Drug Design, Development and Therapy

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CLINICAL TRIAL REPORT

Coenzyme Q10 Impact on Ovarian Reserve Measures and the Intra-Cytoplasmic Sperm Injection (ICSI) Outcomes in Women with Poor Ovarian Response: A Randomized Controlled Study

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Background: Poor ovarian response (POR) is a serious problem that decreases the effectiveness of conventional ovarian stimulation. Its concern is elevated production of reactive oxygen species, causing DNA destruction and mitochondrial malfunction, which contributes to the decline in oocyte quality.

Objective of the Study: This trial aimed to identify the impact of Coenzyme Q10 as an antioxidant on ovarian reserve markers and Intra-cytoplasmic sperm injection results in poor ovarian responders.

Methods: A prospective controlled study included 100 patients classified as poor ovarian responders according to the Bologna criteria. The patients were randomly allocated to two groups. Fifty participants in group A were administrated Coenzyme Q10 plus folic acid for one month prior to the ICSI cycle and through the ICSI cycle. Fifty patients in group B were administrated folic acid only for a similar duration. The primary outcome measured was the count of oocytes obtained. The chemical pregnancy rate was considered a secondary outcome.

Results: The baseline features were equivalent among the groups. CoQ10 markedly improved the oocyte count and peak E2 ($p < 0.001$). Higher levels of antral follicle count at the start of the induction were observed in the treated group ($p = 0.001$). Endometrial thickness was greater in the CoQ10 group than in the control group ($p=0.004$). Significant differences were found in the count of embryos transferred and the percentage of women who underwent no embryo transfer ($p=0.011$). No substantial variations were detected in the gonadotropin doses, induction days, or progesterone levels among the two groups. The chemical and clinical pregnancy rates and completed cycles were equivalent between the two groups, with insignificant differences.

Conclusion: CoQ10 promotes ovarian response to conventional induction and has a beneficial effect on ovarian reserve and embryological measures in poor responders. Despite this, additional investigations are essential to determine its influence on pregnancy rates.

Clinical Trial ID: NCT06405204

Keywords: poor ovarian reserve, oocytes retrieved, Coenzyme Q10, intracytoplasmic sperm injection, infertility

Introduction

The World Health Organization considers reduced fertility to be a global health issue that impacts an extensive percentage of the human population.[1] Moreover, reduced ovarian reserve is a frequent reason for female infertility and an inadequate response of the ovary to controlled stimulation.[1,2]

https://doi.org/10.2147/DDDT.S583321
Received: 21 November 2025
Accepted: 19 February 2026
Published: 2 March 2026

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Poor ovarian reserve is known as a decrease in the quantity and/or quality of oocytes in the ovary, along with a decrease in anti-Müllerian hormone (AMH), a reduction in the antral follicle count, and an increase in follicle-stimulating hormone (FSH). Enhancing the clinical outcomes for females with POR constitutes a major concern in the clinical practice of in vitro fertilization (IVF).[3]

POR is usually age-related. Women in their mid-to-late thirties are frequently observed to have poor ovarian reserve. However, younger women may also be affected. It is thought that the follicular pool experiences a rapid decline when it falls below a threshold value of 25,000 between the ages of 37 and 38.[2]

The prevalence of POR is estimated to range from 6% to 35%,[4] while its incidence is from 9% to 24%.[5]

The pathophysiology of female infertility remains unclear and is poorly understood. Advanced maternal age and decreased ovarian reserve are among the most well-studied pathogenic processes. Both factors are associated with oxidative stress. One pathogenic cause of female infertility, especially POR, is increased oxidative stress.[6]

Furthermore, the build-up of substantial quantities of oxygen-free radicals and reactive oxygen species causes the distortion of mitochondrial DNA. Finally, mutations lead to mtDNA instability within the cells of the ovary, particularly oocytes, which results in mitochondrial dysfunction and lowers oocyte quality.[7]

