

Serum Coenzyme Q10 and Cytochrome C Oxidase Levels in Premature Over Failure

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ABSTRACT

Objective: Premature ovarian insufficiency (POI) is a disease of unknown etiology characterized by the reduction and subsequent loss of ovarian capacity before the onset of physiological menopause. This case-control study was designed to investigate serum coenzyme Q10 and cytochrome C oxidase levels in POI patients.

Material and Methods: A total of 104 patients, 56 POI (Group 1) and 48 healthy controls (Group 2), aged 21-40 years, were included in the study. The control group was selected from fertile patients with normal hormone profiles and regular menstruation. Serum coenzyme Q10 and cytochrome C oxidase levels were measured by ELISA.

Results: When 56 POI patients eligible for the study were evaluated, a significant decrease was found in coenzyme Q10 and Cytochrome C Oxidase concentrations compared to healthy controls. Serum coenzyme Q10 was significantly lower in Group 1 compared to Group 2 (1.77 ± 1.35 ng/mL vs. 3.72 ± 2.68 ng/mL) ($p < 0.001$). Serum Cytochrome C Oxidase levels were also significantly lower in Group 1 compared to Group 2 (2.67 ± 2 ng/mL vs. 6.61 ± 3.05 ng/mL, $p < 0.001$). Serum FSH and LH levels of the POI group were significantly higher than the control group. Serum AMH and estradiol levels were significantly lower in the POI group compared to the controls.

Conclusions: This study showed that serum CoQ10 and cytochrome C oxidase levels were lower in POI cases than in healthy individuals. Our results suggested that a defect in the electron transport chain may play a role in the etiopathogenesis of POI.

Keywords: Coenzyme Q10, Cytochrome C Oxidase, Oxidative Stress, Premature Ovarian Insufficiency.

JMS: 2023; 26(2):23-27 DOI: <https://doi.org/10.33883/jms.v26i2.1265>

INTRODUCTION

Premature ovarian insufficiency (POI), defined as premature ovarian dysfunction or premature ovarian defect, affects approximately 1-2% of women under 40 years of age. POI can have varied clinical presentations. It mostly presents with primary or secondary amenorrhea, infertility, hypogonadotropic hypogonadism, or clinical hypo-estrogenism¹. Although it seems like an isolated organ failure, it may show systemic findings due to a sex steroid synthesis defect. POI negatively affects many functions, including the individual's psychological state and quality of life. The etiology of POI is not known exactly. In addition to many genetic and environmental factors, medications, and surgical interventions can lead to POI.

CoQ10 is a cofactor that regulates the expression of genes required for signalling, transport, and metabolism in human cells. Deficiency in CoQ10 levels can cause many mitochondrial and oxidative stress pathologies, especially aging, recessive autosomal mutations, and carcinogenesis. There are not many studies on whether mitochondrial pathways are damaged in POI patients. This study was designed to investigate the serum levels of cytochrome C and coenzyme-Q10 levels, two of the main electron transporters, to reveal whether electron transport chain pathology plays a role in the etiology of POI.

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How to cite this article: Kalı Z, Çağırır FT, Çılgin H. Serum Coenzyme Q10 and Cytochrome C Oxidase Levels in Premature Over Failure. JMS 2023; 26 (2):23-27

Received: 2023-03-15 Accepted: 2023-06-19

Access this article online



Website:
www.jmsskims.org

DOI:
<https://doi.org/10.33883/jms.v26i2.1265>



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MATERIAL AND METHODS

This case-control study was carried out for one year in Kafkas University Faculty of Medicine, Department of Obstetrics and Gynaecology between 01.03.2017 and 01.03.2018. A total of 104 patients, 56 POIs, and 48 healthy controls, aged 21-40 years, were included in the study. The BMI values of the participants were less than 25. The control group was selected from fertile patients with normal hormone profiles and regular menstruation. The ovarian reserve was evaluated on D3 of the cycle and diagnosis of POI was based on decreased levels of estradiol (E2) (<20 pg/ml), elevated levels of gonadotropin (follicle-stimulating hormone [FSH] >40 IU/l, and LH >20 IU/l, the decreased hormone of anti-Müllerian hormone (AMH) <0.5 ng/ml (<1 ng/ml) and decreased inhibin B.

