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Research Article

LETROZOLE WITH OR WITHOUT GONADOTROPIN AS A FIRST-LINE OVULATION INDUCTION IN ANOVULATORY INFERTILE WOMEN DUE TO POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Objectives: The objective is to evaluate the clinical outcome of using letrozole alone or with gonadotropin as first-line ovulation induction in anovulatory infertile polycystic ovary women**.**

Methods: A prospective single-arm study. 80 infertile polycystic ovarian syndrome (PCOS) women had been recruited between January and October 2017. Letrozole on day 2–3 of the cycle was given. The women are sorted into two groups according to the size of the dominant follicle on day 7 or 8, Group A (letrozole only group) and Group B (letrozole plus gonadotropin).

Results: In our study, the overall pregnancy rate was (67.5%) and ovulation rate was 91.3%. The ovulation rate was significantly higher in Subgroup A than B (97.9% vs. 81.3%). Pregnancy rate was higher in Subgroup A (72.9% vs. 59.4%), but it was statistically not significant. The number of follicles was significantly higher in Subgroup B. Endometrial thickness, miscarriages, ovarian hyperstimulation syndrome, and multiple pregnancies were not statistically significant. Lower cycle number independently and significantly predict clinical pregnancy, while body mass index has a modest effect.

Conclusions: Letrozole alone or in combination with gonadotropin as a first-line treatment in PCOS may be reasonable since this approach may improve the success rate and minimize the overall costs and risks.

Keywords: Clomiphene citrate, Gonadotropin, Letrozole, Ovulation induction, Polycystic ovarian syndrome.

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) prevalence in reproductive-aged women varies from 9% to 18% depending on definitions and populations studied. It is the most common endocrine disorder and accounts for ~80% of women with anovulatory infertility [1]. According to the Rotterdam criteria, diagnosis requires the presence of at least two out of three findings: Hyperandrogenism, ovulatory dysfunction, and polycystic ovaries morphology by ultrasound [2].

Clomiphene citrate (CC), a selective estrogen-receptor modulator, has been used as a first-line ovulation induction treatment in PCOS for decades. Clomiphene has drawbacks, including its overall poor efficacy and an undesirable side-effect profile [3]. Clomiphene resistance, which occurred in 25% of cases, or clomiphene failure often results in the use of more expensive treatment options for infertility [4]. Although adding metformin may show satisfactory results in women resistant to CC [5], the development of effective, simple, and safe treatments for infertility is an important public health goal [6].

Third-generation aromatase inhibitors (e.g., letrozole) have gained an advantage over other endocrine therapies for the treatment of post-menopausal women in both early and metastatic breast cancer [7].

Over the last years, letrozole, an orally active potent aromatase inhibitor, was widely used for ovulation induction. Numerous original articles, reviews, and meta-analysis have been published. Especially, in women with failure or resistance to CC, letrozole was shown to be very effective both in ovulation rate and live birth rate [8]. Pharmacodynamics of letrozole ensures improved endometrial thickness, cervical mucus, monofollicular, and better folliculogenesis. Therefore, these factors may lead to higher pregnancy rates and a greater likelihood of singleton pregnancy [9].

Gonadotropin preparations, either urinary or recombinant follicle stimulating hormone (rFSH), have been used to stimulate ovulation in women who failed to respond to CC [6]. Gonadotropin may lead to the following drawback effect include cost, the risk of multiple pregnancies, hyperstimulation, and cycle cancellation [10]. rFSH used in combination with CC for CC-resistant PCOS was proven to be more effective in improving the ovulation rate than rFSH alone [11].

Taking in consideration, the drawback effect of CC versus benefits of letrozole that mentioned above in one hand, and on the other hand, the previous studies which showed that cotreatment with the letrozole significantly reduced the FSH dose required during controlled ovarian stimulation (COH) in women with unexplained infertility [12,13]; we proposed the possibility of using it alone or in combination with gonadotropins for ovarian induction for an efficacious approach in women with PCOS.

METHODS

This study is a prospective single-arm study. It had been approved by an Ethical and Scientific Committee of the Obstetrics and Gynecology department in Al-Yarmouk Teaching Hospital. Once it had been approved, the recruitment started from January 2017 to October 2017.