Coenzyme Q10 (CoQ10) is a lipid-soluble quinone that functions as a carrier of electrons in the mitochondrial electron transport chain and exerts an antioxidant effect by preventing DNA oxidation and lipid peroxidation. Therefore, CoQ10 may improve DNA control and energy metabolism in oocytes and promote their growth.[8]

Hypogonadism and changes in steroid hormone levels have been linked to decreased plasma levels of CoQ10. Additionally, reduced expression of CoQ10 may contribute to ovarian aging, as a decay in CoQ10 levels is frequently seen in people in their late thirties. It corresponds with a decrease in fertility and the rise in embryo aneuploidy.[9]

CoQ10 can be administered orally before any assisted reproduction technique (ART).[10] Oral preovulatory CoQ10 therapy enhances the reserve of ovaries, reproductive response, and oocyte integrity and restores mitochondrial function by inhibiting oxidative stress-induced DNA harm and apoptosis.[11,12]

Moreover, it enhances the count of cumulus cells around the oocyte and their mitochondrial function, which supports the capability of oocyte development and hence, future reproductive efficacy.[13]

It has been shown that CoQ10 contributes to gene control and reduces oxidative stress with anti-inflammatory and anti-apoptotic responses.[14–18]

According to studies on animals and humans, CoQ10 improves mitochondrial function and ROS levels in oocytes and prevents apoptosis, all of which increase ovarian reserve.[9,19]

Numerous studies have demonstrated the protective properties of CoQ10 against oxidative stress; nevertheless, the mechanisms involved are unexplained.[20–22] Furthermore, despite the extensive use of antioxidants to enhance the IVF outcomes, limited clinical trials have assessed their clinical function in poor ovarian responders. Prior studies lack helpful guidance for therapeutic application as they did not evaluate the benefits of specific antioxidants and concentrated on the general infertile population.[23]

Based on the previously mentioned data, we carried out a study to find how Coenzyme Q10 (CoQ10) could affect ovarian reserve variables and the results of Intra-cytoplasmic sperm injection in patients with a low ovarian reserve.

Patients and Methods

Study Design

A Prospective open-label randomized controlled clinical study was performed at the fertility unit, obstetrics and gynaecology department, Beni-Suef University Hospital, and private centre (El Nada Centre for INF & ICSI) from June 2024 to May 2025.

Ethical Consideration: The trial was accepted by the research ethics committee, Faculty of Medicine, Beni-Suef University (ethics number: FMBSUREC/04062024/Tawfeik), complying with the 1964 Helsinki Declaration. The research was registered at Clinical Trials.gov (number: NCT06405204). This study included 100 patients classified as poor ovarian responders according to the Bologna criteria.[24] The patients were randomly allocated to two groups, by means of a computer-generated random number list, as represented in Figure 1. Fifty patients in group A (intervention

