PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Effect of Maternal Lead Burden on Infant Weight and Weight Gain at One Month of Age Among Breastfed Infants

Luz Helena Sanín, Teresa González-Cossío, Isabelle Romieu, Karen Eileen Peterson, Silvia Ruíz, Eduardo Palazuelos, Mauricio Hernández-Avila and Howard Hu

Pediatrics 2001;107;1016-1023
DOI: 10.1542/peds.107.5.1016

Effect of Maternal Lead Burden on Infant Weight and Weight Gain at One Month of Age Among Breastfed Infants

Luz Helena Sanín, MD, MPH*‡; Teresa González-Cossío, PhD*; Isabelle Romieu, MD, MPH, ScD§; Karen Eileen Peterson, ScD, RD‖; Silvia Ruíz, PhD¶; Eduardo Palazuelos, MD*#; Mauricio Hernández-Avila, MD, ScD*; and Howard Hu, MD, ScD‖**

ABSTRACT. *Introduction.* **Transfer of lead from bone to the bloodstream increases during lactation. However, the effect of maternal lead burden on growth in breastfed newborns is still unknown. This study examined early postnatal growth in a cohort of healthy breastfed newborns in relation to maternal bone lead burden.**

Methods. **Lead levels were measured among 329 mother–infant pairs in umbilical cord blood at birth and in maternal and infant venous blood at 1 month postpartum. Maternal evaluations at 1 month postpartum included lead measures in blood and bone (measured in the tibia and the patella). Blood lead was determined by graphite furnace atomic absorption spectrophotometry. Bone lead was measured by ^{109}Cd Kx-radiograph fluorescence instrument. The primary endpoints were attained weight 1 month of age, and weight gain from birth to 1 month of age, which were analyzed in relation to lead biomarkers and relevant covariates by linear regression models.**

Results. **Infants studied had an average weight gain of 33.1 g/day (standard deviation [SD] = 11.6). Mean infant (at 1 month of age) and maternal blood lead levels were 5.6 μg/dL (SD = 3.0) and 9.7 μg/dL (SD = 4.1), respectively. Mean maternal bone lead levels were 10.1 μg of lead/g (SD = 10.3) and 15.29 μg of lead/g (SD = 15.2) of bone mineral for tibia and patella, respectively. Infant blood lead levels were inversely associated with weight gain, with an estimated decline of 15.1 g per μg/dL of blood lead. Children who were exclusively breastfed had significantly higher weight gains; however, this gain decreased significantly with increasing levels of patella lead. The multivariate regression analysis predicted a 3.6-g decrease in weight at 1 month of age per μg of lead per gram bone mineral increase in maternal patella lead levels.**

Conclusions. **Maternal lead burden is negatively associated to infant attained weight at 1 month of age and to postnatal weight gain from birth to 1 month of age. Additional studies are needed to better understand this source of exposure and to develop interventions to minimize its impact.** *Pediatrics* **2001;107:1016–1023;** ***maternal lead burden, infant weight, weight gain, breastfeeding.***

ABBREVIATIONS. SD, standard deviation; CI, confidence interval.

Recent studies have documented that bone lead stores may be mobilized during pregnancy and lactation.[1–3] Because lead accumulates in bone, women who were chronically exposed to environmental lead during infancy and adolescence may arrive at the age of reproduction with a significant bone lead burden. Because lead crosses the placental barrier freely[4] and because lead is excreted in breast milk,[5] mobilization of bone lead stores may substantially increase lead exposure of the developing breastfed infant.

Environmental lead exposure in Mexico City has been related to 2 primary sources: the use of leaded fuel and the use of traditional lead-glazed ceramics for cooking, storing, or serving foods.[6] For many years, lead was extensively used as an additive in gasoline. However, its use has decreased significantly since 1986,[6] resulting in a decline in umbilical cord blood lead levels from 13.5 μg/dL in 1980 to 6.9 μg/dL in 1996.[7,8] Similar changes have been reported for children living in Mexico City.[9] The resulting decline in ambient air lead levels has increased the relative importance of bone lead stores as a source for lead exposure. Pregnancy and lactation are known to be associated with a marked increase in maternal bone turnover[10,11]; this physiological process may condition lead mobilization from bone stores.[1–3] Thus, bone lead constitutes an important threat, not only to women with ongoing environmental exposures, but also to women enjoying reduced environmental exposures but who have had elevated exposures in the past.

Previously, we studied the biological significance of prenatal lead exposure from maternal bone lead stores and documented lower birth weight in children born of mothers with high levels of bone lead.[12] However, the effect of endogenous sources of lead on growth in human newborns is still not well-documented. In this report, we examine the relationship between lead exposure and postnatal growth and

From the *Centro de Investigaciones en Salud Poblacional, Instituto Nacional de Salud Pública, Cuernavaca, Morelos, México; ‡Universidad Autónoma de Chihuahua, México; §Pan American Health Organization, México; ‖Departments of Maternal and Child Health and Nutrition, Harvard School of Public Health, Boston, Massachusetts; ¶Instituto de Investigacion en Matemáticas Aplicadas y Sistemas, National Autonomous University of Mexico, Mexico; #American British Cowdray Hospital, Mexico; and **Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School and Occupational Health Program, Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts.

