Selenium Supplementation and the Incidence of Preeclampsia in Pregnant Iranian Women: A Randomized, Double-blind, Placebo-controlled Pilot Trial

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SUMMARY

Objective: Recent studies have reported that antioxidant status, including serum selenium concentrations, is altered in women who develop preeclampsia. We wished to examine the effects of selenium supplementation in the prevention of preeclampsia in high-risk pregnant women.

Design: We carried out a randomized, double-blind, placebo-controlled pilot trial. A total of 166 primigravid pregnant women, who were in the first trimester of pregnancy, were randomized to receive 100 μg of selenium ($n=83$; dropouts, $n=22$) or a placebo ($n=83$; dropouts, $n=19$) per day until delivery. The incidence of preeclampsia, serum selenium concentrations, lipid profile and high-sensitivity C-reactive protein status were evaluated at baseline and at the end of the study.

Results: Supplementation with selenium was not associated with any reported major side effects and was associated with a significant increase in mean serum selenium concentrations at term ($p<0.001$). In contrast, mean serum selenium concentrations remained unchanged in the control group ($p=0.63$). The incidence of preeclampsia was lower in the selenium group ($n=0$) than in the control group ($n=3$), although this was not statistically significant ($p>0.05$). After treatment, systolic and diastolic blood pressure, serum total cholesterol, triglycerides, low-density and high-density lipoprotein cholesterol, and high-sensitivity C-reactive protein were significantly increased in both groups compared with pretreatment levels ($p<0.05$).

Conclusion: Our findings indicate that selenium supplementation in pregnant women may be associated with a lower frequency of preeclampsia. [*Taiwan J Obstet Gynecol* 2010;49(2):181–187]

Key Words: high-sensitivity C-reactive protein, lipid, preeclampsia, pregnancy, selenium

Introduction

Preeclampsia is a systemic and serious complication of pregnancy that affects from 2% to 7% of all pregnancies. It is a leading cause of maternal and perinatal mortality and morbidity both in the western world and developing countries [1]. This gestational disorder is characterized

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by hypertension, proteinuria, and edema, and affects multiple organs including the liver, kidneys, brain, and blood clotting system [2]. In spite of the severity and prevalence of preeclampsia, the exact etiology of this disorder remains unknown, although impaired placental perfusion has been proposed as a key factor [3]. Placental underperfusion and ischemia may lead to an excessive production of reactive oxygen species and lipid peroxides, which cause oxidative stress [4,5]. Oxidative stress plays a critical role in endothelial cell dysfunction, which initiates a self-progressing course and clinical manifestations of preeclampsia including hypertension, proteinuria, and edema [2,3,6,7]. Therefore, preeclampsia can be regarded as a state of oxidative stress, and in fact, several lines of evidence support the oxidative hypothesis of preeclampsia. According to previous reports, there is a heightened state of lipid peroxidation in preeclamptic women, whereas the endogenous antioxidant defense systems such as superoxide dismutase and glutathione peroxidase are severely depleted in these subjects [3,5,8,9]. Based on the oxidative hypothesis of preeclampsia, supplementation with antioxidants might help prevent preeclampsia. One of the most important antioxidants in the body is the trace mineral selenium, which is an essential component of a number of antioxidant selenoenzymes such as glutathione peroxidase and thioredoxin reductase [10,11]. Besides, selenium possesses anti-inflammatory properties, which are exerted through a number of mechanisms [12]. A number of studies have reported a decrease in selenium status during pregnancy [13–15]. Moreover, several observational studies have reported a further decrease in selenium status in women with preeclampsia compared with non-preeclamptic pregnant women [8,9,16]. However, there are still insufficient clinical studies evaluating the effectiveness of selenium supplementation in the prevention of preeclampsia.

With regard to the numerous complications of preeclampsia [17,18], the significant reduction in selenium status in preeclamptic women and established antioxidant and anti-inflammatory effects of selenium, we designed the present trial to investigate the impact of selenium supplementation in the prevention of preeclampsia, as well as on the lipid profile and high-sensitivity C-reactive protein (hs-CRP) status, in high-risk pregnant women.

