Postnatal Growth Following Prenatal Lead Exposure and Calcium Intake

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KEY WORDS

lead exposure, prenatal, postnatal, growth

ABBREVIATIONS

CI—confidence interval

MOCEH—Mothers and Children's Environmental Health

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WHAT'S KNOWN ON THIS SUBJECT: Lead is an ubiquitous environmental pollutant, and no safe threshold for blood lead level in children has been discovered yet. Prenatal lead exposure affects growth of children.

WHAT THIS STUDY ADDS: Low level of prenatal lead exposure of <5.0 μg/dL affects postnatal children's growth, which was further intensified by low calcium intake.

abstract

BACKGROUND: The effects on postnatal growth of maternal exposure to low levels of lead during pregnancy have not been well established. In addition, information is limited regarding the protective effect of dietary calcium intake during pregnancy against the effect of lead for fetal and postnatal growth. We investigated the relationship between prenatal exposure to lead and growth at birth and 6, 12, and 24 months postnatal, and evaluated the role of calcium intake against the effect of lead.

METHODS: A total of 1150 pregnant women, and their subsequent offspring, enrolled in a prospective birth cohort study (Mothers and Children's Environmental Health Study), were evaluated. Multivariable regression analysis was conducted to estimate the effects of prenatal maternal blood lead levels on growth at each follow-up.

RESULTS: The blood lead levels of participating mothers were <5.0 μg/dL and mean levels were 1.25 μg/dL during the early (before 20 gestational weeks) and late (at delivery) gestational periods. Prenatal exposure to lead, particularly in late pregnancy, was significantly associated with a reduction in infantile growth at 24 months. When pregnant women had dietary calcium intake at mean or upper level, the association was not significant. In contrast, lower than mean level of calcium intake intensified the adverse effect of prenatal lead exposure on growth in children.

CONCLUSIONS: Prenatal lead exposure <5.0 μg/dL adversely affects postnatal growth and low calcium intake aggravates the effect, indicating more stringent control of lead and sufficient intake of calcium are necessary to help children's health. *Pediatrics* 2014;134:1151–1159

Blood lead levels in the general population have steadily declined in most developed countries due to significant efforts to reduce the presence of lead in daily products, such as gasoline and paint. However, low-level exposure to lead still continues because of the widespread use of lead and its persistent nature.[1,2] The mean blood lead level among childbearing women in the United States was 1.2 μg/dL according to the national survey conducted in 2003–2004, and the level in childbearing Korean women was 1.6 μg/dL by the national survey conducted in 2008–2009.[3,4] Exposure to low-level lead is known to induce a wide range of adverse health effects,[5] and children are particularly sensitive to its effects because of the ongoing development of body organs and the nervous system.[6,7] Therefore, environmental exposure levels that are innocuous in adults could cause adverse effects in children.[8,9]

Although the sensitive period remains undetermined, prenatal exposure to lead is of particular concern because lead is known to cross the placenta and cause adverse birth outcomes, such as preterm birth, low birth weight, and small for gestational age.[1,10–15] Schell et al[12] found that maternal blood lead levels of $\geq$3 μg/dL during the second trimester were associated with reduced head circumference at 6 and 12 months, but had no significant effects at $<$3 μg/dL. Afeiche et al,[16] in a follow-up study of attained child weight, found that prenatal maternal bone lead was associated with lower weight over time among girls up to 5 years of age. However, they did not find a significant association between prenatal lead exposure and height or BMI of children evaluated at 48 months of age.[17] Even though there have been some reports on prenatal lead exposure and postnatal growth, the findings are inconsistent. Our understanding is limited as to whether prenatal low-level lead exposure below the recently proposed reference value of 5 μg/dL in blood, by the Centers for Disease Control and Prevention, affects fetal and child growth.[18,19]

Low dietary calcium increases intestinal absorption of lead, and thereby increases its toxic effects in humans and animals.[20,21] During pregnancy, there is an increased requirement for calcium to support fetal growth; thus, low calcium intake during the prenatal period creates a susceptible window to lead exposure in the growing fetus and infant.[22] However, information concerning the interactions between dietary calcium intake and blood lead levels during pregnancy, and its effect on fetal and child growth, is scarce. Therefore, our objective was to determine whether prenatal low-level lead exposure was associated with child weight and length at birth and 6, 12, and 24 months of age, and to evaluate whether dietary calcium intake modifies the effect of prenatal lead exposure on infant and child growth.