Patients with endocrine disorders, those who received hormone therapy during the last year, smokers, and those with any systemic disease, oligo, or amenorrheic patients were excluded from the study. Peripheral blood chromosome analysis was performed in all patients with POI. Cases with gonadal dysgenesis, sex development disorder, and numerical or structural chromosomal anomaly were excluded from the study.

Sample collection

Venous blood samples were taken into tubes containing EDTA (ethylene diamine tetra acetic acid) as an anticoagulant. Subsequently, all tubes were centrifuged for 15 minutes at room temperature and 3000 g, and the sera were stored at $<-80^{\circ}\text{C}$ for later use.

Measurement of serum cytochrome C oxidase and coenzyme Q10 with ELISA CoQ10 and cytochrome C oxidase levels in venous blood samples were measured with the Human CoQ10/Cytochrome C oxidase ELISA Kits (My bio sure, Inc., Catalog No. MBS281919, CA, USA) using the quantitative sandwich enzyme immunoassay principle. The absorbances of the samples studied per the kit procedure were measured in a Bio-Tek ELx800 (BioTek Instruments, USA) device at a wavelength of 450 nanometers. The concentrations corresponding to all absorbances were calculated in ng/mL with the formula obtained with the help of the standard curve graph. The measuring range of both kits was 0.3120 ng/mL, and the minimum measurable level was 0.078 ng/mL. The intra-

assay CV (Coefficients of Variability) value of the kit was $<15\%$, while the inter-Assay CV value was $<10\%$. Serum FSH, LH, estradiol, and AMH values of the patients were also measured in the blood samples taken on the third day or day 3 of the cycle.

Ethical approval

Ethical approval was obtained from Kafkas University Faculty of Medicine Ethics Committee (Approval No: 80576354-050-99/50, 01/032017). The study was carried out in strict accordance with the criteria of the Declaration of Helsinki, and informed consent was obtained from all participants.

Statistical analysis

Statistical Package for the Social Sciences version 21.0 (SPSS, Chicago, IL) was used for the analysis of all data. Shapiro Wilk test was used to determine whether the data showed normal distribution or not. A parametric t-test or non-parametric Mann-Whitney U test was used for intergroup comparisons. Results were given as mean $\pm$ standard deviation (SD). Spearman's correlation analysis test was used to determine the relationships between parameters. $p<0.05$ was defined as statistically significant for all results.

RESULTS

When 56 POI patients eligible for the study were evaluated, a significant decrease was found in coenzyme Q10 and Cytochrome C Oxidase concentrations compared to healthy controls. Serum coenzyme Q10 was significantly lower in Group 1 compared to Group 2 (1.77 ± 1.35 ng/mL vs. 3.72 ± 2.68 ng/mL) ($p<0.001$). Serum Cytochrome C Oxidase levels were also significantly lower in Group 1 compared to Group 2 (2.67 ± 2 ng/mL vs. 6.61 ± 3.05 ng/mL, $p<0.001$). CoQ10 and cytochrome C oxidase concentrations are detailed in Table 1.

The age, BMI, and miscarriage rates of both groups were similar. However, there was a significant difference between the groups in terms of serum FSH, LH, AMH, and estradiol levels measured on the 3rd day of the cycle (Tables 1 and 2). Serum FSH and LH levels of the POI group were significantly higher than the control group. Serum AMH and estradiol levels were significantly lower in the POI group compared to the controls.

Table 1- Baseline characteristics of both groups of participants.

