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ORIGINAL ARTICLE

The Effect of Maternal Selenium Supplementation on Pregnancy Outcome and the Level of Oxidative Stress in Neonates

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Abstract

Background: Pregnancy is regarded as a condition which is usually accompanied by oxidative stress. This study was undertaken to investigate the effect of maternal selenium supplementation during gestation on the level of oxidative stress in neonates and the pregnancy outcome.

Methods: In this double-blind trial, 179 primigravid pregnant women in the first trimester of pregnancy were randomly assigned to receive 100 µg of selenium (Se group) or a placebo (control group) per day until delivery. The level of oxidative stress and serum selenium concentration was determined in the maternal and umblical cord sera of the subjects. Oxidative stress was measured by means of a novel assay of prooxidant-antioxidant balance (PAB). The incidence of any pregnancy complications and outcomes was also evaluated in all neonates, being fully examined and followed up until 45 days.

Results: Although maternal selenium concentration was significantly higher in the Se group ($p<0.001$), there was no statistically significant differences in the umblical cord selenium content between the two groups. Selenium supplementation was not associated with any significant decrease in PAB values in the Se group. The incidence of neonatal complications and outcomes did not differ significantly between the groups.

Conclusion: Maternal selenium supplementation during pregnancy was safe but was not associated with a significant change in the extent of oxidative stress in neonates.

Keywords: Selenium; Prooxidant-Antioxidant balance; Neonate; Complication; Pregnancy

Introduction

Oxidative stress is defined as an imbalance between the generation of reactive oxygen species (ROS) and the ability of biological antioxidant systems to neutralize these species.[1] Pregnancy is regarded as a condition which is usually accompanied by oxidative stress.[2,3] This is due to the physiological changes that occur during pregnancy including the increase in the basal oxygen intake and consumption as well as elevated metabolic demand, finally leading to the overproduction of reactive oxygen species and decreased activity of antioxidant enzymes.[4,5] On the other

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hand, labor is also a very stressful condition which is itself a cause of significant oxidative stress both in the mother and infant.[6] Moreover, other mechanisms such as exposure to a high oxygen concentration at birth, infection, inflammation and a deficient antioxidant system make the newborn more susceptible to oxidative stress.[7,8] Reactive oxygen species are considered to have a role in the pathophysiology of various neonatal diseases such as bronchopulmonary dysplasia, retinopathy of prematurity, persistent ductus arteriosus, narcotizing enterocolitis, intracranial hemorrhage and hypoxic ischemic encephalopathy.[9-12]

According to the literature, the risk of oxidative stress in neonates depends largely on the maternal antioxidant status which is potentially important for the protection of maternal-fetal unit against free radicals.[3,13,14] As previously stated, pregnancy is considered as a condition that favors oxidative stress and during pregnancy, lower concentrations of antioxidant enzymes have been reported.[2-5] Regarding the significant correlation existing between oxidative status of the mother and neonate,[15] one of the effective strategies against the development of oxidative stress in the newborn is the enhancement of maternal antioxidant system via supplementation with antioxidant compounds.

Selenium is an essential trace micronutrient element which functions in the human body as a key component of some important selenoproteins including the antioxidant enzymes glutathione peroxidases and thioredoxin reductases.[16] Compared with pre-pregnancy levels, lower concentrations of selenium in the whole blood and plasma as well as lower glutathione peroxidase activities have been reported in pregnant women.[17,18] The same trend exists in non-pregnant controls.[19] This decrease in selenium status which is progressive as gestation proceeds may be partly attributed to hemodilution from the blood volume increase associated with pregnancy.[17,19]

In the current study, we sought to investigate the impact of selenium supplementation in pregnant women on the extent of oxidative stress in their newborn. For the evaluation of oxidative stress, we applied a recently developed and modified prooxidant-antioxidant balance (PAB) assay which is a simple, rapid and inexpensive test.[20,21] Furthermore, we looked into the effect of selenium supplementation on the incidence any complications to assess the safety of maternal selenium supplementation during pregnancy for the newborn.

Materials and Methods

Two hundred and eighteen pregnant women with an age range of 16-35 years were assessed for eligibility to participate in this trial. The subjects were selected from women referring to the Obstetrics and Gynecology Department of OM-Albanin Hospital (Mashhad, Iran) between June 2006 and August 2008. The inclusion criteria for selection were gestational age up to 12 weeks with 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 prior history or clinical features of any medical conditions, including thyroid disorders, diabetes, hypertension and infections. Thirty nine individuals were excluded from the study with179 subjects entering the trial. Of these individuals, 13 were excluded because of intolerance to (n=4) or the unpleasant aroma associated with the tablets (n=9). In a double-blind manner, the 166 eligible subjects were randomized to receive 100 µg of selenium, as selenium yeast, daily from the first trimester of their pregnancy until delivery, a period of approximately six months (Se group, n=83), or daily placebo yeast tablets for the same period (control group, n=83). One hundred and twenty-five subjects completed the study (n=61 and 64 for Se and Control groups, respectively). Drop-outs (n=41) mainly comprised those who were ultimately reluctant or unable to comply with the regular consumption of medication (selenium or placebo), or who suffered a miscarriage.

