



# Coenzyme Q10 and/or Vitamin E Supplementation for Polycystic Ovarian Syndrome

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## ABSTRACT

Excessive androgens, insulin resistance, and changing estrogen levels in polycystic ovarian syndrome (PCOS) could affect the metabolic markers and lead to the increment of oxidative stress level. Coenzyme Q10 (CoQ10) is an organic molecule ubiquitously present in cell membranes and mitochondria. It is known to inhibit the peroxidation of cell membrane lipids and reduce the oxidation of circulating lipids, decreasing oxidative stress-induced cell damage. Vitamin E, an exogenous lipid-soluble molecule with antioxidant property, is a direct free radical scavenger that protects the cell membrane from lipid peroxidation and activates intracellular antioxidant enzymes. Some studies suggest that the co-supplementation of CoQ10 and vitamin E has strong synergistic outcomes in women with PCOS. The combination of those antioxidant agents is more likely to have better reproductive and metabolic outcomes.

**Keywords:** Coenzyme Q10, CoQ10, PCOS, polycystic ovarian syndrome, vitamin E.

## ABSTRAK

Kadar androgen berlebih, resistensi insulin, dan perubahan kadar estrogen pada sindrom ovarium polikistik (SOPK) dapat memengaruhi parameter metabolik dan meningkatkan kadar stres oksidatif. Koenzim Q10 (CoQ10) merupakan molekul organik yang banyak ditemukan di dalam membran sel dan mitokondria. Molekul tersebut diketahui dapat menghambat proses peroksidasi lipid membran sel dan mengurangi proses oksidasi lipid dalam sirkulasi, sehingga berdampak mengurangi kerusakan sel yang disebabkan oleh reaksi stres oksidatif. Vitamin E yang merupakan molekul eksogen larut lemak berperan melindungi membran sel dari proses peroksidasi lipid dan membantu aktivasi enzim antioksidan intraseluler. Beberapa penelitian menunjukkan bahwa ko-suplementasi CoQ10 dan vitamin E memberikan dampak signifikan pada wanita dengan SOPK. Kombinasi dua antioksidan tersebut memberikan efek lebih baik dibandingkan pemberian terpisah. **Christian Bobby Irianto, Erick Giovanni Prasetyadi. Suplementasi Koenzim Q10 dan/atau Vitamin E untuk Sindrom Ovarium Polikistik.**

**Kata kunci:** CoQ10, koenzim Q10, sindrom ovarium polikistik, SOPK, vitamin E.

## Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common conditions in reproductive-age women, with a prevalence ranging from 8 - 13%.<sup>1,2</sup> Updated in 2018 by the European Society of Human Reproduction and Embryology (ESHRE) and American Society of Reproductive Medicine (ASRM), PCOS is defined by the presence of two of the three criteria: (a) clinical and/or biochemical hyperandrogenism, (b) ovulatory dysfunction, and (c) polycystic ovaries on ultrasound.<sup>1</sup> Women with PCOS are at higher risk of metabolic abnormalities, obesity, dyslipidemia, hypertension, and cardiovascular diseases (CVD).<sup>2,3</sup> Overweight and obesity seem to exacerbate the progression of various PCOS-related dysfunction, such as anovulation, hyperandrogenism, insulin resistance (IR),

inflammation, and oxidative stress.<sup>4,5</sup> Another sufficient evidence showed that PCOS is strongly correlated with cardiometabolic abnormalities and higher CVD risk.<sup>3</sup>

Oxidative stress is known to contribute to the pathogenesis of PCOS and its metabolic associations.<sup>6</sup> The cell may use various protective mechanisms such as the enzymatic and non-enzymatic antioxidant defenses to defend and repair itself.<sup>7,8</sup> Oxidative stress occurs when there is an imbalance between the oxidants and antioxidants.

Coenzyme Q10 (CoQ10) is known as a potent antioxidant in both reduced (ubiquinol) and oxidized (ubiquinone) forms.<sup>9</sup> It is an organic molecule in cell membranes, mostly in the mitochondria, known for withstanding

continuous reduction and oxidation cycles, which is more likely to inhibit protein, DNA, and lipid oxidation.<sup>10,11</sup> Vitamin E is known for its ability to antagonize oxidative stress by inhibiting the activity of phospholipase A and lipoxygenase function in the reproductive system; the antioxidant effect of vitamin E might reduce the senile oxidative stress reaction that has a detrimental effect on the number and quality of oocytes.<sup>12</sup>

It is hypothesized that the combination of CoQ10 and vitamin E might have an additional effect on metabolic profile and is more likely to have better outcomes than either alone.<sup>2</sup> This review aims to summarize various recent studies on supplementation of CoQ10, vitamin E, or both in PCOS and the possible mechanisms of their therapeutic effects.

