A review of the effect of Coenzyme Q10 in patients with polycystic ovary syndrome

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ABSTRACT

Background: Women with polycystic ovary syndrome are usually suffering from many metabolic disturbances as insulin resistance, so the use of Co enzyme Q10 in those patients improve metabolic changes and insulin resistance resulting in better ovulation.

Mitochondrial dysfunction in the eggs is related to reduction in the oxidative phosphorylation which leads to lower ATP production by mitochondria, also results in deprived reproductive performance, including poor oocyte quality, lessened ovarian store, abnormal conception and unbalanced embryo development.

Objective: The aim of this review is to observe the effects of co enzyme Q10 in PCOS patients by emphasizing many studies that showing the effect of CoQ10 on the metabolic parameters such as (Fasting serum glucose, HbA1c%, total cholesterol, LDL, HDL and triglyceride level).

This article suggested that CoQ10 therapy possess beneficial effect in improving the clinical parameters of PCOS patients including HbA1c%, fasting serum glucose and lipid profile parameters.

Keywords: Coenzyme Q10, polycystic ovary syndrome (PCOS), Glycemic control, lipid profile.

الخلاصة

عادة ما تعاني النساء المصابات بمتلازمة تكيس المبايض من العديد من الاضطرابات الأيضية مثل مقاومة الأنسولين ، لذا فإن استخدام إنزيم Co Q10 في هؤلاء المرضى يحسن التغيرات الأيضية ومقاومة الأنسولين مما يؤدي إلى تحسين التبويض.
يرتبط الخلل الوظيفي في الميتوكوندريا في البيض بتقليل الفسفرة المؤكسدة مما يؤدي إلى انخفاض إنتاج ATP بواسطة الميتوكوندريا ، كما يؤدي إلى ضعف الأداء التناسلي ، بما في ذلك ضعف جودة البويضات ، وتقليل مخزون المبيض ، والحمل غير الطبيعي وتطور الجنين غير المتوازن.

الهدف: الهدف من هذا المرجع هو مراقبة تأثيرات الإنزيم المساعد Q10 في مرضى متلازمة تكيس المبايض من خلال التأكيد على العديد من الدراسات التي توضح تأثير CoQ10 على المعلمات الأيضية مثل (جلوكوز مصل الصيام ، HbA1c٪ ، الكوليسترول الكلي ، LDL، HDL و مستوى الدهون الثلاثية).
اقترحت هذه المقالة أن علاج CoQ10 له تأثير مفيد في تحسين المعلمات السريرية لمرضى متلازمة تكيس المبايض بما في ذلك HbA1c ٪ ، وجلوكوز مصل الصيام ومعلمات ملف تعريف الدهون.

الكلمات المفتاحية: الانزيم المساعد كيو-10، متلازمة تكيس المبايض ، مستوى الكلوكوز بالدم، ملف الدهون.

Introduction

Polycysic ovary syndrome is originally known as the Stein–Leventhal syndrome, it is defined as a common endocrine syndrome that characterized by various signs both reproductive and hyperandrogenic features including irregular menstruation , hyperandrogenism (HA), enlarged ovaries with multiple small follicles appeared as a cyst and ovulation abnormality . (1)

After that fibrosis of the ovaries preventing the release of drooped .follicles (2)

Clinical feature

- Menstruation disorder commonly is seen in PCOS patients such as amenorrhea, prolonged irregular bleeding, and oligomenorrhea.
- High androgen level (hyper- androgenism HA) that results in

  hirsutism which is the growth of hair at seven abnormal sites hair such as, chin, upper lip, back, thighs, chest, upper limb, and abdomen.

  Acne also could be a marker of hyperandrogenism (1)
- Infertility which affecting on PCOS patient who anovulatory due to disorders in issues involving growth and development of follicle which then becomes clogged as follicles with a diameter about (4–8 mm), PCOS patient is also suffering from spontaneous abortion.
- Another feature of PCOS is often encountered is insulin resistance (IR) ,concomitant high insulin level, and obesity. (1).

