

## Relationship between maternal sodium intake and blood lead concentration during pregnancy

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### Abstract

Pb is released from bone stores during pregnancy, which constitutes a period of increased bone resorption. A high Na intake has been found to be negatively associated with Ca and adversely associated with bone metabolism. It is possible that a high Na intake during pregnancy increases the blood Pb concentration; however, no previous study has reported on the relationship between Na intake and blood Pb concentration. We thus have investigated this relationship between Na intake and blood Pb concentrations, and examined whether this relationship differs with Ca intake in pregnant Korean women. Blood Pb concentrations were analysed in 1090 pregnant women at mid-pregnancy. Dietary intakes during mid-pregnancy were estimated by a 24 h recall method covering the use of dietary supplements. Blood Pb concentrations in whole-blood samples were analysed using graphite furnace atomic absorption spectrophotometry. Multiple regression analysis performed after adjustment for covariates revealed that maternal Na intake was positively associated with blood Pb concentration during pregnancy, but only when Ca intake was below the estimated average requirement for pregnant Korean women ( $P=0.001$ ). The findings of the present study suggest that blood Pb concentration during pregnancy could be minimised by dietary recommendations that include decreased Na and increased Ca intakes.

**Key words:** Sodium intake: Calcium intake: Blood lead concentrations: Pregnancy

Pb is a heavy metal that, even at low levels, is considered harmful to maternal and fetal health, causing adverse reproductive outcomes<sup>(1,2)</sup> in pregnant women and neurobehavioural disorders<sup>(3,4)</sup> in their children. Pb binds directly to circulating erythrocytes, with approximately 95% of it accumulating in the skeleton<sup>(5)</sup>. During pregnancy, Pb is released from maternal bone stores into the circulation due to increased mobilisation through bone resorption<sup>(6–8)</sup>. Increased blood Pb concentrations during pregnancy are a health problem for the fetus because Pb is rapidly transferred across the placenta to the fetus<sup>(9)</sup>. We previously found a significant positive correlation between blood Pb concentration in pregnant women and that in the umbilical cord blood<sup>(10)</sup> in populations with low-level Pb exposure. Therefore,

protecting the fetus even from low-level Pb exposure requires efforts to minimise maternal exposure to Pb<sup>(1,9)</sup>.

Pregnancy alters maternal Ca metabolism and bone mineral status in order to supply Ca to the fetus for growth and bone mineralisation<sup>(11,12)</sup>. The associated high Ca requirement is often met by an increased dietary Ca intake and/or mobilisation of Ca in the maternal skeleton<sup>(12)</sup>. Several studies have demonstrated that a higher Ca intake during pregnancy is associated with lower maternal blood Pb concentration due to a decreased bone turnover<sup>(13–15)</sup>. However, most of the studies related to blood Pb concentrations and mineral nutrition in pregnant women have only considered Ca or Ca-providing food groups such as milk and dairy products.

Dietary Na intake has been reported to adversely affect Ca metabolism and bone mass<sup>(16)</sup>. In the Korean population,

**Abbreviations:** EAR, estimated average requirement; MOCEH, Mothers and Children's Environmental Health.

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the intake of dietary Na is 2.5 times higher than the adequate intake, while that of Ca is only 65% of the estimated average requirement (EAR)<sup>(17)</sup>. Ritchie *et al.*<sup>(18)</sup> demonstrated that dietary Na intake is positively associated with urinary Ca excretion during pregnancy. The enhancement of Ca excretion induced by a high salt intake is associated with elevated markers of bone resorption, suggesting that increased urinary Ca excretion due to increased dietary salt intake has an adverse effect on bone mineralisation<sup>(19)</sup>. Experimental animal studies have shown that high Na leads to a decrease in bone mineral content, especially when dietary Ca intake is low<sup>(20,21)</sup>. Thus, it is possible that combining a high Na intake with a low Ca intake during pregnancy could increase blood Pb concentration by increasing bone turnover. Therefore, the present study investigated the relationship between dietary Na intake and blood Pb concentration in pregnant Korean women, and examined whether this relationship differs with Ca intake.

