Letrozole and Clomiphene citrate versus Letrozole alone in ovulation induction for patients with Polycystic Ovarian Syndrome

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is one of the most prevalent endocrine and metabolic conditions in premenopausal women.

Objectives: The goal of this study was to see the efficacy of Letrozole in conjunction with clomiphene citrate versus Letrozole alone in inducing ovulation in PCOS patients.

Patients and methods: This was a randomized clinical trial (RCT) done on a total of 200 patients who came to South Valley University, Obstetrics and Gynecology clinics, after receiving the ethical committee permission and signed informed consent from all participants.

Results: Regarding all treatment outcomes, there were no statistically substantial difference among the two groups as regards the following parameters: ovulation, mature follicle number, endometrial thickness, OHSS, single pregnancy, clinical pregnancy, multiple pregnancy and miscarriage, P>0.05.

Conclusion: this research showed that in terms of infertility therapy in women with PCOS, the combination of letrozole and CC was linked to"Although there is absolute difference between the two groups in favor of the combined use of letrozole plus clomiphene citrate, this difference is not statistically significant". These new findings indicate that this combined therapy might be a low-risk, low-cost infertility treatments.

Key words: Letrozole, Clomiphene citrate, ovulation, induction, Polycystic Ovarian Syndrome

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Introduction

Polycystic ovarian syndrome (PCOS) is one of the most prevalent endocrine and metabolic conditions in premenopausal women. It affects roughly 4% to 8percent of women globally and often results in anovulatory subfertility. In the absence of additional diagnoses, PCOS is defined as a set of characteristics that include both androgen excess and ovarian malfunction (**Jin and Xie, 2018).**

Despite the fact that the actual origin of PCOS is unknown, new data suggests that it is a multigenic disease with significant epigenetic and environmental influences, including diet and lifestyle factors. PCOS is often linked to abdominal adiposity, insulin resistance, overweight, metabolic abnormalities, and cardiovascular disease risk factors (**Escobar-Morreale, 2018).**

Ovulation induction treatments, such as clomiphene citrate (CC), aromatase inhibitors, and gonadotropin therapy, are used to treat infertility (**Tanbo et al., 2018).**

The first-line pharmacotherapy for ovarian stimulation should be clomiphene citrate (CC). In CC-resistant women, second-line treatments such as metformin, laparoscopic ovarian drilling, or gonadotropin medication should be considered (**Tannus et al., 2015).**

Aromatase inhibitors (AIs) are a kind of medication that was first used to induce ovulation in 2001. Since about 2001, clinical investigations have concluded that the AI letrozole is at least as successful as the first-line therapy clomiphene citrate (CC) **(Nguyen et al., 2020).**

When compared to clomiphene citrate, letrozole considerably boosted the rate of ovulation, pregnancy rate, and live birth rate, according to a recent meta-analysis (**Hu et al., 2018).**The goal of this study was to find out how effective Letrozole in conjunction with clomiphene citrate vs Letrozole alone in inducing ovulation in PCO patients.

Patients and methods

This was a randomized clinical comparative trial (RCT) done on a total of 200 patients who came to the Qena University Obstetrics and Gynecology clinic after receiving ethical approval permission and signed informed consent from all patients.

The computer randomly sorted all of the patients into two equal groups: Group I: From the third through the seventh day of the menstrual cycle, 100 individuals were given letrozole 2.5 mg (Femara 2.5 Novartis) twice daily.Group II: From the third to the seventh day of the menstrual cycle, 100 participants received 2.5 mg letrozole twice daily and 100 mg clomiphene (Clomid 50 mg Sanofi Aventis) every day in split doses for five days.

Inclusion criteria: Infertile patients with PCOS in accordance with the revised 2003 Rotterdam Criteria for the diagnosis of PCOS (Table 1) **(ESHRE and Group, 2004; Group, 2004),** clomiphene citrate (CC) resistance cases, age: 20-35 years and body mass index (BMI**)** 19-30.

Exclusion criteria: Chronic disease, any other endocrine condition, male factor of infertility, previous ovarian surgery, endometriosis, hyperprolactineamia and presence of any other factor of infertility.

Methods

All of the participants in the research were exposed to:

Careful history taking: which include, name, age, sex, occupation, special habits, past history of medical or surgical problems.

Thorough clinical examination: includedgeneral, abdominal and local examinations.

