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Comparing Effectiveness of Letrozole versus Postmenopausal FSH in Patients with Clomiphene Citrate-Resistant Polycystic Ovary Syndrome

Obstetrics & Gynecology

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ABSTRACT

Background: Follicle-stimulating hormone (FSH) is known for inducing multi-follicular growth in women. Letrozole (LE) is a third-generation aromatase inhibitor (AI) that is both powerful and selective. It was found to be effective in inducing ovulation, increased pregnancy rate, improve uterine environment, endometrial development with favorable cervical mucus.

Aim of the work: To assess the effectiveness of Letrozole with postmenopausal FSH in the treatment of anovulation in Clomiphene Citrate-Resistant Polycystic Ovary Syndrome.

Patients and methods: This was a randomized-controlled clinical trial involving 200 females with PCOS who were recruited from outpatient clinics at Al-Hussien University Hospital and Kafr EL-Sheikh General Hospital at the start of the study and followed up with after intervention to record the results from June 2020 to June 2021.

Results: The rate of ovulation has slightly been better in the postmenopausal FSH group (58%) compared to the letrozole group (54%), but without a significant difference (P=0.569) with the mean value ± SD for the overall number of follicles throughout activation being considerably larger in the postmenopausal FSH group (2.12 ± 1.35) versus (1.7 ±0.99) in the letrozole group; P=0.05). Out of those ovulating cases, 63% had single follicles compared to 50% in the postmenopausal FSH group and the remaining had multiple follicles, 37% versus 50% in both groups, respectively.

Conclusion: Letrozole and postmenopausal FSH were both beneficial in the treatment of patients with CC-resistant PCOS. Both medications were well tolerated, although letrozole was significantly easier to administer and less expensive.

Keywords: *Polycystic Ovary Syndrome; Letrozole; FSH; Clomiphene Citrate-Resistant.*

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INTRODUCTION

Infertility impacts about 48.5 million couples across the world. The proportion of common etiological factors that contribute to the disease's burden varies by population. [1] PCOS is a prevalent reason for infertility that is linked to chronic anovulation and hyperandrogenaemia.[2]

PCOS is a multifactorial condition that affects 8% to 13% of all reproductive-age females, based on the demographics and terminology utilized. It's the most frequent endocrinopathy that affects females in their reproductive years. PCOS is a multifaceted disorder having reproductive, metabolic, and psychosocial characteristics.[3]

Females with PCOS are also more likely to have other comorbidities like a higher BMI, cardiometabolic disease, mental health issues, and a poorer health-related quality of life (HQoL).[4]

In 75% of patients with PCOS, ovulation stimulation occurs with CC therapy. However, 25% of patients are CC resistant and require alternative treatment. CC is routinely used because of the low costs and the simplicity of administration and management.[5]

Moreover, although there is a 60–85% ovulation rate with CC, the rate of pregnancy is just 10–20% per cycle. Clomiphene resistance, which refers to the continuation of anovulation following normal CC treatment and happens in 15–20% of women, might be responsible for the disparity between ovulation and conception rates. Moreover, CC has the potential to harm the cervical mucus and endometrium.[6]

The persistence of anovulation following normal CC treatment is referred to as CC resistance. For those CC nonresponders, there are adjunctive therapies can be tried.[7] The meaning of clomiphene citrate failure differs, although it is commonly characterised as a failure to conceive despite ovulation during 6 cycles.[8]

Letrozole, an aromatase inhibitor, was first created to treat breast cancer. Letrozole is a nonsteroidal aromatase inhibitor that hinders estrogen biosynthesis in a particular, reversible manner. Letrozole, like CC, has been suggested to stimulate endogenous gonadotropin secretion. Letrozole, on the other hand, does not reduce estrogen receptors in the same way that CC does.[9]

Aromatase inhibitors (AIs), like letrozole or anastrozole, have been used to treat PCOS patients with CC-resistant anovulation in recent times. The hypothalamic-pituitary axis is thought to be free of estrogenic negative feedback if estrogen synthesis is blocked by suppressing aromatization in the ovary. As a result, FSH output rises, increasing the formation of ovarian follicles while lowering the risk of ovulation complications caused by gonadotropins.[10]

