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Original article

Selenium status in pregnancy influences children's cognitive function at 1.5 years of age

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SUMMARY

Background & aims: Selenium deficiency has been shown to affect the neurological development in animals, but human research in this area is scarce. We aimed to assess the impact of selenium status during pregnancy on child development at 1.5 years of age.
Methods: This prospective cohort study was nested into a food and micronutrient supplementation trial (MINIMat) conducted in rural Bangladesh. Using inductively coupled plasma mass spectrometry, we measured selenium concentrations in erythrocyte fraction of blood collected from 750 mothers at gestational week 30, and calculated μg per g hemoglobin. A revised version of Bayley Scales of Infant Development was used to assess children's mental and psychomotor development. A Bangladeshi version of MacArthur's Communicative Development Inventory was used to assess language comprehension and expression. Linear regression analyses adjusted for multiple covariates were used to assess the associations.
Results: Maternal erythrocyte selenium concentrations varied considerably, from 0.19 to 0.87 μg/g hemoglobin (median 0.46 μg/g hemoglobin), and were associated with developmental measures. An increase in erythrocyte selenium by 0.50 μg/g hemoglobin was associated with an increase in children's language comprehension by 3.7 points (0.5 standard deviations; 95% confidence interval: 0.40, 7.1; $p = 0.028$). The same increase in erythrocyte selenium corresponded to an increase in the girls' psychomotor development by 12 points (0.9 standard deviation; 95% confidence interval: 4.3, 19; $p = 0.002$), but much less in boys.
Conclusions: Low prenatal selenium status seems to be disadvantageous for children's psychomotor and language development. Further studies are needed to elucidate the underlying mechanisms of these effects.

1. Introduction

Selenium is a non-metallic micronutrient, which is an essential component of a number of enzyme families, such as glutathione peroxidases and thioredoxin reductases. These enzymes act as antioxidants by catalyzing the breakdown of hydrogen peroxides and lipid peroxides [1]. Selenium is also incorporated into deiodinases, which are responsible for the conversion of the thyroid hormone thyroxine (T4), to its active form, triiodothyronine (T3). All these enzymes are important for early-life development.

The recommended daily intake of selenium varies between 50 and 60 μg/d, depending on gender and age group [1]. During pregnancy, the requirement for selenium increases [2]. The fetal demand is around 4 μg/d, leading to a general recommendation of 60 μg/d for pregnant women [1,2].

In animal models, selenium deficiency has been shown to affect the neurological development in the offspring [3]. Little is, however, known about the effects of selenium deficiency in humans, although many micronutrients have been related to impaired development of the nervous system [3]. Also, low levels of thyroid hormones during the perinatal development are known to induce irreversible motor and intellectual deficits, and in severe cases cretinism [2]. In addition, the developing fetal brain is very susceptible to free-radical damage [4], and gestational stress has

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Abbreviations used

As	arsenic
BAZ	BMI for Age z-score
Cd	cadmium
Ery	erythrocyte
GW	gestational week
HAZ	height for age z-score
HDSS	health and demographic surveillance system
HOME	home observation for measurement of the environment
icddr,b	International Centre for Diarrhoeal Disease Research, Bangladesh
ICPMS	inductively coupled plasma mass spectrometry
LOD	limit of detection
MDI	mental development index
MINIMat	Maternal and Infant Nutrition Interventions in Matlab
Mn	manganese
Pb	lead
PDI	psychomotor development index
Se	selenium
SES	socioeconomic status
T3	triiodothyronine
T4	thyroxine
U	urinary
WAZ	Weight for age z-score
WHZ	Weight for height z-score
Zn	zinc

previously been associated with impaired learning and memory, deficits in attention, and altered social behaviors [5]. The purpose of this prospective cohort study was therefore to clarify if maternal selenium status in pregnancy may influence development in early childhood.

2. Subjects and methods

2.1. Study area and subjects

The study area is Matlab, situated 53 km southeast of Dhaka, Bangladesh. In this area the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) has a hospital and four health care facilities, which support clinical and public health research by providing community based reproductive and child health services. Icddr,b is also running a health and demographic surveillance system (HDSS) in the area, which is updated on a monthly basis via community health workers that visit all households in Matlab. The HDSS contains information about vital events, such as births, deaths and in- and out migration.

