Effects of selenium levels on placental oxidative stress and inflammation during pregnancy: a prospective cohort study

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ABSTRACT

Background: Studies on the impact of Se levels in different pregnancy periods on placental function are limited.

Aim: This cohort study sought to investigate the levels of the trace element Se and to assess their effects on placental oxidative stress (OS) and mRNA expression of inflammatory genes during pregnancy.

Methods: The study population consisted of 2519 pregnant women from the Ma’anshan birth cohort. Se levels were measured in the first and second trimesters of pregnancy and in cord blood using inductively coupled plasma-mass spectrometry (ICP-MS). Placental stress and mRNA expression of inflammatory genes were assessed using RT-PCR.

Results: A statistically significant negative association was noted between Se levels in the second trimester of pregnancy and mRNA expression of placental HO-1 (β = -0.009, p < .01), HIF1α (β = -0.005, p = .010), CRP (β = -0.011, p < .001), and CD68 (β = -0.006, p = .019). A negative association was noted between Se levels in cord blood and mRNA expression of placental HO-1 (β = -0.007, p = .004), HIF1α (β = -0.006, p = .005) and GRP78 (β = -0.009, p = .004). We found that prenatal Se status was associated with placental stress and mRNA expression of inflammatory genes.

Conclusion: Se deficiency during pregnancy, especially in the second trimester, leads to the production of OS and an increase in inflammatory mediators, affecting the growth and development of the fetus. Monitoring of pregnant women’s nutritional status is necessary to prevent nutritional imbalances and deficiencies in important micronutrients in the fetal.
physiological levels, anti-inflammatory mediators are not effectively balanced and can stimulate an inflammatory response [9], resulting in adverse pregnancy outcomes, such as stillbirth [10], intrauterine growth restriction [11–13], preeclampsia [14], premature rupture of membranes [15,16] and spontaneous preterm delivery [17]. However, under normal circumstances, a complex endogenous antioxidant system with both enzymatic and nonenzymatic components can combat the effect of high levels of ROS. Glutathione peroxidase (GPx), catalase (CAT), superoxide dismutase (SOD) and thioredoxin reductase represent some of these enzymes [18–20] that require cofactors, such as micronutrients, to function properly. For instance, glutathione peroxidase requires selenium (Se). Micronutrient deficiency can interrupt mitochondrial respiratory chain activity, which subsequently leads to high levels of electron leakage, thereby increasing ROS production and OS [21]. Importantly, micronutrient deficiencies reduce the cellular protection of the antioxidant system, which is then overwhelmed by free radicals [9,22]. Therefore, adequate maternal micronutrients are essential for placental formation, fetal growth and fetal development.

Se is an essential micronutrient with antioxidant properties that is essential for proper life processes in the body [23]. Diet is the main source of Se, and the amount of Se consumed depends on its concentration in food sources and the amount consumed from these sources. Se in the human body is present in the form of the amino acid selenocysteine in 25 selenoproteins, and the amount of selenoproteins is equal to the level of Se in the human body to some extent [24–26]. Therefore, selenoprotein synthesis is directly affected by serum Se levels. As a component of enzymes, Se includes the antioxidant enzymes glutathione peroxidase (GSH-Pxs), thioredoxin reductase (TrxRs) and selenoprotein P(SePP), among which GPx requires Se to scour free radicals, protecting tissues from ROS and other metabolites of endogenous cell damage, balancing oxidation and antioxidation, and relieving OS [27,28].

Studies have shown that Se is involved in the regulation of fetal and neonatal development [29]. Se deficiency can lead to OS and inflammation, and the process of rapid growth of metabolic changes/lack of sufficient antioxidant defenses makes the developing fetus prone to adverse outcomes including pregnancy complications [30], premature birth [31,32], and abortion [33], among others. It is worth noting that the plasma concentrations of Se in pregnant women and nursing mothers’ decreases with the increasing demand for nutrients for the fetus and neonate, which makes it necessary to continue to provide Se [34]. The daily recommended intake of Se is 60 µg/day for adults, and this value increases to 65 µg/day for pregnant women [35]. Although population studies have shown that Se supplementation is associated with a reduced incidence of preeclampsia and premature rupture of membranes [36–38], the relationship between Se and placental stress and inflammation remains unclear. Therefore, we assessed the effects of prenatal Se levels on placental stress and mRNA expression of inflammatory genes based on a large birth cohort study. Using the proposed approach, we preliminarily studied the relationships among Se status, placental OS, and mRNA levels of inflammatory-related genes.