A total of 80 medically fit infertile women with PCOS had been enrolled in the study after taking informed written consent from all participants and detailed oral and written information concerning the protocol to be used and possible side effect and outcome had been given to them. Modified Rotterdam criteria had been used to diagnose the PCOS. Accordingly, all participating women had ovulatory dysfunction combined with hyperandrogenism and/or ultrasound morphology of polycystic ovary. Thyroid dysfunction, hyperprolactinemia, and other causes of hyperandrogenism had been excluded by

measurement of serum thyroid-stimulating hormone, prolactin, and 17hydroxyprogesterone.

The entire participant had normal tubal patency test and their partner seminal fluid analysis was normal according to the World Health Organization 2010 cutoff points. We asked and encourage overweight and obese women for lifestyle modification before and throughout our study.

All the women were asked to come to the infertility clinic on day 2 or 3 of their menstrual cycle wither it was spontaneously descend or induced by using oral progestin, Provera 5 mg/day (medroxyprogesterone acetate ,Pfizer Pharmaceutical) for 5–10 days.

Baseline transvaginal ultrasound is done, and once no ovarian cyst was seen, oral letrozole 2.5 mg (Femara, Novartis Pharmaceutical) twice daily is given starting from day 2 or day 3 of the cycle for 5 days. The woman is asked to re-come to infertility clinic again at day 7 or day 8 of their cycle for rescanning and according to the size of the dominant follicle at that day the women were divided into two groups. The first group (Group A, letrozole only group) include women who had at least one dominant follicle 10 mm and above at day 7 or day 8 of the cycle. The second groups (Group B, letrozole plus gonadotropin) include women who failed to achieve a dominant follicle of 10 mm and above.

In Group A, the woman will continue to follow-up by transvaginal ultrasound only till mature follicle achieved, while in Group B, the women will start on day 7 or day 8 of the cycle to use gonadotropin in its recombinant form 75 IU subcutaneously (Gonal, Merck Serono Pharmaceutical) on daily bases for 3 consecutive days (total 3 ampoules) then transvaginal ultrasound repeated again. If mature follicle achieved, no further gonadotropin is given and if not another 1 or 2 doses of gonadotropin (total 5 ampoules) are given subcutaneously for another 2 consecutive days and the women reassessed again.

Recombinant human chorionic gonadotropin (HCG) alpha (ovidrel, 250 mcg, Merck Serono Pharmaceutical) was administered subcutaneously when one follicle measured ≥18 mm in diameter. HCG injection was concealed if patients have >3 follicles (15–18) mm [14]. In all women, once mature follicle or follicles are achieved (maximum 2 follicles >16 mm in Group B and ≥17 mm in Group A), couples were instructed to have regular intercourse 2–3 times a week.

The cycle is repeated for 3 consecutive months in each group unless pregnancy happens. If mature follicles did not achieve by a combination of letrozole and 5 daily doses of gonadotropin for 3 consecutive cycles, we considered it as a failure. 1 week after taking HCG, the woman will be asked to come into the laboratory to have progesterone blood draw to confirm ovulation.

2 weeks from HCG, the woman is asked to return for a blood pregnancy test. Transvaginal ultrasonography was done 4 weeks after positive pregnancy test to confirm the presence of gestational sac with fetal pole and fetal heart pulsation, so the clinical pregnancy was identified.

In the study, the primary outcome was clinical pregnancy while the secondary outcome was ovulation, a number of the dominant follicles, endometrial thickness, and adverse treatment outcome in the form of ovarian hyperstimulation syndrome (OHSS), abortion, and multiple pregnancies.

Statistical analysis

Discrete variables are described by number and percentage, Chi-square test or Fisher's exact test was used to analyze these variables. Two samples independent t-test used to analyze the differences in means between two groups. Binary logistic regression analysis used to calculate the odds ratio and their 95% confidence intervals, when the outcome can be categorized into 2 binary levels, and if appropriate probability plot used to present the relationship. SPSS 20.0.0 and Minitab 17.1.0 software package used to make the statistical analysis, p-value considered when appropriate to be significant if <0.05.

RESULTS

Characteristics of the whole group

In the Table 1, we can see the characteristics of the whole study group; the mean age is 26.1 years with 3.8 years standard deviation (SD), the body mass is 26.2±3.0 kg/m^2. More than 70% of the women did not conceive before (57 out of 80) and more than 20% of the women have one or more abortions. The mean duration of infertility is 2.5 years.

