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CLINICAL ARTICLE

Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia

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ABSTRACT

Objective: To assess whether supplementation with Coenzyme Q10 (CoQ10) during pregnancy reduces the risk of pre-eclampsia. *Methods:* Women at increased risk of pre-eclampsia were enrolled in a randomized, double-blind, placebo-controlled trial. Women were assigned to receive 200 mg of CoQ10 or placebo daily from 20 weeks of pregnancy until delivery. The primary outcome was rate of pre-eclampsia. Statistical analyses were by intention-to-treat. *Results:* Of the 235 women enrolled in the trial, 118 were randomized to receive CoQ10 and 117 received a placebo. A total of 197 (83.8%) women were followed-up. The overall rate of pre-eclampsia was 20% (n = 47). Thirty women (25.6%) in the placebo group developed pre-eclampsia compared with 17 women (14.4%) in the CoQ10 group, and this reduction was significant ($P = 0.035$) (relative risk [RR] 0.56; 95% confidence interval [CI], 0.33–0.96). *Conclusion:* Supplementation with CoQ10 reduces the risk of developing pre-eclampsia in women at risk for the condition.
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1. Introduction

Pre-eclampsia is a common disorder of human pregnancy (about 7% of all pregnancies) in which the normal hemodynamic response to pregnancy is compromised. It remains a leading cause of maternal morbidity and mortality and is associated with a significant increase in perinatal mortality [1]. The pathogenesis of pre-eclampsia is still not fully understood, but it is generally accepted that the placenta is implicated in the production of a generalized maternal inflammatory response, which is characterized by activation of maternal vascular endothelial cells and leukocytes [2]. Moreover, in patients with pre-eclampsia, there is an increase in the rate of lipid peroxidation, an increase in lipid availability, and a decrease in the levels of antioxidants such as alpha-tocopherol, ascorbate, beta-carotene, and selenium [2,3].

Coenzyme Q10 (CoQ10) is an essential component of oxidative phosphorylation at mitochondrial level, and also functions to stabilize cell membranes as well as acting as a potent antioxidant [4]. CoQ10 is involved in pathological conditions such as cancer, cardiovascular diseases, and mitochondrial and muscular diseases [5–8].

In 2003, we reported that pregnant women with established pre-eclampsia had significantly lower plasma levels of CoQ10 compared with healthy pregnant and nonpregnant women [9]. These findings have been confirmed by other cohort studies [10,11]. However, these data were collected from women with established pre-eclampsia and, therefore, it was not possible to determine whether the biochemical changes were a cause or a consequence of pre-eclampsia. The aim of the present study was to investigate whether supplementation with CoQ10 during pregnancy reduced the risk of pre-eclampsia in women at increased risk for the condition.

2. Materials and methods

A randomized, double-blind, placebo-controlled trial was conducted between March 6, 2004 and August 27, 2006. The trial recruited women with clinical risk factors for pre-eclampsia (primigravidas, 20 years or younger, and residing in Quito which is at 2800 m altitude). Inclusion criteria were women between 16 and 20 weeks of pregnancy (established by date of last menstrual period and confirmed by ultrasound), not currently taking medication and with no known medical disorders, who attended the prenatal clinic at the Hospital Gineco Obstetrico Isidro Ayora, Quito, Ecuador. Women who were taking vitamin supplements were not excluded from the trial. Participants were evaluated every 4 weeks until the 36th week, and then every 2 weeks up to delivery. Whenever possible trial visits coincided with routine prenatal appointments. The study was approved by the Bioethics Committee at the Biomedical Center, Central University of Ecuador. Written informed consent was obtained from all participants.