Materials and methods

Study design and population

This study was based on the longitudinal Ma’an-shan Anhui Birth Cohort conducted from antenatal clinics of Maternal and Child Health (MCH), Anhui Province, China (05/2013–09/2014). A total of 3474 pregnant women were eligible for this study. Our study excluded 120 spontaneous miscarriages, 2 ectopic pregnancies, 10 stillbirths, 30 therapeutic abortions, 39 pregnant women giving birth to twins, and 754 cases of placenta unavailability. A total of 2519 participants were enrolled in the present study. No serum samples were available from some patients in the first trimester (n = 235) or the second trimester (n = 110) or from the umbilical cord (n = 78). Ultimately, 2284 participants were included in the final analysis of the first trimester, 2409 in the final analysis of the second trimester, and 2441 in the final analysis of umbilical cord serum. Study participant selection is shown in Figure 1. The study subjects were interviewed once in each trimester of pregnancy to collect and update sociodemographic data, including medical data and information on environmental, occupational, and lifestyle factors. Additionally, during each visit and after delivery, biological samples (including urine, blood, cord blood, and placenta) were collected. Detailed procedures for the recruitment of pregnant women and the cohort methodology are described elsewhere [39]. The study protocols were approved by the Ethical Committee of Anhui Medical University (Number: 20131195). All methods were performed in accordance with the relevant guidelines and regulations, including the Declaration of Helsinki.
Serum sample collection and Se assessment

The Se levels in the blood collected from each woman during the first trimesters (8–12 wk) and second trimesters (20–24 wk) of pregnancy and in cord blood at delivery were assessed. Serum samples were aliquoted and stored at −80 °C until analysis. Serum Se was quantified via inductively coupled plasma-mass spectrometry (ICP-MS). Before analysis, the serum was placed on a specimen rocker for at least 1 h after being thawed. Then, the serum was directly diluted 1:25 with a diluent solution (1% (v/v) HNO₃ and 0.05% (v/v) Triton X-100). If flocculation occurred in the serum after thawing, we filtered the serum using a filter head (Millex-HV, 0.45 μm i.d.). Furthermore, in the daily assessment of Se, a strict quality control protocol was performed to ensure the accuracy of measurement. Specifically, first, the standard curve was established on a daily basis. Care was taken to ensure that the standard curve correlation coefficient (r) of Se was > 0.999, and we selected one of the points from the standard curve as a sample to measure its value to further evaluate the merits of the standard curve. Second, the recovery rate of a selected sample as well as the intraday and interday precision of this sample were determined. Third, Y was used as an internal standard element for Se to correct the ionization drift of the machine. The limit of detection (LOD) for Se was 0.20 μg/L. Additionally, we used certified reference
materials (LOT: 1309438) from Seronorm to perform daily quality control. Concentrations below the LOD were replaced by LOD/√2 for statistical analyses [40].

**Placental sample collection and mRNA expression assessment**

Placental tissues were collected from women within 30 min after delivery. To avoid calcification and fascia, after washing with normal saline, the placental lobule was taken, including the full-thickness placenta, and fixed quickly in liquid nitrogen. All tubes were stored at −80°C after being transported to the laboratory [41]. Using TRI reagent (MRC Inc., Cincinnati, OH, USA), total RNA was isolated according to the manufacturer’s protocol. Human subjects participated in this study after informed consent was obtained.

**Analysis of mRNA expression**

All RNA quality was assessed using the Nanodrop® ND-1000 (Nano-Drop), and all RNA used in the analysis had 260/280 values ≥ 1.8. Using the AMV Reverse Transcription System (Promega; Madison, WI, USA), total RNA (1.0 μg) was reverse transcribed into cDNA according to the manufacturer’s instructions. Real-time PCR was performed with a Light Cycler® 480 SYBR Green I Kit (Roche Diagnostics GmbH, Manheim, Germany) using gene primers as listed in Supplementary Table S1. The amplification reactions were run on a Light Cycler® 480II Instrument (Roche Diagnostics GmbH, Mannheim, Germany). The real-time PCR protocol consisted of an initial hold step (95°C for 10 min), followed by 45 cycles of a three-step PCR (95°C for 15 s, 60°C for 15 s, 72°C for 20 s) [42]. All RT-qPCR data were normalized to an endogenous reference RNA, 18SrRNA [31–33]. Delta Ct (ΔCt) was defined as the expression difference between the target mRNA and the normalizing RNA: ΔCt = Ct mRNA− Ct normalizing RNA [43].

