Coenzyme Q₁₀: A Potential Adjunct for Treatment of Antiphospholipid Syndrome and Recurrent Miscarriage

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Abstract: Background: Recurrent Miscarriage (RM) is one of the most frustrating clinical situations wherein most of the cases, neither the engaged obstetrician nor suffering couples know the exact etiology and cause of the disease. About 10-15% of women with RM diagnosed with antiphospholipid syndrome (APS) are characterized by the marked presence of antiphospholipid antibodies (aPLa). There are several scientific reports available on the association between APS and RM; however, scanty data available about the beneficial role of coenzyme Q₁₀ (CoQ₁₀) in APS and APS mediated RM. In the present attempt, we tried to gather information to explain the possible associations between the role of CoQ₁₀ in RM and APS.

Methods: We collected peer-reviewed literature using keywords; antiphospholipid syndrome, CoQ₁₀, endothelial dysfunction, oxidative stress and recurrent miscarriage in online electronic databases, such as Web of Science, Science Direct, Google Scholar, PubMed and Medline. The qualitative analysis of content was done by summarizing interventions and findings of included studies, on the basis of which a conceptual framework was prepared for this narrative review.

Results: The beneficial role of CoQ₁₀ in diverse pathological conditions has been summarized and the evidence suggests that CoQ₁₀ being a potent antioxidant helps in the amelioration of free radical-mediated aPLa production, endothelial damage and mitochondrial dysfunction. The supplementation of CoQ₁₀ overcomes the immune dysregulation in idiopathic RM and APS; thus could be a possible therapeutic adjunct in such diseases.

Conclusion: Based on this review, further comprehensive studies may be conducted to illuminate the beneficial therapeutic effects of supplementing CoQ₁₀ on possible modifiable pathways involved in the progression of RM and APS.

Keywords: Antiphospholipid syndrome, Coenzyme Q₁₀, endothelial dysfunction, oxidative stress, recurrent miscarriage, gestation.

1. INTRODUCTION

Recurrent Miscarriage (RM) is defined as three or more consecutive pregnancy losses prior to 20 weeks of gestation, occurring in 1-3% of women [1, 2]. Various abnormalities are associated with the pathogenesis of RM including chromosomal anomalies, hormonal imbalance, uterine abnormalities, infections, deranged immune system and autoimmune disorders, particularly associated with antiphospholipid antibodies (aPLa) [3]. However, antiphospholipid syndrome (APS) is diagnosed in about 10-15% of women suffering from RM [4] and approximately 50% of cases are idiopathic. In 2006, updated classification criteria of APS includes three or more unexplained consecutive RM before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded. Whereas, fetal losses ≥ 10 weeks of gestation and before 24 weeks of gestation are also strongly associated with aPLa and lupus anticoagulant respectively [5, 6].

Several immune mechanisms are involved in the establishment of the active multifactorial maternal-foetal tolerance [7]: deviation of the systemic maternal immune system toward T helper type 2 (Th2 type) [8], expression of the non-classical HLA-G molecules by trophoblasts thus inhibiting maternal NK cell attack [9], promoting apoptosis of activated Fas⁺ maternal lymphocytes through FasL expression by the syncytiotrophoblast [10, 11], down-
regulation of NKG2D receptor on maternal peripheral blood mononuclear cells (PBMC) by placental exosomes carrying NKG2D ligands [12, 13] and indoleamine-2,3-dioxygenasedemediated tryptophan degradation that suppresses the immune response by the inhibition of T lymphocyte proliferation [14]. This review, however, is emphasized mainly on the role of CoQ10: thrombophilic mechanism, mitochondrial and endothelial dysfunction and oxidative stress in RM and APS. There is no such clear evidence about the cause of this syndrome and mechanistic pathways involved in its occurrence due to the complexity of auto-antibodies and their multiple target sites [15]. Therefore, instead of acellular level, a multi-targeted approach should be envisaged at the molecular level at which aPLa participates actively and ultimately contributes to increased RM cases burden. Since, CoQ10 is known to correct all the aforesaid abnormalities viz. oxidative stress, endothelial and mitochondrial dysfunction etc. being a potent antioxidant and also an important part of the mitochondrial electron transport chain. Thus, an association has been made on the basis of available scientific literature mainly emphasized on the role of APS in RM and its overcome strategies.