To ensure double-blind allocation the principle investigator, who was not directly involved with the clinical team, used a random number sequence generated by computer software (Epi Info 6.04, Bethesda, MD, USA) to allocate the participants to either the treatment or placebo group. Neither the trial staff nor the participants knew the treatment allocation. Women randomized to the treatment group received 100-mg softgel capsules containing an enhanced-absorption

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CoQ10 formula (Q-absorb; Jarrow Formulas, Los Angeles, CA, USA). Women in the placebo group received identical-looking softgel capsules produced by the same manufacturer. Both products were packaged in identical plastic bottles identifiable only by the patient allocation number. Each patient was provided with a bottle containing a 1-month supply of trial medication. The women were told to take 2 softgels each day (1 in the morning and 1 in the afternoon). Acceptable compliance was defined as taking at least 80% of the softgels. The women were instructed to leave all remaining softgels in the bottle so that they could be counted later.

At the start of the trial, a 10 mL venous blood sample was collected from each participant to determine baseline plasma levels of CoQ10 and total cholesterol. A 10 mL blood sample was then collected from each trial participant every 4 weeks up to the 36th week and then every 2 weeks until delivery. Samples taken at delivery were obtained when the women were admitted to hospital, before labor started.

The samples were immediately transferred into heparinized polypropylene vials and gently mixed by inversion. Samples were centrifuged at 4 °C for 10 minutes at 1200 ×*g*; the plasma fraction was transferred into another vial and stored in 500 μL aliquots at −40 °C until assayed as previously described [9]. Samples were measured in duplicate and the mean value was used.

Plasma cholesterol was determined in duplicate samples using a spectrophotometer (Eppendorf, Hamberg, Germany) and a Cholesterol Liquicolor test kit (Human GmbH, Wiesbaden, Germany).

The primary outcome in the study was pre-eclampsia, defined as a blood pressure greater than 140/90 mm Hg on at least 2 occasions more than 6 hours apart and proteinuria greater than 300 mg/dL (2+ or greater by dipstick on 2 occasions 4–24 hours apart) appearing in the second trimester of pregnancy [12].

We estimated that a sample size of 206 women would have a statistical power of 80% (2-tailed alpha level of 0.05) to detect a reduction in the risk of pre-eclampsia among the women from 20% to 6%. Data are presented by group as number (%) or mean ± SD as appropriate. Primary outcome (occurrence of pre-eclampsia) is reported by intention-to-treat analysis using the Fisher exact test. Plasma levels of CoQ10 in each group were compared using 1-way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test. Differences in CoQ10 levels between the treatment and placebo group were compared using unpaired *t* test. All analyses were performed using GraphPad InStat version 3.01 for Windows (GraphPad Software, La Jolla, CA, USA). $P<0.05$ was considered significant. The study was registered at: www.clinicaltrials.gov; No. TNC00300937.

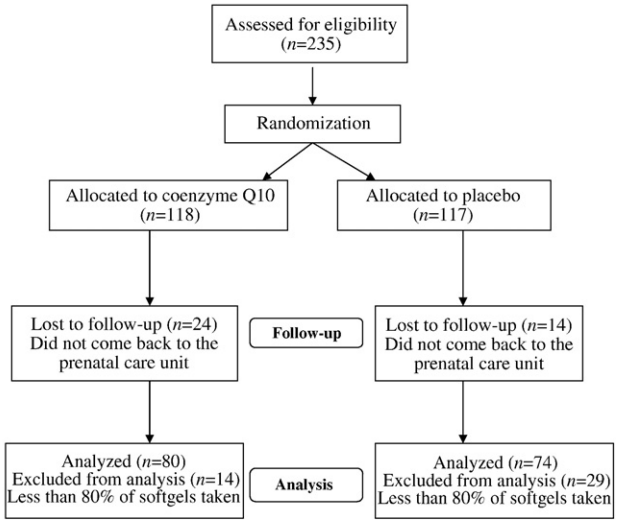

Fig. 1. Trial profile.