**Statistical analysis**

Descriptive statistics for maternal demographic and clinical characteristics were calculated according to study outcomes using the mean ± standard deviation (SD).

The correlation between Se levels in each trimester of pregnancy and cord blood was examined using the Pearson linear correlation coefficient. Pearson correlation analysis was also used to explore potential associations between placental stress and mRNA levels of inflammation-related genes. The Pearson correlation coefficients between various placental inflammatory mRNAs were statistically significant and ranged from 0.064 to 0.831 (Supplementary Table S2).

Multiple linear regression models were used to analyze the association between serum Se and placental stress and inflammatory mRNA. We evaluated two main models: Model 1 represented our crude model, and Model 2 was conducted with adjustment for potential confounders. The evaluated covariates that were identified from the literature were as follows: maternal age, race (Han ethnicity, other), residence in the previous 6 months (village, city), poverty status (yuan/RMB < 2 500, 2 500–4 000, > 4 000), education (< high school, > high school), smoking (yes, no), alcohol consumption (yes, no), parity (nulliparous, parous), method of delivery, pregnancy complication, infant sex, and multiple micronutrient supplementation before pregnancy, in the first trimester, in the second trimester, and in the third trimester (including Se).

For all statistical analyses, two-sided tests and a 5% (i.e. p-value < .05) level of significance were used. Analyses were performed using SPSS 16 for Macintosh (SPSS, Inc., Chicago, IL, USA).

**Results**

**Population characteristics**

Ultimately, 2,519 participants were enrolled in the study. The mean age and pre-pregnancy BMI of the pregnant women were 26.34 years and 20.57 kg/m², respectively. Most of the participants lived in cities, and 60.06% of them had received higher education. Most pregnant women had no history of drinking (92.02%) or smoking (95.91%). Most pregnant women did not take additional micronutrient supplements (including Se) at different stages of pregnancy (first (75.31%), second (90.23%) and third (92.02%) trimesters). Additionally, study participant characteristics, including maternal age, race, maternal complications, residence in the previous 6 months, poverty status, parity, maternal complications, and method of delivery, were also investigated. The detailed questionnaire for these 2519 women is provided in Table 1.

**Se level during pregnancy**

Se levels in the blood collected in each trimester of pregnancy and in cord blood, are presented in Table 2, and correlations between microelement levels in each period are shown in Table 3. The mean Se levels were 74.27 ± 16.32 μg/L in the first trimester, 71.91 ± 15.91 μg/L in the second trimester, and 45.37 ± 13.63 μg/L in cord blood. The weakest
A correlation was observed between Se levels in the different trimesters of pregnancy and cord blood (correlation coefficients ranged from 0.139 to 0.259). Indicators of placental inflammatory factors and inflammation-associated mRNA, including the OS indicator heme oxygenase-1 (HO-1), hypoxia stress index hypoxia inducible factor 1α (HIF1α), endoplasmic reticulum stress index glucose regulated protein 78 (GRP78), proinflammatory cytokines interleukin-1 (IL-1), c-reactive protein (CRP), classically activated macrophage (M1) biomarker cluster of differentiation 68 (CD68), and macrophage (M2) biomarker cluster of differentiation 206 (CD206), exhibited values of 1.03 ± 1.42, 0.56 ± 1.43, 1.31 ± 1.97, 0.90 ± 1.42, 1.31 ± 2.25, 1.95 ± 1.92, and 1.39 ± 1.63, respectively.

| Table 1. Study population characteristics (N = 2 519). |
|-----------------------------------------------|
| **Characteristics** | n (%) |
| Age | 26.34 ± 3.56* |
| Pre-pregnancy BMI (kg/m²) | 20.57 ± 2.78* |
| Education | |
| ≤ High school | 1 066 (39.94) |
| > High school | 1 513 (60.06) |
| Residence in the previous 6 months | |
| Village | 266 (10.56) |
| City | 2 253 (89.44) |
| Family monthly incomeb | |
| Low | 647 (25.68) |
| Middle | 1 091 (43.32) |
| High | 781 (31.00) |
| Cigarette smoking | |
| Yes | 103 (4.09) |
| No | 2 416 (95.91) |
| Alcohol consumption | |
| Yes | 201 (7.98) |
| No | 2 318 (92.02) |
| Micronutrient supplementation before pregnancyc | |
| Yes | 184 (7.30) |
| No | 2 335 (92.70) |
| Micronutrient supplementation during the first trimesterc | |
| Yes | 622 (24.69) |
| No | 1 897 (75.31) |
| Micronutrient supplementation during the second trimesterc | |
| Yes | 246 (9.77) |
| No | 2 273 (90.23) |
| Micronutrient supplementation during the third trimesterc | |
| Yes | 201 (7.98) |
| No | 2 318 (92.02) |
| Maternal complication | |
| Gestational diabetes | 329 (13.06) |
| Preeclampsia | 45 (1.19) |
| Pregnancy-induced hypertension | 94 (3.73) |
| Intrahepatic cholestasis of pregnancy | 146 (5.80) |