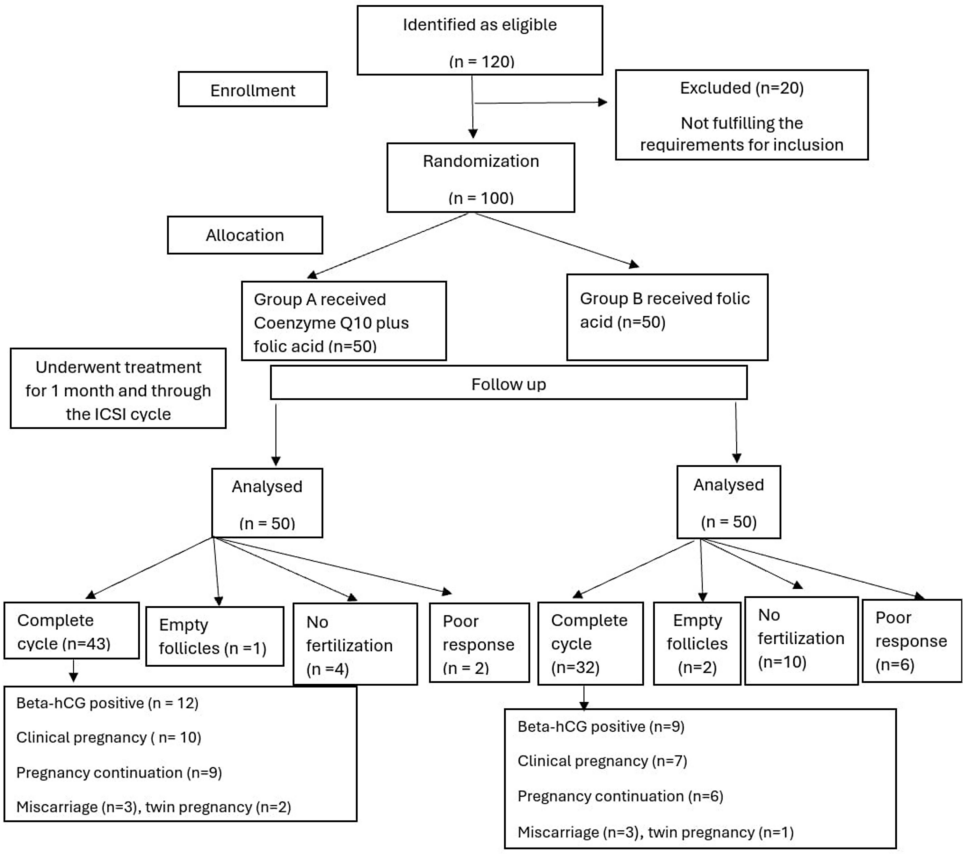

Figure 1 Flow chart outlining patient enrollment, allocation, follow up, and analysis.

group) consumed Coenzyme Q10 (Synapse CoQ10 200 mg®, Synapse Pharm, Egypt) two times daily plus Folic acid (Folic acid 500 µg®, Mepaco Medifood, Egypt) once daily for 1 month before the start of the ICSI cycle and through the ICSI cycle. Fifty patients in group B (control group) consumed only folic acid (Folic acid 500 µg®, Mepaco Medifood) once daily for a similar period. Doses and therapy duration are within the safe and effective range used in fertility studies.[5,9,25] The study began on the fifth day of the menstrual cycle before the cycle intended for gonadotropin induction, and supplements were taken until the trigger day. All the candidates submitted informed written consent and retained the option to withdraw from the trial at any moment. We minimized the risk of measurement variability by using standardized ultrasound protocols and having all scans performed by the same experienced operator.

Stimulation Protocol

According to the center's standard operating procedures, patients started receiving injections of recombinant FSH (rFSH, Gonal-F; Merck-Serono, Italy) on days two and three of their menstruation. The daily dosage ranged from 300 to 450 IU. It was altered depending on individual factors, including age, body mass index (BMI), antral follicle count (AFC), hormonal profile, and prior ovarian response. Starting day 6 of stimulation until trigger day, the patients were given 0.25 mg of the GnRH antagonist Cetrorelix (CETROTIDE 0.25mg/d, Merck Serono, Germany) subcutaneously daily to suppress the pituitary. The last stage of follicular maturation was initiated by administering an hCG injection (Ovidrel amp 0.25 mg) once at least two follicles had grown to a diameter of 18 mm. Oocytes were obtained thirty-six hours after hCG was administered.

Sample Size

G*power software version 3.1.9.2 (Germany) was utilized to determine the sample size. The Sample size for each arm was estimated using α=0.05, power (1-β)=0.8, and effect size derived from the mean and standard deviation (SD) for

quantitative variables and percentages for qualitative variables, according to previously published studies with similar populations and outcomes, which reported comparable clinical parameters in poor ovarian responders undergoing assisted reproductive techniques.[9,26–29]

Study Population

Inclusion Criteria

- Age: 25–45 years
- Women who are infertile and meet one of the following characteristics of an impaired ovarian response:
  - Fewer than seven antral follicles were observed
  - Levels of anti-Mullerian hormone below 1.2 ng/mL.