1.1. Role of APS in RM

APS is an autoimmune thrombophilic condition that is marked by the presence of antibodies that recognize and attack phospholipid-binding proteins, rather than phospholipid itself. Several obstetric complications including RM, early delivery, oligohydramnios, prematurity, intraterine growth restriction, fetal distress, fetal or neonatal thrombosis, pre-eclampsia/ eclampsia, HELLP syndrome, arterial or venous thrombosis and placental insufficiency are related to APS [16]. Albeit APS mediated fetal loss emerged as the most apparent reason in recent decades, aPLa have shown to increase the cellular adhesion molecules (CAMs) such as intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and E-selectin in vitro [17]. In addition, tissue factor (TF) up-regulation has been advocated as an important mechanism to explain the pro-thrombotic effects of aPLa [18, 19] that may lead to fetal loss/ miscarriage. Vascular Endothelial Growth Factor (VEGF) may stimulate TF expression in monocytes through its receptor tyrosine kinase fms like tyrosine kinase (Flt-1) and its expression was (VEGF & Flt-1) found to be increased in APS patients [20]. aPLa induces TF expression by activating, simultaneously and independently, the phosphorylation of MEK-1/ ERK proteins, and the p38 MAPK-dependent nuclear translocation and activation of nuclear factor kappa B (NFkB) / Rel proteins [21]. Convincing evidence exists that aPLa induces endothelial cells and monocyte activation and a pro-coagulant and pro-inflammatory phenotype in vitro and in vivo. Also, oxidative stress-induced modification of phospholipids has been linked to the formation of aPLa in the APS [22].

1.2. Role of Endothelial Dysfunction and Oxidative Stress in APS Mediated RM

Apart from the thrombophilic condition in APS patients and dysregulated immune system; endothelial dysfunction is one of the underlying features of RM. Endothelial dysfunction is characterized by reduced vasodilation, which is a pro-inflammatory state and shows pro-thrombotic properties. It is associated with several types of cardiovascular disease, such as hypertension, coronary artery disease, chronic heart failure, peripheral artery disease, diabetes, and chronic renal failure where the mechanism of action involves nitric oxide generation and oxidative stress [23]. However, its implications in pre-eclampsia and RM have also been studied [24]. Oxidative stress-induced damage has been hypothesized to play a role in spontaneous abortion, idiopathic recurrent pregnancy loss, hydatidiform mole, defective embryogenesis, and drug-induced teratogenicity [22]. Increased ROS resulting in the oxidation of phospholipids and low density lipoproteins, thus subsequently leads to the altered antigenic properties of phospholipids and aPLa production. The role of ROS in the aPLa mediated pro-adhesive state was also studied and found that it acts as the second messenger by activating p38 mitogen-activated protein kinase (p38 MAPK) thereby helping in controlling VEGF up-regulation [25]. The human placenta is hemochorial and an adequate uteroplacental circulation is required for successful pregnancy. There are reports which demonstrated that 10-12 weeks of gestation is a crucial time for the establishment of maternal circulation in the placenta [26, 27]. Early stages of development i.e. right from fertilization to differentiation takes place in micro-oxygen environment to protect the embryo from harmful effects of free radicals. Further, aberrant placentaation also seems to be involved in early spontaneous abortion [28]. Abnormal placentation leads to placental oxidative stress and syncytiotrophoblast dysfunction, and it has also been proposed as a cause of early abortion [22]. Increased generation of active oxygen forms was demonstrated in granulocytes with the help of spontaneous luminal dependent chemiluminescence in the recurrent abortion patients compared to healthy women [29] and the immunological effects of antioxidant have shown that vitamin E not only prevented fetal wastage but also optimized IL6 and VEGF placental levels for prevention of abortion in mice [30]. Anticardiolipin antibodies (aCL) also seem to play an important role in oxidative stress by inducing nitric oxide (NO) and superoxide production, resulting in enhanced levels of plasma peroxynitrite, a powerful pro-oxidant substance [31].