Table 1
Demographic and clinical characteristics at enrolment of the women included in the study [a]

Characteristics	CoQ10 group (n = 118)	Placebo group (n = 117)	*P* value
Age, y	17.4 ± 1.9	17.6 ± 2.1	0.44
Systolic blood pressure, mm Hg	105.5 ± 10.3	105.9 ± 10.4	0.76
Diastolic blood pressure, mm Hg	67.0 ± 7.6	66.7 ± 7.9	0.76
Plasma CoQ10 (μmol)/cholesterol (mmol) ratio	0.139 ± 0.06	0.134 ± 0.05	0.48

3. Results

Of 235 women initially enrolled in the trial, 197 (83.8%) attended at least 2 visits and were followed-up (Fig. 1). On the basis of the pill count, 154 women (65.5%) were compliant; the percentage was significantly higher in the CoQ10 supplementation group (85.1% vs 71.9%, $P = 0.02$). Less than 10% of women were taking multivitamin supplements at enrolment. The last woman delivered on September 3, 2006. The demographic characteristics at enrollment did not differ between women in the CoQ10 group and those in the placebo group (Table 1).

Mild gastrointestinal symptoms were the most common adverse effects, but the difference was not significant between the groups (1.3% CoQ10 vs 1.5% placebo; $P = 0.84$). Only 2 pregnancies resulted in preterm delivery (before 36 weeks of pregnancy) and both were in the placebo group. The incidence of low birth weight (less than 2500 g) was similar in the placebo group (12.3%) compared with the CoQ10 group (10.0%). There was no perinatal mortality. Mean birth weight was 2981 ± 387 g in the CoQ10 group compared with 2938 ± 396 g in the placebo group; and the average duration of pregnancy was 39.1 ± 1.4 weeks in the CoQ10 group compared with 39.1 ± 1.5 weeks in the placebo group. Neither birth weight nor pregnancy duration was significantly different between the groups.

The overall rate of pre-eclampsia was 20% ($n = 47$); 17 women in the CoQ10 group and 30 in the placebo group. Supplementation with CoQ10 significantly reduced ($P = 0.035$) the risk for pre-eclampsia from 25.6% in the placebo group to 14.4% in the CoQ10 group (relative risk [RR] 0.56; 95% confidence interval [CI], 0.33–0.96).

Baseline levels of CoQ10 (corrected by plasma cholesterol) were similar in the CoQ10 and placebo groups (Table 1). Plasma levels of CoQ10 increased significantly compared with the baseline value ($P<0.0001$) at each assessment stage in the CoQ10 group (Fig. 2). However, the increase was not significant compared with the levels

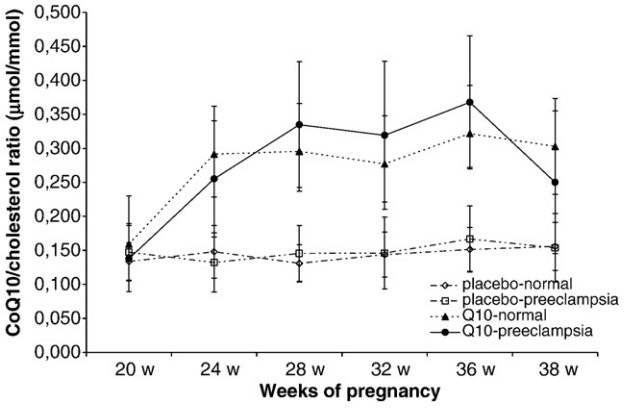

Fig. 2. Plasma coenzyme Q10 (CoQ10)/cholesterol (μmol/mmol) ratio in women with healthy pregnancy and those with pre-eclampsia.

obtained at 24 weeks (Fig. 2). This finding was independent of the development of pre-eclampsia (Fig. 2). Plasma concentrations of CoQ10 in the women in the placebo group who developed pre-eclampsia showed no statistically significant differences compared with women in the placebo group who did not develop the condition (Fig. 2).