Exclusion Criteria

- Any metabolic or endocrine condition, including diabetes, thyroid dysfunction, and hyperprolactinemia
- Any pathology of the pelvis, including uterine anomalies and hydrosalpinx.
- Any male-factor infertility, including azoospermia or Oligo-Astheno-Teratozoospermia (OAT).

Statistical Analysis

SPSS version 27 was utilized for all tests, and the Raincloud plot was performed using the DataTab free version. The mean ± standard deviation (SD) was used to define normally distributed continuous data. The median (Interquartile Range [IQR]) was chosen for continuous data that were not normally distributed. When comparing normally distributed continuous data, the Student's *t*-test was chosen. The Mann–Whitney *U*-test was applied to analyse non-normally distributed continuous data, such as progesterone levels, total units of gonadotropins, and AFC, at the first visit. Categorical variables (eg, type of infertility, cycle completion, count of embryos transferred, pregnancy rates, etc.) were analysed using the chi-square test. A p-value of less than 0.05 was accepted as statistically significant for each test.

Results

The baseline features of the two groups were equivalent, without discernible variations found ($p > 0.05$) (Table 1). The infertility features were also similar, without noticeable variations observed ($p > 0.05$) (Table 1).

The Comparison of the antral follicle count (AFC) at two-time points (first visit and beginning of induction) revealed significant findings. At the first visit, no significant changes in AFC were found between the two groups ($p = 0.430$) (Figure 2). However, at the beginning of induction, significant differences were found ($p= 0.001$) (Figure 3).

Table 1 Baseline and Infertility Characteristics of the Studied Groups

Baseline	CoQ10 Group (no=50)	Control Group (no=50)	P-value
Age (years) (mean±SD)	35.9±3.2	36.4±3.8	0.393
BMI (kg/m^2) (mean±SD)	29.2±2.7	29.5±2.7	0.646
Type of infertility			0.096
1ry, n (%)	36(72.0%)	28(56.0%)	
2dry, n (%)	14(28.0%)	22(44.0%)	
Period of infertility (years) ^	5.0(3.0,8.0)	5.0(4.0,8.0)	0.250
Basal FSH (IU/mL) ^	11.8(10.9,13.2)	12.0(10.6,13.5)	0.812

(*Continued*)

Table 1 (Continued).

Baseline	CoQ10 Group (no=50)	Control Group (no=50)	P-value
Basal LH (IU/mL) ^	8.0(7.0,9.1)	9.0(7.0,10.0)	0.095
Basal E2 (pg/mL) ^	51.5(42.0,64.5)	49.5(44.7,66.0)	0.890
Baseline AMH (ng/mL) ^	0.6(0.5,0.8)	0.6(0.3,0.8)	0.528

Notes: ^ [median (IQR)].
Abbreviations: BMI, body mass index; FSH, follicular stimulating hormone; LH, luteinizing hormone; E2, estradiol hormone; AMH, anti-Mullerian hormone.

The primary outcomes of oocyte retrieval, maturity, and fertilization significantly varied between the two groups (p <0.001) (Table 2).

Concerning induction parameters, the CoQ10 group did not show substantial variations in days of induction (p= 0.848) or total units of gonadotropins (p= 0.836) when compared to the control group (Table 2).

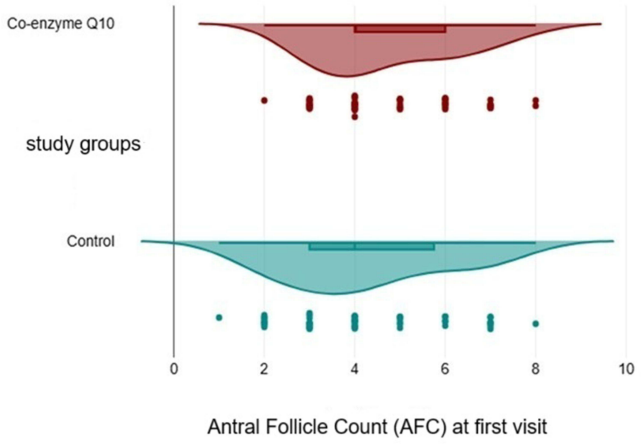

Figure 2 Rain cloud plot illustrating the distribution of antral follicle count (AFC) at first visit in the CoQ10 and control groups.