## Subjects and methods

### Study subjects

The subjects of the present study participated in the Mothers and Children's Environmental Health (MOCEH) study, which is a multi-centre (Seoul, Ulsan and Cheonan) birth cohort study in South Korea. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all subjects provided a written informed consent. The study was reviewed and approved by the three institutional review boards at the Ewha Womans University School of Medicine, Dankook University Hospital and Ulsan University Hospital, and it has been described in detail elsewhere<sup>(22)</sup>. Of a total of 1824 women who participated in the MOCEH study between August 2006 and October 2011, we excluded thirty-one women who were pregnant with twins, thirteen with congenital anomaly, twenty-four with spontaneous abortion, three with intra-uterine growth retardation and thirty-nine with pregnancy complications (hypertension and/or diabetes). Of the 1714 pregnant women, we excluded 112 without blood Pb concentrations and 189 whose dietary intake data were not collected and 168 without gestational age at blood sampling. Blood Pb follows a U-shaped pattern during pregnancy<sup>(9)</sup>, and hence we excluded a further 155 women with a gestational age at blood collection of <12 or >30 weeks. Therefore, 1090 subjects were finally included in the analysis performed in the present study. Pre-pregnancy BMI was calculated using the self-reported height and weight. Using a structured questionnaire, trained personnel interviewed the participants to obtain demographic and socioeconomic data and information on health-related behaviours.

### Dietary assessment

Dietary intake data for 1 d before blood sampling were obtained by well-trained dietary interviewers using 24 h recall. Dietary intakes were analysed using a computerised nutrient-intake assessment software program (CAN-Pro 3.0; Korean Nutrition Society). Information on self-reported supplement use was

obtained by asking about the type (vitamins, minerals and others) and brand name of supplements, and the amounts and frequencies of their use. The total intake of each nutrient was calculated by adding the amounts from all supplements to the dietary intake. Ca intake data, including supplements, were compared with the EAR of the Korean Dietary Reference Intake<sup>(23)</sup>.

### Blood lead concentration

Maternal blood samples were drawn after a 12 h overnight fast by a trained technician or nurse using standard venepuncture. The whole-blood samples were stored at -70°C until analysis. The samples were diluted to 1:20 with a matrix modifier (0.2% HNO<sub>3</sub>, 0.5% Triton X-100 and 0.2% ammonium phosphate), and were transferred to pyrolytic-coated partitioned tubes. Pb concentrations in the whole-blood samples were analysed using graphite furnace atomic absorption spectrophotometry (AAnalyst HCA 800; Perkin Elmer) in a biorepository centre at the Blood Bank Laboratory of the NeODIN Medical Institute. The limit of detection for Pb in the whole blood was 1.2 µg/l.

### Statistical analysis

Statistical analyses were performed using the SPSS statistical package (version 12.0; SPSS). Blood Pb concentrations and dietary Na intakes of the subjects were log-transformed in order to normalise the distributions. Data are expressed as means and standard deviations (for continuous variables) or as numbers and percentages (for categorical variables). Multiple regression analysis was used to examine the relationship between Na and Ca intake and blood Pb concentration after controlling for potential confounders, including maternal age (continuous variable), pre-pregnancy BMI (continuous variable), maternal education (less than high school/high school, college, or university or higher education) and gestational age at the time of blood collection (continuous variable). Whether the relationship between dietary Na intake and blood Pb concentration at mid-pregnancy differs with Ca intake was tested in the multiple regression analysis after controlling for potential confounders. Differences were considered significant at the 5% level.

## Results

Our subjects were aged 30.1 (SD 3.6) years, and pre-pregnancy BMI was 21.5 (SD 3.3) kg/m<sup>2</sup> (Table 1). Approximately, 52.8% of the subjects had a university or higher education, and 86.2% of them were passive smokers. The average total Ca intake was 593.0 (SD 335.4) mg/d, and approximately 22% of the subjects took Ca supplements. The dietary Na intake was 4113.9 (SD 2456.9) mg/d. The whole-blood Pb concentration was 14 (SD 6) µg/l, and the gestational age at blood sampling was 18.9 (SD 3.8) weeks.