	Group-1 (POI)	Group-2 (Control)	p-values
Age(years)	22.23±5.8	29.23±5.8	0.406
BMI(kg / m ²)	22±1.5	23.0±2.0	0.918
Gravida	2.7 ± 1.8	3.4±2.1	0.062
Parity	1.4 ± 0.7	2.0 ± 1.3	0.13
Miscarriage	0.4±0.6	0.5±0.7	0.514
AMH (ng/mL)	0.4±0.6	1.8±1.32	0.001
Inhibin B (pg/mL)	24.0 ± 0.8	49.6 ± 8	0.024
FSH (mIU/mL)	41.50±37.50	5.6 ± 4.2	0.001
LH (mIU/mL)	26±24	3.52±2.34	0.001
E2 (pg/mL)	20±17.50	39.75±26.64	0.001
CoQ10 (ng/mL)	1.77±1.35	3.72±2.68	0.001
Cytochrome C (ng/mL)	2.67±2	6.61±3.05	0.001

Table 2 - The prognostic value of maternal serum coenzyme-Q10 and Cytochrome C Oxidase levels for prediction of POI.

Variables	95% CI(%)					
	Sensitivity	Specificity	PPV	NPV	PLR	NLR
Coenzyme-Q10(≤2.42)	83.9 (71.6-92.3)	91.7 (80-97.7)	92.2 (82-96.8)	83 (72.7-89.9)	10 (3.9-25.9)	0.18 (0.1-0.3)
Cytochrome C(≤2.99)	75.6 (60.4-87.1)	62.7 (49.1-74.9)	60.7 (51.6-69)	77 (58.4-77)	2(1.4-2.9)	0.39(0.2-0.68)

PPV: Positive predictive value, NPV: Negative predictive value,

CI: Confidence interval, PLR:

Positive likelihood ratio, NLR: Negative likelihood ratio.

DISCUSSION

Although the etiology of POI is not clear, genetic, autoimmune, idiopathic, enzymatic, and iatrogenic causes play a role³. The oxidative phosphorylation system (OXPHOS), known as the mitochondrial electron transport chain, includes electron transport systems and many functional enzyme complexes in the inner mitochondrial membrane, as well as CoQ10 and cytochrome C. Electrons in the complex I and II enzymatic pathways are first transferred to CoQ10. Subsequently, these electrons are transferred to complex III (cytochrome reductase) by CoQ10 and then complex IV is activated. Complex IV reduces O₂ for H₂O production. Finally, the cycle ends by producing adenosine triphosphate (ATP) with complex V^{4,5}. In light of this information, it is obvious that the cell needs CoQ10 for energy production and metabolic activities. Energy requirement for germ cell development, oogenesis, and oocyte maintenance is an absolute requirement. Consistent with this, CoQ10 has been reported to increase ovulation and proliferation of bovine embryos in vitro. CoQ10 is also known to lead to an improvement in the functions of ATP-producing cells⁶.

Mutations in genes encoding the mitochondrial multiprotein complex may cause many clinical diseases^{7,8}. Since mutations in more than fifty genes have been reported in POI, CoQ10 and cytochrome oxidase functions may be defective⁹. Mutant genes in POI may contribute to POI formation as they affect DNA repair, gonadal development, DNA replication, functions of hormones, and adaptive immunity¹⁰. POI occurs as a component of Perrault syndrome associated with hypogonadotropic hypogonadism. Being part of an autosomal recessive syndrome is important evidence of the genetic basis of POI. The demonstration of muscle CoQ10 defect in addition to the partial defect of cytochrome C oxidase, which is mitochondrial enzymes, in Perrault syndrome suggests that CoQ10 and cytochrome oxidase defects may be present in the etiology of POI^{11,12,13}.

There is also clinical evidence that CoQ10 has a role in the etiology of POI. The decrease in aneuploidy rates and the increase in clinical pregnancy rates in IVF/ICSI (in vitro fertilization/ Intracytoplasmic sperm injection) patients given coenzyme Q10 supplementation are one of the most important indicators of the role of CoQ10 in follicle development¹⁴. Similarly, the increase in the number of antral follicles in patients with a low ovarian reserve who are supplemented with CoQ10 concurrently with androgens is another clinical data showing the efficacy of CoQ10¹⁵. When all these studies and our findings are evaluated together, they provide supporting evidence that coenzyme Q10 and cytochrome C oxidase may have a role in early ovarian failure.