The neonates included in the study were all those who were delivered from participant mothers. For each newborn, a sequence of examinations was performed by a neonatologist in the three intervals of 3-5, 10-15 and 30-45 days of birth. Each subject gave written consent to participate in the study. The study protocol was approved by the Ethics Committee for Clinical Research of Mashhad University of Medical Sciences (MUMS).

For all the newborns, the required parameters including gender, weight, length, gestational age, head circumference and Apgar scores in the first and fifth minutes of birth were determined. Head circumference was measured at the level of occipital protuberance and frontal. The body weight of each subject was measured with a standard scale to an accuracy of 0.1 gram. The Apgar score was evaluated in the first and fifth minutes of birth in the labor room. The gestational age was measured in terms of weeks from the last menstrual period and accordingly an immature newborn was defined as a newborn with

gestational age<37 weeks and a mature newborn as a newborn with gestational age≥37 weeks.

The newborn complications which were evaluated included newborn mortality, immaturity, pathologic icterous, birth asphyxia, intraventricular hemorrhage (IVH), Apgar score at the fifth minutes<7, and respiratory distress syndrome. The newborn anomalies evaluated included hydrocephaly, torticolli, fetal dent, hypospadiasis, mandibular hypoplasia, imperforated anus, valgus metatars, and developmental dysplasia of the hip.

Maternal and umblical cord blood samples were collected after birth and centrifuged at 2500 rpm for 15 min at room temperature to obtain the serum. Hemolyzed samples were excluded from analysis. Serum was stored at -20°C prior to analysis.

Serum selenium was determined by electrothermal atomic absorption spectrometry with Zeeman background correction using a palladium chloride chemical modifier.[22,23]

To assess the oxidative stress level in the newborns, a modified PAB assay was applied based on a previously described method.[20,21]

All statistical analyses were performed using SPSS software (version 11.5, Chicago, IL, USA). The values were expressed as mean±SD (for normally distributed data) or median and interquartile range (for non-normally distributed data). The group comparisons were carried out using *t* test (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data). Categorical data were compared by Fisher's Exact test. A two-tailed *p*-value of <0.05 was considered as statistically significant.

Results

Effect of Selenium Supplementation on the İncidence of Complications in Newborns

Newborn parameters including gender, gestational age, birth weight, birth length, head circumference and Apgar scores at the first and the fifth minutes of birth did not differ significantly between the Se and control groups ($p>0.05$, Table 1). There was also no significant difference in newborn complications (mortality, immaturity, pathologic icterous, asphyxia, intraventricular hemorrhage (IVH), Apgar score at the fifth minutes<7 and respiratory distress syndrome) and anomalies (hydrocephaly, torticolli, fetal dent, hypospadiasis, mandibular hypoplasia, imperforated anus, valgus metatars and developmental dysplasia of the hip) between the newborns in the Se and control

Table 1: Characteristics of neonates in the Se and control groups.

Parameter	Se group	Control group	*P* value
Male (%)	55.8	58.2	0.85
Gestational age (weeks)	39.0 (39.0-40.0)	39.0 (38.0-40.0)	0.97
Birth wieht (g)	3085.3±622.2	3069.0±551.1	0.88
Birth length (cm)	50.0 (49.0-51.0)	50.0 (48.0-51.0)	0.76
Birth head circumflax (cm)	34.4±1.4	34.5±2.9	0.53
Apgar at 1 min (n)	9.0 (8.0-9.0)	9.0 (8.0-9.0)	0.63
Apgar at 5 min (n)	9.0 (9.0-9.0)	9.0 (9.0-9.0)	0.66

Values are expressed as percentile, mean±SD or median and interquartile range.

Table 2: Comparison of the occurences of neonatal complications and anomalies between Se and control groups.

	Parameter	Se group (%)	Control group (%)	*P* value
	Congenital anomaly	0	1.6	1.00
Mortality	Infection	1.9	0	0.45
	Immaturity	1.9	1.6	1.00
	Immaturity	7.7	9.2	1.00
	Pathologic icter	1.7	1.6	1.00
	Birth asphixia	7.7	7.9	1.00
Morbidity				
	Respiratory distress syndrome	8.3	9.5	1.00
	IVH	0	3.1	0.50
	Apgar < 7	3.4	4.7	1.00
	Congenital anomaly	3.8	6.0	0.69

IVH: Intraventricular hemorrhage.

groups (p>0.05, Table 2).