Diagnosis

Criteria used to diagnose PCOS have been described by three groups:

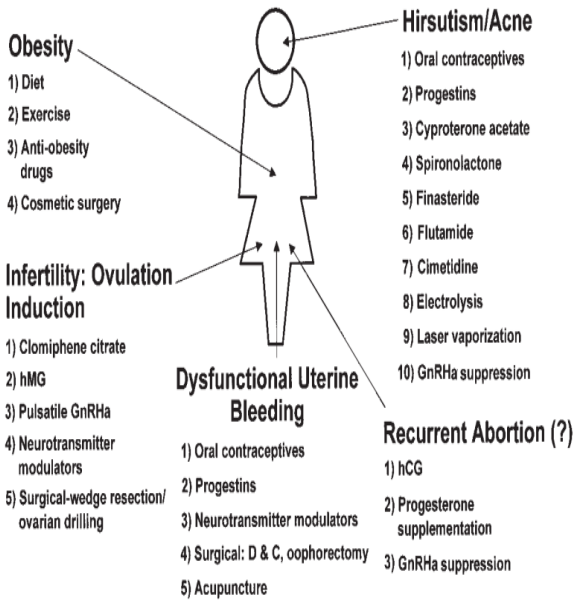
- ✓ National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD)
- ✓ Rotterdam criteria or European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM)
- ✓ Androgen Excess and PCOS Society(AES)(3)

Every one of these groups considers PCOS after exclusion of other disorder

NIH/NICHD and (AES) both of these criteria consider the PCO if patients having features of hyperandrogenism as hirsutism, or hyperandrogenemia including (high testosterone level, low sex hormone-binding globulin (SHBG) concentration. Rotterdam criteria permit the diagnosis of PCOS deprived of the existence of hyperandrogenemia / hyperandrogenism, ovulatory disorder and multiple small cysts in the ovaries are diagnosed as PCOS. (4)

Another difference of Rotterdam criteria is that it doesnot include menstrual irregularity or ovulation disorder for diagnosis while NIH/NICHD criteria excepts diagnosis of PCOS if the patient having regular menstrual cycle and subclinical ovulation disorder.(1).

Management



Treatment of PCOS depends on improving the symptoms such as reducing high insulin level, re-establish fertility, treating hirsutism and / acne, correction of the menstrual disturbances with prevention of hyperplasia and cancer of the endometrium.

Weight reduction and exercise decrease the insulin level, slight weight reduction (5%) could result in improving ovulation and regulate menstruation, decreasing diabetes and cardio-metabolic occurrence.

Oral contraceptive pills (OCP's) are considered as the first-line Pharmacological agent for treating hirsutism. Combined OCPs the other option which regulates menstruation, reduces hirsutism and acne. But the use of (OCP) may worsen glucose metabolism (1).

Antiandrogenic agent as Spironolactone, / Flutamide acts as a competitive inhibitor for androgen receptors and reducing androgen production.

Flutamide is a selective antiandrogenic drug deprived of progesterone action used for hirsutism treatment. It is used as an assistant agent because of its high cost and hepatocellular toxicity.(3).

Insulin sensitizing drugs such as thiazolidinediones group and Metformin improve insulin resistance, and it could reduce androgen levels. Metformin reduces weight, while thiazolidinediones rise weight because of fluid retention .(5).

D-chiro-inositol might improve insulin resistance and treat PCOS patient

Clomiphene citrate (CC) partially selective estrogen receptor modulator and it's considered the drug of choice for inducing ovulation in PCOS female

Selective aromatase inhibitors such as Anastrozole and Letrozole are new ovulation induction agents.

If PCOS women suffered from hyperprolactinemia then dopaminergic agonist as Bromocriptine was used to treat this condition.(3).