The significantly lower levels of coenzyme-Q10 and cytochrome C in patients in the POI group compared to controls support the role of these two mitochondrial enzymes in the causation of POI. Adequate mitochondrial number and functions are indispensable for healthy follicular development. The use of pharmacological agents such as CoQ10 for the regulation of mitochondrial functions leads to an increase in mitochondrial mass and plays a role in the improvement of mitochondrial functions¹⁶. CoQ10 supplementation provides significant improvement in oocyte competence, especially in aging oocytes. Consistent with this, it has been reported that coenzyme Q10 supplementation improves mitochondrial gene expression in oocytes and improves ovarian function, thereby reducing

follicle loss due to premature aging^{16,17}. While CoQ10 improves follicle development with its dehydroepiandrosterone (DHEA) like effect, it may delay early follicular aging. Indeed, DHEA treatment increases the pregnancy rate in patients with early ovarian failure, reduces the possibility of miscarriage, and increases the success of IVF treatment. The fact that CoQ10 supplementation increases the level of CoQ10 in some tissues such as sperm, plasma, and muscle is proof that it has a similar effect in ovaries and oocytes¹⁶⁻¹⁸.

Our study is important in terms of presenting the clinical data showing the change in CoQ10 and cytochrome oxidase levels in POI cases. Our findings suggest that the development of POI can be slowed down by replacing these two mitochondrial enzymes. Consistent with our data, it has been reported that CoQ10 supplementation can protect the ovarian reserve by preventing both physiological ovarian aging and mitochondrial ovarian aging¹⁹. Detection of defective genes related to the mitochondrial function or metabolism in Perrault syndrome and increased apoptosis are other pieces of evidence showing the role of mitochondrial enzymes in the development of POI²⁰⁻²³. To make clearer comments on this subject, clinical studies investigating serum FSH, LH, and AMH levels by CoQ10 supplementation in patients with premature ovarian aging are needed.

CONCLUSION

This study showed that serum CoQ10 and cytochrome C oxidase levels were lower in POI cases than in healthy individuals. Our results suggested that a defect in the electron transport chain may play a role in the etiopathogenesis of POI. To make a clearer conclusion, it is very important to evaluate the effect of CoQ10 supplementation on clinical and laboratory results in patients at risk of POI. To clarify the precise role of CoQ10 in POI, improvement in vasomotor symptoms and serum AMH and AFC levels should be evaluated.

ACKNOWLEDGMENT

For his support in the design of the study and obtaining the laboratory data, Dr. We would like to thank Hasan Çilgin.

FUNDING

There is no financial contribute by any foundation source.

CONFLICT OF INTEREST

The Authors declare that they have no conflict of interests

REFERENCES

1. Homer HA. Understanding oocyte ageing: can we influence the process as clinicians? *Curr Opin Obstet Gynecol.* 2021; 33: 218-224.
2. Yeh TS, Ho JD, Yang VW, Tzeng CR, Hsieh RH. Calcium stimulates mitochondrial biogenesis in human granulosa cells. *Ann NY Acad Sci.* 2005; 1042: 157-62.
3. Kovanci E, Schutt A. Premature ovarian failure: clinical presentation and treatment. *Obstet Gynecol Clin North Am* 2015;42:153-61.
4. May-Panloup P, Chretien MF, Malthiery Y. Mitochondrial DNA in the oocyte and the developing embryo. *Curr Top Dev Biol* 2007; 77: 5183.
5. Gendelman M, Roth Z. Incorporation of coenzyme Q10 into bovine oocytes improves mitochondrial features and alleviates the effects of summer thermal stress on developmental competence. *Biol Reprod.* 2012; 87: 118.
6. Stojkovic M, Westesn K, Zakhartchenko V. Coenzyme Q10 in submicron-sized dispersion improves development, hatching, cell proliferation, and adenosine triphosphate content of in vitro-produced bovine embryos. *Biol Reprod.* 1999; 61: 5417.
7. Koene S, Rodenburg RJ, Van der Knaap MS. Natural disease course and genotype-phenotype correlations in complex I deficiency caused by nuclear gene defects: what we learned from 130 cases. *J Inherit Metab Dis.* 2012; 35: 737-47.
8. Distelmaier F, Koopman WJ, Van den Heuvel LP. Mitochondrial complex I deficiency: from organelle dysfunction to clinical disease. *Brain.* 2009; 132: 833-42.
9. Qin Y, Jiao X, Simpson JL et al. Genetics of primary ovarian insufficiency: new developments and opportunities. *Hum Reprod Update.* 2015; 21: 787808.
10. Tucker EJ., Grover SR., Bachelot A. Premature Ovarian Insufficiency: New Perspectives on Genetic Cause and Phenotypic Spectrum. *Endocrine Reviews*, 2016; 37: 609-635.