The two subgroups after day 7

All the included women (80 women) were started on letrozole therapy, then transvaginal ultrasound was done at day 7 or 8 of the cycle, and after that, the women were sorted into two groups according to the size of the dominant follicle at that day, in the first group (Group A) with the size more than 10 mm, while the other group (Group B) includes women with <10 mm follicle. Table 2 shows the results of

Table 1: The characteristics of the whole group (n=80 women)

Variables	Value
Mean age in years±SD	26.1±3.8
Mean BMI±SD	26.2±3.0
Parity (number of women; %)	
Null	57; 71.2
1	17; 21.2
2	5; 6.2
3	1; 1.2
Abortion (number of women; %)	
0	63; 78.8
1	13; 16.2
2	4; 5
Mean duration of infertility (years)±SD	2.5±1.1

SD: Standard deviation, BMI: Body mass index

Table 2: Comparison between the characteristics of the subgroup A (letrozole only) and subgroup B (letrozole and gonadotropin)

Variables	Subgroup A (n=48)	Subgroup B (n=32)	p value
Mean age in years±SD	24.4±2.0	28.6±4.5	<0.001
Mean BMI±SD	24.5±1.9	28.6±2.7	<0.001
Parity (number of women; percent)			0.089
Null	39; 81.2	19; 56.2	
1	7; 14.6	10; 31.2	
2	2; 4.2	3; 9.4	
3	0; 0.0	1; 3.1	
Abortion (number of women; %)			0.747
0	38; 79.2	25; 78.1	
1	7; 14.6	6; 18.8	
2	3; 6.3	1; 3.1	
Mean duration of infertility (years)±SD	2.1±0.7	3.2±1.3	<0.001

SD: Standard deviation, BMI: Body mass index

the comparison between the characteristic of two groups, where the Group A contains 48 women, while Group B contains 32 women. There is a significant difference in the age, where the mean age is 28.6 years in Group B versus 24.4 years in Group A (p<0.001). Furthermore, the body mass index (BMI) was higher in Group B (p<0.001). The parity status and previous history of abortion were not significantly different between the two groups; this is on the contrary with the duration of infertility where the Group B has a longer duration of infertility with a statistically significant difference.

Outcome of treatment

Table 3 shows the different levels of outcome of the whole group whether they continue on letrozole (Subgroup A), or they received gonadotropin in addition to letrozole (Subgroup B), the pregnancy occurred in 54 women (67.5%), and the success of ovulation was 91.3%, with cumulative mean number of cycles 2.3 (SD±0.8). The mean endometrial thickness was 8.7 mm, and we had three miscarriage out of 54 pregnancies.

In 70% of the women, they developed only one dominant follicle and 26% of women developed two follicles. We had three cases of mild OHSS, while we had two women with twin pregnancy.

Comparison of the outcome between the two subgroups

Women in Subgroup A developed one dominant follicle in 97.9%, while more than 70% of women in Group B developed two dominant follicles (p<0.001), the number of cycles, and endometrial thickness showed no significant difference between the two subgroups.

The success of ovulation was significantly higher in Subgroup A than B (97.9% vs. 81.3%, p=0.015). Furthermore, we reported the higher percentages of pregnancy in Subgroup A than B (72.9% vs. 59.4%), but it was statistically not significant (p=0.2).

Table 3: The different levels of the outcome of the whole group

Variable	Number of women; %
Number of the follicle (s)	
1	53; 70.7
2	20; 26.7
3	2; 2.7
Mean endometrial thickness (mm)±SD	8.7±0.5
Mean size of follicles (mm)±SD	19.1±1.4
Mean cumulative number of cycles±SD	2.3±0.8
Pregnancy	54; 67.5
Successful ovulation	73; 91.3
Miscarriage (percent per pregnant ladies)	3; 5.6 (3 out of 54 women)
OHSS	3; 3.8

OHSS: Ovarian hyperstimulation syndrome, SD: Standard deviation

As mentioned above, we reported three cases of abortion, 2 in the letrozole group and one in the second group; this difference was statistically not significant.

Although the three reported cases of mild OHSS were seen in the Subgroup B, again the difference was statistically not significant (Table 4).

Lower cycle number independently and significantly predict clinical pregnancy, while BMI has the modest effect to predict clinical pregnancy, in which the lower the BMI, the better the outcome (BMI lower than 24.3 had the best outcome to predict clinical pregnancy), as illustrated in Table 5 and Fig. 1.

DISCUSSION

A normogonadotrophic anovulatory PCOS woman (WHO 2) shows high variation in ovarian response to ovulation induction. Treatment form in this group should become more individually tailored, and therefore, it seems reasonable to implicate new approaches to the conventional WHO 2 anovulation treatment protocol [15].

