Effects of menstrual cycle and oral contraceptive use on serum levels of lipid-soluble antioxidants

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KEY WORDS
Menstrual cycle
Oral contraceptive use
Coenzyme Q10
Antioxidant

Objective: The purpose of this study was to examine the influence of menstrual cycle and oral contraceptive use on serum levels of lipid-soluble antioxidants.

Study design: In this cross-section study, nonfasting blood samples were collected twice from 10 healthy premenopausal women during the follicular phase (between days 8 and 11) and the luteal phase (between days 18 and 22) of their same menstrual cycle. In addition, blood samples from 15 premenopausal women who used oral contraceptive for at least 6 months and 40 women who did not use oral contraceptive were collected randomly at any day of the menstrual cycle. Serum levels of coenzyme Q10, α-tocopherol, γ-tocopherol, β-carotene, α-carotene, and lycopene were determined using high pressure liquid chromatography.

Results: Serum coenzyme Q10 and α-tocopherol levels were significantly lower during the follicular phase compared with the luteal phase of the same menstrual cycle (P < .05). Oral contraceptive use also significantly decreased coenzyme Q10 and α-tocopherol (P < .001). Other antioxidant levels were comparable.

Conclusion: Alterations in coenzyme Q10 and α-tocopherol levels during the menstrual cycle and in oral contraceptive users should be taken into consideration, concerning the future antioxidant research in premenopausal women. Further studies are needed to investigate the potential role of endogenous and exogenous ovarian hormones on oxidative stress in women.

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Oxidative damage caused by oxygen free radicals has been implicated in the pathogenesis of a large number of chronic diseases.1 Lipid-soluble antioxidants coenzyme Q10 and α-tocopherol can neutralize free radical and are thus postulated potentially to decrease the risk of major diseases, such as cancer and cardiovascular disease (CVD).2,3 Ovarian hormones, primarily estrogens, possess antioxidant properties and have been postulated to protect against CVD.4 Although the fluctuations in ovarian hormone levels during the menstrual cycle increasingly are believed to play a significant role in the cause of many disorders and diseases in women, several studies were conducted to determine whether plasma


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Women who consumed coenzyme Q10 or multivitamin using any medications or hormonal contraceptives. November 2004 were recruited, with informed consent. Bronx, New York, between January 2002 and gynecology clinics at the Bronx-Lebanon Hospital Center. Among the remaining 55 women, 15 women were OC users for a minimum period of 6 months, and 40 women did not use OCs. Significantly lower serum levels of coenzyme Q10 and α-tocopherol were detected during the follicular phase of the menstrual cycle, when compared with the luteal phase, in healthy premenopausal women.

Material and methods

The Institutional Review Board approved the study protocol. In this cross-section study, 65 nonpregnant women with regular menstrual cycles, who attended the gynecology clinics at the Bronx-Lebanon Hospital Center, Bronx, New York, between January 2002 and November 2004 were recruited, with informed consent. All subjects came from the same catchment area and had a similar socioeconomic composition and were not using any medications or hormonal contraceptives. Women who consumed coenzyme Q10 or multivitamin supplementation or women who had irregular menstrual cycles were excluded from the study. No dietary restrictions were imposed on any of the subjects. Ten healthy women (median age, 33 years; range, 28-44 years) with regular menstrual cycles (27-29 days) were studied at 2 time points during the same menstrual cycle. Nonfasting venous blood samples were obtained in the follicular phase (between days 8 and 11) and in the luteal phase (between days 18 and 22) of their menstrual cycle. Subjects in this group were not taking any steroid medication and placebo phase. Serum was separated by centrifugation within 1 to 2 hours and stored at −70°C for no > 7 days. Serum levels of coenzyme Q10, α-tocopherol, γ-tocopherol, β-carotene, α-carotene, and lycopene were measured by the high pressure liquid chromatography methods, as described previously. The coefficients of variation were <8% for all nutrients. Serum 17β-estradiol and progesterone levels were measured by the radio immunoassay method in the clinical laboratory at our institution. Statistical analyses were performed with the Student t test, and by Wilcoxon paired-sample test between the luteal phase and follicular phase. Significance was defined by a probability value of <.05.

Results

A total of 65 non-smoking premenopausal women were enrolled in this study. Most of the study subjects were Hispanic (60%) and black (38%) women, and most of them were representatives of an inner-city population. Of these 65 women, 10 women who were not taking any OC participated in the menstrual cycle–antioxidant study. In these 10 women, serum levels of estradiol increased from 84 ± 20 pg/mL in the follicular phase to 205 ± 60 pg/mL in the luteal phase (P < .01), and progesterone levels changed from 0.7 ± 0.3 ng/mL to 6.0 ± 2 ng/mL (P < .01). Progesterone levels in all subjects during the luteal phase were > 3 ng/mL. Among the remaining 55 women, 15 women were OC users for a minimum period of 6 months, and 40 women did not use OCs. Significantly lower serum levels of coenzyme Q10 and α-tocopherol were detected during the follicular phase of the menstrual cycle, when compared with the luteal phase, in healthy premenopausal women (P < .05, Wilcoxon paired-sample test).