Materials and Methods

Subjects

A total of 218 primigravid pregnant women aged 16–35 years were assessed for eligibility to participate in this trial. Subjects were selected from women attending the Ommolbanin Hospital, Mashhad, Iran. The inclusion criteria for selection were as follows: gestational age up to 12 weeks, and with no indications for termination of the pregnancy. Exclusion criteria included the use of any drugs, except routine supplements of folic acid and ferrous sulfate, and a prior history or clinical features of any medical conditions, including thyroid disorders, diabetes, hypertension and infections. Thirty-nine individuals were excluded from the study with 179 subjects entering the trial. Of these 179 subjects, 13 were excluded because of intolerance to the tablets ($n=4$) or their unpleasant aroma ($n=9$).

For each participant, a questionnaire with information about past medical history, family history of preeclampsia, last menstrual period, smoking habits and consumption of any supplement was completed. Each subject gave written consent to participate in the study. The study protocol was approved by the ethics committee for clinical research of the Mashhad University of Medical Sciences.

Study design and medications

A randomized, double-blind, placebo-controlled design was used in which the 166 eligible participants were randomly assigned to one of the following groups: the first group comprising 83 pregnant women who were given 100 μg of selenium yeast daily from the first trimester of their pregnancy until delivery for a period of approximately 6 months (Se group), and the second group comprising 83 pregnant women for whom daily placebo yeast tablets were provided for the same period (control group). A total of 125 subjects completed the study ($n=61$ and $n=64$ for Se and control groups, respectively) (Figure). The prescribed selenium dose was in agreement with the National Academy of Sciences' guidelines that established an upper limit of 400 μg/day for selenium intake [19].

Selenium yeast tablets and matched placebo yeast tablets were provided by Pharma Nord (Vejle, Denmark).

Definition of preeclampsia and hypertension

The main outcome of our study was the incidence of preeclampsia. We defined preeclampsia by the new development of proteinuria. For women with pre-existing proteinuria, the diagnosis of preeclampsia was based on development of hypertension, as defined below, or after identification of clinical or biochemical markers or at least one additional feature of preeclampsia such as HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Hypertension was defined as systolic blood pressure (SBP) = 140 mmHg and diastolic blood pressure (DBP) = 90 mmHg according