Franik *et al*. reviewed 26 RCTs (5560 women) using Cochrane database systemic review at 2014 on the use of aromatase inhibitors for subfertile women with polycystic ovary and end up with a conclusion that letrozole had a better pregnancy and live birth rate than CC and the complication of OHSS was rare [16].

Brown and Farquhar at 2016 did a review of 28 RCTs (3377 women) comparing clomiphene and other antiestrogens for ovulation induction in PCOS and went out with a conclusion that gonadotropin was more effective than clomiphene in the rate of live birth and ongoing pregnancy [17].

The use of letrozole in combination with gonadotropin had been assessed by several studies, especially in clomiphene-resistant cases. Xi *et al*. at 2015 did a prospective study on the use of letrozole-gonadotropin versus clomiphene-gonadotropins in clomiphene-resistant infertile women with PCOS and found out that letrozole-gonadotropin use significantly reduced the duration and total gonadotropin dose needed for stimulation and that the rate of monofollicular development was significantly higher in comparison, this, in turn, supports the concept that letrozole combined with gonadotropin reduces the risk of hyperstimulation [18].

Malhotra *et al*. did a prospective randomized trial on letrozole alone or letrozole gonadotropin combination as the first line for superovulation in women with unexplained infertility undergoing intrauterine insemination and went out in a conclusion that better number of follicles and improved ET result in higher pregnancy rate in letrozole-human menopausal gonadotropin (HMG) protocol in comparison to letrozole alone protocol and letrozole-HMG should be preferred over letrozole as the first line for superovulation in unexplained infertility [19].

Table 4: Comparison between the outcome of the subgroup A (letrozole only) and subgroup B (letrozole and gonadotropin)

Variable	Number of women; %		p value
	Group A (48)	Group B (32)	
Number of the follicle (s)			<0.001
1	47; 97.7%	6; 22.2%	
2	1; 2.1%	19; 70.4%	
3	0	2; 7.4%	
Mean endometrial thickness (mm)±SD	8.7±0.5	8.8±0.5	0.312
Mean size of follicles (mm)±SD	18.8±1.2	19.6±1.5	0.009
Mean cumulative number of cycles±SD	2.4±0.7	2.1±0.9	0.103
Pregnancy	35; 72.9%	19; 59.4%	0.205
Successful ovulation	47; 97.9%	26; 81.3%	0.015
Miscarriage (percent per pregnant ladies)	2; 5.7%	1; 5.3	1.0
OHSS	0	3; 9.4%	0.060

OHSS: Ovarian hyperstimulation syndrome, SD: Standard deviation

Table 5: Multivariate analysis of the predictors of a successful pregnancy for all women

Variables	OR (95% CI)	p value
Cycle number	0.021 (0.002–0.215)	0.001
BMI	0.527 (0.256–1.084)	0.082
Mean size of follicle	1.524 (0.822– 2.825)	0.181
Age	1.329 (0.858–2.058)	0.203
Type of therapy	1.376 (0.003–547.188)	0.917
Parity	3.639 (0.423–31.338)	0.240
Abortion	1.550 (0.460–5.225)	0.480
Duration of infertility	0.621 (0.230–1.676)	0.347
Mean number of follicle	0.224 (0.010–4.845)	0.340
Endometrial thickness	2.442 (0.422–14.137)	0.319
Day in the cycle	1.763 (0.557–5.582)	0.335
Day of stimulation	1.070 (0.216–5.312)	0.934

R^2=0.442 (Cox and Snell). OR: Odds ratio, CI: Confidence intervals, BMI: Body mass index

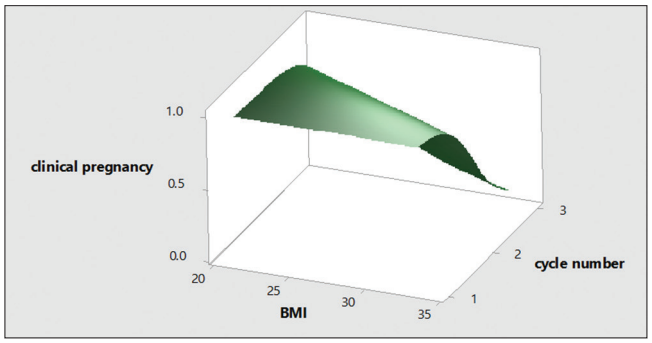

Fig. 1: Surface plot of the instant relationship between body mass index and cycle number to predict clinical pregnancy

Arya *et al*. at 2017 did retrospective cohort study on ovulation induction and COH using letrozole gonadotropin combination in PCOS and other fertility cases and end up in a conclusion of letrozole-low-dose gonadotropins combination appears to be effective across different causes of infertility for superovulation. The letrozole-low dose gonadotropin combination resulted in high rate of monofolliculogenesis, low occurrence of multiple gestations, and no case of OHSS or cycle cancellation [20].

