

Effect of Short Term Supplementation of Coenzyme Q10 on Cumulative Pregnancy Rates in Young Infertile Women with Polycystic Ovarian Syndrome

Meryem KURU PEKCAN^a,
Aytekin TOKMAK^a,
Gülnur ÖZAKŞİT^a

^aDepartment of Obstetrics and Gynecology,
Zekai Tahir Burak Women's Health Care
Training and Research Hospital,
Ankara, TURKEY

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Correspondence:
Meryem KURU PEKCAN
Zekai Tahir Burak Women's Health Care
Training and Research Hospital,
Department of Obstetrics and Gynecology,
Ankara, TURKEY
meryemkuru@gmail.com

ABSTRACT Objective: To investigate the effect of coenzyme Q10 (CoQ10) supplementation on ovulation induction (OI) and intrauterine insemination (IUI) outcomes in polycystic ovary syndrome (PCOS) patients with clomiphene citrate (CC) failure or resistance. **Material and Methods:** A total of 130 nulliparous infertile patients diagnosed with PCOS were included in this prospective study. The first group of patients who were unable to conceive after the first treatment with CC received CoQ10 treatment at a dosage of 100 mg/bid for one month (study group). The other group (control group) received no treatment with CoQ10. The two groups were compared with each other in terms of cycle characteristics and success of the treatment for the subsequent three months. **Results:** The study group included 66 patients and the control group involved 64 patients. No statistically significant differences were observed between the groups in terms of age, body mass index (BMI), and infertility type. All the study participants had previously received similar medical treatments for infertility. Duration of infertility was significantly longer in the study group as compared to that in the control group (3.4 ± 1.5 vs. 2.9 ± 1.1 years). Cumulative pregnancy rates were observed to be 18 (27.3%) and 21 (32.8%) in the study and control group, respectively. **Conclusion:** Short term CoQ10 supplementation was not found to be an effective adjuvant therapy for cumulative pregnancy rates in young infertile women with PCOS who have undergone ovulation induction with intrauterine insemination. Yet, this treatment may prove to be effective on some other subgroup of women.

Keywords: Clinical pregnancy; clomiphene citrate failure; coenzyme Q10; infertility; PCOS

The polycystic ovary syndrome (PCOS) is an endocrinopathy affecting 5% to 7% of the women in their reproductive age.¹ In addition to the effects on the reproductive system, it also causes metabolic and psychological problems. Gonadotropins (GTs) are preferred in patients who do not respond to clomiphene citrate (CC) treatment. However, GT treatment costs are high and require close monitoring.²

PCOS has been found to be associated with dysfunction in mitochondria.³ Coenzyme Q10 (CoQ10), also known as ubiquinone, is a fat-soluble substance which may additionally be considered as a vitamin. It is a component of the electron transport chain and participates in aerobic cellular respiration, which generates energy in the form of ATP. CoQ10, mainly found in the inner membrane of mitochondria, also possesses antioxidant properties and is used in the treatment of many diseases like cardiovascular disorders and diabetes mellitus.⁴⁻⁶

CoQ10 has been shown to play a role in the treatment of mitochondrial disorders in animals.⁷ It has been suggested that pre-treatment with CoQ10 leads to improved ovarian response and embryo quality in young women undergoing in-vitro fertilization procedure to improve the decreased ovarian reserves.⁸ It has been observed that the metabolic and endocrine dysfunctions in patients with PCOS improve with the maintenance of CoQ10 as it ameliorates insulin and lipid metabolism.⁹ In addition, CoQ10 reduces oxidative stress, which results in increased lipolysis of triglycerides, thus contributing to endothelial metabolism in a positive manner.¹⁰

In this regard, the authors hypothesized that CoQ10 supplementation may contribute to improving oocyte quality and ovulation in infertile women with PCOS. Hence, this study aimed to evaluate the effect of CoQ10 supplementation on ovulation induction (OI) and intrauterine insemination (IUI) outcomes in PCOS patients with CC failure.

MATERIAL AND METHODS

This study was designed as a prospective non-randomized controlled study involving 130 female patients and was conducted between March and August 2016 in a tertiary level maternity hospital in the capital city of Turkey, Ankara. The study protocol was approved by the institutional ethics committee (Date and decision number: 09.29.2015-62) and it conforms to the provisions of the Declaration of Helsinki. Informed consent was obtained from each participant prior to the initiation of the study.