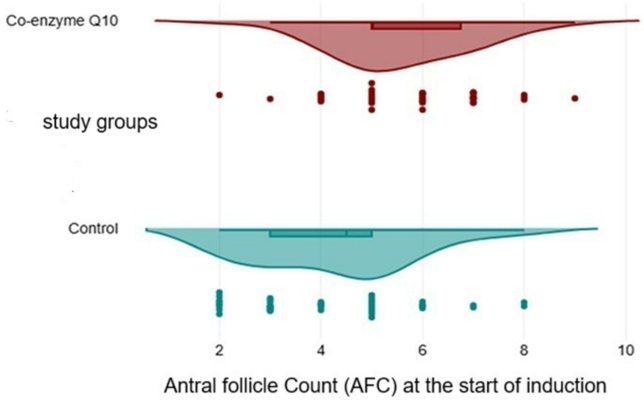

Figure 3 Rain cloud plot showing the difference in antral follicle count at the start of induction between the two groups.

https://doi.org/10.2147/DDDT.S583321

Table 2 Primary Outcomes and Induction Parameters of the Studied Groups

Variables [Median (IQR)]	CoQ10 Group	Control Group	P-value
No. of retrieved oocytes	(n=47) 5.0(4.0,6.0)	(n=42) 4.0(3.0,5.0)	<0.001*
No. of mature oocytes	(n=47) 5.0(3.0,6.0)	(n=42) 3.0(2.0,4.0)	<0.001*
No. of Fertilized oocytes	(n=43) 3.0(2.0,5.0)	(n=32) 2.0(0.0,3.0)	<0.001*
Days of induction	(n=48) 12.0(11.0,13.0)	(n=44) 12.0(11.0,13.0)	0.848
Total units of gonadotropins (IU)	(n=48) 5625.0(4950.0,5925.0)	(n=44) 5600.0(4950.0,5850.0)	0.836

Notes: *P-value is significant.
Abbreviation: IU, international unit.

The CoQ10 group showed significantly higher peak E2 levels (1096.0 pg/mL) than the control group (p <0.001) (Figure 4). Endometrial thickness on the trigger day significantly changed between the two groups (p= 0.004) (Figure 5).

Percentages of completed cycles, empty follicles, and no fertilization did not substantially differ between the two groups (p = 0.089) (Table 3).

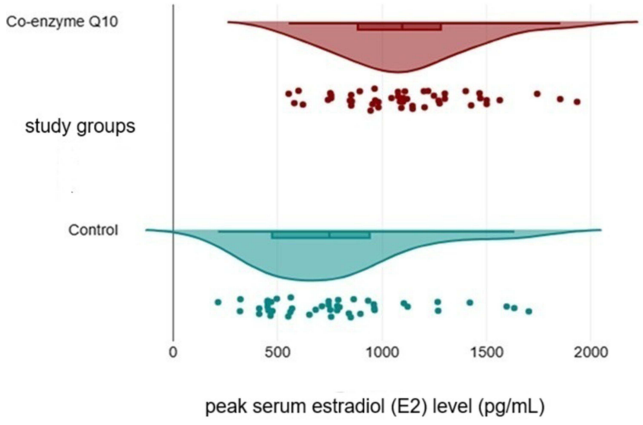

Figure 4 Rain cloud plot of Peak serum estradiol (E2) levels in the CoQ10 and control groups.