Received for publication Aug 16, 1999; accepted Aug 24, 2000.

Reprints requests to (M.H.-A.) Instituto Nacional de Salud Pública, Av Universidad 655, Col Sta Ma Ahuacatitlán, Cuernavaca, Morelos, México, CP 62508. E-mail: mhernan@insp3.insp.mx

size at 1 month of age in healthy, breastfed infants. Lead exposure was determined by measuring blood lead levels at birth and at 1 month of age and Kx-radiograph fluorescence measured maternal bone lead—as an indicator of bone lead burden—and maternal blood lead levels at 1 month postpartum.

METHODS

Sample Selection

We examined baseline data of 617 women who were subsequently enrolled in a randomized trial to assess the effect of calcium supplementation on blood lead levels during lactation. Data collection methods have been detailed elsewhere.[13] Briefly, between 1994 and 1995, 2910 potential study participants were interviewed at 3 maternity hospitals in Mexico City. Of these women, 1382 were found to be eligible for the trial. Exclusion criteria included no intention to breastfeed; logistics that would interfere with data collection, such as living outside of Mexico City; and conditions related to calcium metabolism and requirements, such as multiple fetuses, preeclampsia, or pregnancy-related hypertensive disorders; psychiatric, kidney, or cardiac disease; gestational diabetes; history of repeated urinary infections; family or personal history of kidney stone formation; seizure disorder requiring daily medications; and ingestion of corticosteroids. Also excluded from the study were premature neonates (<37 weeks) or newborns with low birth weight (<2000 g). Baseline information on health status and social and demographic characteristics as well as written consent were obtained from all 1382 eligible participating mothers. Umbilical cord and maternal venous blood specimens were obtained at delivery from 82% of newborns and 98% of the women participating in the study.

At 1-month postpartum (± 5 days), participants were invited to attend our research center. Of the 1382 initially eligible mother–infant pairs, 617 (44.6%) agreed to participate in the trial. At this time, an interview questionnaire was used to assess social and demographic characteristics, reproductive history, maternal and infant perinatal health, infant feeding practices (exclusive vs partial breastfeeding), and known risk factors for blood lead, documented in our previous studies.[6]

Anthropometry

Experienced obstetric nurses using standard procedures collected anthropometry data on nude newborns within the first 12 hours of delivery. Maternal and infant anthropometry at 1 month after delivery was collected by our project personnel, previously trained and standardized following the technique described by Habicht,[14] using calibrated beam scales (Oken model TD16, Oken, Naucalpan, Mexico) read to the nearest 10 g.

Lead Measurements

We measured blood lead concentrations in umbilical cord and venous blood samples from the infant at 1 month of age. Maternal blood lead levels were determined at delivery and at 1 month postpartum. All samples were analyzed by graphite furnace atomic absorption spectrophotometry instrument (Perkin-Elmer 3000, Perkin-Elmer, Norwalk, CT) at the metals laboratory of the American British Cowdray Hospital in Mexico City. The laboratory standardization program of the Wisconsin State Laboratory of Hygiene (Madison, WI) provided external quality control with blind specimens varying from 2 to 88 μg/dL. Our laboratory maintained acceptable precision and accuracy during the study time (correlation = 0.98; mean difference: 0.71 μg/dL; standard deviation [SD] = 0.68).

Additional lead measurements included the determination of maternal bone lead. Measurements were obtained from the participants' midtibia shaft (cortical bone) and patella (trabecular) using a spot-source ^{109}Cd Kx-radiograph fluorescence instrument constructed at Harvard University and installed in a research facility in Mexico. The physical principles, technical specifications, validation, and use of this and other Kx-radiograph fluorescence instruments have been described in detail elsewhere.[15,16] Briefly, the instrument uses a ^{109}Cd γ-ray source to provoke the emission of fluorescent photons from target tissue that are then detected, counted, and arrayed on a spectrum. Net lead signal is determined after subtraction of Compton background counts, using a linear least-squares algorithm. The lead fluorescent signal is then normalized to the elastic or coherently scattered radiograph signal, which arises predominantly from the calcium and phosphorous present in bone mineral. For the present study, 30-minute measurements were taken at the midshaft of the left tibia (cortical bone) and at the left patella (trabecular bone) after each region had been washed with a 50% solution of isopropyl alcohol.

The analysis presented is restricted to 53.3% of the participants of the trial (n = 329) with complete information for all variables of interest. We excluded from the analyses 24.9% (n = 154) because of refusal to participate in this part of the study, 12.8% (n = 79) because of missing umbilical cord blood lead levels, and 8.1% (n = 41) because of questionable bone lead measurements. Potential sources of errors in these measurements included movement of the limb out of the measurement field or extreme thickness of overlying tissue. Each of these individuals had estimates of uncertainty that were >10 μg of lead/g for the tibia or 15 μg of lead/g of bone mineral for the patella. The remaining participants were excluded because of missing information or errors in the following variables: maternal height (n = 12) and date of birth (n = 2).

