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Effect of Coenzyme Q10a and Clomiphene Citrate for Ovulation Induction in Patients with PCOS as Compared to Clomiphene Citrate alone

Abstract: To evaluate the effects of coenzyme Q10A and clomiphene citrate taken in addition to other drugs to stimulate ovulation in people with polycystic ovarian syndrome. The Department conducted the study of Obstetrics and Gynecology, Pakistan Ordinance Factory (POF), Wah Cantonment, Rawalpindi from Mar 2019 to Feb 2021 By using a lottery, all of the patients were split into two random groups. Group A was given Coenzyme Q10A 60mg daily from day 1 of the cycle thrice a day and clomiphene citrate 150mg/day from days 2-6 of the cycle, and Group B was given only clomiphene citrate 150mg/day from 2-6 day of cycle for 5 days. The follicular growth and maturation were observed on days 10, 12, and 14 of the cycle with transvaginal ultrasound. Ovulation was confirmed by measuring serum progesterone level on day 21 of the cycle. Patients were followed for 3 cycles. The mean number of mature follicles in Group A was 1.63±0.49 and 1.3±0.47 in Group B (p-value=0.01). The analysis of either of the groups' ovulation statuses revealed that in 70% of patients (n=21) in Group A and 36.67% (n=11) in Group B, ovulation was initiated (p value= 0.01). We concluded that the outcome of combined coenzymeQ10A and clomiphene citrate is significantly better for patients with polycystic ovarian syndrome; inducing ovulation is more effective with clomiphene citrate alone.

Key Words: Poly Cystic Ovary, Combined Coenzymeq10a, Clomiphene Citrate

Introduction

For women who are fertile, polycystic ovarian syndrome is the most prevalent endocrine condition. It affects 2%-20% of women in this age group, varying in different parts of the world [Deswal [2020](#)]. Women suffer from oligomenorrhea, subfertility (75% of PCOS cases), hirsutism, obesity (50% of cases), acne, hoarseness of voice, and hyperinsulinemia [Joham [2022](#)]. Subfertility is a major problem in women suffering from PCOS, which occurs due to oligo-ovulation or anovulation for which they take multiple alternative therapies. [Celik [2019](#)] Couples become frustrated when they cannot conceive despite multiple treatments for ovulation induction, like food or drug supplements. Women

with PCOS are given three cycles of clomiphene citrate for ovulation induction but despite increasing the dose of clomiphene citrate in each cycle, 20% to 25% of patients fail to conceive, so there was a need to add some drug with clomiphene citrate to increase the chances of ovulation and pregnancy [Peker [2021](#)], [Izhar [2022](#)] A new hope for increasing fertility in such patients is the use of coenzymeQ10A. It is less expensive and is a safer option for patients as compared to gonadotrophin hormones, ovarian drilling, and other alternative options available for patients resistant to clomiphene citrate treatment. [Karamali [2022](#)]

Coenzyme Q10A is a lipid-soluble mitochondrial enzyme found in the inner membrane of

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mitochondria. It is an electron acceptor for the mitochondrial electron transport chain and produces energy in the form of ATP. [Badr 2021] It acts as an antioxidant and membrane stabilizer. The largest number of mitochondria is found in oocytes in the body where they provide energy and protect against oxidative stress [Ibrahim 2020].

The objective of this study is to ascertain the combined effect of coenzyme Q10A and clomiphene citrate in patients with PCOS as compared to clomiphene citrate alone. Gonadotrophins and ovarian drilling are used as an alternative in clomiphene citrate-resistant patients but they are expensive and not safe for patients. Coenzyme Q10A is less expensive and safe for patients so it can be very beneficial in developing countries like Pakistan where most patients are non-affording. There are few studies available on its use internationally and no study available regarding its use and benefits in Pakistan. If we do research regarding its use in female subfertility, it could prove to be a miracle for infertile couples. It is a new hope for clomiphene citrate-resistant patients with PCOS.