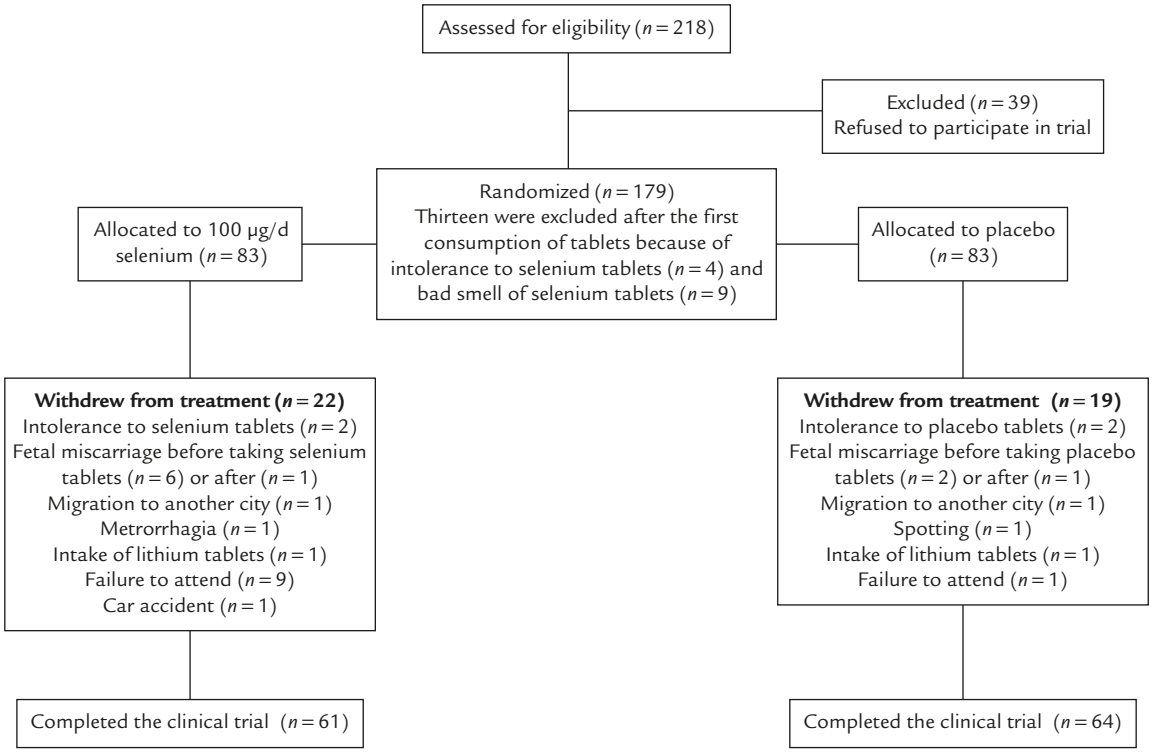

Figure. Flow chart of the trial.

to the US Sixth Joint National Committee criteria [20]. We defined gestational hypertension as a DBP ≥ 90 mmHg after 20 weeks of pregnancy or in the early postnatal period (up to 48 hours).

Anthropometric and other measurements

Anthropometric parameters including weight, height, and body mass index were measured. Weight was measured using a standard scale, with the subjects dressed in light clothing after an overnight fast. Blood pressure was measured twice using a standard mercury sphygmomanometer, while the patients were seated and resting. The systolic blood pressure was defined as the appearance of the first sound (Korotkoff phase 1) and the diastolic blood pressure was defined as the disappearance of the sound (Korotkoff phase 5) during deflating of the cuff. Body mass index was calculated as weight (in kilograms) divided by the square of height (in meters).

Lipid profile and hs-CRP

Lipid profile comprising total cholesterol, triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol was determined at baseline and at the end of trial. The post-trial samples were not fasting samples, while the pre-trial ones were collected after fasting. Serum lipid profile was measured by routine enzymatic methods using commercial kits. Serum hs-CRP was measured by a polyethylene glycol-enhanced immunoturbidimetric method with an Alcyon analyzer (Abbott Laboratories, Abbott Park, IL, USA).

Serum selenium analysis

Serum selenium concentrations were determined by electrothermal atomic absorption spectrometry with Zeeman background correction using a palladium chloride chemical modifier. Typical between-batch precision (coefficient of variation) was 3.7% [21,22].

Statistical analysis

All statistical analyses were performed using SPSS version 11.5 software (SPSS Inc., Chicago, IL, USA). Values are expressed as mean ± standard deviation or median and interquartile range. The group comparisons were assessed by χ^2 test, Fisher exact test, independent samples paired *t* test or Wilcoxon signed rank test (in the case of serum triglycerides and hs-CRP). A two-tailed *p* value of < 0.05 was considered statistically significant.

Results

Demographic data

There were no significant differences in age, anthropometric indices, socioeconomic state, past medical history (miscarriage and infertility history), and family history (incidence of preeclampsia, diabetes, hypertension and

Table 1. Demographic characteristics of selenium (Se) and control groups at baseline*

	Se group ($n=83$)	Control group ($n=83$)	p
Age (yr)	21.6±2.5	21.6±3.4	0.91
Weight (kg)	58.5±10.2	56.5±9.8	0.16
Height (cm)	156.7±5.8	156.7±6.3	0.99
BMI (kg/m^2)	23.8±3.8	23.0±4.0	0.16
Waist circumference (cm)	77.1±11.6	74.9±8.2	0.13
Hip circumference (cm)	95.8±12.1	94.8±7.9	0.50
Waist to hip ratio	0.8±0.08	0.8±0.06	0.14
Education			0.89
Illiterate or lower than diploma	42 (50.6)	44 (53.0)	
Diploma	36 (43.4)	35 (42.2)	
Higher than diploma	5 (6.0)	4 (4.8)	
Family history			
Preeclampsia	11 (13.3)	18 (21.7)	0.13
Diabetes	2 (2.4)	5 (6.0)	0.17
Hypertension	5 (6.0)	5 (6.0)	0.93
Hyperlipidemia	4 (4.8)	5 (6.0)	0.79