2. COENZYME Q10 (COQ10): AN ANTIOXIDANT

CoQ10 also known as ubiquinone is endogenous lipophilic molecule composed of a redox active quinone ring and a hydrophobic tail. It participates in the transfer of electrons in the mitochondrial respiratory chain and increases the expression of mitochondrial uncoupling proteins, an effect which is anti-apoptotic that leads to a reduction in free radical generation i.e. antioxidant effect. The reduced form of CoQ10 is a powerful antioxidant that prevents the free radicals mediated oxidation of lipids within the mitochondrial membrane [32]. It is transported in the plasma primarily by low-density lipoprotein (LDL) while some proportion is also carried by high density lipoprotein (HDL) and very low density lipoprotein (VLDL) [33]. There is evidence that CoQ10 has anti-inflammatory properties: decreasing the secretion of pro-inflammatory cytokine tumor...
necrosis factor-alpha (TNF-α) and chemokines like Macrophage inflammatory protein-1 alpha (MIP-1α) and Regulated upon activation, normal T cell expressed and secreted (RANTES) [34, 35]. Earlier, Groneberg et al. studied the molecular mechanisms to explain the pleiotropic effects of CoQ10 on human CaCo-2 cells line. They stated that CoQ10 targets the expression of many genes involved in cell signaling, metabolism, embryonic development and nutrient transport [36]. Later on, in *silico* analysis suggested that signaling pathways of G-protein coupled receptors, JAK/ STAT, and Integrin contain a number of CoQ10 sensitive genes. Further analysis revealed the involvement of CoQ10 in the regulation of ILS, thrombin, vitronectin, vitronectin receptor, and C-reactive protein via the transcription factor NFκB1 and cell culture experiment results showed the anti-inflammatory effect of CoQ10 via NFκB1 dependent gene expression [37]. Also, there is considerable data available suggesting its beneficial role in a broad spectrum of pathological conditions such as preventing atherosclerosis, cardiac failure, hypertension, exercise-induced muscular injury, improving endothelial function, sperm motility, reducing the incidence of pre-eclampsia and mitigate migraine as well. These properties constitute the basis for its clinical applications and as a food supplement [38].

2.1. Role of CoQ10 in APS and Endothelial Dysfunction

The effect of CoQ10 in APS has been recently studied and it was shown that the CoQ10 pre-incubation of healthy monocytes before aPLa treatment decreased oxidative stress, altered membrane potential and reduced the expression of Tissue factor (TF), Vascular endothelial growth factor (VEGF) and its receptor Flt-1 [39]. Protease-activated receptors (PARs) are the mediators of TF signaling activities in APS [40, 41]. Accordingly, PAR 1 and PAR 2-induced signaling is directly involved in the constitutive p38 MAPK activation [42]. Thus, an increased expression of pro-inflammatory cytokine VEGF and its receptor Flt-1 was found in patients with aPLa [20]. CoQ10 was found to reduce the PAR-2 expression thereby decreasing the p38 MAPK activation and subsequent NFκB activation [39].

CoQ10 was reported to have a direct effect on endothelial function also. Oral CoQ10 supplementation has been shown to ameliorate cardiac contractility and endothelial dysfunction in coronary heart failure patients [43]. CoQ10 also improves endothelium-dependent relaxation and endothelium-bound extracellular superoxide dismutase (ecSOD) activity by counteracting the rate of nitric oxide to peroxynitrite by superoxide anions [44]. A meta-analysis of randomized controlled trials also quantified the effect of CoQ10 on the endothelial function which was found beneficial in patients with endothelial dysfunction [45].

3. KEY RESEARCH QUESTIONS

- Whether, CoQ10 can favorably alter the pro-thrombotic cytokines/ chemokines milieu and adhesion molecules induced by aPLa which results in repeated pregnancy losses in known cases of APS?
- Whether, CoQ10 being a powerful antioxidant, can decrease oxidative stress thereby preventing endothelial damage, which has been implicated in idiopathic RM cases?