Moreover, gonadotrophin (FSH) ovulation stimulation started in the 1960s, and there is a significant amount of observational data to support the use of FSH ovulation induction in CCR or clomiphene-citrate-failure PCOS people.[11] However, the comparative efficacy of these therapies for patients with CCR-PCOS also remains unclear.[12]

The aim of this work has been to evaluate the efficacy of the Letrozole drug against postmenopausal FSH in the treatment of anovulation in CC-Resistant PCOS.

PATIENTS AND METHODS

This was a randomized-controlled clinical trial involving 200 females with PCOS who were recruited from outpatient clinics at Al-Hussien University Hospital and Kafr EL-Sheikh General Hospital at the start of the study and followed up with after intervention to record the results from June 2020 to 2021.

Randomization: Simple randomization using computer-generated numbers for randomizing the selected subjects was done.

Subjects were allocated into 2 groups: Group I, which consisted of 100 women that got letrozole, and Group II, which consisted of 100 women that got postmenopausal FSH.

Ethical Approval:

Approval of ethical committee was obtained from quality education assurance unit, Al-Azhar university faculty of medicine, Egypt. Verbal consent was taken from all cases and controls a before participation in this study. The nature and aim of this work were fully discussed with all the ladies who accepted to take part in the research. Any participant in the study had the option to withdraw from the study without affecting the medical care she received.

Inclusion criteria: Age from 21–35 years old, clomiphene citrate resistance, i.e., failing to ovulate following taking 150 mg of CC for five days in one cycle, normal serum prolactin, thyroid stimulating hormone, and 17-OH progesterone, no systemic diseases, and no gonadotropin or other hormonal medication therapy in the previous three months.

Exclusion criteria: Infertility caused by causes other than PCOS, lesions of the uterus cavity, or ovarian cysts, women with an ovarian surgery history, endometriosis complications, or pelvic adhesion, other endocrine illnesses, or a history of hepatic, renal, or thyroid disorders, and women who did not have therapies after registration as per the established routine or dropped out during therapies.

Every patient was exposed to:

History taking.

Clinical examinations were done including: Measurement of weight, height, and BMI
using the formula: BMI= weight (kg) / [height (m)]^2, general and abdominal examination for hyperandroginism signs, and cardiac and chest examination.

Ultrasound Examination: Transvaginal ultrasound examination for PCO diagnosis and for detection of any uterine or ovarian mass or abnormalities for example: uterine fibroid, ovarian cyst, pelvic endometriosis. The ultrasound equipment used was (MINDRAY, China) via a 3.5-5-MHz transabdominal probe and 5-9 MHz.

Investigations: On the second day of menstruation, all patients had their hormone levels (such as FSH, LH, and testosterone (T)) measured in their venous blood. Hysterosalpingography was used to confirm each woman's patent fallopian tube. As per the WHO's amended guidelines, their male partners' semen analytical parameters were normal.[13]

Intervention:

Group I: 100 cases received letrozole (FEMARA 2.5 MG, Novartis company) (dose: 5.0 mg/d^{-1} on the 3rd –7th days of the menstrual period for five consecutive days). If the patient did not conceive, the therapy has been repeated for another cycle.

Group II: 100 cases received postmenopausal FSH (Fostimon, IBSA) administered starting with a 75 IU ampoule daily from cycle day 5 days. If the patient did not conceive, the therapy has been repeated for another cycle.

If the patient is menstruated we started from 3 days. If the patient with amenorrhea we did withdrawal of the cycle by progesterone for 5days

Transvaginal Ultrasonographic evaluation of ovulation reponse: On day 11, as well as every 1–3 days afterwards, all participants were observed by transvaginal ultrasonography measurements of the average follicular diameter and serial tests of LH and estradiol concentrations till a follicle reached a diameter of ≥18 mm.

Duration of therapy: Both groups received the treatment of ovulation induction till success of pregnancy or for one cycles.