Methodology

The Department of Gynecology and Obstetrics conducted this randomized controlled experiment. Pakistan Ordinance Factory Hospital Wah Cantt from Mar 2019 to Feb 2021. Using the WHO calculator and the Level of significance, the sample size was determined: 5%, Power of test: 99%, Confidence level: 95%, Population standard deviation: 0.295, Population mean number of follicles in group A: $1.85 + 0.295$ [2]. Population means number of follicles in group B: $1.30 + 0.295$. [El Rafea 2014] Sample size turned out to be 60. Consecutive non-probability sampling was the method employed for sampling. All women of reproductive age (18-45) with patent fallopian tubes proved by hysterosalpingography having polycystic ovary syndrome were included in the study. Women having thyroid disorder, hyperprolactinemia, hypercorticism, or any other medical disorder, women who were using drugs which interact with coenzyme Q10A like lipid-lowering drugs, beta-blockers, tricyclic antidepressant, antihypertensive, hypoglycemic drugs, chemotherapeutic drugs were not allowed to participate in the study.

The research was initiated after obtaining approval from the ethical committee of POF Hospital, Wah Cantt, and permissions from all concerned departments were also acquired. Each patient who

presented had their informed consent obtained in the Obstetrics and Gynaecology Department of MCH Center, POF Hospital, Wah Cantt, fulfilling the inclusion criteria of the study. Demographic details, treatment given to patients, number of treatment cycles given to patients, number of growing and mature follicles formed, and ovulation rate were entered in a designed proforma. Every patient was split up into two arbitrary groups by lottery method. Group A was given coenzyme Q10A and clomiphene citrate. Coenzyme Q10A 60mg was given daily from day 1 of the cycle, thrice a day, and clomiphene citrate 150mg/day was given from day 2-6 of the cycle. Group B was given clomiphene citrate 150mg/day from 2-6 days of the cycle for 5 days then follicular growth and maturation were observed on days 10, 12, and 14 of the cycle with transvaginal ultrasound under the supervision of seniors. Ovulation was confirmed by measuring serum progesterone level on day 21 of the cycle. All patients were followed for 3 cycles.

All of the collected data was entered and examined using the statistical software for social sciences (version SPSS 22.0). A descriptive analysis was done. Quantitative variables like age, weight, BMI, and number of mature follicles, were measured as mean and standard deviation. Qualitative variables like ovulation status and socioeconomic status (SES) were measured as frequency and percentage. For qualitative factors such as ovulation status, chi-square was utilized as the significance test. For quantitative variables, the use of an independent sample t-test, such as the number of developed follicles. P-values below 0.05 were regarded as significant. Age, BMI, and SES were among the effect mediators that were regulated through stratification, and the chi-square test was used after stratification.

Results

When clomiphene citrate was used alone vs. coenzyme Q10A for ovulation induction in patients with a condition known as polycystic ovarian syndrome, the outcomes were similar, using a total of 60 cases (30 in each group) that met the selection criteria. The distribution of ages revealed that 76.67% (n=23) in Group B and 80% (n=24) in Group A were in the age range of 18 to 30 with a mean age of 27.3 ± 3.69 years in Group A and 27.43 ± 3.58 years in Group B. Mean BMI was calculated as 28.9 ± 1.84 in Group A and 29.33 ± 1.76 in Group-B. The Socioeconomic status was recorded as 66.67% (n=20) in Group A and 56.67% (n=17) in Group B

for the lower class. A higher mean number of mature follicles in Group A was reported i.e. 1.63 ± 0.40 , as compared to Group B (p-value=0.01). (Table No. 1)

Table 1

Number of Mature Follicles (N=60)

Mature follicles	Group-A (n=30)		Group-B (n=30)		p-value*
	Mean	SD	Mean	SD	
	1.63	0.49	1.3	0.47	0.01

*Independent sample t-test

Both groups' ovulation statuses were contrasted. 70% (n=21) in Group A and 36.67% (n=11) in Group B were found to have a significant shift; the p-value was 0.01. (Table Number 2).