In spite of the significantly higher maternal serum selenium concentration in the Se group compared with that in the control group (p<0.001, Table 3), there was no significant difference in the umblical cord serum selenium levels between the two groups (p=0.294, Table 3). Supplementation with selenium was not associated with a significant decrease in the umblical cord PAB values in the Se group compared with that in the control group (p=0.190, Table 3).

Discussion

In the present study, we found no significant effect of selenium supplementation (100 µg/day) on neonatal parameters and outcomes during the postpartum 45-day follow-up period. In a previous trial among 913 HIV-infected pregnant women, it was reported that selenium supplementation (200 µg/day) was not associated with a significant effect on pregnancy outcomes, neonatal parameters and mortality, but it reduced the risk of child mortality after 6 weeks. These findings were based on a longer follow-up (until 6 months after delivery) and larger supplementation dose (200 µg/day).[22] In another trial, postnatal selenium supplementation in very low birth weight infants was not found to improve neonatal outcomes.[23]

In spite of the significantly higher maternal serum selenium concentrations in the supplemented vs. non-supplemented group (p<0.001), there was no significance difference in cord selenium levels between the groups (p>0.05). To the best of our knowledge, to date there has been no report about the level of selenium in Iranian neonates. The mean selenium concentration which was measured in the cord blood of the subjects was higher than that of those in countries like Germany, Finland, Slovenia and Poland,[24-27] while being lower than that of those in Japan, Turkey and California in the USA.[28-30] These differences in selenium status are probably due to the regional and geographical variability in the selenium content of soil and plant foods because selenium enters food chain primarily through plants (as reviewed by Rayman).[31] The cord blood selenium in our study was approximately 63% of the maternal selenium. In contrast to some studies,[18,29,27] our findings is consistent with the majority of previous reports on the concentration of selenium in maternal and cord blood.[26,32-35] Lower levels of cord selenium compared to maternal selenium concentrations might be attributed to the high metabolic demands by the fetal tissues or the action of metallothionein-1. Metallothionein-1 is a heavy naturally occurring metal-binding protein in human placenta that sequesters some metals including selenium and can influence the distribution of selenium between serum and tissues. However, other mechanisms such as limited transport of selenium across the placenta may also be responsible for the lower cord selenium concentration.[35]

Regarding the good correlation existing between the maternal and cord selenium concentration,[15] maternal selenium deficiency is considered to be a contributory factor in the causation of oxidative stress in the neonate which is characterized by increased lipid peroxidation and impaired development of the immune system in the neonate.[36,37] However, the findings of our study indicate that selenium supplementation during gestation does not lead to a significant change in the extent of oxidative stress in the neonate. Our results also showed that there was no significant difference in the incidence of neonatal anomalies and outcomes between the groups. This major finding confirms that selenium supplementation during pregnancy is safe and is not associated with any side effect for the neonate. This safety for the neonate is especially important for the mothers who may wish to benefit from selenium supplementation during pregnancy and protect themselves against the heightened state of oxidative stress and decreased selenium status that occur during pregnancy.[2-5,17-19]

The method applied here for the estimation of oxidative stress was a modified PAB assay which has been recently developed by our group.[21] Briefly, in this method total prooxidant and antioxidant capacities are measured in a single assay and a redox index

Table 3: Comparison of maternal and umblical cord selenium concentrations and PAB values between Se and control groups

Parameter	Se group	Control group	*P* value
Maternal selenium (µg/L)	168.6±36.4	119.4±33.4	< 0.001
Cord selenium (µg/L)	106.3±18.2	101.9±15.9	0.29
PAB (AU)	37.2 (26.1-121.0)	30.8 (24.0-45.5)	0.19

Values are expressed as mean±SD or median and interquartile range. PAB: prooxidant-antioxidant balance. AU: arbitrary unit.

is obtained. This method has been calibrated against a series of well-known oxidants and antioxidants and its response has been found to be linear.[20] Finally, the simple, rapid and inexpensive procedure of this method poses the probability of its application as a routine clinical laboratory test for the assessment of oxidative stress in neonates, who are extremely vulnerable to free radical damage, and also the choice of an effective prophylaxis for those who are at an increased risk of developing oxidative stress.

The major limitation of the current study was the duration of follow-up period. With a longer follow-up, we would be able to obtain a better assessment of the impact of selenium supplementation on neonatal abnormalities and outcomes that may occur later than 45 days of life. Besides, determination of selenoprotein levels such as selenoprotein P could have been helpful for a better understanding of selenium status in both mothers and neonates.

In summary, the findings of our 45-day follow-up indicated that maternal selenium supplementation during pregnancy was safe for the newborns but was not associated with a lower risk of oxidative stress. The results also suggest that the modified PAB assay might be useful (e.g. as a screening test) for the evaluation of oxidative status in the newborns. However, further and larger clinical research in various physiological and pathological states related to oxidative stress, and especially in pregnant women, who are selenium deficient, is required to confirm the feasibility and potency of this method as a clinical laboratory test.

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