Statistical Analysis:

In the present study, statistical analyses of data have been performed employing SPSS version 23(Chicago, IL, USA). The Shapiro–Wilks test has

been employed to determine whether variables have a normal distribution. The mean ± SD, or median and range, have been utilized to represent numerical data. Categorical data was summarized as percentages. The comparison between 2 groups with quantitative data for before and after and parametric distribution has been done using the paired t-test, whereas the comparison between 2 groups with quantitative data for before and after and non-parametric distribution has been conducted utilizing the Wilxon Rank test. The Kolmogorov-Smirnov test has been conducted to detect the parameter distribution pattern normality. For normally distributed data, the t-test was employed; otherwise, the Mann-Whitney test was employed. Qualitative variables were also assessed by the chi-squared χ^2test. The margin of error accepted has been set at 5%, with a 95% confidence interval. Significant has been deemed as a P value of < 0.05.

RESULTS

		Letrozole group (N= 100)	Postmenopausal FSH group (N= 100)	P-value
Age (years)	Range	20–35	21–34	0.104
	Mean ± S. D	26.9 ± 3.06	26.23 ± 2.72	
20-25 (years)	N (%)	36(36%)	46(46%)	0.204
26-30 (years)	N (%)	51(51%)	47(47%)	
31-35 (years)	N (%)	13(13%)	7(7%)	
BMI (Kg/m^2)	Range	19.5–38	19.5–35	0.093
	Mean ± S. D	26.79± 2.71	26.04± 3.49	
18.5-25 (kg/m^2)	N (%)	36(36%)	51(51%)	0.004**
26-30 (kg/m^2)	N (%)	56(56%)	33(33%)	
>35 (kg/m^2)	N (%)	8(8%)	16(16%)	
Duration of infertility (years)	Range	1.5–7.5	1.5–7.5	0.372
	Mean ± S. D	2.8± 1.05	2.68± 0.92	

Table 1: Age distribution, BMI and duration of infertility in group I (letrozole group) and group II (Postmenopausal FSH group).

The mean age ± SD was (27.06 ± 3.28 vs. 25.84 ± 4.32) in letrozole group and Postmenopausal FSH group, respectively. In terms of age, there have been no statistically significant differences between the two groups (P=0.104). There have been statistically significant differences between the two study groups in terms of the percentage of instances in each age group (P=0.204). Most of cases aged between 26-30 years old (51% vs 47% in both studied groups respectively.

There has been a non-significant difference between the examined groups concerning the BMI of patients (P > 0.05), where the average BMI of cases in the letrozole group was 26.79± 2.71, ranging from 19.5 to 38 kg/m2 and the average BMI of cases in the postmenopausal FSH group was 26.04± 3.49 kg/m2 , ranging from 19.5 to 35 kg/m2. Most of cases had their BMI ranged between 26-30 kg/m2 (56% and 33% in both studied groups respectively.

We discovered no difference in the mean length of infertility between the two groups studied (P=0.372) (Table 1).

		Letrozole group (N= 100)			Postmenopausal FSH group (N= 100)			P-value
Number of patients with amenorrhea:								
Oligomenorrhea	N	75			70			0.866
	%	75%			70%			
Amenorrhea	N	25			30			
	%	25%			30%			
Total	N	100			100			
	%	100.0%			100%			
Hormonal profile:								
2nd day LH (IU/mL)	Range	7.98	–	15.5	8.52	–	16.5	0.106
	Mean ± S. D	12.02	±	1	12.28	±	1.24	
2nd day FSH (IU/mL)	Range	3.9	-	7.3	3.9	-	7.99	0.476
	Mean ± S. D	5.95	±	0.65	6.03	±	0.87	
2nd day LH/FSH	Range	1.5	-	3.27	1.39	-	3.22	0.390
	Mean ± S. D	2.04	±	0.25	2.07	±	0.29	
Basal Estradiol (E_2) (pg/ml)	Range	39	-	61	39	-	66	0.002
	Mean ± S. D	49.35	±	4.84	51.75	±	6.09	

Table 2: Number of patients with amenorrhea and mean of Hormonal profile in group I (letrozole group) and group II (Postmenopausal FSH group).

