Pediatrics and Neonatology (2012) 53, 334–339

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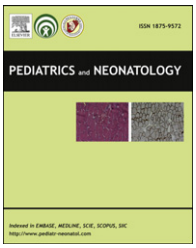

ORIGINAL ARTICLE

Effect of Prenatal Selenium Supplementation on Cord Blood Selenium and Lipid Profile

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Received Apr 14, 2011; received in revised form Mar 5, 2012; accepted Mar 15, 2012

Key Words
antioxidant;
cord blood;
lipid profile;
newborn;
selenium

Background: Selenium is an essential trace element and as a component of selenoproteins it plays a key role as an antioxidant. We aimed to evaluate the effect of selenium supplementation during pregnancy on cord blood selenium content and lipid profile.
Methods: This trial was performed on 166 eligible women who were randomized to receive 100 μg of selenium, as selenium-yeast (Se group) or a placebo-yeast tablet (placebo group). Umbilical cord blood samples were collected at the time of delivery and selenium concentration and lipid profile were measured.
Results: Triglyceride levels were found to be significantly higher in the Se group than in the placebo group ($p = 0.01$). However, no significant difference in cord blood selenium was observed between the groups nor were there any significant correlations between cord blood selenium and lipid profile parameters.

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http://dx.doi.org/10.1016/j.pedneo.2012.08.008

Conclusion: Our findings suggest that selenium supplementation in pregnant women may be associated with an increased cord-blood triglyceride level, although total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol levels did not change significantly. The clinical significance of the increased cord triglyceride concentration needs to be evaluated.

1. Introduction

Selenium is an essential trace element and a key component of important enzymes, including the antioxidant glutathione peroxidase and the iodothyronine deiodinases.[1] A number of selenoenzymes play key roles in protecting against oxidative damage.[2] The mammalian fetus is sensitive to reactive oxygen species (ROS) during development. Fetal cell growth *in vitro* has been shown to be impaired in a dose-dependent manner in the presence of ROS.[3] Antioxidant vitamin treatment increases the number of zygotes and improves the transformation of zygotes to blastocytes *in vitro*.[4] Micronutrient deficiency during pregnancy may lead to growth and developmental delay of fetal organs and may adversely affect immune function.[5] Antioxidant defenses are dependent on micronutrient status; the immune system is compromised in malnourished pregnant women and their neonates are small for gestational age (SGA).[6] One effective strategy for preventing the development of oxidative stress in the newborn may be by enhancing maternal antioxidant status via supplementation with nutrients such as selenium.[7] In the current study, we sought to investigate the effect of selenium supplementation during pregnancy on umbilical cord selenium content and on cord blood-lipid profile.

2. Methods

Two hundred and eighteen pregnant women age 16-35 years were assessed for eligibility to participate in this randomized double-blind placebo-controlled trial. Study participants were selected from women referred to the Obstetrics and Gynecology Department of Ghaem Hospital (Mashhad, Iran) between June 2007 and June 2009. Inclusion criteria for selection were gestational age up to 12 weeks and no indications for terminating the pregnancy. Exclusion criteria included the use of any drugs except routine supplements of folic acid and ferrous sulfate and a history or clinical features of any medical conditions including thyroid disorders, diabetes, hypertension, hyperlipidemia, and infections. The Ethics Committee of the Mashhad University of Medical Science (MUMS) approved this study and all individuals signed informed consent. In this trial, eligible individuals were randomly assigned to receive 100 μg of selenium as a selenium-enriched yeast tablet (Se group) or a placebo-yeast tablet (placebo group) daily for the last 6 months of pregnancy. Individuals were alternatively allocated to tablets coded A or B, with the first code chosen randomly. The dose of selenium used was in agreement with the National Academy of Sciences' guidelines that established a safe upper limit of 400 μg/day for selenium intake.[8] Both the placebo and the selenium-enriched yeast tablets were provided by Pharma Nord (Vejle, Denmark). Maternal groups were similar for parameters such as anthropometric indices (weight, length, body mass index), socioeconomic status (education and career), medical history (infertility and miscarriage), complete blood count, and blood typing. Study physicians, research nurses, and participants were unaware of the assignment groups (tablets were administered as A or B). Before administration of the tablets, the participants were asked to sign a written consent form and complete a questionnaire providing details of age, weight, height, blood pressure, date of last menstrual period, contraceptive methods, smoking habit, alcohol use, and consumption of routine supplements during pregnancy. On delivery, umbilical cord blood was collected. Serum selenium concentration and lipid profile were measured in these samples.