Looking on all the studies together may justify adopting the use of letrozole as first-line ovulation induction in anovulatory infertility in PCOS and may possibly justify adopting the use of gonadotropin in combination with letrozole when the first one failed to achieve ovulation in the same cycle. In our study, the overall pregnancy rate was 67.5% (54/80), we reported the higher percentages of pregnancy in Subgroup A than B (72.9% vs. 59.4%), but it was statistically not significant (p=0.2). The ovulation rate was 91.3% (73/90). The success of ovulation was significantly higher in Subgroup A than B (97.9% vs. 81.3%, p=0.015). Depending on CD 7 ultrasound, the administration of low doses of exogenous FSH starting at that day can help to achive single dominant follicle selection in most of the women who fail to show a response to letrozole alone. This may explain the high rate of ovulation in both groups collectively. In those who did not show a response (8.7%), the amount of exogenous FSH might have been too low to extend the window sufficiently for the selection of dominant follicles. In our study, number of follicle was monomolecular in 97.9% in Group A, while 26% of women developed 2 follicles in more than 70% in Group B (p<0.001). The number of cycles, endometrial thickness, miscarriage, twine, and OHSS showed no significant difference between the two subgroups. Looking into most of our study results, it goes with most of the results of the abovementioned literature [18-20].

By comparing demographic characters between Group A and Group B, we found significant differences regarding women age, BMI, and period of infertility. The use of prediction models may help to choose an individualized treatment pathway per PCOS woman in addition to CD7 ultrasound. In our ovulation induction protocol, we used fixed dose of letrozole (5 mg) only, not 2.5 mg or 7.5 mg, protocol was supported by the retrospective study of Badawy *et al*. and randomized control trial of Polyzos *et al*. both showed that 5 mg letrozole was more effective than other doses in the term of pregnancy rate [21,22]. Furthermore, in our protocol, we used 75 IU rFSH, not 50 IU or 100 IU, the dose that was supported by Streda *et al*. study at 2012 who showed that 50 IU daily is the appropriate starting dose to support ovulation, but the disadvantage may be an increased risk of cycle cancellation due to low ovarian response [23].

On the other hand , Akbari et al. use letrozole 5 mg in combination with gonadotropin 100 IU and compare it with clomiphene gonadotropin combination regime in unexplained infertility and they start adding gonadotropin on day 6-8 day of the menstrual cycle depending on that day response, and they went out in a conclusion that letrozole is a good alternative to CC, or it can be a first-line drug in ovarian stimulation and treatment of anovulation. Use of letrozole can induce ovulation comparable to CC without any adverse effect on endometrium and with comparable pregnancy rate and lower abortion rate compared with CC [24]. Based on Akbari *et al*. study, Pourali *et al*. at 2017 did a randomized trial on the same subject with the same study design and ended up with the same conclusion [24,25]. Malhotra *et al*. in their study also advocate using letrozole gonadotropin combination as a first-line treatment for unexplained infertility [19].

On the other hand, Kiran Chaudhary *et al*. at 2015 compare the efficacy of letrozole and low-dose gonadotropin combination with clomiphene and low-dose gonadotropin combination as a COH regime before intrauterine insemination in patients with unexplained infertility, and they found no significant differences in their primary and secondary outcome. In their study, they used 5 mg letrozole with 150 IU of gonadotropin but started at day 9 [26].

The last studies above [19, 24-26] advocating using letrozole with gonadotropin as a first-line treatment in unexplained infertility. Using letrozole alone or in combination with gonadotropin in the current study as a first-line treatment in PCOS may be reasonable since this approach may improve the success and minimize costs and risks, but it has a limitation regarding the sample size.

CONCLUSION

Letrozole alone or in combination with gonadotropin as a first-line treatment in PCOS may be reasonable since this approach may improve the success rate and minimize the overall costs and risks.

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AUTHOR CONTRIBUTIONS

Concept and collection of data, writing the article and critical review of the article, and final approval of the article - Fadia J Alizzi.

CONFLICT OF INTEREST

Fadia J Alizzi declares that she has no conflict of interest.

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