FSH, follicle-stimulating hormone; LH, lutenizing hormone; E2, Estradiol FSH, follicle-stimulating hormone; LH, lutenizing hormone; E2, Estradiol

The percentage of patients with amenorrhea was comparable in both groups (25% in the letrozole group versus 30% in the postmenopausal FSH group), with the remaining cases, 75% and 70% having oligomenorrhea, respectively, in both groups without statistically significant differences (P = 0.866). (P = 0.866). There has been a non-significant diff erence between the two examined groups concerning the average of 2nd day LH & FSH hormones, as the mean of LH hormone was 12.02± 1 in letrozole group compared to 12.28±1.24 in postmenopausal FSH group, (P=0.106). Also, the mean FSH level was 5.95±0.65 in letrozole group compared to 6.03±0.87 in Postmenopausal FSH group, (P=0.476). Moreover, nearly similar ratio between LH/FSH levels was detected among both studied groups (P=0.390). However, Estradiol hormone was significantly higher in postmenopausal FSH group (51.75±6.09) compared to letrozole group (49.35± 4.84), (P=0.002) (Table 2).

		Letrozole group (N= 100)			Postmenopausal FSH group (N= 100)			P-value
Endometrial thickness at hCG (mm)	Range	6	–	10.1	6	–	10.9	0.021
	Mean ± S. D	9.89	±	1.94	10.52	±	1.88	
Ovulation:								
Negative	N	46			42			0.569
	%	46%			42%			
Positive	N	54			58			
	%	54%			58%			
Total	N	100			100			
	%	100.0%			100%			

Table 3: Mean of Endometrial thickness at hCG (mm), and ovulation results in group I (letrozole group) and group II (Postmenopausal FSH group)

The mean of endometrial thickness (ET) at HCG injection was among group I (letrozole group) and group II (postmenopausal FSH group). The mean of endometrial thickness at the time of HCG injection ± SD in group I was 9.89 ± 1.94 mm versus 10.52 ± 1.88 in group II. There has been a statistically significant increase in the thickness of endometrium at the HCG administration time in the postmenopausal FSH group compared to that in the letrozole group (P=0.021). The rate of ovulation was slightly better in the Postmenopausal FSH group (58%) compared to the letrozole group (54%), but without a significant difference (P=0.569) (Table 3).

		Letrozole group (N= 46)			Postmenopausal FSH group (N= 58)			P-value
Total number of follicles	Range	1	–	4	1	–	5	0.05
	Mean ± S. D	1.7	±	0.99	2.12	±	1.35	
Single follicle	N (%)	29(63%)			29(50%)			0.183
Multiple Follicles	N (%)	17(37%)			29(50%)			
Pregnancy rate	No	73(73%)			64(64%)			0.171
	Yes	27(27%)			36(36%)			

Table 4: Mean number of follicles and pregnancy rate in groups I (letrozole) and II (Postmenopausal FSH group).

The mean value ± SD for the overall follicle number throughout activation was significantly larger in the postmenopausal FSH group (2.12 ± 1.35) vs. (1.7 ±0.99) in the letrozole group; P=0.05). Out of those ovulating cases 63% had single follicles compared to 50% in postmenopausal FSH group and the remaining had multiple follicles 37% versus 50% in both groups respectively. There have been no significant differences between the rates of pregnancy in groups I (letrozole group) and II (Postmenopausal FSH group) (Table 4).

	Letrozole group (N= 100)	Postmenopausal FSH group (N= 100)	p-value
Number of Patient have follicle	54	58	0.023*
Rupture follicle	50	40	0.001*
Non Rupture follicle	4	2	0.002*

Table 5: Comparison between two groups according to number of patient have follicle, Rupture follicle and Non Rupture follicle.

There is a highly significant difference between the two groups when it comes to ruptured and non-ruptured follicles, but there is also a significant difference when it comes to the number of patients with follicles.