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### Polycystic Ovarian Syndrome (PCOS)

Polycystic ovarian syndrome (PCOS) is one of the most common endocrinopathies in women during their reproductive age, and it has significant reproductive, metabolic, and psychological impact.<sup>1</sup> This syndrome is known to be associated with rapid pulses of gonadotropin-releasing hormone (GnRH), excessive luteinizing hormone (LH), and insufficient follicle-stimulating hormone (FSH), which lead to excessive ovarian androgen production and ovulatory dysfunction.<sup>13</sup> The etiology of PCOS is not clearly understood, but it is thought to be multifactorial.<sup>1,2,13</sup>

Insulin resistance (IR) and compensatory hyperinsulinemia are found in 75% to 95% women with PCOS, accompanied by severe metabolic disorders and their complications.<sup>4</sup> IR stimulates ovarian and adipose tissue androgen production and inhibits sex hormone-binding globulin (SHBG) synthesis in the liver through hyperinsulinemia.<sup>14</sup> Along with IR, risk of diabetes mellitus, gestational diabetes, and impaired glucose tolerance (IGT) also significantly increased in women with PCOS. This risk is known to be independent of body mass index (BMI), age, and ethnicity, which add to further health and cost burden.<sup>1</sup>

A study conducted by Chen, *et al.*<sup>5</sup> indicates that oxidative stress (OS) has an impact on metabolic diseases and thus contributes to the pathogenesis of PCOS. The oxidative stress results in high levels of reactive oxygen species (ROS) and therefore may cause further cell damage.<sup>4,5</sup> ROS is derived from cell metabolism product, particularly from the oxygen molecule, including oxygen ions, free radicals, and peroxides. This is a worrisome product because of its ability to oxidize protein, lipid, and also DNA.<sup>5</sup>

Various studies in women with PCOS also showed increased malondialdehyde (MDA) levels, a common marker of oxidant-mediated damage, and reduced capability to scavenge harmful free radicals, known as the total antioxidant capacity (TAC).<sup>4</sup> The concentration of MDA was significantly higher in infertile PCOS than fertile PCOS women.<sup>13</sup> MDA is commonly known as an aldehyde derived from the peroxidation of polyunsaturated fatty acids. It has the role to form the "advanced lipoxidation end-products," which is considered to be a biomarker of OS.<sup>6</sup>

Higher ROS levels found in mitochondria of PCOS women are related to mitochondrial dysfunction, which may lead to oxidative damage to DNA and other intracellular abnormalities. Thus, supplementing antioxidants has been proposed to be one of the strategies to improve mitochondrial function.<sup>15</sup>

### Coenzyme Q10 (CoQ10)

CoQ10, in both reduced (ubiquinol) and oxidized (ubiquinone) forms, is a liposoluble benzoquinone with an important role in eliminating free radicals and inhibiting the oxidation of lipid as well as protein.<sup>9,10</sup> As an antioxidant found in most aerobic microorganisms, CoQ10 has a critical role in cellular biogenesis and oxidative balance, particularly in the inner mitochondrial layer, either by scavenging ROS or by regenerating vitamin E, which may further inhibit the lipid peroxidation process.<sup>16</sup>

CoQ10 is provided with notable antioxidant and anti-inflammatory properties; its depletion can worsen the unwanted consequence of inflammatory processes.<sup>9</sup> Current studies showed that supplementation of CoQ10 significantly increases the levels of TAC and Superoxide Dismutase (SOD) activities, as well as decreases the level of MDA.<sup>16</sup> CoQ10 may benefit women with PCOS by modulating the insulin and adiponectin receptors, thus improving glycemic control and enhancing triglyceride lipolysis. These effects emphasize the importance of CoQ10 supplementation in glucose metabolism and lipid profile for PCOS women.<sup>10</sup>