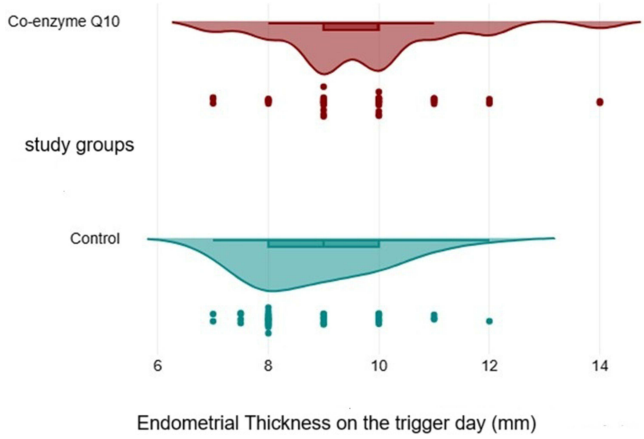

Figure 5 Rain cloud plot of endometrial thickness on the trigger day in the CoQ10 and control groups.

Table 3 Secondary Outcomes, Cycle Completion, and Embryo Transfer of the Studied Groups

Outcomes	CoQ10 Group	Control Group	P-value
Progesterone (ng/mL) [median (IQR)]	(no=43) 1.1(0.9,1.6)	(no=32) 1.0(0.8,1.6)	0.106
Complete cycle, n (%)	(no=50) 43(86.0%)	(no=50) 32(64.0%)	0.089
Empty follicles, n (%)	1(2.0%)	2(4.0%)	
No fertilization, n (%)	4(8.0%)	10(20.0%)	
Poor response, n (%)	2(4.0%)	6(12.0%)	
Embryo transfer, n (%)	(no=50)	(no=50)	0.011*
−1Embryo transferred	3(6.0%)	8(16.0%)	
−2 Embryos Transferred	30(60.0%)	18(36.0%)	
−3 Embryos Transferred	10(20.0%)	6(12.0%)	
-No transfer	7(14.0%)	18(36.0%)	
beta.hCG positive, n (%)	12/43(27.9%)	9/32(28.1%)	0.983
Clinical pregnancy (%)	10/43(23.3%)	7/32(21.9%)	0.888
Continue, n (%)	9/12(75.0%)	6/9(66.7%)	0.676
Miscarriage, n (%)	3/12(25.0%)	3/9(33.3%)	
Twin			0.792
No, n (%)	7/9(77.8%)	5/6(83.3%)	
Yes, n (%)	2/9(22.2%)	1/6(16.7%)	

Notes: *P-value is significant.
Abbreviation: hCG, human chorionic gonadotropin.

The count of embryos transferred significantly varied among the two groups, and the percentage of women who underwent no embryo transfer was substantially diminished in the CoQ10 group in comparison with the control group (p = 0.011). Progesterone levels did not substantially differ between the two groups (p = 0.106) (Table 3).

Concerning secondary outcomes, the positive beta-HCG rate of 27.9% in the CoQ10 group resembled that of the control group (p = 0.983). No noticeable variations were demonstrated in clinical pregnancy rates (P = 0.888), lower miscarriage rates (p = 0.676), or twin pregnancies (p = 0.792); however, CoQ10 appeared to demonstrate promising outcomes (Table 3).

Discussion

This study was designed to show how Coenzyme Q10 (CoQ10) affected the measures of ovarian reserve and the results of intracytoplasmic sperm injection in patients with low ovarian reserve. Our findings demonstrated that CoQ10 markedly promoted the count of retrieved, M2, and fertilized oocytes. These results were consistent with those reported by Xu et al who demonstrated an increased count of retrieved and fertilized oocytes.[9] This finding could be attributed to the antioxidative effect of CoQ10 and its impact on energy production in the oocyte.[30,31] In contrast to our results, Caballero et al did not observe any significant enhancement in the count of retrieved or M2 oocytes, which may be explained by the limited sample size and insufficient statistical power of this trial.[32] Additionally, we observed that the total gonadotropin units and induction days did not vary between the CoQ10 and the control groups. These findings aligned with Bentov et al, who demonstrated equivalent results in poor ovarian responders taking 600 mg of CoQ10 for