Side effect	Letrozole group (N= 100)	Postmenopausal FSH group (N= 100)	p-value
• **Breast pain**	3	1	0.312
• **Hot flashes**	4	2	0.407
• **Bloating/abdominal discomfort**	3	5	0.470

• Dizziness • Headache	3	4	0.700
• Acne • Weight gain	1	5	0.097
• Injection site soreness and redness	0	5	0.024*

Table 6: Comparison between two groups according to side effects

There had been a significant difference between both groups regarding injection site soreness and redness, but not in terms of breast pain, hot flashes, bloating, abdominal discomfort, dizziness, headache, acne and weight gain (Table 6).

DISCUSSION

Results of the current work revealed that both groups were matched by age (P=0.104), BMI (P=0.093). The mean length of infertility was 1.5 to 7.5 years in both groups (P=0.372).

In line with our results, another recent study with the same purpose reported a non-significant difference between letrozole and HMG in terms of age, height, body weight, BMI, or exhibiting signs and symptoms.[10]

Our findings revealed that the average age ± SD was (27.06 ± 3.28 vs. 25.84 ± 4.32) in letrozole group and Postmenopausal FSH group, respectively. In respect of the percentage of instances in each age group, there were statistically significant differences among both the two study groups (P=0.204). Most of cases aged between 26-30 years old (51% vs 47% in both studied groups respectively.

In agreement with our results, Abd-Allatif et al.[14] in evaluating the effectiveness of aromatase inhibitors (letrizole), clomiphene citrate, and recombinant (FSH) on ovulation induction in PCOS, found that the age of women ranged between 20 and 37 years old, and the mean ages were 24.65 years in group I, 25.86 years in group II, and 27.02 years in group III, with no statistically significant difference.

When Seyedoshohadaei and colleagues[15] compared the impacts of clomiphene-estradiol valerate and letrozole, they found that there had been no significant age difference between the groups investigated, which was in agreement with our study.

Regarding BMI, our results revealed that the average BMI of sufferers in the letrozole group was 26.79±2.71, ranging from 19.5 to 38 kg/m^2 and the average BMI of sufferers in the postmenopausal FSH group was 26.04± 3.49 kg/m^2, ranging from 19.5 to 35 kg/m^2.

Ibrahim et al.[16] stated that the average BMI in their study was 29.11 ± 1.62 (26.6–32.87) & 29.21 ± 1.72 0.773(26.67–33) kg/m^2 in both the letrozole and LOD groups.

In accordance with this, in cases of CC resistance, El-Naggar[17] reported that the mean BMI in the short therapy group was 27.86 and 28.59 kg/m^2 in the long therapy group. BMI was insignificant between two groups (P value = 0.215).

The nature of PCOS in Egyptian patients may explain the higher mean BMI in our research.

Obesity is also linked to PCOS, which impacts 6–12% of reproductive-age women.[18]

According to the duration of infertility, we found no difference in the mean duration of infertility between the two investigated groups (P=0.372). It ranged from 1.5-7.5 years with an average of 2.8± 1.05 years in the letrozole group and 2.68± 0.92 years in the post-menopausal FSH group.

And according to Abd-Allatif et al.[14], Seyedoshohadaei et al.[15], and Ibrahim et al.[16], there have been no statistically significant differences in the average length of infertility between their studied PCO groups. It ranged from 1 to more than 6 years in both studies.

In addition, our results revealed that the percentage of patients with amenorrhea was comparable in both studied groups (22% in the letrozole group versus 23% in the postmenopausal FSH group), and that of the remaining cases, 78% and 77% had oligomenorrhea, respectively, in both groups without statistically significant differences (P=0.866). Moreover, there have been non-significant differences between the investigated groups concerning the percentage of cases with hyperandrogenism (65% & 68% in both groups, respectively (P > 0.05).

Consistent with our findings, Xi et al. [19] stated that the rate of amenorrhea in their CCR–PCO cases was 29% in the letrozole + HMG group, 31.3% in the CC + HMG group, and 26.8% in the HMG-only group, with their remaining cases having oligomennorrhea, which was not statistically significant (P > 0.05).