Mitochondria are known to have a significant

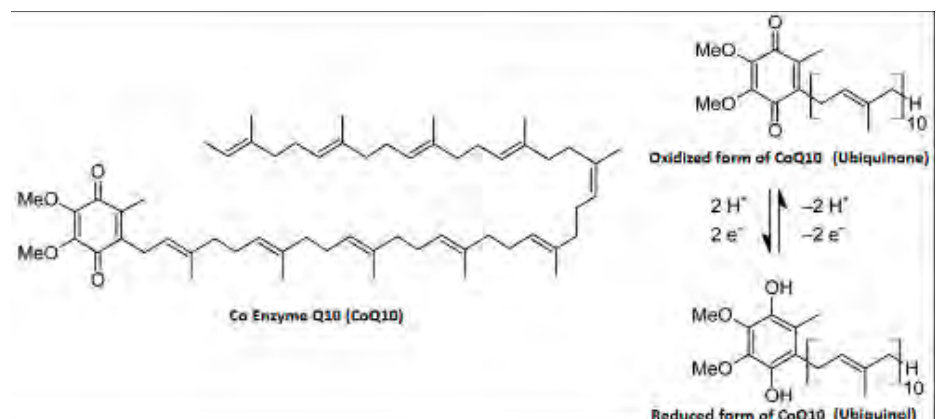
role in the fertilization process and embryonic development. CoQ10, which is mostly found in the inner membrane of mitochondria, shows a direct effect on cellular ATP production and results in ovarian function improvement. In addition, CoQ10 also acts as an antiapoptotic, while apoptosis is known as the main mechanism of follicular atresia.<sup>11,15,17</sup>

It has been demonstrated that up to 900 mg/day of CoQ10 supplementation is well tolerated and relatively safe for healthy adult women with PCOS.<sup>15</sup>

### Vitamin E

Vitamin E, also known as  $\alpha$ -tocopherol, is a lipid-soluble substance with antioxidant properties. This substance can antagonize the oxidative stress reactions caused by free oxygen radicals and antioxidant imbalance through non-enzymatic processes. Studies showed that vitamin E deficient women are prone to have pregnancy-related problems, such as infertility, miscarriage, premature delivery, hypertension-related pregnancy problems.<sup>12</sup>

A study on the effects of magnesium and vitamin E co-supplementation showed a significant increase in total antioxidant capacity (TAC);<sup>18</sup> the combination also significantly reduces hirsutism and the level of serum high-sensitivity C-reactive protein.<sup>18</sup> Another study showed a significant decrease in serum triglycerides following vitamin E supplementation compared to the placebo group.<sup>3</sup> The mechanism of vitamin E's capability to improve lipid profile is still unknown. However, the antioxidant property of vitamin E is postulated to improve lipid



Picture 1. Chemical structure of CoQ10<sup>9</sup>



## ANALYSIS



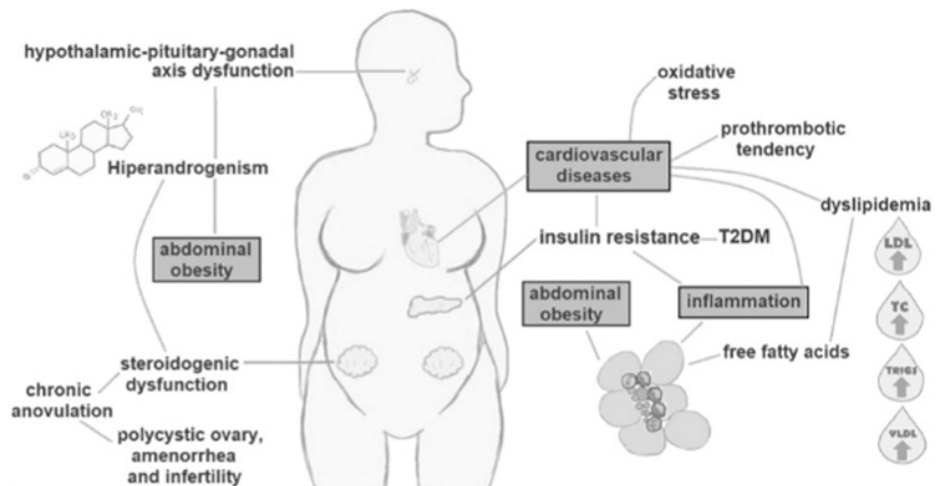
metabolism by reducing oxidative stress reactions. The capability of vitamin E to suppress various signaling pathways such as JAK-STAT3, NF- $\kappa$ B, and JAK-signal transducer also contributes to its anti-inflammatory and antioxidative effects.<sup>3,18</sup> A synergistic approach was also found between omega-3 fatty acids and vitamin E after a 12-week co-supplementation on women with PCOS, which resulted in significant improvement in insulin resistance indices and level of total and free testosterone.<sup>19</sup> The doses of vitamin E used in various studies are quite diverse, ranging from 100 mg/day to 400 mg/day.<sup>12,18</sup>