60 days.[33] However, Xu et al revealed a significant reduction in gonadotropin units required for ovarian induction and an insignificant decrease in stimulation durations, which may be attributed to differences in CoQ10 dose and therapy duration, as the latter study used a higher dosage (600 mg) for a longer duration (2 months).[9] Regarding hormonal response, the peak E2 serum concentration on the trigger day significantly altered between the two groups, which aligned with the finding of Xu et al,[9] but contrasted with Bentov et al, who demonstrated no significant difference in mean E2 serum concentration on the trigger day, due to the underpowered sample size of this study.[33] According to our results, CoQ10 significantly improved endometrial thickness on the trigger day, which could be attributed to the decrease in oxidative stress in endometrial cells and the prevention of lipid peroxidation by CoQ10.[8] Nevertheless, Xu et al did not show any marked variation in endometrial thickness on the day after the hCG injection.[9] Additionally, AFC significantly increased at the start of induction after CoQ10 administration in comparison to the control group, suggesting a positive correlation between CoQ10 and AFC levels through promoting ovarian function and folliculogenesis.[34] However, Xu et al found that AFC was comparable prior to and following CoQ10 therapy.[9] In Comparison with the control group, CoQ10 was linked to a higher percentage of completed cycles without statistical significance, which aligned with the findings of Xu et al, and could reflect insufficient sample size.[9] The chemical and clinical pregnancy rates were equivalent between the CoQ10 and the control groups without reaching statistical significance, which aligned with those reported in prior studies, demonstrating the limited power of sample size to detect clinical outcomes.[9,32] The rate of pregnancy continuation and multiple pregnancies was slightly increased in the CoQ10 group, with insignificant differences. CoQ10 demonstrated a lower miscarriage rate with no significant difference, which aligned with those reported by Xu et al as the sample size was not sufficient.[9] The percentage of women who underwent no embryo transfer was markedly lowered in the CoQ10 group, which was in line with the results of Xu et al, which could be explained by the enhancement in mitochondrial function and energy production, leading to oocyte maturation, fertilization, and embryonic development.[9] Contrary to our data, Bentov et al showed that the CoQ10 and control groups had comparable frequencies of high-quality embryos at 48 and 72 h.[33] Additionally, Caballero et al found no variation in implantation rate per embryo transfer.[32] Both studies reported underpowered sample sizes, as mentioned above.[32,33] We also noticed an insignificant change in the levels of progesterone detected on the trigger day between the two groups, which aligned with the study by Bentov et al.[33] Moreover, the current trial confirmed the reports of the study by Iwes et al on 81 infertile women aged 20–42, with both normal and poor ovarian reserve, which showed that follicular fluid CoQ10 levels were favorably associated with both the quality of the embryo and the probability of becoming pregnant in females receiving intracytoplasmic sperm injection (ICSI), supporting the supplementation of CoQ10 in women performing IVF to promote the quality of oocytes and embryo.[35]

Age-associated drop in human oocyte quality has been related to increased reactive oxygen species and/or mitochondrial disorders in the reproductive field because mitochondria are necessary for proper meiotic spindle aggregation, chromosomal separation, development, fertilization, and embryo growth.[36] Therefore, a plausible explanation for this age-related reduction in ovum quality could be inadequate CoQ10 levels.[37] Compelling data indicate that oxidative stress in ovarian ageing is a significant pathogenic factor in POR.[38] Mitochondrial malfunction caused by increased oxidative stress could be closely linked to adverse reproductive outcomes, low ovarian response, and disturbed embryo growth.[30] CoQ10 exerted a crucial role in the respiratory mitochondrial chain, providing an antioxidant effect.[9] Hence, CoQ10 could alleviate DNA damage, enhance mitochondrial function, and maintain energy production.[39] As mitochondria are the organelles with the highest proportion in oocytes, CoQ10 could facilitate oocyte maturation via energy metabolism in oocytes and granulosa cells.[8,40] Additionally, CoQ10 have shown positive correlation with antral follicle count and endometrial thickness through promoting ovarian function and folliculogenesis and reducing oxidative stress, thereby achieving improvement in ovarian reserve measures and better ICSI outcomes.[8,34] Levels of CoQ10 in the follicular fluid have been proven to demonstrate a beneficial effect on the quality of oocyte and embryo.[41] A prospective study included 30 women aged 31–46 receiving IVF and observed that oral administration of 200 mg/day CoQ10 for 30–35 days enhanced follicular fluid content and oocyte quality, particularly in females over 35.[25] Preclinical research suggests that CoQ10 enhances oocyte mitochondrial function, ATP synthesis, and the maintenance of ovarian reserve, targeting critical elements of reproductive aging at the cellular level. Clinical evidence, including meta-analysis of randomized controlled trials, indicates that CoQ10 supplementation in poor ovarian responders performing ICSI correlates with better ovarian