No statistically significant differences were found among both the two CCR PCO groups (with respect to amenorrhea as reported by Liu et al. [20] but with a smaller percentage of amenorrhea in their cases (11.2 % &17.1%).

As regards biochemical laboratory findings, our findings showed that there was a non-significant difference among both studied groups regarding the mean of 2nd day LH & FSH hormones as the mean of LH hormone was 12.02± 1 in letrozole group compared to 12.28±1.24 in postmenopausal FSH group, (P=0.106). Also, the mean FSH level was 5.95±0.65 in letrozole group compared to 6.03±0.87 in Postmenopausal FSH group, (P=0.476). Moreover, nearly similar ratio between LH/FSH levels was detected among both studied groups (2.04 ± 0.25 vs 2.07± 0.29) in both groups respectively (P=0.390).However, Estradiol hormone was significantly higher in postmenopausal FSH group (51.75±6.09) compared to letrozole group (49.35± 4.84), (P=0.002).

Former studies on CCR-PCO cases with trials of different therapeutic regimens through randomizing their cases found no statistically significant difference between both groups concerning hormonal profiles prior to therapy. [10, 15, 20]

In their study to assess the efficiency and effectiveness of letrozole and CC combination with HMG in CC-resistant infertile females with PCOS, Xi et al. (19) discovered a non-statistically significant difference in average age, BMI, or menstruation patterns (oligomenorrhea or amenorrhea) between the three patient groups. The duration of infertility was similar in all groups. Biochemical markers like LH, FSH, testosterone plasma concentrations, and the LH/FSH ratios did not show any significant differences. On transvaginal sonographies, all of the women examined displayed morphological characteristics of PCOS.

Regarding reproductive outcomes, the mean thickness of endometrium increased statistically significantly at the time of HCG injection in the postmenopausal FSH group (10.52 ± 1.88mm) than in the letrozole group (.89 ± 1.94 mm) (P=0.021).

Moreover, the rate of ovulation was slightly greater in the postmenopausal FSH group (58%) compared to the letrozole group (54%), but without a significant difference (P=0.569) with the mean value ± SD for the overall number of follicles throughout activation being considerably larger in the postmenopausal FSH group (2.12 ± 1.35) versus (1.7 ±0.99) in the letrozole group (P=0.05). Out of those ovulating cases 63% had single follicles compared to 50% in postmenopausal FSH group and the remaining had multiple follicles 37% versus 50% in both groups respectively

Then, among those who had ovulation in group I, 22 women (22%) got pregnant with singleton pregnancies, and 5 cases had multiple pregnancies, while eight women had miscarriages, and in group II, 28 women (28%) got pregnant with singleton pregnancies, and 8 cases had multiple pregnancies, while a miscarriage occurred in 13 women. There was no statistically significant difference between both groups concerning pregnancy rates (P = 0.171), multiple pregnancy rates (P = 0.390), or abortion rates (P = 0.249).

Some studies have demonstrated that letrozole and gonadotropins are successful in managing patients with CC resistant PCOS, [21, 22]. However, research evaluating letrozole and gonadotropins in females having CC-resistant PCOS has either been retrospective or focused on patients who underwent intra-uterine insemination (IUI). [23, 24]

There is a paucity of randomized trials that compare letrozole with gonadotropins.

In a study comparing the two therapies, Hassan et al.[25] found that the letrozole group completed 186 cycles, 50 of which were ovulatory cycles and eight of which were multi-follicular cycles. In the uFSH group, 189 cycles have been performed; 62 were ovulatory and 31 were multi-follicular. Although there had been no significant differences in ovulation rates among the two groups, multi-follicular cycles were significantly more common in the FSH group. They also found that ovulation happened in 33 (47%) of the letrozole-treated ladies, and 21 (30%) of them became pregnant. All of the pregnancies were singletons, and two of the ladies miscarried. In the uFSH group, 40 (57%) women ovulated, 24 (34%) of them became pregnant, 2 of whom had twins, and 3 of whom suffered miscarriages. Ovulation, pregnancy, miscarriage (p > 0.999), and twin pregnancy rates did not differ significantly between the groups.