Two hundred and eighteen pregnant women were assessed for eligibility to participate in this trial. Thirty-nine individuals did not meet the inclusion criteria and were excluded from the study. Of the 179 individuals who entered the trial, 13 dropped out because of intolerance to the tablets ($n = 4$) or the unpleasant aroma associated with them ($n = 9$). One hundred twenty-five individuals completed the study (61 in the Se group and 64 in the placebo group, Figure 1). Because some of the women did not eventually deliver their babies in our hospitals; we were only able to collect umbilical cord-blood samples from 34 and 32 participants in the Se and placebo groups, respectively. Samples were analyzed in a single laboratory. Blood was centrifuged at 2500 rpm for 15 minutes at room temperature to obtain serum. Serum lipid profile parameters including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured by routine enzymatic methods using commercial kits. Serum selenium was determined by electrothermal atomic absorption spectrometry with Zeeman background correction using a palladium chloride chemical modifier.

All statistical analyses were performed using SPSS 11.5, Chicago, IL. Values were expressed as mean ± standard deviation. The group comparisons were assessed by the Student *t*-test or the Mann-Whitney U test. Pearson and Spearman correlation tests were performed for normally and non-normally distributed data. A two-tailed $p < 0.05$ was considered statistically significant.

3. Results

Basic and clinical findings including sex, gestational age, birth weight, birth length, birth head circumference, and

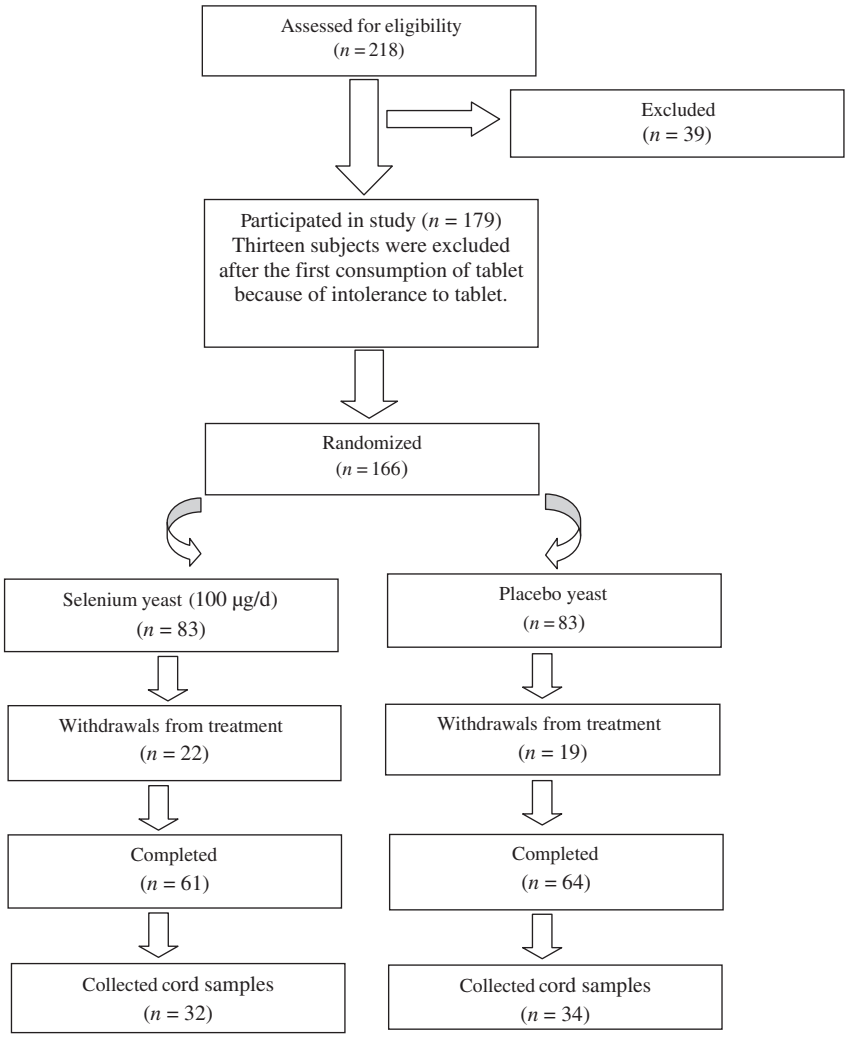

Figure 1 Flowchart of patient allocation in the study.