Investigations: Basal Follicular stimulating hormone FSH at day 3, basal Luteinizing hormone (LH), thyroid stimulating hormone, serum prolactin level, serum progesterone on the day 21 of the cycle and 2D and 3D ultrasound to measure ovarian volume and endometrial thickness and exclude any local pelvic pathology.

Induction of ovulation: The drugs (letrozole and clomiphene) were begun in patients with oligomenorrhea following induction of bleeding with short period progesterone to induce menstruation, and in patients with normal cycles, the treatments (letrozole and clomiphene) were started on the third day of the cycle.

Outcomes: Primary outcome: Serial vaginal ultrasounds were performed on day 11, 13 and 15 of the cycle to determine: No of mature follicles, incidence of ovulation rate, endometrium thickness and its pattern, timing the date of Human chorionic gonadotrophin injection 2 Ampoule IM (10,000 IU) (Choriomon 5000 I.U IBSA) for every patient when the mature follicle reached the size (18-22 ml). Secondary outcome: Pregnancy rate (chemical and clinical), multiple pregnancy rate and miscarriage rate.

Follow up: All patients in both groups underwent follow up to detect pregnancy in cases of missed periods and +ve pregnancy test cases were followed up to the end of first trimester of pregnancy to detect the rate of clinical pregnancy and incidence of miscarriage.

Ethical considerations: The following are some of the ethical research issues in the study: The research design was submitted to the local ethics committee for approval. Before taking part in the trial, all of the patients completed an informed consent form. The study's purpose and goal were explained to the participants by the researcher.

Statistical analysis and data interpretation: The data was entered into the computer and evaluated by IBM SPSS Corp.'s software, which was released in 2013. Version 22.0 of IBM SPSS Statistics for Windows. IBM Corporation, Armonk,NY. Number and percent were used to describe qualitative data. After evaluating normality using the Kolmogrov-Smirnov test, quantitative data were reported using average (minimum and maximum) for non-parametric data and average, standard deviation for parametric data. The significance of the obtained findings was determined at the (0.05) level.