As indicated in Table 2, multiple regression analysis performed after adjustment for maternal age, pre-pregnancy BMI, total energy intake, use of Ca supplement, urinary

**Table 1.** General characteristics, dietary intake and blood lead concentrations at mid-pregnancy in Korean pregnant women  
(Mean values and standard deviations; number of participants and percentages)

	Total subjects ( <i>n</i> )	Mean	SD
Characteristics			
Age (years)	1082	30.1	3.6
Height (cm)	1020	161.2	4.8
Pre-pregnancy weight (kg)	1071	55.8	8.9
Pre-pregnancy BMI (kg/m <sup>2</sup> )	1015	21.5	3.3
Local centres	1090		
Seoul			
<i>n</i>		287	
%		26.3	
Ulsan			
<i>n</i>		435	
%		39.9	
Cheonan			
<i>n</i>		368	
%		33.8	
Education	1034		
Less than high school/high school			
<i>n</i>		284	
%		27.5	
College			
<i>n</i>		204	
%		19.7	
University or higher education			
<i>n</i>		546	
%		52.8	
Monthly household income	1019		
< \$2000			
<i>n</i>		283	
%		27.8	
\$2000–4000			
<i>n</i>		546	
%		53.6	
> \$4000			
<i>n</i>		190	
%		18.6	
Passive smokers	999		
Yes			
<i>n</i>		861	
%		86.2	
No			
<i>n</i>		138	
%		13.8	
Dietary nutrient intake	1090		
Energy (kcal/d)		1829.2	492.1
Energy (kJ/d)		7653.4	2058.9
Carbohydrate (% energy)		61.4	10.1
Protein (% energy)		15.5	3.6
Fat (% energy)		23.9	8.0
Total Ca (mg/d)		593.0	335.4
Na (mg/d)		4113.9	2456.9
Ca supplement users	1090		
<i>n</i>		240	
%		22.0	
Blood Pb concentrations (µg/l)	1090	13.9	6.3
Gestational age at blood sampling (weeks)	1090	18.9	3.8
Urinary cotinine concentration (µg/g creatinine)	1030	40.9	287.3

cotinine concentration, gestational age at blood collection and local centres showed that dietary Ca intake was inversely, but not significantly ( $P=0.120$ ), associated with blood Pb concentration, whereas dietary Na intake was positively associated with blood Pb concentration ( $P=0.016$ ). However, when Ca intake was dichotomised at the EAR for pregnant women (840 mg/d), dietary Na intake was positively and significantly

associated with blood Pb level only among women with low dietary Ca intake ( $P=0.001$ ) (Table 3).

## Discussion

Bone resorption is significantly higher during pregnancy than before pregnancy<sup>(24)</sup>, and blood Pb concentration is known to

**Table 2.** Coefficients from multiple regression analysis between dietary sodium intake and total calcium intake, and blood lead concentration at mid-pregnancy\*

( $\beta$  Coefficients with their standard errors)

	Blood Pb concentration at mid-pregnancy		
	$\beta$	SE	P
Na intake	0.089	0.037	0.016
Total Ca intake	-0.050	0.032	0.120

\*Blood Pb concentration, and dietary Ca and Na intakes were log-transformed and adjusted for maternal age, pre-pregnancy BMI, total energy intake, use of Ca supplements, urinary cotinine concentration, gestational age at blood collection and local centres.

increase during periods of bone resorption such as pregnancy and lactation<sup>(6,9)</sup>. Many researchers have demonstrated that even a low concentration of Pb can have adverse effects on fetal growth and development<sup>(1,3,25)</sup>, which makes it important to identify factors that influence bone resorption in pregnancy. Studies of the effects of dietary nutrient intake on bone metabolism have focused on Ca as the major element contributing to bone mass<sup>(16,26)</sup>. However, other nutrients, including Na, also have been reported to affect Ca metabolism<sup>(27)</sup>. Several investigators have demonstrated that dietary Na intake affects Ca excretion independently of other dietary factors, and have suggested that a Na intake within the range for a normal diet is an important determinant of bone Ca loss<sup>(18,28)</sup>. Sekine *et al.*<sup>(29)</sup> reported that dietary Na intake is inversely related to the change in bone mass during pregnancy and postpartum periods in healthy women. These results suggest that a high Na intake could enhance blood Pb concentration during pregnancy by increasing bone resorption.