The inclusion criteria were as follows: nulliparous women aged 20 to 35 years affected with PCOS, follicle-stimulating hormone (FSH) levels below 12 mIU/mL, estradiol (E₂) levels < 80 pg/mL, no history of any additional diseases and, normal hysterosalpingogram and normal spermiogram parameters of the husband. Women who reported the use of multivitamin supplementation, except for folic acid and those who did not wish to undergo the IUI procedure were excluded from the study.

Also, women diagnosed with PCOS according to the revised Rotterdam consensus were eliminated from the study.¹¹

The patients in the first group of PCOS, who were unable to conceive even after the first round of treatment with CC in the author's clinic, were administered CoQ10 supplementation at a dose of 100 mg BID for one month (study group), before implementing the next treatment modality. The other group received no treatment with CoQ10 (control group). The patients were then subjected to OI and IUI procedure either until the time they conceived or at least for three months. According to the clinical measures practiced by the authors, CC is employed as the first step in the treatment modality for infertile PCOS patients. Women, who were still not able to conceive, were then treated with GTs as the next step. In CC-resistant (defined as a failure to ovulate even after receiving 150 mg of CC daily for at least three cycles) patients, the authors use CC and GT sequentially for controlled ovarian stimulation. Thus, the patients were subsequently treated with different OI agents, which were customized according to each patient. Multiple clinicians were involved in the treatment of the study participants.

The groups were compared with each other in terms of cycle characteristics and treatment success. Characteristics of the final treatment cycle of each study participant were recorded. Demographic, hormonal [FSH, LH, E₂, thyroid stimulating hormone (TSH), prolactin (PRL)] and clinical features of patients were also noted. Transvaginal ultrasonography was used to determine follicular growth and endometrial thickness. Recombinant human chorionic gonadotropin (hCG) at a dose of 250 mcg was administered subcutaneously when the diameter of at least one or two follicles was ≥ 17 mm. Semen specimens were collected following masturbation and were prepared by the swim up technique. IUI was performed 34-36 h after hCG administration. A single IUI was performed using a flexible intrauterine cannula (TecnoCath insemination catheter, Ankara, Turkey). All patients who were treated with GTs received support in the luteal phase in the form of vaginal progesterone,

starting on the day of IUI until pregnancy testing. The clinical pregnancy rate was defined as a visualization of a fetal heartbeat at six weeks of pregnancy after IUI.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) for Windows (IBM Corp., Amarak NY, USA) was used for data analysis. Kolmogorov-Smirnov test was applied for the normal distribution of continuous variables. Numerical variables were expressed as mean±standard deviation or median (minimum-maximum), whichever appropriate. Categorical variables were shown as number (percentage). The mean differences of normally distributed variables between groups were assessed by the parametric Student’s t-test while median values of non-normally distributed variables were assessed by the non-parametric Mann-Whitney U test. Differences between categorical variables were evaluated using the Chi-square or Fisher’s exact test. A p-value <0.05 was considered to be statistically significant.

RESULTS

The study group included 66 patients while the control group included 64 patients. No statistically significant differences between the groups were observed in terms of age, BMI and infertility type. Duration of infertility was significantly longer in the study group as compared to that in the controls (3.4±1.5 vs. 2.9±1.1 years, p=0.031). The demographics and baseline hormone levels are depicted in Table 1. No significant differences were observed in the baseline hormone parameters (FSH, LH, E₂, TSH, and PRL) or the existent and previous cycle characteristics (Table 2). The medical treatment previously administered to the patients for infertility was also similar. No relevant side effects were reported in the patients taking CoQ10 treatment. No significant relationship was found between mature follicle size and clinical pregnancy outcomes in either of the groups. Cumulative pregnancy rates were observed to be 18 (27.3%) and 21 (32.8%) in the study and control group, respectively (p=0.491).

TABLE 1: Demographics and baseline hormone levels of the patients.