11. Sarikaya E, Ensert CG, Gulerman HC. Hypergonadotropic hypogonadism, progressive spinocerebellar ataxia and late onset sensorineural hearing loss: Case report and literature review. *BJMG* 2011; 14: 77-88
12. Wang H, Sun X, Lin MS, Ferrario CM, Van Remmen H, Groban L. G protein-coupled estrogen receptor (GPER) deficiency induces cardiac remodeling through oxidative stress. *Transl Res*. 2018; 199: 39-51.
13. Gironi M, Lamperti C, Nemni R, et al. Late-onset cerebellar ataxia with hypogonadism and muscle coenzyme Q10 deficiency. *Neurology* 2004; 62: 818-820.
14. Bentov Y, Hannam T, Jurisicova A. Coenzyme Q10 supplementation and oocyte aneuploidy in women undergoing IVF-ICSI treatment. *Clin Med Insights Reprod Health*. 2014; 8:316.
15. Gat I, Mejia SB, Balakier H, et al. The use of coenzyme Q10 and DHEA during IUI and IVF cycles in patients with decreased ovarian reserve. *GynecolEndocrinol*. 2016; 32: 534-7.
16. Ben-Meir A, Burstein E, Borrego-Alvarez A, et al. Coenzyme Q10 restores oocyte mitochondrial function and fertility during reproductive aging. *Aging Cell*. 2015; 14: 887-895.
17. Bentov Y, Casper RF. The aging oocyte can mitochondrial function be improved? *Fertil Steril*. 2013; 99: 1822.
18. Bentov Y, Esfandiari N, Burstein E. The use of mitochondrial nutrients to improve the outcome of infertility treatment in older patients. *Fertil Steril*. 2010; 93: 272-5.
19. Özcan P, Fıçıcıoğlu C, Kizilkale Ö. Can Coenzyme Q10 supplementation protect the ovarian reserve against oxidative damage? *Journal of assisted reproduction and genetics*. 2016; 33: 1223-30.
20. Raimundo N, Song L, Shutt TE. Mitochondrial stress engages E2F1 apoptotic signaling to cause deafness. *Cell*. 2012; 148: 716-26.
21. Huhtaniemi I, Hovatta O, La Marca A, et al. Advances in the Molecular Pathophysiology, Genetics, and Treatment of Primary Ovarian Insufficiency. *Trends in Endocrinology & Metabolism*. 2018; 29: 400-419.
22. Lee HJ, Park MJ, Joo BS, Joo JK, Kim YH, Yang SW, Kim CW, Kim KH. Effects of coenzyme Q10 on ovarian surface epithelium-derived ovarian stem cells and ovarian function in a 4-vinylcyclohexene diepoxide-induced murine model of ovarian failure. *Reprod Biol Endocrinol*. 2021; 19: 59.
23. Meldrum DR, Casper RF, Diez-Juan A, Simon C, Domar AD, Frydman R. Aging and the environment affect gamete and embryo potential: can we intervene? *Fertil Steril*. 2016; 105: 548-559.