Coenzyme Q10

CoQ10 (ubiquinone or ubidecarenone) is a lipid-soluble molecule that exists in every cell. It possesses 2,3 dimethoxy-5 methyl-6 decaprenyl benzoquinone group which is bind to a side-chain of isoprenoid unit of specified length between 6–10 subunits, it is redox-active substance that institutes in the plasma membrane ,it plays a key role in the electron transport chain of the mitochondria generating proton gradient, which lead to the production of ATP that considered as the energy source of the body. (6).

The reduced form of Co Q10 (ubiquinol) considered as a potential antioxidant therefore, it is used as antiaging supplement and for management of mitochondrial disorders. (7).

Functions of Co Q

- ✓ The plasma membrane of most cells contains CoQ -dependent NADH-oxidase which regulates the cytosolic ratio of NAD+ / NADH ratio and ascorbate reduction and is involved in the regulation of cell growth and differentiation. (8).
- ✓ CoQ 10 is considered as a lipophilic antioxidant which endogenously synthesized and act as an efficient preventer of oxidation of DNA, proteins, and lipids. Effective enzyme systems always attempt to maintain this molecule in the reduced active form.(9).
- ✓ Opening the transition pore of the mitochondrial membrane permits the translocation of large molecules up to 1500 Da in size, which leads to a failure of mitochondrial functions , CoQ10 prevents the opening of these pores, so it is stabilizing apoptotic proceedings such as ATP diminution, the release of cytochrome to the cytosol, cas, depolarizing the potential of the mitochondrial membrane and DNA destruction (10).
- ✓ Uncoupled proteins which existing in the mitochondrial inner membrane translocating protons from outside to the inside of this membrane which lead to the proton gradient

made by the respiratory chain is detached from oxidative phosphorylation and producing heat in its place. (11).

These protons brought from fatty acids to these uncoupled proteins with the support of oxidized CoQ, which is a necessary cofactor in this method (11).

- ✓ CoQ exerts multiple anti-inflammatory effects by influencing the expression of (NF-κB)1-dependent genes. Apparently, uptake of CoQ into lymphocytes and monocytes initiates the release of mediators and signal substances into the blood that subsequently modify such expression in a variety of tissues(4).
- ✓ Anti-atherosclerotic properties resulted by preventing LDL oxidation, also reducing lipid peroxides that are associated with lipoproteins in producing atherosclerotic injuries, diminishing the size of these lesions in the aorta(1).
- ✓ CoQ reduces b2-integrin CD11b in monocytes levels, which antagonize interactions between monocyte–endothelial cell. (12).
- ✓ CoQ helps counteract the endothelial dysfunction by stimulating endothelial release of nitric oxide (1).
- ✓ CoQ facilitates sulfide oxidation in yeast and disulfide bonds institution into bacterial proteins. (13).

Pharmacokinetic

CoQ is lipid-soluble substance its absorption is enhanced with a fatty meal after absorption it is reduced to ubiquinol form then transported to the liver added to (VLDL)/LDL particles and released to blood.

CoQ given is orally poorly absorbed but improved by the addition of emulsifier Chopra et al. use polysorbate 80 to CoQ_{10} supplements to enhance absorption.

CoQ_{10} is present in many tissues but high-level present in tissue (heart, kidney, liver, and muscle) which possess high metabolic activity, in ubiquinol form in high concentration in the mitochondria.

Biosynthesis drop with age CoQ_{10} is metabolized in almost all tissue mainly excreted by the biliary and fecal route, with a small portion eliminated in the urine. (14).

Side effect and drug interaction

CoQ10 is found naturally in the body, so it's a well-tolerated supplement, some mild side effect might occur including gastric upset such as (low appetite nausea, vomiting, diarrhea, dyspepsia) and dizziness.(14).