During pregnancy, maternal Ca requirement increases due to the growing fetus, and the associated responses include increased Ca absorption and/or bone turnover, and reduced Ca excretion<sup>(12,24)</sup>. Aguado *et al.*<sup>(30)</sup> reported that bone mineral density is lower in pregnant women with a low Ca intake. When maternal Ca is insufficient, bone demineralisation may occur due to Ca homeostasis, which leads to an

increased blood Pb concentration<sup>(9)</sup>. However, in the present study, we found no association between Ca intake and blood Pb concentration. Approximately 74% of our subjects did not meet the EAR for Ca intake during pregnancy (840 mg/d), whereas the mean dietary Na intake was 4113.9 mg/d, which is more than 2.7 times the adequate intake. Carbone *et al.*<sup>(31)</sup> suggested that populations that consume lower amounts of Ca are the most sensitive to the effects of Na-induced bone resorption. Thus, in the present study subjects, dietary Na intake may be more relevant than Ca intake for determining bone resorption and the subsequent increase in blood Pb concentration during pregnancy.

We found a positive association between dietary Na intake and blood Pb concentration at mid-pregnancy, but this disappeared for high total Ca intakes ( $\geq 840$  mg/d). This observation could indicate that Ca and Na share a common transport mechanism in the kidney, and so when Ca intake is low, it is Na rather than Ca that plays a major role in determining how much Ca is excreted<sup>(32,33)</sup>. Several studies have found that the modulating effects of Na excretion on Ca excretion were more sensitive with a lower Ca intake<sup>(25,34)</sup>. Ilich *et al.*<sup>(35)</sup> reported that adequate Ca intake appears to alleviate the deleterious effects of salt intake on bone metabolism. An animal experimental study has shown that a high salt intake leads to a decrease in bone mineral density in rats fed a low-Ca diet<sup>(20)</sup>. Pb is released from bone stores into the circulation during periods of bone resorption, such as pregnancy<sup>(36,37)</sup>. An increased blood Pb concentration can have demonstrable adverse effects on fetal growth, including cognitive and behaviour development<sup>(3,25,38)</sup>, making it important to minimise the blood Pb concentration during pregnancy. Considering that maternal Na intake may be a major factor influencing the blood Pb concentration via increased bone mineralisation, an adequate Ca intake in pregnant women could negate the positive relationship between dietary Na intake and blood Pb concentration.

The present study was subject to a few limitations. First, we did not measure bone mineral density. This is usually achieved using dual-energy X-ray absorptiometry, but this method is unsuitable for application to pregnant women. Second, a 24 h recall method might not be sufficient to assess the usual daily intake due to large intra-individual variabilities in food and nutrient intakes. However, possible bias was minimised by employing trained dietitians using standard protocols in order to help the subjects reflect on their daily diet. There is also a report available from a study which was conducted as a part of the Korea National Health and Nutrition Examination Survey in 2009<sup>(39)</sup>. This report has shown that the values for total energy and other nutrients, obtained from each interview, were not much different; 1.1% for energy and 0.84% for Na intake, from an additional 1 d, 24 h dietary recall to an original 1 d dietary interview. Third, we did not consider the potential effects of the overall diet or other minerals which also have been linked to bone health. We tried to analyse whether other minerals such as K and Mg have any influences on the present data. For K, we found no relationship between maternal K intake and blood Pb concentration ( $r = 0.374$ ,  $P = 0.438$ ) and for Mg, the database in CAN-Pro

**Table 3.** Coefficients from multiple regression analysis between dietary sodium intake and blood lead concentration at mid-pregnancy according to total calcium status\*

( $\beta$  Coefficients with their standard errors)

	Blood Pb concentration at mid-pregnancy*			
	Dietary Na intake			P
	n	$\beta$	SE	
Total Ca intake				
Less than EAR	751	0.141	0.043	0.001
Above EAR	233	-0.010	0.075	0.894

EAR, estimated average requirement.

\*Blood Pb concentration and dietary Na intakes were log-transformed and adjusted for maternal age, pre-pregnancy BMI, total energy intake, use of Ca supplements, urinary cotinine concentration, gestational age at blood collection and local centres.



3.0 (nutrient-intake assessment software program; Korean Nutrition Society) was insufficient to carry out the statistical analysis. Nonetheless, to the best of our knowledge, this is the first study involving a large cohort demonstrating a positive association of maternal dietary Na intake with blood Pb concentration during pregnancy.

In conclusion, we found that maternal Na intake was positively associated with blood Pb concentration at mid-pregnancy when the total Ca intake was below the EAR (840 mg/d). The findings of the present study suggest that adequate Ca with a low Na intake may play a beneficial role in decreasing the blood Pb concentration in pregnant women. The present results might not be applicable to other populations that consume diets that are high in Ca and low in Na.

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