Variables	Study group	Control group	p-value
	(treated with CoQ10) (n=66)	(n=64)	
Age (years)	25.4 ±3.8	24.7 ±3.6	0.272
BMI (kg/m ²)	24.7 ±4.0	24.2 ±4.5	0.461
Primary infertility n (%)	57 (86.5)	60 (93.8)	0.438
Infertility duration (years)	3.4 ±1.5	2.9 ±1.1	0.031
Treatment n (%)			0.059
CC+IUI	48 (72.7)	36 (56.3)	
GT+IUI	10 (15.2)	21 (32.8)	
CC+GT+IUI	8 (12.1)	7 (10.9)	
E ₂ (pg/mL)	37.3 ±17.4	42.0 ±16.9	0.119
FSH (U/L)	6.8 ±1.7	6.6 ±1.8	0.475
LH (U/L)	7.5 ±3.9	8.6 ±5.1	0.310
Prolactin (ng/mL)	12.8 ±5.2	12.6 ±4.9	0.819
TSH (U/L)	2.2 ±1.0	2.3 ±1.1	0.684

Note: Data are expressed as mean ±standard deviation and number (percentage). CoQ10: coenzyme Q10, BMI: Body mass index, CC: Clomiphene citrate, GT: Gonadotropin, IUI: Intrauterine insemination, E₂: Estradiol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone. A p-value <0.05 is considered statistically significant.

TABLE 2: Cycle characteristics of the patients in the study and control groups.

Variables	Study group	Control group	p-value
	(treated with CoQ10) (n=66)	(n=64)	
Stimulation duration (days)	14.5 ±3.3	14.0 ±2.6	0.332
Endometrial thickness on day of hCG (mm)	8.6 ±2.4	8.6 ±1.8	0.658
Current cycle cancellation n (%)	5 (7.8)	1 (1.5)	0.112
Previous CC cycles	2 (1–6)	3 (1–6)	0.931
Previous GT cycle	0 (0–3)	0 (0–3)	0.542
Previous IUI	2 (0–6)	2 (0–6)	0.092
Previous cycle cancellation n (%)			0.765
1	5 (7.8)	2 (3)	
2	1 (1.6)	2 (3)	
3	0	1 (1.5)	
CC dose used (mg)	50 (50–150)	100 (50–150)	0.017
GT starting dose (IU)	37.5 (37.5–75)	37.5 (25–75)	0.980
GT total dose (IU)	554 ±230	749 ±598	0.424
Follicle size (mm)	17.9 ±1.1	18.0 ±0.9	0.396
Cumulative pregnancy rate n (%)	21 (32.8)	18 (27.3)	0.491

Note: Data are expressed as mean ±standard deviation, median (minimum-maximum) and number (percentage). hCG: Human chorionic gonadotropin, CC: Clomiphene citrate, GT: Gonadotropin, IUI: Intrauterine insemination. A p-value <0.05 is considered statistically significant.

DISCUSSION

The main goal of this study was to assess the short term effect of CoQ10 supplementation on pregnancy rates in women with PCOS who underwent OI and IUI because of CC failure or resistance. To the best knowledge of the authors, data on the effects of CoQ10 administration on pregnancy rates in women with PCOS are scarce. This study, however, demonstrated that this treatment option is not an effective adjuvant therapy for assessing cumulative pregnancy rates in women with PCOS.

Maternal micronutrient intake affects the developmental phases of pregnancy and, their deficiency negatively affects both, placental development and fetal growth.^{12,13} However, only a little information is available on the most appropriate combination of vitamin or nutrients that may be useful for human reproduction.¹⁴ Lifestyle factors can also affect fertility and the inappropriate diet may cause subfertility. In one study, a combination of lifestyle factors was found to lower the risk of anovulatory subfertility by 69%.¹⁵ A wide range of observational studies have reported that a support in the form of multiple micronutrients increases pregnancy rate.^{16,17} Preconception nutrition is important because it affects critical steps of pregnancy including fertility, implantation, fetal growth, and placental development.¹² Micronutrient use may be beneficial in preventing some adverse pregnancy outcomes.¹⁸ The literature reports a few studies stating that micronutrient reinforcement may have beneficial effects. Besides their use as supportive treatment in infertility, some beneficial effects of micronutrient supplementation were also seen in the preconception period. They are cost-effective and well-tolerated drugs with no significant side effects. In the present study, CoQ10 was well tolerated by all patients with no side effects observed.