- HMG–CoA reductase inhibitors (statin) is Cholesterol reducing agents, these drugs hindering synthesis of cholesterol also blocking the biosynthesis of CoQ10 leading to its exhaustion, causing myopathy and rhabdomyolysis, in severe cases, these side effects can be eliminated by CoQ10 supplement administration .

- Anticancer agents (doxorubicin and daunorubicin) are considered as good anticancer drugs but lead to irreversible damage to the mitochondria of the myocyte, CoQ10 supplementation during chemotherapy diminish this S/E without compromise their anticancer effect.(15).

- Adjustments of dose in diabetic patients who taking glyburide, tolazamide with CoQ10 to prevent hypoglycemia, because CoQ10 improve glycemic control in diabetic patients. also, these drugs reduce the endogenous CoQ10 level.

- Beta-cell function and insulin sensitivity may be improved by CoQ10 which decreases insulin requirements in diabetic patients (16).

- Beta-blockers obstructing CoQ10-dependent enzymes and decrease endogenous CoQ10.
- CoQ10 has an structure similar to vitamin K, so if the patients take anticoagulant therapy may require dosage adjustment of anticoagulant and INR monitoring .

Indication

- **Treatment of coenzyme Q10 deficiencies**

Patients with primary or secondary CoQ10 deficiency show symptoms improvd after treatment with administration of CoQ10 supplement orally.

2,400 mg day in the adult patients while in pediatric patients the dose should not exceed (30 mg/kg) daily given as three separated doses daily. (17)

- **Mitochondrial disorders**

CoQ10 is used in treating patients suffering from mitochondrial disorders due to CoQ10 is decreased in the muscle of patients with mitochondrial myopathy . (17)

- **Fibromyalgia (FM)**

Is a chronic disorder with indefinite causes with patient suffering from weakening fatigue, pain, allodynia, stiffness of the joint and migraine headache?

FM presented with CoQ10 deficiency have a significant improvement of symptoms with CoQ10 treatment.(18)

- **Cardiovascular disease**

Heart failure (HF) is a loss of contractility due to an energy exhaustion in the mitochondria if there is low levels of CoQ10 endogenously.

Treatment with oral CoQ10 supplement might improve contraction of the heart in stable HF and alleviate endothelial disorder (19) (20).

- **Atherosclerosis**

(Ubiquinol) obstructs the peroxidation of lipid in the cell membrane and inhibits the lipoprotein that presents in the blood. Nutritional supplements with CoQ10 lead to prevent low-density lipoprotein for beginning of lipid peroxidation . (21).

Dyslipidemia

Hypercholesterolemia and are generally treated with hydroxyl methyl glutaryl coenzyme A reductase inhibiter (“statins”) which block the CoQ10 and cholesterol synthesis.

Coenzyme Q10 exhaustion may be the cause of statin- myopathies so supplementation with Coenzyme Q10 is greatly suggested in preventing myopathy resulted from statin therapy.(22).

- **Hypertension**

CoQ10 might reduce blood pressure by reduction the peripheral resistance, protecting nitric oxide which causes peripheral arteries relaxation, and decreasing blood pressure.

CoQ10 may augment prostaglandin prostacyclin (PGI_2) production which is considered as a potent vasodilator so its suggested to act as an assistant antihypertensive agent (23).

- **Neurological conditions**

Parkinson’s disease (PD)

CoQ10 might be playing a key role in the cellular abnormality that found in Parkinson’s patient due to low levels of CoQ10 that observed in blood and platelet mitochondria and plasma of PD patients .(24).

Huntington's disease (HD) is a neurodegenerative disorder that is caused by an enlargement of DNA sequence CAG trinucleotide repeat in the HD encoding gene which leads to progressive death of striated neurons.

The therapeutic strategy reduces the reactive oxygen radicals might improve the neurodegeneration process by using CoQ10 which acts as antioxidants. (25).

Alzheimer's disease (AD)

Alzheimer's disease is related to oxidative damage which occurs due to mitochondrial dysfunction .