**Data are presented as mean±standard deviation or n (%). BMI=body mass index.*

hyperlipidemia) between the Se and control groups. Similarly, baseline SBP and DBP, lipid profile, hs-CRP and serum selenium concentrations were not significantly different between the Se and control groups.

There were also no significant differences between the groups for delivery state, amniotic fluid properties, sex of the neonate, neonatal abnormalities, age of pregnancy, and neonatal state. The demographic data for the patients and controls are presented in Table 1.

Serum selenium concentrations

There was no significant difference in serum selenium concentrations between the two groups at baseline (Table 2). Supplementation with selenium was associated with a significant increase in serum selenium concentrations ($p<0.001$; Table 2). In contrast, serum selenium concentrations remained unchanged by the end of the trial in the control group ($p=0.63$; Table 2).

Effect of selenium supplementation on the incidence of preeclampsia

There was no incidence of preeclampsia in the Se group compared with 4.7% ($n=3$) in the control group. However, this decrease was not statistically significant, which is probably because of the insufficient number of participants in the study.

Effect of selenium supplementation on lipid profile and serum hs-CRP

At the end of the trial, there were significant increases in total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol in both the Se group ($p<0.001$, $p<0.001$, $p<0.001$ and $p=0.001$, respectively; Table 2) and control group ($p<0.001$, $p<0.001$, $p<0.001$ and $p=0.007$, respectively; Table 2). Similar to selenium concentrations, serum hs-CRP concentrations increased significantly in both groups by term ($p<0.001$; Table 2).

Discussion

There has been a great deal of interest in the use of antioxidant supplementation as a preventive strategy against preeclampsia [7,23,24]. However, the results of trials on the efficacy of using vitamin C and vitamin E supplementation in high-risk pregnant women have not been promising [25,26]. Therefore, based on the current findings, supplementation with vitamins C and E is not recommended as part of clinical practice for reducing the risk of preeclampsia [27].

Selenium is an essential trace element present in biologic systems as a component of selenoproteins such as glutathione peroxidase and thioredoxin reductase, and is involved in antioxidant protection and anti-inflammatory effects [10–12]. In cases of selenium deficiency, supplementation with selenium is associated with enhanced enzymatic antioxidant activity [28] and reduced lipid peroxidation [29]. Selenium concentrations in whole blood and plasma significantly fall during pregnancy compared with pre-pregnancy or non-pregnancy concentrations, and this decrease is progressive as

Table 2. Comparison of clinical and biochemical parameters pre- and post-trial*†

Parameters	Se group			Control group		
	Pre-trial	Post-trial	p‡	Pre-trial	Post-trial	p‡
SBP (mmHg)	100.1 ± 10.5	111.4 ± 8.6	< 0.001	101.9 ± 11.4	111.2 ± 11.1	0.002
DBP (mmHg)	62.5 ± 8.4	70.2 ± 9.2	< 0.001	62.9 ± 11.5	69.2 ± 9.4	0.03
Cholesterol (mg/dL)	177.3 ± 60.2	222.4 ± 50.2	< 0.001	165.9 ± 53.4	206.1 ± 50.3	< 0.001
TG (mg/dL)	88.0 (62.0–98.0)	211.0 (141.7–245.2)	< 0.001	80.0 (73.0–103.0)	181.5 (144.5–223.5)	< 0.001
LDL-C (mg/dL)	113.8 ± 55.0	132.0 ± 41.2	< 0.001	104.4 ± 49.8	115.2 ± 23.2	< 0.001
HDL-C (mg/dL)	48.8 ± 10.4	59.3 ± 11.0	0.001	46.8 ± 8.6	58.6 ± 10.1	0.007
hs-CRP (mg/L)	5.2 (1.5–7.6)	25.4 (8.8–52.1)	< 0.001	4.1 (1.8–7.6)	43.3 (8.9–89.3)	< 0.001
Se (μg/L)	122.5 ± 23.2	168.6 ± 36.4	< 0.001	122.9 ± 26.9	119.4 ± 33.4	0.63
Incidence of preeclampsia, *n* (%)	0 (0)			3 (4.7)		0.25§