There were no statistically significant differences in the demographic characteristics between the women who developed pre-eclampsia and those who did not. The mean systolic blood pressure at 20 weeks of pregnancy in women who later developed pre-eclampsia was 106.5 ± 11.9 mm Hg and the mean diastolic blood pressure was 66.3 ± 8.4 mm Hg. None of the women who developed pre-eclampsia had proteinuria greater than 30 mg/dL at the beginning of the study, but by the end of pregnancy (38–40 weeks), mean systolic blood pressure was 127.5 ± 12.5 mm Hg and mean diastolic blood pressure was 88.5 ± 8.3 mm Hg; all of these women had proteinuria greater than 30 mg/dL.

The 47 women who developed pre-eclampsia had similar baseline plasma levels of CoQ10 compared with the 107 women who remained normotensive at 20 weeks of pregnancy (0.143 ± 0.05 vs 0.136 ± 0.05 μmol/mmol, respectively; $P = 0.42$) and also at 36 weeks of pregnancy (0.271 ± 0.185 vs 0.241 ± 0.14 μmol/mmol, respectively; $P = 0.27$).

4. Discussion

The results of this study support the hypothesis that coenzyme Q10 (100 mg twice a day) supplementation given prophylactically from 20 weeks of pregnancy leads to a reduction in the rate of pre-eclampsia in women at risk for the condition.

Although the rate of pre-eclampsia in the population studied was slightly higher than reported previously [13,14], the baseline plasma concentrations of CoQ10 were similar to those reported in other populations of pregnant or nonpregnant women [15,16].

The role of CoQ10 in placental function is probably related to its activity as an essential component of mitochondrial complexes I and III, in addition to its well-known antioxidant properties [17,18].

Poor placentation is an important predisposing factor for pre-eclampsia. The proposed "2-stage model" [19] in which reduced placental perfusion (stage 1) leads to the maternal syndrome (stage 2) is likely to provide a simplified, yet largely accurate, description of the origin of severe early-onset pre-eclampsia, but may be less relevant for later-onset milder pre-eclampsia [20]. The proposed role of the placenta in the pathology of pre-eclampsia is also strongly supported by the rapid resolution of symptoms after delivery.

In 3 large studies [21–23] conducted with women at high risk for pre-eclampsia, high doses of vitamin C and vitamin E showed a lack of efficacy in preventing the condition, despite consistent evidence for a state of oxidative stress [2,3]. However, the absence of benefit and evidence of unfavorable outcomes in those studies cannot be extrapolated to other antioxidants, including CoQ10. These findings should not detract from the potential importance of oxidative stress in pre-eclampsia.

On the basis of these studies and the analysis of a further 7 studies, a recent Cochrane meta-analysis [24] does not support routine antioxidant supplementation during pregnancy to reduce the risk of pre-eclampsia. However, the results of the present study will add to the debate and support the design of larger trials, particularly because of the complex bioenergetic and antioxidant function of CoQ10. For example, a recent study by Tiano et al. [25] revealed a positive effect of CoQ10 on endothelial function, and this could have particular importance in pre-eclampsia in which endothelial dysfunction is recognized to play a pathogenetic role [13].

The selection of the dosage of 100 mg CoQ10 twice a day was based on the hypothesis that during pregnancy nutrient requirements are increased. With higher doses of CoQ10 the effects might be more evident since the plasma levels of CoQ10 in women receiving supplementation did not continue to increase after 24 weeks of pregnancy.

However, the reason why women who were supplemented with CoQ10 and then developed pre-eclampsia had higher plasma levels of CoQ10 than women in the placebo group who also developed pre-eclampsia is not clear. The small number of women who developed pre-eclampsia and the considerable variation in the results might be confounding factors.

In conclusion, CoQ10 supplementation starting at 20 weeks of pregnancy appears to be a safe and well tolerated intervention, and resulted in a significant reduction in the rate of pre-eclampsia. More clinical studies are needed to investigate this further.

Acknowledgments

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