The use of quinone therapy has be improve the clinical symptoms and the disease biomarkers (26).

Cancer:

Reduced CoQ10 levels in the plasma of ladies with breast cancer with a worse prognosis and shorter disease-free intervals. The use of the high doses of doxorubicin resulted in CoQ10 exhaustion and cardiotoxicity.

CoQ10 supplementation avoids cardiac damage and another side effect which is caused by an anticancer agent without.(27).

Diabetes

Diabetes is a chronic metabolic disease which results in either absolute or relative lack of insulin action and/or insulin secretion.

CoQ10 levels in patients with type 2 diabetes are reduced producing diabetic cardiomyopathy which is reversed by CoQ10 administration. It has been verified that ubiquinone treatment for about twelve weeks results in improving the nerve conduction in patients with diabetic neuropathy, it also reducing oxidative stress without causing the side effect . (28).

Male infertility

CoQ10 can be measured in the semen its percentage relates to the number and motion of the sperm.

If CoQ10 is given to patients with azoospermia suffering from infertility may lead to rising in the level of CoQ10 in sperm cells, seminal plasma, and improving sperm motion (29).(30).

- **Migraine**

Migraine is considered a mitochondrial disorder because of compromised energy metabolism.

Presently CoQ10 supplementation with riboflavin suggested widely because it is safe and effective as prophylaxis for migraine. (31)(31).

Down´s syndrome (DS)

It is an abnormality in chromosome number 21 that is associated with a multipart phenotype, its pathology is mainly due to oxidative stress, suggesting that oxidative imbalance adds to the clinical manifestation of DS.

CoQ10 treatment in DS patient reduces oxidative signs in plasma, and also improve DNA repair mechanisms through variation in the DNA repairing enzymes (32).

Aging

During the aging process, low CoQ10 level is considered as one of the contributing factors in the progression of different chronic diseases in the elderly.

Maintaining CoQ10 levels at cell membranes by dietary supplementation or by enhancing the biosynthesis can be a good approach to enhance health during aging (33).

Cosmetic

Antioxidants topically applied in the management of photoaged and chronologically aged skin.

CoQ10 in the skin acts as an antioxidant its level in the epidermis layers 10-times higher levels than in the dermis layer of the skin. Reduction of the antioxidant systems efficiency has been projected as a cause of skin ageing, so CoQ10 is widely used now a day as anti-ageing product. (34).

The major quantity of mitochondria is present in oocytes. The role of the mitochondria contributes to the type of eggs and plays a key role in the fertilization process and fetus development. Dysfunction in the mitochondria may add to the beginning of metabolic syndromes such as obesity, IR, dyslipidemia, and an increased chance of heart disease. (35).

The effect of Coenzyme Q10 in PCOS patients

- In the mitochondria CoQ10, play a role in the electron transferring in the respiratory chain, and produce ATP in the cell.

- CoQ10 is a lipophilic antioxidant produced in the bodies and it can decrease oxidative stress in the ovary also could protect DNA from damage due to free radicals. Ubiquinol (reduced form), it impedes lipid peroxidation in the living membranes.

- It stabilizes the plasma membranes by preserving their flexibility. The fluidity of the membrane's effects on the membrane receptors, enzymes, and carriers, so it's important for maintaining the physical performance of the membrane.

- CoQ10 is considered a micronutrient its uptake by tissue associates with the degree of CoQ10 deficiency in the tissue, acting as an antiapoptotic agent, where apoptosis is the chief mechanism in follicular cohort atresia. (36).

Conclusion

This review study concludes that

Coenzyme Q10 supplementation in PCOS patient result in significant decreases is glycated hemoglobin, also cholesterol levels, LDL, and triglycerides are significantly reduced. HDL is not affected after CoQ10 supplement administration. There is no difference regarding BMI in patients after supplementation with CoQ10.

Conflict of interest: There is no conflict of interest.