METHODS

Study Population and Growth Assessment

This research was conducted as a part of MOCEH (Mothers and Children's Environmental Health) study, which is a multicenter prospective hospital and community-based birth cohort study. The study has investigated the effects of environmental hazards on the health of mothers and their children in South Korea. Three regional centers in the study were located in Seoul, Cheonan, and Ulsan cities. Each center has a community-based network of a university hospital, local clinics, and community public health centers. Women who lived in these cities were enrolled in the first trimester. The participants fulfilled the inclusion criterion of age $>$18 years. Written informed consent was obtained at the initial visit from all enrolled mothers on behalf of themselves and their children. All protocols were approved by the Institutional Review Board of Ewha Womans University, Dankook University Hospital, and Ulsan University Hospital. A total of 1751 pregnant women were enrolled in the MOCEH, which was conducted in South Korea from May 2006 to December 2010 according to previously described study protocols.[23]

The study subjects were restricted to those in which maternal and cord blood lead levels were assessed, and postnatal growth measurements were performed. Overall, 1475 participants were eligible for enrollment in the study, after excluding subjects lost to follow-up before birth (n = 276). Of these 1475 women, 325 were excluded for the following reasons: low birth weight ($<$2500 g, n = 41); preterm birth (gestational week $<$37, n = 39); and missing information on maternal age (n = 47), BMI (n = 115), education level (n = 11), and gestational week (n = 35). Additionally, subjects with $>$2 SD for mean maternal blood lead levels (n = 25) and child birth weight or length (n = 12) were further excluded. Finally, 1150 pregnant women and their infants were included in the analysis (Fig 1). When we compared the characteristics of pregnant women at recruitment and their newborns at birth between the final and excluded participants, we did not find significant differences (Supplemental Table 5). Some infants did not reach the age of follow-up or were lost to follow-up, hence the numbers of children included in the analysis were 796, 717, and 628 for weight, and 781, 711, and 620 for length measures, at 6, 12 and 24 months, respectively. Those who were lost to follow-up were compared with the participants followed up at 6,12, and 24 months, respectively, but