Shi and his co-workers[10] discovered that the number of ovulatory cycles in the letrozole group was 53.6% compared to 64.7% in the HMG group, with multiple follicle number in the letrozole group being 13 (10.4 %) and in the HMG group being 30 (25.2 %), and that the difference between the two groups was statistically significant (P < .01), also they found that endometrial thickness was not significantly different between the two groups on the day of HCG injection (P > .05). The pregnancy rates in the two groups were comparable (P >.05), and the letrozole group had a lower abortion rate (2%) than the HMG group, though the differences were not statistically significant (P > .05). HMG group had a much greater rate of multiple pregnancies than the letrozole group, with a statistically significant difference (P < .05).

In a major randomized, single-blind clinical study, Ganesh et al. [26] compared the impact of letrozole, CC plus recombinant FSH, and recombinant FSH alone on CC-resistant PCO. In CC resistant PCOS patients having IUI, they found no significant differences in pregnancy rates between letrozole and rFSH.

Likewise, Jee et al.[27] found no significant differences in pregnancy rates between letrozole and the combination usage of CC and hMG in IUI patients. In a retrospective analysis of 132 patients having unsuccessful CC therapy and various reasons for infertility, Quintero et al.[23] discovered that the cumulative pregnancy rate following 3 cycles of gonadotropins was greater than that of letrozole.

Liu et al.[20] reported that while comparing letrozole to LOD in treating CC-resistant PCOS, the endometrium in the LE group was significantly thicker compared to the LOD group on the day of hCG injection. Moreover, on the day of hCG injections, ovulation in the letrozole group was better synchronized with endometrial growth than in the LOD group, owing to LE activating more follicles than LOD.

We found no differences in the frequencies of multiple pregnancies between the two groups, but it may be owing to the relatively small specimen size to detect such a difference.

FSH is known for inducing multi-follicular growth in women.[28] Quintero et al.[23] and Hassan et al.[25] had a similar result.

According to a systematic analysis by Goudarzi et al.[24], in patients having CC resistant PCOS (n¼307), rFSH exhibited greater multiple pregnancy ferquency compared to laparoscopic ovarian diathermy. This implies that to identify a significant difference, a larger sample size is required.

As regard side effects, our results revealed that cases in postmenopausal FSH group had increased risk to develop ovarian hyperstimulation syndrome (OHSS) as there were 7 women in Postmenopausal FSH group vs. 3 in letrozole group developed OHSS but without statistically significant difference between both studied groups

According to Shi et al. [10], the letrozole group had a lower rate of ovarian cysts and OHSS than the HMG group, and the differences were statistically significant (P < .05).

Ovarian hyperstimulation syndrome is a significant iatrogenic consequence of fertility therapy with hMG mixed with hCG due to increased E2 levels, which appear as enlarged multicystic ovaries.[29]

One crucial aspect to keep in mind is cost efficacy. The letrozole cycle cost is about 200 Egyptian pounds (LE). Postmenopausal FSH costs about 850 LE. Without a significant difference in ovulation or conception rates, every uFSH cycle costs four times as much as a letrozole cycle. As a result, letrozole therapy was significantly less expensive than uFSH therapy.

CONCLUSION

Letrozole and post-menopausal FSH were both found to be beneficial in the treatment of patients with CC-resistant PCOS. Both medications were well tolerated, but letrozole was easier to administer and more cost-effective. Furthermore, it has been demonstrated to enhance ovulation and pregnancy rates in women with refractory CCR-PCOS. Thus, letrozole might be regarded as a first-line therapy for PCOS.

Recommendations:

We recommended to use both drug on treatment of patient with PCO. We recommended to use letrazole on induction of ovulation in the patient on the clomphine citrate resistant patient with PCO as letrazole is more tolerant and Chipper than FSH. Also we recommended for more studies with multi central and more number of patients.

Conflict of interest : none

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