References

1. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2013;6(1):1–13.
2. Priyanka Kantivan Goswami, Anubha Khale SO. Natural remedies for polycystic ovarian syndrome (PCOS) : A review. Int J Pharm Phytopharm Res [Internet]. 2012;1(6):396–402. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L368610055%0Ahttp://www.eijppr.com/may_jun_2012/15.pdf
3. Maqbool M, Gani I. POLYCYSTIC OVARIAN SYNDROME-A MULTIFACETED DISEASE : A REVIEW. 2019;10(March).
4. Azziz R. Diagnosis of polycystic ovarian syndrome: The Rotterdam criteria are premature. J Clin Endocrinol Metab.

2006;91(3):781–5.
5. Legro RS. Polycystic ovary syndrome: Current and future treatment paradigms. Am J Obstet Gynecol. 1998;179(6 II):101–8.
6. Barakat A, Shegokar R, Dittgen M, Mu RH. Coenzyme Q10 oral bioavailability : effect of formulation type. 2013;431–51.
7. Wang Y, Hekimi S. Understanding Ubiquinone. Trends Cell Biol [Internet]. 2016;xx:1–12. Available from: http://dx.doi.org/10.1016/j.tcb.2015.12.007
8. Dewailly D, Lujan ME, Carmina E, Cedars MI, Laven J, Norman RJ, et al. Definition and significance of polycystic ovarian morphology: A task force report from the androgen excess and polycystic ovary syndrome society. Hum Reprod Update. 2014;20(3):334–52.
9. Dewailly D, Pigny P, Soudan B, Catteau-jonard S, Decanter C, Poncelet E, et al. Reconciling the Definitions of Polycystic Ovary Syndrome : The Ovarian Follicle Number and Serum ¨ llerian Hormone Concentrations Aggregate with the Markers of Hyperandrogenism. 2010;95(September):4399–405.
10. Homburg R. What is polycystic ovarian syndrome? A proposal for a consensus on the definition and diagnosis of polycystic ovarian syndrome. Hum Reprod. 2002;17(10):2495–9.
11. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2013;98(12):4565–92.
12. Döring F, Schmelzer C, Lindner I, Vock C, Fujii K. Functional connections and pathways of coenzyme Q10-inducible genes: An in-silico study. IUBMB Life. 2007;59(10):628–33.
13. Bentinger M, Tekle M, Dallner G. Coenzyme Q - Biosynthesis and functions. Biochem Biophys Res Commun [Internet]. 2010;396(1):74–9. Available from: http://dx.doi.org/10.1016/j.bbrc.2010.02.147
14. Mortensen SA. Coenzyme Q 10. JACC Hear Fail. 2015;3(3):270–1.
15. Conklin KA. Coenzyme Q10 for prevention of anthracycline-induced cardiotoxicity. Integr Cancer Ther. 2005;4(2):110–30.
16. Bhagavan HN, Chopra RK. Coenzyme Q10: Absorption, tissue uptake, metabolism and pharmacokinetics. Free Radic Res. 2006;40(5):445–53.
17. Garrido-Maraver J, Cordero M, Oropesa-Avila M, Fernández-Vega A, de la Mata M, Pavon A, et al. Clinical applications of coenzyme Q10. Front Biosci (Landmark Ed. 2014 Jan 6;19:619–33.
18. Cordero MD, Cano-García FJ, Alcocer-Gómez E, de Miguel M, Sánchez-Alcázar JA. Oxidative stress correlates with headache symptoms in Fibromyalgia: Coenzyme Q 10 effect on clinical improvement. PLoS One. 2012;7(4):6–11.
19. Greenberg S, Frishman WH. Co-enzyme Q10: A new drug for cardiovascular disease. J Clin Pharmacol. 1990;30(7):596–608.
20. Littarru GP, Tiano L. Clinical aspects of coenzyme Q10: An update. Nutrition [Internet]. 2010;26(3):250–4. Available from: http://dx.doi.org/10.1016/j.nut.2009.08.008
21. Witting PK, Pettersson K, Letters J, Stocker R. Anti-atherogenic effect of coenzyme Q10 in apolipoprotein E gene knockout mice11Dedicated to Lars Ernster for his pioneering contributions to research into coenzyme Q and his genuine passion and enthusiasm we were privileged to experience. Free Radic Biol Med. 2000;29(3–4):295–305.
22. Qu H, Guo M, Chai H, Wang WT, Ga ZY,

