone in the treatment of CC-resistant PCOS patients with letrozole 5mg/d, obtaining ovulation rate 79.3% (295/372), the cycle pregnancy rate was 23.39% (87/372), The ovulation rate was better in the letrozole group than in the CC-recombinant FSH, but in the single-use recombinant FSH group. There was no significant difference in pregnancy rate and abortion rate between the 2 group [14]. In agreement with our result Gregoriou O et al showed that As expected there was a trend for an increased number of mature follicles >18 mm at the time of hCG administration in the gonadotropin group as well as higher peak E2 levels. None of these differences, however, reached statistical significance [15].

In current study we found that there was insignificant difference between two groups as regard Size of dominant follicle, Endometrial thickness at hCG (mm) p-value 0.151, 0.926 respectively.

In agreement with our result Shi S et al showed that the endometrial thickness was measured on the day of HCG injection. There was no significant difference between the two groups (*P*>.05) [13].

But in Gregoriou O et al showed that The endometrium measured on the day of hCG administration was significantly thicker in the gonadotropin group than in the letrozole group (8.2 2.1 vs. 7.1 2.3, P<.02) [15].

In current study, we found that OHSS, discontinuation due to OHSS, positive pregnancy test, was higher in FSH recombinant group but differences didn't reach significance.

In agreement with our result Shi S et al showed that the incidence of ovarian cysts and the incidence of OHSS in the letrozole group were lower than those in HMG group, and the difference was statistically significant (*P*<.05). The cycle pregnancy rate of the 2 groups was similar (*P*>.05), and the ratio of abortion in the letrozole group was lower (2%) than HMG group, but the difference was not statistically significant (*P*>.05).

The multiple pregnancy rate in HMG group was significantly higher than that in the letrozole group, and the difference was statistically

significant (*P*<.05). The live birth of the 2 groups was similar (*P*>.05) [13].

Another study by Gregoriou O et al showed that nine patients conceived in the gonadotropin group for a PR per initiated cycle of 14%. Four patients conceived after the first cycle, three after at the second, and two after the third cycle.

Six patients conceived in the letrozole group (8.9%); three conceived after the first cycle, two after the second, and one after the third cycle. There was no difference in PR/cycle between the two groups. One ectopic pregnancy occurred in the letrozole group and two first trimester miscarriages in the gonadotropin group. All pregnancies were singletons. There was no difference in the take home baby rate between the two groups (28% vs. 20%, P>.05) [15].

Also Busso CE et al agree with our result as showed that No significant differences were observed between both groups in terms of pregnancy rates per started cycle or per IUI, although slightly better outcome was obtained with letrozole. However, as cancellation and miscarriage rates were higher (although not significant) in the Letrozole group, the take home baby rate per started cycle was comparable between both groups [16].

5. CONCLUSIONS

In the current study it can be concluded that there was non-significant difference between two groups in relation to ovulation, number of follicles, size of dominant follicle, endometrial thickness at day of HCG injection it was reported that OHSS, discontinuation due to OHSS, positive pregnancy test, was higher in FSH recombinant group but differences didn't reach significance level.

CONSENT AND ETHICAL APPROVAL

Informed and written consent have been obtained from the patients after acquiring permission of the medical and ethical committee of Tanta University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/71992