Mitochondria perform important functions in the fertilization stage and play a significant role in embryonic development.¹⁹ The fact that oocyte does not increase the number of mitochondria during ripening may result in poor quality embryo development.^{20,21} Mitochondrial disorders also play a

role in the development of metabolic disorders (such as diabetes mellitus, cardiovascular diseases, dyslipidemia).²² In animal studies, it was observed that CoQ10 increased reproductive success by 30%. This effect of CoQ10 is directly related to the effect of cellular ATP production in mitochondrial-mediated electron transfer in the respiratory chain. In addition, CoQ10 has been shown to improve ovarian function in patients with PCOS who do not respond to CC therapy.²³

CoQ10 is an oil-soluble antioxidant synthesized in the human body. It protects the ovaries against free radical damage and reduces oxidative stress in the ovary. A study observed that CoQ10-treated mice had a significantly higher CoQ10 concentration in their ovaries.²² CoQ10 also inhibits lipid peroxidation in the biological membranes. It has the ability to regenerate the oxidized form of vitamin E. Lipoproteins are possibly protected from oxidative damage due to these effects of CoQ10.²⁴ CoQ10 behaves like an antiapoptotic, and this is the main mechanism that explains the essential role of CoQ10 in follicular atresia.²⁵ The positive effects of CoQ10 use on the developing embryos have also been emphasized in the previous experimental studies. Its use in in-vitro bovine embryo culture resulted in more extensive blastocysts and greater internal cell masses.²⁶

In one study, it was reported that combined treatment using CoQ10-CC significantly increases clinical pregnancy rates in women with CC-resistant PCOS.²⁷ The CoQ10 group has been associated with an improved ovarian response, which is likely to have a better clinical pregnancy success rate as compared to that of the control group. In contrast to this study, such an effect of CoQ10 treatment in PCOS patients who have previously experienced CC failure or resistance in their OI cycles could not be observed. The patient cohort of the present study was younger and has favorable reproductive features as compared to that in the said study. In the aforementioned study, there was no difference in terms of ovulation and clinical pregnancy rates among the weak and obese PCOS patients in the CoQ10 group. Therefore, in response to CoQ10, it was concluded that body weight had no effect as

opposed to other OI agents such as GT, and CoQ10 could be added to oral ovulation induction agents such as CC, which is promising in terms of treatment success. CoQ10 and CC combination has been suggested as it is cheap, effective and stimulates follicular development safely in CC-resistant patients. On the contrary, the authors of this study found that CoQ10 treatment is ineffective. This difference may be due to the dose or time of use of CoQ10.

The present study had some limitations. CoQ10 levels in plasma or serum were not evaluated. Also, metabolic parameters and biomarkers of inflammation or gene expression could not be assessed in this study. The other limitations of the present study include the short treatment duration, daily dosage of CoQ10 supplementation and limited follow-up time. The results of this study may be interpreted as negative data because of the inclusion of patients with relatively favorable prognosis. In addition, there are many factors affecting treatment success in infertile women and a cause-effect relationship between CoQ10 supplementation and pregnancy rates cannot be established. However, the authors deliberate that this study presents some valuable clinical information because of its prospective design.

CONCLUSION

This study demonstrates that short term CoQ10 supplementation is not an effective adjuvant therapy for cumulative pregnancy rates in young in-

fertile women with PCOS who have previously undergone OI with IUI. However, it is quite possible that this treatment would prove to be effective in another subgroup of women. Therefore, larger prospective randomized studies are needed to test the beneficial effects of CoQ10 on the treatment success of infertile women with PCOS.

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Conflict of Interest

There exists no conflict of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, shareholding and similar situations in any form.

Authorship Contributions

Idea/Concept: Meryem Kuru Pekcan; **Design:** Meryem Kuru Pekcan, Aytekin Tokmak; **Control/Supervision:** Gülnur Özakşit; **Data Collection and/or Processing:** Meryem Kuru Pekcan, Gülnur Özakşit; **Analysis and/or Interpretation:** Meryem Kuru Pekcan, Aytekin Tokmak; **Literature Review:** Meryem Kuru Pekcan, Aytekin Tokmak; **Writing the Article:** Meryem Kuru Pekcan, Aytekin Tokmak; **Critical Review:** Gülnur Özakşit, Aytekin Tokmak.

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