Results

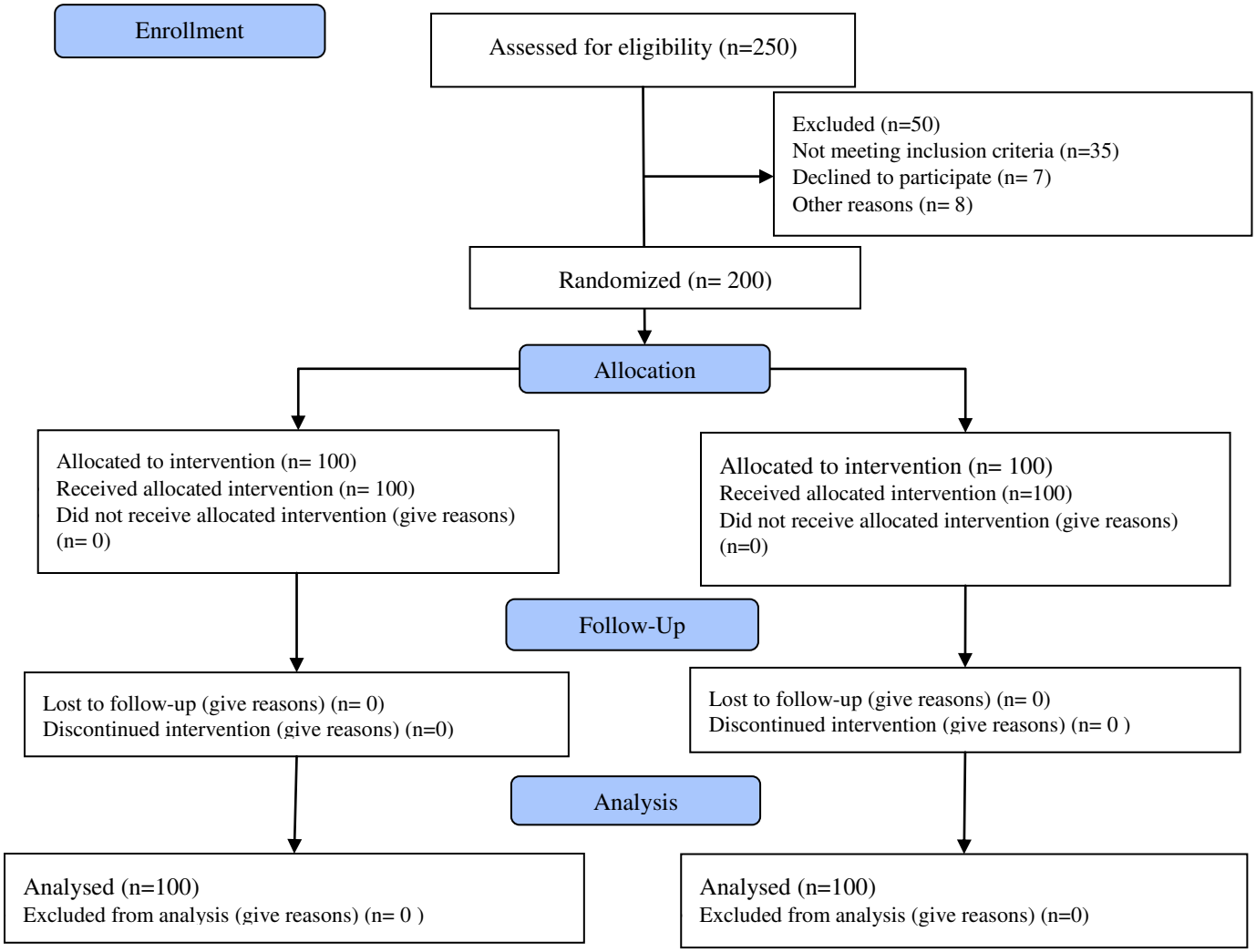

Fig.1.Consort flow chart showing study design

The demographic characteristics of the studied groups were presented in (**Table.1**). There were no statistically significant differences among both groups regarding all the demographic features (age, sex, height and BMI) **(P>0.05).**

Table 1. Demographic characteristics of the studied groups:

	GI n=100	GII n=100	test of significance	P value
Age/years Mean±SD	27.08±4.44	27.99±4.84	t=1.38	p=0.168
Weight/kg Mean±SD	71.90±4.46	71.91±4.28	t=0.016	p=0.987
Height/cm Mean±SD	1.64±0.055	1.65±0.057	t=1.57	p=0.117
Body mass index (kg/m^2) Mean±SD	26.94±2.58	26.51±2.19	t=1.26	p=0.209

t:Student t test

Table (2) demonstrates compliant distribution among studied groups. There were no statistically significant differences among both groups regarding oligo/anovulation as well as hyperandrogenism **(P>0.05).**

Table 2. Compliant distribution between studied groups:

	GI n=100(%)	GII n=100(%)	test of significance	P value
Oligo/anovulation + infertility Yes	38(38.0) 62(62.0)	42(42.0) 58(58.0)	χ^2=0.333	p=0.564
Hyperandrogenism + infertility +ve	56(56.0) 44(44.0)	66(66.0) 34(34.0)	χ^2=2.10	p=0.147

χ^2=Chi-Square test, p: probability

Table (3) demonstrates the laboratory findings among studied groups. There were no statistically significant differences among both groups regarding all laboratory investigations (FSH, LH, TSH, prolactin and progesterone) **(P>0.05).**

Table 3. Laboratory findings among studied groups:

	GI n=100	GII n=100	test of significance	P value
FSH (IU/mL) Mean±SD	4.93±0.83	5.0±0.85	t=0.588	p=0.557
LH (IU/mL) Mean±SD	12.58±3.94	11.73±3.70	t=1.57	p=0.118
TSH (IU/mL) Mean±SD	2.21±0.82	2.42±0.84	t=1.76	p=0.08
Prolactin (IU/mL) Mean±SD	15.43±4.72	16.34±4.61	t=1.38	p=0.169
Progesterone (IU/mL) Mean±SD	11.61±2.04	11.53±2.15	t=0.270	p=0.788

t:Student t test

Tables (4) illustrate the distribution of ovarian volume and endometrial thickness according to the studied groups. There were no statistically significant differences among both groups regarding ovarian volume as well as endometrial thickness **(P>0.05).**

Table 4. Distribution of ovarian volume and endometrial thickness according to the studied groups:

	GI n=100	GII n=100	test of significance	P value
Ovarian volume/cc Mean±SD	11.94±0.84	12.07±0.86	t=1.08	p=0.279
Endometrial thickness /mm Mean±SD	9.45±1.11	9.54±1.185	t=0.511	p=0.610

t:Student t test

Table (5) demonstrates the distribution of the studied groups according to treatment outcome.There were no statistically significant differences among both groups regarding all the treatment outcomes (Ovulation, mature follicle number, endometrial thickness, OHSS, single pregnancy, clinical pregnancy, multiple pregnancy and miscarriage) **(P>0.05).**

Table 5. Distribution of the studied groups according to treatment outcome:

	GI n=100	GII n=100	test of significance	P value
Ovulation n(%)				
-ve	21(21.0)	19(19.0)	χ^2=0.125	p=0.724
+ve	79(79.0)	81(81.0)		
Mature follicle number median (range)	3.0(0.0-6.0)	3.0(0.0-6.0)	Z=1.21	P=0.226
Endometrial thickness/mm median (range)	10.0(8.0-12.0)	10(8-12)	Z=0.293	P=0.769
OHSS n(%)				
-ve	97(97.0)	99(99.0)	FET	P=0.621
+ve	3(3.0)	1(1.0)		
Single pregnancy n(%)				
-ve	73(73.0)	76(76.0)	χ^2=0.237	p=0.626
+ve	27(27.0)	24(24.0)		
Clinical pregnancy n(%)				
-ve	7(67.0)	75(75.0)	χ^2=1.55	p=0.213
+ve	33(33.0)	25(25.0)		
Multiple pregnancy n(%)				
-ve	97(97.0)	98(98.0)	FET	P=1.0
+ve	3(3.0)	2(2.0)		
Miscarriage n(%)				
-ve	96(96.0)	97(97.0)	FET	P=1.0
+ve	4(4.0)	3(3.0)		

Z: Mann Whitney U test FET: Fischer exact test χ^2:Chi-Square test

Discussion

PCOS is often linked to abdominal adiposity, insulin resistance, overweight, metabolic disturbances, and cardiovascular disease risk factors. PCOS is a simple condition to diagnose and treat, needing just the careful use of a few well-established diagnosing tests and suitable management procedures to address hyperandrogenism, ovarian dysfunction, and the

resulting metabolic abnormalities(**Escobar-Morreale, 2018**).

This was a clinical randomized trial conducted at Outpatients clinic of Qena University and Qena General Hospitals on a total of 200 who were diagnosed with an infertility and PCOS aimed to compare between the use of Letrozole in combination with clomiphene citrate and letrozole alone in ovulation induction for patients with PCOs.

To the best of our knowledge, there were limited researches that compared between such combinations versus letrozole alone. The majority of prior researches were mainly emphasized on comparing among both drugs individually (Letrozole versus clomiphene citrate).

Concerning the demographic characteristics (age, sex, height and BMI) in the current study, both groups demonstrated insignificant differences (P>0.05).

Such results indicated that both groups were comparable and the demographic characteristics were not interfering with net results of the study.

In terms of, compliant distribution, laboratory findings, distribution of ovarian volume and endometrial thickness both groups demonstrated insignificant differences (P>0.05).

With regard to ovulation rate, the current study demonstrated that, when compared to letrozole alone, letrozole and CCcombination was linked to an increase in ovulation rate, however such increase not reached the statistical significance (79 versus 81) (P>0.05).

Of note, the only study that compared among these groups was conducted by Mejia and his colleagues who focused their research on women between the ages of 18 and 40 who had infertility and PCOS.

They demonstrated that, When compared to women who got letrozole alone, those who received the letrozole and CCcombination had a statistically greater ovulation rate (27 of 35 women [77 percent] vs. 15 of 35 women [43 percent])(**Mejia et al., 2019**).

This research provided preliminary findings that supported their unique hypothesis that using a combination treatment for ovulation induction is more effective than using a single drug alone. It allows for the use of alternative treatments rather than gonadotropins, which are expensive and risky. Different considerations must still be taken into account. One reason is that this was not a live birth experiment, but rather a single ovulation attempt. It's still unclear if several ovulations can be maintained in order to increase pregnancy rates.(**Kaur et al., 2019**).

Prior to **Hajishafihaand his colleagues**, conducted a prospective cohort study on 100 patients who were resistant to CC alone (6 cycles) and letrozole alone (4 cycles) and found an 82.9 percent (213/257 cycles) follicular development rate using 5 mg letrozole + 100 mg CC/day for 5 days from day 3 to 5, compared to 2.5 mg letrozole and 50 mg CC used in this investigation (**Hajishafiha et al., 2013**).