*Mean ± SD.

bLow income for < 2000 RMB per month, middle income for 2500–4000 RMB per month, and high income for > 4000 RMB per month.

cMultiple micronutrient supplementation including Se.

| Table 2. Characteristics of the exposure and outcome variables. |
|-------------------------|--------|--------|--------|--------|
| Variables | Serum Se concentration (µg/L) | Placental stress (N = 2 519) | Placental inflammation (N = 2 519) |
| | in 1st trimester of pregnancy (N = 2 284) | in 2nd trimester of pregnancy (N = 2 409) | in cord blood (N = 2 441) | HO-1 | | HIF1α | | GRP78 | | IL-1 | | CRP | | CD68 | | CD206 |
| | Mean | SD | Min | Max | Mean | SD | Min | Max | Mean | SD | Min | Max | Mean | SD | Min | Max |
| | 74.27 | 16.32 | 11.74 | 214.32 | 71.91 | 15.93 | 25.77 | 188.25 | 45.37 | 13.63 | 14.25 | 177.61 | 1.03 | 1.42 | –4.53 | 7.60 | 0.56 | 1.43 | –6.43 | 7.77 | 1.31 | 1.97 | –10.13 | 7.57 | 0.90 | 1.42 | –4.09 | 5.81 | 1.31 | 2.25 | –6.29 | 7.00 | 1.95 | 1.92 | –6.74 | 7.74 | 1.39 | 1.63 | –4.37 | 6.40 |
Table 4 presents the associations of maternal Se levels in the first and second trimesters of pregnancy in cord blood and with placental stress and mRNA expression of inflammatory genes. In the adjusted model, a statistically significant negative association was observed between Se levels in the second trimester of pregnancy and placental HO-1 \((\beta = -0.009, p < .01)\), HIF1\(\alpha\) \((\beta = -0.005, p = .010)\), GRP78 \((\beta = -0.011, p < .001)\), CRP \((\beta = -0.007, p = .033)\) and CD68 \((\beta = -0.006, p = .019)\) mRNA expression. A negative association was noted between Se levels in cord blood and placental HO-1 \((\beta = -0.007, p = .004)\), HIF1\(\alpha\) \((\beta = -0.006, p = .005)\) and GRP78 \((\beta = -0.009, p = .004)\) mRNA expression.

Discussion

Pregnancy is an exceptional condition of enhanced demand for various nutrients. Poor maternal nutritional status during pregnancy may affect children’s cognitive function, psychomotor ability, intelligence, and behavioral maturity [44,45]. Micronutrient supplements that are widely recommended during pregnancy can have a major impact on the fetus. This large sample-based Ma’anshan-Anhui Birth Cohort study indicated that Se status during pregnancy was inversely correlated with placental stress and inflammation. Alternatively, it should be noted that the significant effects of Se status on placental stress are observed mainly in serum from the second trimester and cord blood, and the effects of Se status on placental inflammation were found mainly in the second trimester of pregnancy. These results indicate that achieving and maintaining an optimal trough level for prophylaxis during pregnancy or supplementing the diet with Se may help reduce the generation of placental OS. Correspondingly, after Se supplementation or maintenance of an optimal Se status during pregnancy, the expression levels of related inflammatory mRNAs may decrease rapidly. This study shows that Se plays an important role in ensuring the safety of the fetus during pregnancy, especially in the second trimester.