**Data are presented as mean ± standard deviation or median (interquartile range); †pre-trial samples but not post-trial samples were collected fasted; ‡paired t test or Wilcoxon signed rank test; §Fisher exact test. Se = selenium; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglycerides; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein.*

gestation proceeds [13–15]. Furthermore, epidemiologic studies have shown that selenium status in preeclamptic patients is significantly decreased both in serum and toenail specimens [8,9,16]. As expected, the activity of glutathione peroxidase is also decreased in preeclampsia as a function of selenium depletion [30]. In spite of these findings, there are few clinical trials investigating the efficacy of selenium supplementation in preventing the incidence of preeclampsia. The results of our trial suggested that selenium supplementation is associated with a decrease in the incidence of preeclampsia in pregnant women at risk of developing the disease. However, the small number of participants in our study is a limiting factor that may have led to this decrease being nonsignificant.

To the best of our knowledge, there has been only one trial investigating the influence of selenium supplementation in preeclamptic women. In this study, Han and Zhou [31] reported the beneficial effect of supplementation with 100 μg of selenium per day in the prevention of pregnancy-induced hypertension and gestational edema in a group of Chinese pregnant women. Their study population comprised 100 pregnant women at high risk of preeclampsia ($n = 52$ in the Se group and $n = 48$ in the control group) in certain selenium deficient regions of China that had been previously reported to have a high prevalence of preeclampsia [31].

The low incidence of preeclampsia in our study population, in spite of the greater number of participants compared with the only similar previous study [31], is probably due to the relatively high serum selenium concentrations. The mean serum selenium concentrations in our study are higher than those reported in most parts of Europe, including the United Kingdom [32–35]. Mean selenium concentrations in our study are even higher than reported values in other provinces of Iran, and are similar to the selenium status in the population of North America [36–39].

In the current study, the increase in lipid profile parameters in both groups is consistent with previous reports and could be attributed to the hormonal changes during pregnancy and effect of female sexual hormones, in particular estrogen, on lipid metabolism [40]. During pregnancy, the activity of hepatic lipase is increased and that of lipoprotein lipase is decreased, which lead to the elevation of triglyceride concentrations [40]. These changes in lipid parameters are even more remarkable during preeclampsia, and as a result, a casual relationship has been proposed between dyslipidemia, in particular hypertriglyceridemia, and the development of preeclampsia [41,42]. However, the hypothesis that dyslipidemia always precedes the clinical manifestations of preeclampsia and may be used as a predictor of the disorder is still inconsistent and has been not confirmed by the findings of some studies, including our study [43]. The increase in hs-CRP concentrations in both groups in our study could be due to the profound inflammatory changes during pregnancy as described elsewhere [44]. However the increase in the Se group was less than that in controls, which is probably because of the effect of selenium on hs-CRP status and the inverse relationship that exists between them [45,46]. Another important explanation for the rise of these parameters is that the post-trial samples were not fasting samples while the pre-trial ones were collected after fasting.

In summary, the findings of the present randomized, double blind, placebo-controlled pilot trial indicate that selenium supplementation in Iranian

pregnant women, who have a higher selenium status than those of UK and other European countries, is safe and may be associated with a lower incidence of preeclampsia. The main limitation of our pilot study was the relatively small study population. Therefore, any definitive judgment about the efficacy of selenium supplementation in pregnancy for the purpose of preventing the development of preeclampsia will depend on the results of future trials with a larger number of participants.

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