As a consequence, they recommend giving a combination of the two drugs first to PCOS patients who are resistant to clomiphene and letrozole as single agents, followed by more aggressive treatment or surgery. This combination might possibly be used as a first-line therapy to stimulate ovulation in severe cases of PCOS to save time and money (**Hajishafiha et al., 2013**).

Metformin-taking subjects were included in the current research. a comprehensive review and network analysis indicated that CC and metformin together had greater ovulation rates (odds ratio 1.55, 95 percent CI 1.02–2.36) but equal live birth rates when compared to CC alone(**Wang et al., 2017**).

Additionally, **Wang and his colleagues** demonstrated that, In women with WHO group II anovulation, letrozole and the combination of clomiphene and metformin are superior to clomiphene alone in terms of ovulation and conception. When compared to clomiphene alone, letrozole is the only medicine that considerably increases the rate of live birth (**Wang et al., 2017**).

Regarding, mature follicle number as well as endometrial thickness (ET), the current study demonstrated that, both groups demonstrated insignificant differences (P>0.05).

In the same line, **Harira, (2018)** demonstrated that there was no substantialvariance among (CC+ Letrozole) compared to (Letrozole+HMG) in terms of endometrial thickness (9.6±1.7 versus 9.8±1.5) (P=0.41).

While **Harira, (2018)** was in disagreement with the current study in terms of number of mature follicle as he reported that, there was substantial increase in number of follicle ≥18 mm among (CC+ Letrozole) compared to (Letrozole+HMG).

On the contrary, **Meija et al (2019)** demonstrated that, in terms of both ET and mature

follicle number, there were statistically considerable variations among the two groups. They found that as compared to letrozole alone, the combination groups had a significantly higher ET (8.3± 3.6 vs 6.2± 2.2) (P=0.006). Additionally, the number of women with follicles >15 mmconsiderably increased in the combination group compared to letrozole alone (9 versus 19) (P=0.02), and the number of follicles >10 mm increased considerably in the combination group compared to letrozole alone (P<0.001).

In terms of, OHSS, single pregnancy clinical pregnancy, multiple pregnancies and miscarriage, the current study demonstrated that, both groups demonstrated comparable outcomes.

In accordance, **Meija et al (2019)** displayed that, In the PP analysis;There were no statistically substantial variations among the two groups in terms of conception, pregnancy, or live birth. In neither group, there were any multiple-gestation pregnancies. The two therapy groups had equal rates of pregnancy loss among women who conceived. As a result, they suggested that a significantly higher sample size be used to discover variations in these outcomes.

Similarly, **Harira, (2018)** demonstrated that, the pregnancy rate did not show any statistical significant variance in both groups (P value = 0.45) ; 32 patients (30.1%) in group A compared with 27 patients (25.4%) in group B. Four cases were aborted in group A and three cases in group B. Four cases had twin pregnancy in group A compared with three cases only in group B. Also, there was no significant varianceamong them regarding ovarian hyperstimulation; two cases with combined clomid in Letrozole group and one case only in Letrozole and hMG group

Concerning adverse effects, it's worth noting that the side-effect profiles of these two medications were remarkably comparable in the current trial, with no congenital anomalies reported.

In the same line, **Meija et al (2019),**In terms of negative consequences, the results were similar. There was no discernible variation in the profile of adverse effects among the two groups. Headaches (41%), weariness (22%), and stomach discomfort or cramping were the most often reported adverse effects in the letrozole group (19 percent). Hot flashes (31percent), headache (28percent), and stomach discomfort or cramping were the most often reported adverse effects in the letrozole and CC group (19 percent). Due to irritation, just one participant out of 32 declared they would not take the combined regimen again.

Despite the fact that the research was not powered to evaluate a variance in congenital birth abnormalities across groups, they can report that there were no congenital birth problems among the four live babies.

Conclusion

In terms of infertility therapy in women with PCOS, the combination of letrozole and CC was linked to" Although there is absolute difference between the two groups in favor of the combined use of letrozole plus clomiphene citrate, this difference is not statistically significant".. These new findings indicate that this combined therapy might be a low-risk, low-cost infertility therapy. However, more research needs to be done in areas with a large number of people to back up the current findings.

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