Shi DZ. Effects of coenzyme Q10 on statin-induced myopathy: An updated meta-analysis of randomized controlled trials. J Am Heart Assoc. 2018;7(19):1–11.
23. Rosenfeldt FL, Haas SJ, Krum H, Hadj A, Ng K, Leong JY, et al. Coenzyme Q10 in the treatment of hypertension: A meta-analysis of the clinical trials. J Hum Hypertens. 2007;21(4):297–306.
24. Shults CW. Effects of Coenzyme Q10 in Early Parkinson Disease. Arch Neurol. 2002;59(10):1541.
25. Naia L, Ribeiro MJ, Rego AC. Mitochondrial and metabolic-based protective strategies in Huntington's disease: The case of creatine and coenzyme Q. Rev Neurosci. 2012;23(1):13–28.
26. Wadsworth TL, Bishop JA, Pappu AS, Woltjer RL, Quinn JF. Evaluation of coenzyme Q as an antioxidant strategy for Alzheimer's disease. J Alzheimer's Dis. 2008;14(2):225–34.
27. Bank G, Kagan D, Madhavi D. Coenzyme Q 10: Clinical update and Bioavailability. Complement Health Pract Rev. 2011;16(2):129–37.
28. Hernández-Ojeda J, Cardona-Muñoz EG, Román-Pintos LM, Troyo-Sanromán R, Ortiz-Lazareno PC, Cárdenas-Meza MA, et al. The effect of ubiquinone in diabetic polyneuropathy: A randomized double-blind placebo-controlled study. J Diabetes Complications [Internet]. 2012;26(4):352–8. Available from: http://dx.doi.org/10.1016/j.jdiacomp.2012.04.004
29. Balercia G, Buldreghini E, Vignini A, Tiano L, Paggi F, Amoroso S, et al. Coenzyme Q10 treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. Fertil Steril [Internet]. 2009;91(5):1785–92. Available from: http://dx.doi.org/10.1016/j.fertnstert.2008.02.119
30. Florou P, Anagnostis P, Theocharis P, Chourdakis M, Goulis DG. Does coenzyme Q10 supplementation improve fertility outcomes in women undergoing assisted reproductive technology procedures? A systematic review and meta-analysis of randomized-controlled trials. J Assist Reprod Genet. 2020;37(10):2377–87.
31. Markley HG. CoEnzyme Q10 and riboflavin: the mitochondrial connection. Headache. 2012;52 Suppl 2:81–7.
32. Tiano L, Busciglio J. Mitochondrial dysfunction and Down's syndrome: Is there a role for coenzyme Q 10? BioFactors. 2011;37(5):386–92.
33. Hernández-camacho JD, Bernier M, López-lluch G. Coenzyme Q 10 Supplementation in Aging and Disease. 2018;9(February):1–11.
34. Fisher GJ, Kang S, Varani J, Bata-Csorgo Z, Wan Y, Datta S, et al. Mechanisms of photoaging and chronological skin aging. Arch Dermatol. 2002;138(11):1462–70.
35. Cummins JM. The role of mitochondria in the establishment of oocyte functional competence. Eur J Obstet Gynecol Reprod Biol. 2004;115(SUPPL.):23–9.
36. Martelli A, Testai L, Colletti A, Cicero AFG. Coenzyme Q10: Clinical applications in cardiovascular diseases. Antioxidants. 2020;9(4):1–26.