An increased expression of cell adhesion molecules and tissue factors *via* activation of endothelial cells, monocytes, platelets and complement system is the hallmark of pro-thrombotic event. APS is ensayed by mitochondrial dysfunction and subsequent activation of nuclear factor kappa B-1 (NFκB-1) gene *via* phosphorylation of p38 mitogen-activated protein kinase resulting in pro-thrombotic/ pro-inflammatory gene expression that further contributes to endothelial dysfunction and RM. Also, an imbalance between the pro-oxidant/ antioxidants milieu resulting in the reactive oxygen species (ROS) mediated endothelial damage is another underlying feature of APS mediated RM. CoQ10, being a powerful antioxidant, prevents oxidative damage by scavenging free radicals and assists in regeneration of Vitamin E. CoQ10 exerts its anti-inflammatory effects *via* NFκB-1 dependent gene expression thereby decreasing the production of pro-inflammatory cytokines. Low levels of CoQ10 were found to be associated with high levels of inflammatory cytokines and vascular endothelial biomarkers. Furthermore, CoQ10 also ameliorate overexpression of pro-thrombotic and endothelial markers and mitochondrial dysfunction, the characteristic features of APS (Fig. 1). In a recent randomized placebo-controlled clinical trial, CoQ10 supplementation in patients with APS beneficially modulated overexpressed inflammatory and thrombotic markers without showing any clinically significant side-effects [46]. Earlier, Noia G [47] & Noia G [48] in two different studies measured the levels of CoQ10 in RM cases and found it to be low when compared to normal fertile women. In addition, the lower CoQ10 levels have also been reported in pre-eclampsia women suggesting its potential use as an early diagnostic biomarker for the prediction of pre-eclampsia [49]. Moreover, CoQ10 has already been used clinically during pregnancy and its supplementation reduced the risk of pre-eclampsia in women who were at increased risk for the condition [50]. Earlier, the same group quantified plasma CoQ10 levels in women with pre-eclampsia and found these to be significantly lower than in healthy pregnant women [51]. Recent findings from our laboratory corroborate the promising immunomodulatory effects of CoQ10 in idiopathic recurrent miscarriages. The experiments performed on PBMCs isolated from women with the history of recurrent pregnancy loss revealed that IFN-γ- producing T cells and pro-inflammatory cytokine levels as well as ROS levels, were significantly increased. However, exposure of PBMCs to CoQ10 resulted in a dramatic reversal of such effects [52]. In another study, CoQ10 deficiency was found to be associated with neonatal multiorgan failure. It would be important to evaluate the potential therapeutic effects of CoQ10 supplementation in pregnant women with family history showing a homozygous c.545T>G, p.(Met182Arg) alteration in COQ2 resulting in CoQ10 deficiencies [53]. CoQ10 content in amniotic fluid is also associated with obstetrics complications such as fetal growth retardation,
which is consistent with a report linking CoQ10 levels and pregnancy complications [54]. Contrary to the beneficial role of CoQ10 supplementation, an animal study suggested that CoQ10 supplementation in rats increases the oxidative stress during pregnancy [55]. A double blind placebo-controlled randomized trial designed to compare the post-meiotic oocyte aneuploidy rate following in vitro fertilization and intra-cytoplasmic sperm injection in patients supplemented with CoQ10 versus placebo revealed no significant difference in outcome [56]. The later findings are consistent with earlier results from the same group highlighting the central role of CoQ10 in ameliorating mitochondrial dysfunction and oxygen free radicals in the process of oocyte aging and senescence [57]. Owing to this, it is rational to believe that ROS-mediated aPLa production and endothelial damage as well as mitochondrial dysfunction are pathophysiologic indicators of APS, ultimately resulting in RM. CoQ10 supplementation could thus be beneficial to overcome the effects of altered antioxidant enzymes, pro-thrombotic/ pro-inflammatory markers and endothelial/ mitochondrial dysfunction. CoQ10 could thus be regarded as a therapeutic adjunct and might open new therapeutic strategies.

**CONCLUSION**

Based on the foregoing, it is increasingly clear that CoQ10 may act as a key player in the management of APS, APS-mediated RM and idiopathic RM. Hence, CoQ10 supplementation may prove to be a rational therapeutic option in the management of these complex and debilitating clinical conditions.

**ABBREVIATIONS**

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>aPLa</td>
<td>Anti-Phospholipid Antibody</td>
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<td>APS</td>
<td>Antiphospholipid Syndrome</td>
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<td>CoQ10</td>
<td>Coenzyme Q10</td>
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<tr>
<td>Flt-1</td>
<td>Fms Like Tyrosine Kinase</td>
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<tr>
<td>NFkB</td>
<td>Nuclear Factor Kappa B</td>
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<td>RM</td>
<td>Recurrent Miscarriage</td>
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<td>TF</td>
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<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
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**CONSENT FOR PUBLICATION**

Not applicable.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES