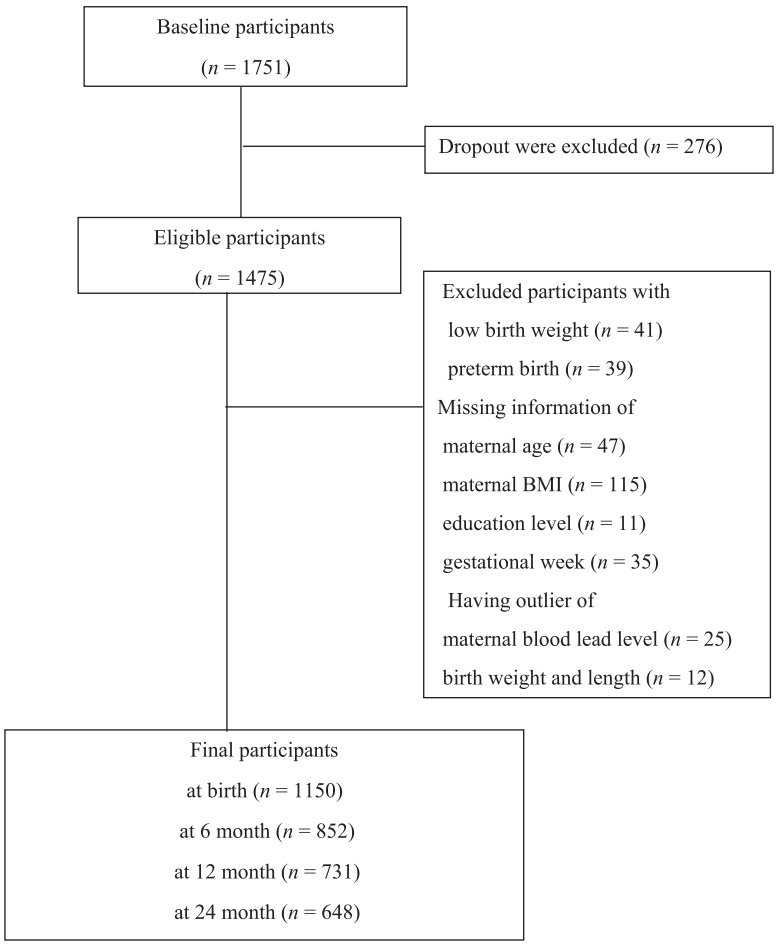

FIGURE 1
The application of exclusion criteria.

there was no difference in mother's blood lead concentration, age, education, pre-pregnancy BMI, or gestational age (t = 1.96; $P > .05$ for all covariates, respectively)

Trained nurses investigated maternal prenatal characteristics by using questionnaires that addressed maternal demographic factors, socioeconomic status, and previous obstetric history. Dietary data were collected by 24-hour recall for intake. Experienced, well-trained dietary interviewers instructed the respondents to recall and describe all of the foods and beverages that they had consumed over the past 24 hours. Information about portion sizes was gathered according to defined units by writing down on a form. The food items most frequently eaten were set as models in a defined unit and were shown to the subjects to increase the accuracy of their reporting. The household portions in each subject's record were converted to weights (in grams). The subjects' dietary intakes of nutrients and food groups were quantified using a computer-aided nutritional analysis program (CAN-Pro 3.0; Korean Nutrition Society, Seoul, Korea).Gestational ages were estimated based on the onset times of last menstrual periods. First ultrasonographic estimations of gestational age were used when last menstrual periods were deemed unreliable, or when there was significant discordance of dating (>10 days) between ultrasonographic findings and last menstrual period; 129 estimates of gestational age were based on ultrasound. After delivery, birth-related information, including gestational age, birth weight and length of newborns, gender, and obstetric complications, were obtained from delivery records. Weights and lengths at 6 and 12 months were taken by using an infantometer (DS-B02 model; Dong Sahn Jenix Co. LTD, Seoul, Korea) by laying infants on the center of a scale, and were read to 1 decimal place for weight (0.1 kg) and length (0.1 cm). At 24 months of age, weights and lengths were obtained by using an automatic measuring station for weight and length (DS-102 model; Dong Sahn Jenix Co. LTD) by standing on the center of the scale on both feet, and placing their heels, bottom, back, and posterior head on the measuring rod. For the measurement, only light clothes without socks, shoes, and any accessories were permitted for infants.

When participants visited the hospital after birth, mothers were asked to complete questionnaires regarding change of demographic characteristics, family disease history, environmental conditions, and maternal alcohol consumption since the previous visit.

Maternal Blood Lead Measurements

Whole-blood samples were obtained in metal-free tubes during early pregnancy before gestation week 20 and at delivery, which was considered representative of the late gestational period. Cord blood samples were also collected from infants. The blood samples were frozen and stored at −20°C. For measurement of lead levels, the samples were brought to room temperature and vortexed after thawing. In total, 0.1 mL of blood was diluted with 0.1% Triton X-100. The samples were mixed well using a vortex mixer and assayed by atomic absorption spectrometry on the Analyst 100 instrument (Perkin-Elmer, Norwalk, CT) by using a graphite

tube atomizer (HGA 800; Perkin-Elmer GmbH, Uberlinger, Germany). Lead concentrations were quantified in the deuterium background correction mode. For internal quality assurance and control purposes, commercial reference materials were obtained from Bio-Rad (Lyphocheks Whole Blood Metals Control; Bio-Rad, Hercules, CA). An internal control was used for each series of analyses. The limit of detection was 0.15 μg/dL and no sample had levels below the limit of detection.

Statistical Analysis

Blood lead concentrations are log transformed due to non-normal distribution. Age-specific length and weight *z* scores were calculated by WHO Anthroplus software (Department of Nutrition for Health and Development, WHO, Geneva, Switzerland).[24] We selected covariates based on biological (eg, gender and maternal and gestational age) and environmental considerations (eg, maternal BMI, education and participating clinics). Multivariable linear regression analysis was used to estimate the effects of prenatal maternal and cord blood lead levels on infant growth. The dependent variables were length-for-age and weight-for-age *z* scores, and the independent variables were child gender, maternal age, maternal education, and maternal BMI before pregnancy, gestational age, and participating clinics. Generalized additive models were applied to confirm the linearity of the relationships between maternal blood lead levels and infantile growth variables. The relation of calcium intake and maternal lead level and *z* scores of growth was examined. To explore change in growth by mother's calcium intake combined with lead exposure, stratified analysis was performed after dividing the subjects into 2 groups by mother's mean daily calcium intake at enrollment. Calcium-stratified analysis was conducted with the linear regression model controlling for the same covariates as the main analysis. Interaction between lead and calcium was calculated by adding the multiplicative interaction term between lead and calcium intake in the corresponding model.

We defined statistical significance as $P < .05$. Data were analyzed by using SAS version 9.3 (SAS Institute, Inc, Cary, NC) and R version 2.14.1 (The Comprehensive R Archive Network: http://cran.r-project.org).

RESULTS

In the study population for maternal blood lead during pregnancy and infantile growth measurements, mean maternal age was 30.2 years and mean gestational period was 39 weeks (Table 1). Forty percent of the study population had an education level lower than university, and one-quarter of the study population had what was considered to be a low income level. There were 47.4% ($n = 546$) infant girls. Mean infantile length and weight at birth and 6, 12, and 24 months of age were 50.6, 69.7, 76.8, and 87.3 cm, and 3.3, 8.5, 10.1, and 12.5 kg, respectively. Infant boys had higher weight and length than infant girls throughout the follow-up time, up to 24 months. The mean blood lead level of all participating mothers was 1.25 μg/dL in the early and late gestational periods and the mean calcium intake of mothers at the time of enrollment was 541 mg per day (Table 2).

The regression analyses for maternal blood lead levels and child weights and lengths are shown in Table 3. We found that lead levels of late pregnancy were negatively associated with *z* scores of weight for age ($\beta = -0.28$, confidence interval [CI] -0.48 to -0.09) and length for age ($\beta = -0.28$, CI -0.49 to -0.06) at 24 months. This result indicates that a 1-μg/dL increase in late pregnancy lead level decreased weight and length at 24 months by 0.28 kg and 0.51 cm, respectively.

To confirm our assumption of linear relationship between maternal blood

TABLE 1 General Characteristics of Study Subjects

Parameter	Total		Boys		Girls	
	n	Mean (SD)/[%]	*n*	Mean (SD)/[%]	*n*	Mean (SD)/[%]
Mothers						
Mother's age, y	1150	30.2 (3.6)	604	30.3 (3.76)	546	30.1 (3.6)
Pre-pregnancy BMI[a]	1150	22.8 (3.3)	604	22.9 (3.44)	546	22.7 (3.1)
Education [%]						
< University	464	[40.3]	250	[41.3]	214	[39.2]
≥University	686	[59.7]	354	[58.7]	332	[60.8]
Income, thousand KRW/mo [%]						
Up to 2000	294	[25.6]	150	[24.8]	144	[26.3]
>2000	855	[74.4]	453	[75.2]	402	[73.6]
Children						
Gestational age, wk	1150	39.0 (1.0)	604	38.9 (1.08)	546	39.1 (1.0)
Weight, kg						
At birth	1150	3.3 (0.3)	604	3.3 (0.3)	546	3.2 (0.3)
6 mo	823	8.5 (0.9)	439	8.8 (0.9)	384	8.1 (0.8)
12 mo	730	10.1 (1.0)	391	10.4 (0.9)	339	9.8 (1.0)
24 mo	648	12.5 (1.3)	347	12.8 (1.3)	301	12.1 (1.2)
Length, cm						
At birth	1077	50.6 (2.1)	565	50.9 (2.1)	512	50.3 (2.0)
6 mo	852	69.7 (2.8)	453	70.4 (2.7)	399	68.8 (2.7)
12 mo	731	76.8 (2.7)	393	77.4 (2.8)	338	76.0 (2.5)
24 mo	644	87.3 (3.1)	343	88.0 (3.2)	301	86.6 (2.9)

n indicates number of children in the model.
[a] Weight in kilograms/height in m^2.

TABLE 2 Distribution of Maternal Lead Level and Calcium Intake

Parameter	*n*	Mean (SD)	Minimum	25%	Median	75%	Maximum
Early pregnancy blood lead level,[a] μg/dL	1131	1.25 (1.46)	0.25	0.98	1.29	1.65	2.63
Late pregnancy blood lead level,[a] μg/dL	914	1.25 (1.52)	0.26	0.98	1.27	1.64	2.52
Cord blood lead,[a] μg/dL	897	0.91 (1.57)	0.11	0.71	0.93	1.19	1.90
Total calcium intake, mg/d	1110	541.00 (243.39)	42.37	359.50	506.69	697.90	1977.29

n indicates number of children.

[a] Maternal pregnancy blood lead levels are expressed in geometric mean and geometric SD.

lead levels at late pregnancy and child weights and lengths, we examined the shape of the relationships by using generalized additive models. Figure 2 shows the linear inverse association between late pregnancy blood lead levels and *z* scores of weight and length for age at 24 months.

Calcium intake was negatively associated with early and late maternal lead level ($r = -0.09$, $P < .01$, and $r = -0.05$, $P = .15$, respectively), but was not significantly positively associated with the weight and length *z* scores at 24 months ($r = 0.03$, $P = .42$, and $r = 0.05$, $P = .18$, respectively). When we stratified subjects based on the calcium intake of mothers at enrollment, during pregnancy, significant associations remained only in the group of calcium intake less than the mean level (Table 4). We found significant associations between the early-pregnancy lead levels and birth *z* scores, and the late-pregnancy

TABLE 3 Association Between Log Transformed Maternal Pregnancy Lead Levels and Children's Weight and Length *z* Scores at Birth and 6, 12, and 24 Months (β, CI)

Parameter	Unadjusted for Calcium Intake			Adjusted for Calcium Intake			*P* for Interaction Between Lead and Calcium[b]
	n	β[a]	95% CI[a]	*n*	β[a]	95% CI[a]	
Early pregnancy lead level							
Weight *z*-scores							
At birth	1123	−0.05	−0.16 to 0.06	1052	−0.05	−0.16 to 0.07	.008
6 mo	796	−0.02	−0.18 to 0.13	746	−0.03	−0.19 to 0.13	.29
12 mo	717	−0.08	−0.24 to 0.07	677	−0.10	−0.26 to 0.06	.84
24 mo	628	−0.05	−0.22 to 0.11	591	−0.05	−0.23 to 0.12	.73
Length *z*-scores							
At birth	1019	0.01	−0.14 to 0.17	953	0.01	−0.15 to 0.18	.53
6 mo	781	−0.18	−0.37 to 0.004	733	−0.17	−0.37 to 0.02	.01
12 mo	711	0.01	−0.17 to 0.21	669	0.04	−0.15 to 0.24	.06
24 mo	620	−0.15	−0.34 to 0.04	584	−0.15	−0.35 to 0.04	.83
Late pregnancy lead level							
Weight *z*-scores							
At birth	909	−0.04	−0.17 to 0.08	852	−0.01	−0.15 to 0.12	.06
6 mo	659	−0.11	−0.29 to 0.07	618	−0.15	−0.34 to 0.03	.37
12 mo	594	−0.11	−0.29 to 0.07	560	−0.15	−0.34 to 0.03	.17
24 mo	520	−0.28	−0.48 to −0.09*	488	−0.33	−0.53 to −0.13*	.50
Length *z*-scores							
At birth	824	−0.11	−0.30 to 0.06	770	−0.07	−0.25 to 0.11	.82
6 mo	641	−0.10	−0.31 to 0.11	603	−0.05	−0.28 to 0.16	.50
12 mo	589	0.10	−0.11 to 0.32	553	0.10	−0.12 to 0.33	.04
24 mo	515	−0.28	−0.49 to −0.06*	484	−0.30	−0.53 to −0.08*	.15
Cord blood lead level							
Weight *z*-scores							
At birth	891	0.06	−0.06 to 0.19	841	0.08	−0.04 to 0.21	.29
6 mo	647	0.08	−0.08 to 0.26	612	0.10	−0.07 to 0.28	.37
12 mo	586	0.04	−0.12 to 0.22	558	0.06	−0.10 to 0.24	.15
24 mo	498	−0.01	−0.21 to 0.17	472	−0.01	−0.21 to 0.18	.94
Length *z*-scores							
At birth	812	0.11	−0.05 to 0.29	766	0.14	−0.03 to 0.32	.67
6 mo	628	0.07	−0.14 to 0.28	592	0.11	−0.11 to 0.33	.27
12 mo	580	0.19	−0.01 to 0.41	550	0.22	0.01 to 0.44	.18
24 mo	491	0.02	−0.19 to 0.24	466	0.004	−0.22 to 0.22	.50

n indicates number of children included in the model. *$P < .05$.

[a] Parameter (β) and 95% CIs estimated using generalized linear regression model adjusted for mother's age, education, pre-pregnancy BMI, gestational age (wk), gender of the child, and clinic location.

[b] *P* for interaction between lead and calcium is calculated by adding the multiplicative interaction term between lead and calcium intake in the corresponding model.

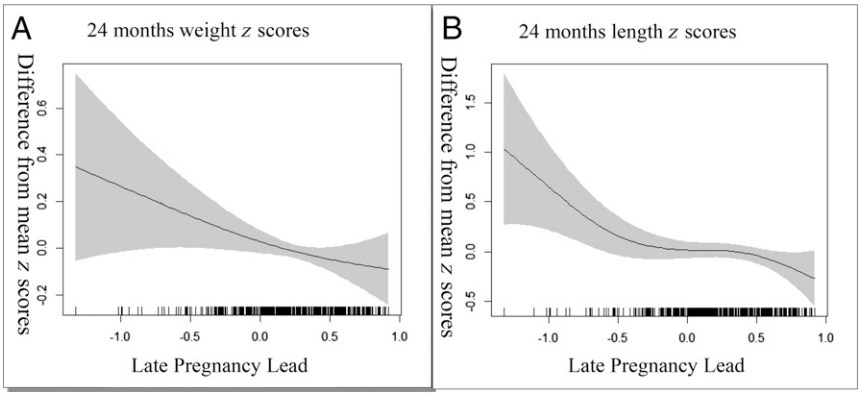

FIGURE 2
Significant inverse relation between log-transformed late pregnancy lead and 24-month weight and length-for-age *z* scores after adjusting for the covariates. Smoothing function of late pregnancy lead was used.

TABLE 4 Association Between Log-Transformed Maternal Pregnancy Lead Levels and Children's Weight and Length *z* Scores Stratified by Mother's Calcium Intake at Birth and 6, 12, and 24 Months (β, 95% CI)

	< Mean Calcium Intake (541 mg/d)			≥ Mean Calcium Intake (541 mg/d)		
	n	β[a]	95% CI[a]	*n*	β[a]	95% CI[a]
Early pregnancy lead level						
Weight-for-age *z* scores						
At birth	567	−0.18	−0.34 to −0.01*	485	0.09	−0.07 to 0.26
6 mo	375	−0.04	−0.28 to 0.19	371	0.01	−0.21 to 0.24
12 mo	357	−0.13	−0.36 to 0.09	320	−0.07	−0.30 to 0.15
24 mo	304	−0.11	−0.35 to 0.13	287	−0.02	−0.28 to 0.23
Length-for-age *z* scores						
At birth	508	−0.02	−0.26 to 0.22	445	0.03	−0.19 to 0.26
6 mo	374	−0.23	−0.51 to 0.04	359	−0.07	−0.35 to 0.19
12 mo	356	−0.14	−0.42 to 0.14	313	0.20	−0.08 to 0.48
24 mo	302	−0.16	−0.45 to 0.12	282	−0.16	−0.43 to 0.11
Late pregnancy lead level						
Weight-for-age *z* scores						
At birth	460	−0.11	−0.31 to 0.08	392	0.09	−0.09 to 0.28
6 mo	315	−0.16	−0.45 to 0.11	303	−0.14	−0.39 to 0.10
12 mo	298	−0.31	−0.59 to −0.04*	262	0.01	−0.24 to 0.27
24 mo	247	−0.41	−0.71 to −0.11*	241	−0.26	−0.54 to 0.01
Length-for-age *z* scores						
At birth	410	−0.01	−0.29 to 0.27	360	−0.12	−0.37 to 0.13
6 mo	313	0.10	−0.23 to 0.44	290	−0.14	−0.44 to 0.15
12 mo	297	−0.09	−0.43 to 0.23	256	0.30	−0.08 to 0.62
24 mo	247	−0.45	−0.80 to −0.10*	237	−0.20	−0.48 to 0.08
Cord blood lead level						
Weight-for-age *z* scores						
At birth	457	0.008	−0.16 to 0.18	384	0.17	−0.01 to 0.36
6 mo	316	0.20	−0.04 to 0.46	296	0.01	−0.23 to 0.26
12 mo	303	−0.06	−0.31 to 0.19	255	0.28	−0.02 to 0.47
24 mo	247	0.002	−0.27 to 0.28	225	−0.04	−0.33 to 0.24
Length-for-age *z* scores						
At birth	411	0.10	−0.14 to 0.36	353	0.18	−0.06 to 0.43
6 mo	309	0.20	−0.11 to 0.52	283	0.06	−0.25 to 0.37
12 mo	302	0.05	−0.24 to 0.36	248	0.40	0.09 to 0.72
24 mo	246	0.07	−0.24 to 0.40	220	−0.05	−0.37 to 0.26

n indicates number of children included in the model. *$P < .05$.
[a] Parameter, β, and 95% CIs estimated by using generalized linear regression model adjusted for mother's age, education, pre-pregnancy BMI, gestational age (wk), gender of the child, and clinic location.

lead levels and weight *z* scores from 12 months to 24 months, and length *z* scores at 24 months of age, in the low calcium intake group (Supplemental Figure 3). The regression coefficient estimates increased by almost 100% in the lower calcium intake group compared with the high calcium intake group.

DISCUSSION

This study showed that a prenatal maternal blood lead level <5 μg/dL was significantly associated with reduction in attained infantile growth at 24 months of age. This adverse effect was more pronounced in the less calcium intake group. The mean blood lead level for study participants was 1.25 μg/dL, which was much lower than 5 μg/dL, a reference value proposed by the Centers for Disease Control and Prevention. Although blood lead levels have been decreasing in developed countries due to public awareness and governmental regulations, this result raised concerns regarding low-level exposure to lead in susceptible populations.[25] It has been suggested that prenatal growth and development is highly susceptible to various environmental pollutants.[26]

Maternal lead exposure during pregnancy was reported to negatively affect gestational length and to increase the risk of preterm and small-for-gestational age infants.[1,11,12,14,25,27] However, in these studies, the lead levels in maternal blood were >5 μg/dL, thus the effects of the very low levels currently observed in developed countries are still to be thoroughly evaluated. In addition, environmental constraints on fetal growth may not only affect birth outcomes, but also have lasting effects on postnatal growth.[16] Furthermore, the consequences of reduced infantile growth are far from negligible, because even a small reduction could affect health outcomes significantly in later life.[28] Previously, Afeiche et al[16] reported that prenatal lead exposure was associated with lower

weight over time in girls up to 5 years of age. Some authors have suggested that intrauterine nutrient restriction, besides causing intrauterine growth retardation or low birth weight, had significant long-term influences on body weight and energy homeostasis in offspring.[29–31]

Although the pathophysiologic mechanisms underlying the adverse effects of lead on fetal and child growth have not been established, the disruption of thyroid signaling by lead in maternal blood could be a potential mechanism.[16] Dearth et al[32] found that maternal rats exposed to lead at levels similar to human exposure levels during gestation, decreased estradiol and insulinlike growth factor-1 levels in offspring. Because insulinlike growth factor-1 is a primary mediator of growth hormone, these findings suggested that disruption of estrogen or growth hormone also may contribute to reduced infantile growth.

Calcium demands increase significantly during pregnancy to fulfill the requirements of the growing fetus. Increase in dietary calcium during pregnancy could inhibit the harmful effect of prenatal lead exposure on fetal development.[21] Because lead can substitute for calcium in Ca^{2+} (calcium)/Na^{2+} (sodium) adenosine triphosphate pumps within the intestinal lumen, absorption of lead would be increased in calcium deficiency. Hence, calcium insufficiency could intensify the harmful effects of lead on child growth, as gastrointestinal lead absorption is the major pathway of its uptake.[33]

We found that blood lead levels during late pregnancy affected postnatal growth at 24 months. The early programming of postnatal growth caused by intrauterine exposure to lead may result from the separate influence of maternal blood lead levels either during the early or late gestational period. However, little is known about the critical period of sensitivity to lead exposure during pregnancy. In the current study, maternal blood lead during the late-pregnancy period was found to have adverse effects on postnatal growth, whereas we did not observe significant effects for the early-pregnancy lead levels.

However, in the low calcium intake group, early-pregnancy lead levels also affected birth weight in children. Although the calcium requirement for fetal growth is much increased in the last trimester, changes in calcium metabolism also could occur in early pregnancy. Because bone resorption appears to increase in early pregnancy, low calcium intake during early pregnancy would further aggravate bone resorption.[34] Increased demineralization of bone helps to mobilize lead to the blood and the consequent increase in lead levels during early pregnancy could affect birth weight.[35] In the case of calcium deficiency, lead substitutes calcium at the calcium-binding sites in the osteoblasts. This alters the functioning of the calcium-binding proteins like cyclic adenosine monophosphate, protein kinase C, and the calcium-dependent cell functions like coupling hormonal and local signal response of the Ca^{+2} messenger system in the osteoblast.[36] This alteration in the activity of calcium-binding protein disrupts the hormonal action of parathyroid hormone and vitamin D3, which affects the development and regulation of skeletal mass.[37] However, because maximum fetal development takes place during late pregnancy, low calcium intake during the last trimester may affect postnatal growth more by decreasing the width of the growth plate in bones and their mineralization.[38]

The strengths of the current study merit discussion. First, we investigated the effects of very low blood lead levels on fetal and infantile growth. All subjects included in this study had a blood lead level of <5 μg/dL, and intensive exclusion criteria minimized the impact of the influence of outliers on the results. Thus, the study provides additional information on the potential health effects of exposure to lead at levels encountered in developed countries. Second, we investigated the effect of intrauterine lead exposure on infantile growth up to 24 months, and the longitudinal component to the study design allowed us to evaluate the effects of intrauterine lead exposure over time. Third, we found lower calcium intake intensified the adverse effects of lead exposure on infantile growth, whereas higher calcium intake ameliorated the effects, suggesting the possibility of dietary prevention of harmful effects of lead during pregnancy. We also conducted analysis considering breast feeding (Supplemental Table 7) and child's calcium intake (Supplemental Table 8), where the results remained unchanged.

On the other hand, the study also had its limitations. First, the number of participants reduced considerably during the follow-up period, and, thus, some variables associated with loss to follow-up could have biased our results. However, we did not find significant differences between the participants and those who were lost to follow-up (Supplemental Table 6). Second, the racial factor may limit generalization of our results to other racial groups because all participants were Koreans. Third, although we adjusted for potential confounders, such as smoking exposure and maternal obesity, exposure to other pollutants could have biased the results, should they have correlated concomitantly with exposure to lead and child growth.

CONCLUSIONS

Maternal blood lead levels during late pregnancy were found to be associated with the reduction in attained infantile weight and length at 24 months of age. We

also found that less calcium intake during pregnancy intensified the harmful effect of prenatal lead exposure on infantile growth. This study may have important implications to the management of lead exposure in susceptible populations, such as pregnant women, particularly with insufficient calcium intake.

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