Stratification controlled effect modifiers such as age, BMI, and socioeconomic status (SES). Table No. 3 displays the post-stratification chi-square test findings.

Table 2

Comparison of Ovulation Status across both Groups (N=60)

Ovulation	Group-A (n=30)		Group-B (n=30)		p-value*
	No. of patients	%	No. of patients	%	
Yes	21	70	11	36.67	0.01
No	9	30	19	63.33	
Total	30	100	30	100	

*Chi-square test

Table 3

Stratification for Ovulation Status with Regards to Age, BMI, and SES

Variables	Categories	Group	Ovulation status		P value
			Yes	No	
Age	18-30 years	A	17	7	0.01
		B	8	15	
	31-45 years	A	4	2	0.39
		B	3	4	
BMI	Up-to 30	A	16	8	0.01
		B	7	15	
	>30	A	5	1	0.19
		B	4	4	
	Lower	A	14	6	0.53
		B	4	13	
SES	Middle	A	6	1	0.51
		B	5	2	
	Higher	A	1	2	1.0
		B	2	4	

Discussion

The most frequent endocrine disorder impacting

reproductively mature women is called polycystic ovarian syndrome, or PCOS. The links between PCOS and oxidative stress, obesity, insulin

resistance, hyperandrogenism, and aberrant lipid profiles are now well established. It has been discovered recently that PCOS is linked to mitochondrial malfunction, which lowers egg quality by impairing meiotic spindle shape and chromosomal misalignment, ultimately leading to oocyte death [Zhang 2019],[Wang 2021]

Coenzyme Q10 (CoQ10) is a fat-soluble coenzyme that is present in the inner membrane of the mitochondria and functions as an antioxidant in addition to being essential for the synthesis of cellular energy. It has been utilized as a nutritional supplement to treat a range of conditions, such as high cholesterol, diabetes mellitus, cardiovascular disease, and immune system disorders in HIV/AIDS patients. It has also been utilized as an anticancer agent for the cure of breast cancer. [Sifuentes 2022] additionally, it is frequently utilized as an ingredient in cosmetic goods like some shampoos and conditioners. Animal studies have provided increasing evidence that CoQ10 may play a part in the treatment of mitochondrial illnesses because it has been shown to significantly increase the viability of hen and old mouse eggs[Cirilli 2021]. It's unclear if humans get the same enhancements from eggs as mice. The current controlled trial aimed to compare the efficacy of coenzyme Q10A in combination with clomiphene citrate for inducing ovulation in patients with polycystic ovarian syndrome.

In our study, the mean number of mature follicles in Group A (combination group) was 1.63 ± 0.49 and 1.3 ± 0.47 in Group B (clomiphene citrate alone group), and the p-value was 0.009. In comparison of ovulation in both groups was completed, demonstrating that 70 % (n=21) in Group A and 36.67% (n=11) in Group B, the p-value was 0.0097 showing a notable distinction.

According to another study use of coenzyme Q10A and clomiphene citrate in patients with clomiphene citrate-resistant PCOS improves follicular maturation, ovulation rate, endometrial thickness, and pregnancy rate. The study reports that follicles with size >18mm in patients who use coenzyme Q10A and clomiphene citrate were 1.85 ± 0.27 and in the clomiphene citrate group were 1.30 ± 0.32 . The ovulation rate in the coenzyme Q10A group was 65.9% and the clomiphene citrate group was 15.5%. The clinical pregnancy rate in the coenzyme Q10A group was 37.7% and the other group was 6%. [Sharideh 2020]. According to Benton et al., patients receiving IVF/ICSI treatment who took coenzyme Q10A supplements as opposed to placebo had a lower

aneuploidy rate and a higher pregnancy rate [Benton 2014]. There is another study conducted by Turri which showed the presence of Coenzyme Q10 in follicular fluid although the biochemical and exact function of coenzyme Q10 in follicular fluid was not clear we can use it in infertile patients to evaluate its role in ovulation induction and pregnancy [Turri 2012]. Our results are supported by this study.