Apgar scores at first and fifth minutes did not show any significant difference between neonates in the Se and placebo groups ($p > 0.05$) (Table 1). The umbilical cord serum- selenium concentration was comparable in Se and placebo groups ($p > 0.05$, Table 2). Maternal serum selenium concentrations increased in the Se group by the end of the trial (122.5 ± 23.2 μg/L at baseline and 168.6 ± 36.4 μg/L posttrial; $p < 0.001$) whereas no significant change was

Table 1 Basic and clinical findings of study neonates.*

Parameter	Se group	Placebo group	*p*-value
Gestational age (wk)	39.0 (39.0—40.0)	39.0 (38.0—40.0)	>0.05
Sex (% female)	44.2	41.8	>0.05
Weight (g)	3085.3 ± 622.2	3069.0 ± 551.1	>0.05
Length (cm)	50.0 (49.0—51.0)	50.0 (48.0—51.0)	>0.05
Head circumference (cm)	34.4 ± 1.4	34.5 ± 2.9	>0.05
Apgar score (first min)	9.0 (8.0—9.0)	9.0 (8.0—9.0)	>0.05
Apgar score (fifth min)	9.0 (9.0—9.0)	9.0 (9.0—9.0)	>0.05

* Values are expressed as percentage, mean ± standard deviation or median (interquartile range).

Table 2 Comparison of cord serum selenium and lipid profile in selenium and placebo group.*

Parameter	Group		*p*-value
	Selenium group (*n* = 32)	Placebo group (*n* = 34)	
Selenium (μg/L)	106.3 ± 18.2	101.9 ± 15.9	0.29
Total cholesterol (mg/dL)	96.7 ± 55.7	79.6 ± 39.9	0.16
Triglyceride (mg/dL)	56.0 (41.0—105.0)	38.5 (32.7—67.0)	0.01
LDL-C (mg/dL)	58.0 ± 39.6	45.1 ± 27.2	0.13
HDL-C (mg/dL)	23.0 ± 8.5	20.2 ± 8.1	0.17

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

* Values express as mean ± standard deviation for normally distributed data and median interquartile range for non-normally distributed data.

observed in the placebo group (122.9 ± 26.9 μg/L at baseline and 119.4 ± 33.4 μg/L posttrial; $p > 0.05$). There was no significant difference in total cholesterol, LDL-C, and HDL-C in cord blood serum between Se and placebo groups ($p > 0.05$), whereas the triglyceride level was significantly higher in the Se group ($p = 0.01$, Table 2). With respect to the bivariate correlations, we did not find a significant correlation between cord-serum selenium and the lipid profile parameters of total cholesterol, triglycerides, LDL-C, and HDL-C ($p > 0.05$; Table 3).

4. Discussion

Pregnancy is often regarded as a condition of oxidative stress. Several factors are responsible for this type of stress, including increased oxygen intake and consumption, high metabolic demand, and labor-associated stress.[9] Previous reports have confirmed elevated levels of lipid peroxides and reduced antioxidant enzyme activities in the blood circulation of pregnant women. In addition, the placenta is a major source of lipid peroxides and oxidative stress. This increased lipid peroxidation along with the exposure to high oxygen concentration at birth, inflammation, and an immature antioxidant defense system make the neonates, especially those who are preterm, susceptible to oxidative stress.[10] Oxidative stress has been suggested to be implicated in the pathophysiology of multiple pregnancy complications such as preterm premature rupture of membranes, bronchopulmonary dysplasia, intrauterine growth restriction, persistent ductus arteriosus, intracranial hemorrhage, and fetal death.[11]

As selenoproteins might be expected to have a protective effect against oxidative damage to lipoproteins such as LDL, supplementation with selenium may have a beneficial effect during pregnancy. However, clinical trials investigating the effect of prenatal selenium supplementation on cord blood lipid profile are lacking. In observational studies, serum selenium concentrations have been reported to be positively and significantly correlated with serum cholesterol. This correlation was found to remain significant after adjustment for age and body mass index.[12] Lipoproteins, apolipoproteins, and in particular triglycerides increase significantly in maternal serum during pregnancy, which may be due to hormonal changes and increased hepatic lipase activity.[13]

The results of our trial indicated that selenium supplementation is associated with an increase in serum triglyceride concentration in cord blood (56.0 vs. 38.5 mg/dL, $p = 0.01$). However, total cholesterol, LDL-C, and HDL-C did not change significantly post-trial. Therefore, although the clinical effect of increased cord triglycerides remains to be evaluated, daily administration of 100 μg selenium to pregnant women during the second and third trimesters does not seem to be associated with a negative effect on the newborn's total cholesterol, LDL-C, and HDL-C values.