There is only a few research on the effect of vitamin E alone on PCOS patients.<sup>3,12,18</sup> As an antioxidant capable of reducing pro-oxidative stress factors and promoting antioxidative stress markers, vitamin E plays an essential role in reducing oocyte apoptosis, improving oocyte maturation and endometrial proliferation.<sup>3,12</sup> Additionally, one study with multiple micronutrients (MMN) supplementation also showed a supportive effect in women with anovulatory infertility or unexplained infertility who were undergoing ovulation induction.<sup>12</sup> These antioxidants warrant further research to assess which antioxidant or its combination is superior to another.<sup>12</sup>

### CoQ10 and Vitamin E

Co-supplementation of CoQ10 and vitamin E might have a robust synergistic outcome on metabolic profile and also as antioxidants in women with PCOS than either alone.<sup>2,3</sup> Ubiquinol, a reduced form of CoQ10, is known to prevent vitamin E oxidation.<sup>2,11,15</sup> It is also known for the ability to regenerate vitamin E back from its oxidized form, which later can lead to the inhibition of lipid peroxidation.<sup>11,15,17</sup>

Patients with PCOS are more prone to endocrine and metabolic profile impairment.<sup>2,14</sup> One study<sup>2</sup> showed that CoQ10 supplementation for 8 weeks, with or without additional vitamin E supplementation, resulted in serum fasting blood sugar



**Figure 2.** Biochemical pathway involved in the pathophysiology of PCOS.<sup>13</sup>

T2DM = Type 2 Diabetes Mellitus; LDL = Low-Density Lipoprotein; TC = Total Cholesterol; Trigs = Triglycerides; VLDL = Very Low-Density Lipoprotein

and homeostatic model assessment of insulin resistance (HOMA-IR) reduction.<sup>2,19</sup> Another 8-week CoQ10 and vitamin E co-supplementation study showed a significant reduction in serum total testosterone levels and free androgen index (FAI).<sup>2</sup> Moreover, this co-supplementation provided some beneficial effect on sex hormone binding globulin (SHBG) level but failed to show any effect with the supplementation of either CoQ10 or vitamin E alone.<sup>2,3,20</sup>

Hyperandrogenemia is one of many key pathogenic roles in PCOS. It is strongly associated with insulin resistance and androgen excess.<sup>2,12</sup> The combination of CoQ10 and vitamin E supplements may presumably improve sex hormones concentrations by improving insulin resistance. It is suggested that the association of insulin resistance and sex hormones concentration comes in two key pathway: (1) Insulin resistance is correlated with SHBG synthesis reduction and a greater level of free androgens; (2) Insulin resistance increases androgen production through a synergistic action with Luteinizing Hormone (LH) in theca cells.<sup>2</sup>

Reportedly, CoQ10 and vitamin E supplementation is also known to have

some positive impact on cardiovascular risk. Using the ratio of Atherogenic Coefficient (AC) and Atherogenic Index of Plasma (AIP), both are new potential markers to predict cardiovascular risk. The supplementation of CoQ10 and/or vitamin E could reduce AIP and provided a more significant reduction in AC.<sup>3</sup> A study<sup>3</sup> showed that neither CoQ10 nor vitamin E alone had any significant role on HDL-C or LDL-C levels. In contrast, a significant improvement in HDL-C and LDL-C levels was obtained by co-supplementing CoQ10 and vitamin E altogether.<sup>3,10</sup>

### Conclusion

PCOS is associated with increased oxidative stress that may result in some significant reproductive and metabolic issues. CoQ10 and vitamin E are known as potent antioxidants, and both work synergistically to amplify the beneficial effects. Co-supplementation of CoQ10 and vitamin E in PCOS patients showed a more promising result than supplementation with either CoQ10 or vitamin E alone. Further studies are needed to determine the appropriate dose for each supplement, along with another antioxidant or its combination that may work concomitantly for PCOS patients.

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