The present prospective cohort study is an addition to a longitudinal study on the associations between exposure to arsenic through drinking water and other pollutants in pregnancy and child development in Matlab [6]. The cohort was nested in the Maternal and Infant Nutrition Interventions in Matlab (MINIMat), a food and micronutrient supplementation trial during pregnancy [7]. The women were recruited in early pregnancy, at gestational week 8 (GW 8) on average, between November 2001 and October 2003. The criteria for the pregnant women's enrollment in the trial were: viable fetus, gestational age less than 14 weeks by ultrasound examination, no severe illness, and written consent for participation [7]. All women recruited in the trial were randomized into two different food groups and three different micronutrient supplementation groups, resulting in a total of six groups [7]. The micronutrient supplementation, which was initiated at GW 14, consisted of either 30 mg of iron and 400 μg of folic acid, 60 mg of iron and 400 μg of folic acid (WHO's standard supplementation for pregnant women), or a multiple micronutrient capsule containing 30 mg of iron and 400 μg of folic acid, as well as 13 other micronutrients, including 65 μg of selenium in the form of sodium selenite, 15 mg zinc and 150 μg iodine [7]. The women were also randomized to receive food supplementation (608 kcal of energy and 18 g of vegetable protein provided six days a week) directly after recruitment (around GW 9) or according to common practice (around GW 20) [7]. Venous blood samples were collected around GW 14 and 30.

Out of the 4436 pregnant women recruited to the trial, 3267 had singleton live births with anthropometry measures at birth. The infants born from August 2002 to September 2003 ($n = 2853$) were selected for developmental assessments at 1.5 years of age, and for evaluation of the impact of the supplementation and arsenic exposure [6]. In total, 2112 of the children (72%) had their development assessed at 1.5 years. The main reasons for loss to follow-up were being away from home on visits ($n = 351$), refusal ($n = 185$), death ($n = 89$), moving out of area ($n = 52$), disability ($n = 5$) and illness at the time of testing ($n = 59$) [6]. From the mothers recruited to the MINIMat trial throughout 2002 ($n = 2119$), we analyzed available blood samples from 900 women for toxic and essential elements in blood. Reasons for missing blood samples were refusal and blood samples being used for other purposes. Of the 900 women with blood samples analyzed, 729 children had their development tested at 1.5 years of age. These mothers were slightly older (mean: 26.6 *vs* 26.2 years; $p = 0.032$) and had slightly lower BMI (19.9 *vs* 20.2 kg/m^2; $p = 0.041$) and lower SES (−0.24 *vs* 0.03; $p = 0.012$), compared to those who had no selenium measurements.

The project was approved by the research and ethical review committees at icddr,b and the Ethical Committee at the Karolinska Institutet. The study was conducted in accordance with the Helsinki Declaration. The main caretakers gave their written consent at recruitment in the MINIMat trial [7], and again before the developmental testing of the children at 1.5 years of age [6].

2.2. Sample collection and selenium analysis

The most commonly used biomarker of selenium status is the concentration in plasma [8,9]. However, plasma selenium tends to saturate at high concentrations [9], and is also influenced by inflammatory response [8]. Selenium is incorporated into glutathione peroxidase in the erythrocytes, but the selenium concentrations may rise above enzyme saturation in the erythrocytes [9], probably due to binding to hemoglobin [1]. Therefore, erythrocyte selenium (Ery-Se) is suggested as a suitable biomarker of long-term selenium status [1], and was used as such in the present study. To adjust for differences in hematocrit, Ery-Se was expressed as μg/g hemoglobin (Hb) [8].

Blood samples were collected in 5.5 mL Li-heparin tubes at the health care facilities, and the samples were then transported chilled to the hospital laboratory. The samples where centrifuged for separation of plasma and erythrocytes, and the erythrocyte fraction was kept frozen during transportation to Karolinska Institutet, Sweden, for analysis of selenium and other elements. Hemoglobin

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