El Refaeey A. et al. conducted another investigation in a prospective randomized controlled trial, the efficacy of oral coenzyme Q10 (CoQ10) in combination with clomiphene citrate for ovulation induction in patients with clomiphene-citrate-resistant polycystic ovarian syndrome (PCOS) was evaluated. A total of 101 clomiphene citrate-resistant PCOS infertile women were randomized to receive clomiphene citrate alone (50 patients, 71 cycles) or clomiphene citrate plus CoQ10 (51 patients, 82 cycles). The outcome goals included the number of follicles, blood levels of oestradiol and progesterone, endometrial thickness and ovulation, clinical pregnancy, and loss rates. Follicles larger than 14 mm and greater than 18 mm were detected in significantly higher numbers in the CoQ10 group. The endometrial thickness of the CoQ10 group was significantly greater (8.82 ± 0.27 mm) on the day of human chorionic gonadotrophin than it was for the other group (7.03 ± 0.74 mm).

In the CoQ10 group, ovulation took place in 54/82 cycles (65.9%), while in the control group, it happened in 11/71 cycles (15.5%). The CoQ10 group had a considerably higher clinical pregnancy rate (19/51, 37.3%) than the control group (3/50, 6.0%). Ovulation and clinical pregnancy rates are increased when CoQ10 and clomiphene citrate are combined in the medical care of PCOS Patients who have clomiphene citrate resistance. They came to the conclusion that it is an efficient and secure substitute that should be taken into account before laparoscopic ovarian excavation or gonadotrophin therapy.

According to Abdelaziz El Refaeey and colleagues, all patients handled CoQ10 well, and no side effects were noted. [Lakshmi 2018] In contrast to other ovulation induction techniques like gonadotrophins, The lack of statistically significant differences in the rates of clinical pregnancy and ovulation between PCOS patients with lean and obese body types in the CoQ10 group implies that body weight has no bearing on the responsiveness to CoQ10. More patient-centered research is recommended in order to validate these findings. Patients in the control group were instructed not to take any medication—

especially CoQ10—unless specifically approved by their treating physician while taking clomiphene citrate, to avoid bias. Additionally, they were told not to take medications like beta-blockers and tricyclic antidepressants that have been demonstrated to interfere with CoQ10.

CoQ10 seems like a good adjuvant to use in addition to oral ovulatory drugs like clomiphene citrate. The combination of CoQ10 and clomiphene citrate has been demonstrated to be safe, cost-efficient, and reliable in stimulating follicular growth for curing clomiphene-citrate-resistant PCOS. Before turning to more complex treatments like gonadotrophins and laparoscopic ovarian drilling, this combination can be used with effectiveness.

The results of our study are encouraging however our data is based on a single-center study and other multicenter studies are required to validate our results. The most appropriate CoQ10 dosage and duration of treatment need to be investigated further. Furthermore, more research is needed to determine whether it is possible to change the cardiovascular risk factors, hyperandrogenism symptoms, and hormonal and metabolic profiles as a result of CoQ10 therapy. This is especially true for PCOS [Martelli [2020](#)]. When comparing CoQ10 to other medical

ovulation induction techniques for PCOS patients resistant to clomiphene citrate compared to gonadotrophins, it is less costly, produces results faster than metformin, and doesn't need to be closely watched during or after treatment [Martelli [2020](#)], [Testai [2021](#)]. Therefore, CoQ10 might be a useful substitute in underdeveloped nations and for women over 35 who need a quicker course of treatment. [Lakshmi [2018](#)]

Conclusion

When compared to clomiphene citrate alone, we concluded that the combination of coenzyme Q10A and clomiphene citrate considerably improves the outcome of inducing ovulation in patients with polycystic ovarian syndrome.

Author's Contribution

Iqra Nadeem: Data collection, Data analysis, and result compilation.

Sara Malik: Data collection and analysis.

Humaira Nasir: Supervised whole study.

Sana Hassan: Data collection and study design.

Sadia Ikram: Data analysis.

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