Several previous observational studies have reported a positive association between serum selenium concentrations and lipid levels.[14] However, the findings of intervention studies have been less clear. Selenium deficiency has been reported to be linked with reduced lipid levels.[15] With regard to clinical studies, there have been three reports on the effect of selenium supplementation on plasma lipids.[16–18] Findings of trials by Luoma et al.[16] and Yu et al.[17] did not show any significant effect of selenium on plasma lipids. However, a recently published robust trial by Rayman et al.[18] showed modest reductions in total and non–high-density lipoprotein cholesterol levels on supplementing either 100 μg/day or 200 μg/day of high-selenium yeast. However, at a higher dose (300 μg/day), no significant effect was observed on total or non–high-density lipoprotein cholesterol levels although HDL-C was significantly increased.

The mean baseline selenium concentration in maternal serum of both selenium and placebo groups was reported to be higher than the mean selenium concentration in non-pregnant women in other countries, including India, Spain, Poland, Norway, Estonia, and the Netherlands.[19–24] Furthermore, the levels found in the current study were also higher than those reported in non-pregnant women from other parts of Iran.[25,26] The difference in selenium status is probably due to the regional and geographic variability in the selenium content of soil and plant foods.[27,28] Selenium administration in pregnant women did not increase the cord blood-serum selenium significantly. The cord blood serum selenium in our study was lower than that of maternal serum selenium, which is consistent with most previous reports, such as the study of Gathwala et al.[29] that reported the cord-blood serum selenium as 54.17 ± 13.4 μg/kg (ppb). In comparison with the normal range (50–150 ppb), this reported cord blood-selenium concentration may be considered as a low normal value. Makhoul et al.[30] reported cord blood serum selenium to be 60–70% that of maternal serum selenium. A possible explanation for the observed low cord blood-serum selenium levels might be the uptake of selenoprotein P via apoE R2 receptor in the placental tissue. Selenoprotein P is synthesized and secreted by the liver and comprises most of the plasma selenium content.[31] Uptake of

Table 3 Correlation of cord serum selenium level with components of lipid profile in cord blood serum.

Parameter	Se group		Placebo group		Total	
	R	*p*	r	*p*	r	*p*
Total cholesterol	0.16^{sp}	0.37	-0.20^{sp}	0.27	0.01^{sp}	0.95
Triglyceride	-0.09^{sp}	0.60	-0.10^{sp}	0.60	-0.04^{sp}	0.76
LDL-C	0.37^{sp}	0.13	-0.17^{sp}	0.35	0.08^{sp}	0.51
HDL-C	0.24	0.18	−0.52	0.77	0.13	0.30

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; sp = Spearman correlation coefficient.

selenium by apoE R2 (a member of the lipoprotein receptor family) has been shown previously in the testis and the brain.[32] Lower levels of cord blood selenium compared with maternal selenium concentrations might be attributed to the high metabolic demands of the fetus or the action of metallothionein-1. Metallothionein-1 is a metal-binding protein in the human placenta that sequesters some metals and can influence the distribution of selenium between serum and tissues.[30] However, the exact mechanism for the selenium gradient between maternal and neonatal serum is not yet clear.[8] Indeed, some factors such as age, dietary regimen, physical activity, and disease may affect serum selenium concentration. Another important factor that could affect the serum selenium level is the acute phase/inflammatory response. Previous studies have shown a negative association between plasma selenium concentrations and selenoprotein expression with inflammation.[33,34] Therefore, measurement of inflammatory markers would help give a more reliable interpretation of selenium status in different conditions. The results of our trial may have been influenced by the level of selenium intake in our soils and foods, which led to a relatively high selenium concentration in participating women. In addition, larger multicenter trials, preferably with different doses of selenium and in regions of different selenium status, would be helpful to confirm the efficacy of prenatal selenium supplementation on cord blood lipid profile.

5. Conclusion

Selenium supplementation in Iranian pregnant women may increase triglycerides levels in cord blood, although no effect was found on total cholesterol, LDL, and HDL levels. The advantages and disadvantages of high levels of serum triglycerides in infants need to be evaluated. Most fatty acids in human milk are in the form of triglycerides, and lipids represent approximately 50% of the calories in human milk. It must be noted that the relatively small number of participants (completers) who were evaluated in the current study may have affected the interpretation of our results. Therefore, the current findings need to be confirmed by future large-scale trials with better characterization of maternal selenium and glucose tolerance status.

Acknowledgments

This work was financially supported by the Research Council of the Mashhad University of Medical Sciences. The authors would like to thank all study participants as well as Pharma Nord, (Vejle, Denmark), which donated selenium and placebo tablets.

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