response, greater retrieval of oocytes and high-quality embryos, elevated estradiol levels, and improved clinical pregnancy outcomes, while decreasing cycle cancellation and miscarriage rates. These results correspond with a mechanistic hypothesis that proposes mitochondrial strengthening and oxidative stress reduction as primary mechanisms through which CoQ10 may confer reproductive advantages.[42]

We did not observe significant consideration of pregnancy rates, possibly because improving clinical pregnancy rates required not only high-quality embryos but also appropriate immunological and coagulation functions, along with consideration of the psychological condition of the infertile females. Promoting clinical pregnancy rates needed a multifaceted approach rather than dependence on a singular strategy, as any anomaly at any point could lead to unsuccessful embryo implantation. The antioxidant may be just one of the factors.[43]

The optimum dosage and duration of therapy are still uncertain.[9] In our research, there was statistical significance in the ovarian reserve markers when CoQ10 was administered in a dosage of 200 mg twice daily for 1 month before the ICSI cycle and through the ICSI cycle. However, a prior trial by Caballero et al showed insignificant change in the number of M2 oocytes when CoQ10 was consumed at a dose of 600 mg twice daily for 3 months. Nevertheless, the sample size of the latter trial could be underpowered to assess substantial change.[32]

The primary strength of this study was that the baseline and infertility features were equivalent between the participants, providing a solid foundation for evaluating the influence of CoQ10 on ovarian reserve parameters and ICSI results without baseline confounding effects. Randomization was performed without bias. Laboratory and clinical approaches were comparable for all participants.

The main limitation of this study was that our findings could not detect statistical significance in the clinical consequences and results of ICSI cycles, including pregnancy and miscarriage rates and completed cycles. Therefore, our recommendation is to increase the sample size and the period of therapy in future studies. Other limitations were a small sample size, a lack of blinding, and a short duration of therapy.

Conclusion

Given the significant positive effects observed of Coenzyme Q10 on oocyte retrieval, maturity, fertilization, and embryological outcomes. It is recommended as a beneficial supplement for poor ovarian responders undergoing ICSI. Clinicians may consider incorporating CoQ10 supplementation into the treatment regimen for this population to improve ovarian reserve markers such as AFC. The interpretations of these findings can highlight the study limitations, including small sample size and open-label design, to detect the impact of CoQ10 on pregnancy rates. Therefore, further well-designed randomized studies with larger sample sizes and longer follow-up periods are essential to explore their effects on the frequencies of clinical pregnancy and live birth.

Data Access

All relevant data are within the paper and its supporting files.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Faculty of Medicine, Beni-Suef University (protocol code FMBSUREC/04062024/Tawfeik, 4/6/2024).

Informed Consent

Informed consent was obtained from all subjects involved in the study. Written informed consent was obtained from the patients. Participation was voluntary, and patients had the right to withdraw from the study at any time, without affecting their medical care.

Acknowledgments

Acknowledgments of all participants in this research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

Funding

The authors extend their appreciation to the Deanship of Scientific Research and Graduate at King Khalid University for funding this work through small group Research Project under grant number RGP1/59/46.

Disclosure

The authors declare no conflict of interest.

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