γ-Tocopherol, β-carotene, α-carotene, and lycopene levels were comparable between the follicular and luteal phases of the menstrual cycle. OC use significantly

<table>
<thead>
<tr>
<th>Table</th>
<th>Serum levels of antioxidants during the follicular and the luteal phases in the same premenopausal women and in women who used OCs and control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant</td>
<td>Menstrual phase</td>
</tr>
<tr>
<td></td>
<td>Follicular: Group 1 (n = 10)</td>
</tr>
<tr>
<td>Coenzyme Q10 (µg/dL)</td>
<td>0.50 ± 0.3*</td>
</tr>
<tr>
<td>α-Tocopherol (mg/L)</td>
<td>4.60 ± 1.0*</td>
</tr>
<tr>
<td>γ-Tocopherol (mg/L)</td>
<td>1.09 ± 0.4</td>
</tr>
<tr>
<td>β-Carotene (µg/dL)</td>
<td>27.9 ± 6.2</td>
</tr>
<tr>
<td>α-Carotene (µg/dL)</td>
<td>3.9 ± 2.3</td>
</tr>
<tr>
<td>Lycopene (µg/dL)</td>
<td>35.5 ± 13.2</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD.
* P < .05, group 1 vs group 2, by Wilcoxon paired-sample test.
† P < .001, group 3 vs group 4, by the Student t test.

α-tocopherol levels fluctuate by phase of the menstrual cycle. However, relatively little research has been focused on menstrual cycle–related changes in lipid soluble antioxidant coenzyme Q10. We investigated the influence of menstrual cycle phase and oral contraceptive (OC) use on serum levels of coenzyme Q10, α-tocopherol, γ-tocopherol, β-carotene, α-carotene, and lycopene in healthy premenopausal women.
decreased serum levels of coenzyme Q_10_ and \( \alpha \)-tocopherol \((P < .001, \text{by the Student } t \text{ test})\) in premenopausal women. Serum levels of \( \gamma \)-tocopherol, \( \beta \)-carotene, \( \alpha \)-carotene, and lycopene were comparable between OC users and nonusers (Table).

Comment

We examined the influence of ovarian hormones during the follicular and luteal phases of the menstrual cycle on serum levels of lipid-soluble antioxidants in healthy premenopausal women. Our data demonstrate significantly lower coenzyme Q_{10} and \( \alpha \)-tocopherol levels during the follicular phase, when compared with the luteal phase, in women with regular menstrual cycles, whereas other antioxidants \(( \gamma \)-tocopherol, \( \beta \)-carotene, \( \alpha \)-carotene, and lycopene\) were not altered significantly. We also studied the effects of exogenous ovarian hormones on levels of the same antioxidants in a separate subgroup of premenopausal women who were OC users for at least a 6-month duration. The results show that the use of OC significantly lowered the serum levels of coenzyme Q_{10} and \( \alpha \)-tocopherol, compared with the levels in non-OC users. \( \gamma \)-Tocopherol, \( \beta \)-carotene, \( \alpha \)-carotene, and lycopene levels were comparable between both groups. Similarly, we observed a decrease in serum levels of coenzyme Q_{10} with the use of hormone replacement therapy (unpublished data). The limitations of our present study include small sample size and the fact that all blood samples were nonfasting. Blood samples from OC users were collected irrespective to placebo or the steroid medication phase, and blood samples from non-OC users were taken randomly at any day of the menstrual cycle. This may explain the differences between serum levels of \( \alpha \)-tocopherol in non-OC users and the levels that were obtained in the follicular phase. It is noteworthy that, unlike water soluble antioxidants where plasma levels are related directly to daily intake, lipid-soluble antioxidants levels are related directly to lipid stores and not influenced appreciably by fluctuations by daily intake.

Several reports have demonstrated a nonsignificant fluctuation in plasma levels of \( \alpha \)-tocopherol by phase of the menstrual cycle. Lanza et al\textsuperscript{6} reported significantly lower (12%) plasma \( \alpha \)-tocopherol levels during menses (days 1 and 2) than during the luteal phase in subjects with controlled-diет conditions, but not in a free-living group. Recently, Reimer et al\textsuperscript{7} reported 12% lower serum \( \alpha \)-tocopherol levels during the follicular phase compared with the luteal phase. We observed 28% lower serum levels of \( \alpha \)-tocopherol in the follicular phase compared with the luteal phase. The lower energy intake in the follicular phase likely explains lower intake of several key nutrients compared with the luteal phase. This may have a significant impact on serum levels of lipid-soluble antioxidants. Dietary interventions may be important for women’s health, especially among young OC users, because of the impact of diet, nutrition, and weight patterns on many conditions, which include CVD, the leading cause of death in women.

Although the relation between estrogen and CVD events remains unclear, there is a substantial body of observational studies that points toward a cardioprotective role for estrogen in healthy women. Estrogen, which acts through 1 of its receptors, stimulates COX-2 production, which boosts prostacyclin, prostaglandin I\(_2\), which in turn protects the heart from atherosclerosis in female mice by restraining both oxidant stress and platelet activation. Oxygen free radicals can cause oxidative damage to lipids and proteins and contribute to the development of CVD. Lipid-soluble antioxidants are important natural cellular defense agents that protect lipids and protein molecules from oxidation. Coenzyme Q_{10} and \( \alpha \)-tocopherol are lipid-soluble free radical scavengers that are located together in cell membranes capable of neutralizing oxygen free radicals and are thus, postulated potentially to decrease the risk of CVD.

The precise molecular mechanisms of action of antioxidants remain poorly understood. Dietary antioxidants are protective agents that can counteract oxidative stress and potentially re-establish a healthy cellular redox balance. Our findings demonstrate the varying effects of endogenous and exogenous ovarian hormones on lipid-soluble antioxidant levels and should be taken into consideration in future antioxidant research. If our findings are confirmed by larger studies, women who receive OCs may be considered for coenzyme Q_{10} and/or \( \alpha \)-tocopherol supplementation. The potential value, if any, for coenzyme Q_{10} and \( \alpha \)-tocopherol supplementation in OC users and the effect of menstrual cycle phase on oxidative stress deserve further investigation.

References