The prospective study design and assessment of Se levels in each trimester of pregnancy as well as in maternal (at delivery) and cord blood samples are important advantages of this study. We measured Se levels in the first \((74.27 \mu g/L)\) and second \((71.91 \mu g/L)\) trimesters of pregnancy and cord blood \((45.37 \mu g/L)\), as shown in Table 2. These values are higher than the 48.3 \(\mu g/L\) in the first trimester of pregnancy, 42.3 \(\mu g/L\) in the second trimester of pregnancy, and 31.1 \(\mu g/L\) in cord blood reported in the Polish mother and child cohort study [45]. Interestingly, the \(> 100 \mu g/L\) Se levels reported in the other two studies [46,47] were significantly higher than those noted in our study. The differences between studies may be due to dietary differences and regional differences between studies. However, all the findings support the notion that the appropriate level of Se is beneficial during the gestational period. As shown in Table 3, we found that Se levels in the first and second trimesters and in cord blood exhibited a weak positive correlation based on Pearson correlation analysis. Therefore, to some extent, the earlier Se was supplied, the better the Se level would be during pregnancy.

A large number of studies have shown that Se plays an important role in the development of diseases. Liu [39] found that Se content in children’s hair is negatively correlated with the incidence of Kashin-Beck disease. A U-shaped association is potentially noted between Se content and Keshan disease in children. A preliminary cohort explored the relationship between serum Se levels in the first trimester of pregnancy and the risk of gestational diabetes and preterm
Linear regression analyses of the association between Se levels and inflammatory factors and stress factors in the placentas (l, 95\%CI).

| Placental stress | Placental inflammation |
|------------------|------------------------|
| HO-1             | IL-1                   |
| First trimester  | N = 2284               |                      |
|                 | 0.004 (±0.002, 0.006)  | 0.005 (±0.004, 0.007) |
| Second trimester | N = 2409              |                      |
|                 | 0.003 (±0.003, 0.006)  | 0.004 (±0.005, 0.008) |
| Cord blood      | N = 2181              |                      |
|                 | 0.002 (±0.001, 0.004)  | 0.002 (±0.004, 0.007) |

CI: confidence interval; Model 1: the crude model; Model 2: adjusted for maternal age, pre-pregnancy BMI, race, education, residence in the previous 6 months, poverty status, smoking status, alcohol consumption, parity, method of delivery, maternal complication, infant sex, multiple micronutrient supplementation before pregnancy, first trimester, second trimester, third trimester (including Se).

Table 4. Linear regression analyses of the association between Se levels and inflammatory factors and stress factors in the placentas (l, 95\%CI).

The limitations of this study are worth noting. Firstly, human exposure to Se and its various chemical species can occur through food, water, and air, and diet serves as major source of human Se exposure. However, we cannot include dietary habits in the statistical analysis due to the complexity of the sample.
and high variability in Se content in foods even within small geographical areas. Secondly, we did not evaluate whether a correlation existed between other trace elements and Se levels. For example, some studies have reported that trace elements, such as iodine and zinc, also have an antioxidant effect, whereas the potential effects of various micronutrients on OS have not been completely studied. Additionally, the lack of additional mechanistic research and failure to establish a link between Se concentration and a disease mechanism are also limitations of this research. Our investigations demonstrate the importance of Se status during pregnancy and its correlation with OS and inflammation indicators. In addition, these results also support the relevant evidence regarding the cause of diseases during pregnancy, and it is worth noting that in-depth mechanistic research may have far-reaching significance.

Conclusion

Micronutrients have an important impact on the health of pregnant women and growing fetuses. Prenatal Se levels are associated with placental stress and inflammation. This cohort study revealed that Se deficiency during pregnancy may lead to the generation of OS and an increase in inflammatory mediators, mainly in the second trimester, thus affecting fetus growth and development. Therefore, the nutritional status of women during pregnancy must be carefully monitored to prevent nutritional imbalance and the lack of important micronutrients and avoid adverse effects on the fetus. Preeclampsia is a persistent hypertensive gestational disease characterized by high blood pressure and proteinuria that presents during the second trimester of pregnancy and is largely related to the release of free radicals by the placenta. Due to the early time points included in our work and time and funding constraints, we failed to correlate the effects of Se supplemetations on placental stress and inflammation with diseases. In future studies, we will focus on the impact of antioxidant and inflammatory effects produced by Se supplemetations during pregnancy on improving or alleviating a series of pregnancy complications, such as eclampsia.

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Ethics approval and consent to participate

The study was approved by Ethical Committee of Anhui Medical University (Number: 20131195). Written informed consent was obtained from all participants. All methods were performed in accordance with the relevant guidelines and regulations, including Declaration of Helsinki.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. Data are available from the corresponding author.

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