Statistical Analyses

We had 2 main outcome variables: weight gain from birth to 1 month of life and attained weight at the same time point. Univariate and bivariate statistics, tabulations, and distribution plots were examined for all variables. To identify outliers, we assumed that the maximum growth that an infant could achieve between birth and the first month of life was equal to the change from the 10th percentile at birth to 90th percentile at 1 month of the National Center for Health Statistics/World Health Organization reference growth curves.[17] Thirteen infants whose growth was outside this expected scale were considered outliers and were excluded from the analysis.

In a first step, we used ordinary least-squares multiple regression analyses[18] to identify important determinants of weight and weight gain at 1 month of age. Selection of covariates was based on known predictors of infant growth.[19,20] Variables included in the models were infant age, gender, breastfeeding practices (exclusive vs partial), and infant health problems during the first month of life (doctor or hospital visits because of gastrointestinal or respiratory illness); maternal characteristics, such as age, parity (first born vs other), maternal anthropometry (calf circumference and height), and education level (complete elementary or less vs seventh grade or more); and the hospital of recruitment (social security vs others). Our final multivariate base model included only those variables that were retained in the model after a backward stepwise elimination, with selection criteria set at $P < .10$.

In the second step, we added to the base model data regarding our lead biomarkers. Each variable was included one at a time, as well as in combinations. Lead measurements were used as continuous and categorical variables using indicator variables for blood lead (zero for value ≤10 and 1 for values >10 μg/dL) and the quartile distribution for bone lead measurements. The quartile cutoff points for tibia lead were: 4.2, 9.7, and 15.7 μg of lead/g of bone mineral, and for patella lead were: 4.9, 13.9, and 24.5 μg of lead/g of bone mineral.

We explored the hypothesis of residual effect of maternal bone lead levels on infant growth by adding to the model the bone markers after adjusting for maternal and infant blood lead levels at birth and at 1 month of age. In addition, we tested the potential interactions among the different lead biomarkers and between lead biomarkers and breastfeeding patterns.

As a final step, to test the robustness of our models, we used more rigid criteria for the bone lead measurements, ie, by including only those measurements with imprecision lower than 8 and 11 for tibia and patella, respectively, and excluding bone lead values with point estimates below 0. However, because results were essentially unchanged, we present only those obtained with the full set of data. We performed all analyses with Stata Software (*Stata Statistical Software, Release 5.0*, Stata Corporation, College Station, TX).

RESULTS

Of the 1382 eligible mother–infant pairs, 476 (34.4%) completed the 1-month postpartum evalua-

tions including infant's anthropometric and blood lead measurements. Participants and nonparticipants did not differ regarding maternal age, education, parity, birth weight, or umbilical cord blood lead levels (Table 1). The groups included and excluded from the analysis were similar, except for slightly higher blood and bone lead levels among women who were included in the analysis (Table 1).

Umbilical cord blood and infant blood lead concentration at 1 month of age were 6.8 μg/dL (SD = 3.8) and 5.6 μg/dL (SD = 3.0), respectively. Close to 14% and 8% of umbilical cord and infant blood lead values exceeded the 10-μg/dL cutoff point. Maternal blood lead levels at 1 month postpartum ranged from 2.2 to 60.1 μg/dL with a mean of 9.7 μg/dL (SD = 4.1). Mean maternal tibia lead was 10.1 (SD = 10.3) μg of lead/g of bone mineral and patella lead burden was 15.2 (SD = 15.2) μg of blood/g of bone mineral. The number of measurements with point estimates <0 were 28 for tibia (8.5%) and 36 for patella (10.1%). We observed statistically significant associations among the different lead biomarkers. Maternal blood and bone lead levels were strong and significant predictors of infant blood lead levels, both at birth and at 1 month of age (Table 2).

Participants in the study were followed for an average of 31 days (range: 23–58 days) from birth. Over the study, the newborns had an average weight gain of 33.1 g/day (SD = 11.6). Mean weight attained at 31 days of life was 4187 g (SD = 544).

Using bivariate regression models with infant age included as a covariate, variables related positively to weight gain were gender (male), exclusive breastfeeding, and no history of a hospital visit because of respiratory or gastrointestinal disease ($P < .10$; Table 3). Attained weight at 1 month was positively associated with age and being a male, with maternal height, calf circumference, and education, and negatively associated with primiparity (Table 3).

We then examined the relationship between lead biomarkers and infant growth adjusted for infant age and multiple relevant covariates (Table 4). In these multivariate models, all lead biomarkers were inversely related to weight gain and attained weight at 1 month of age. However, significant associations were only observed between infant blood lead level at 1 month and weight gain, and between maternal patella lead level and attained weight at 1 month of age.

Infant blood lead levels were inversely associated with lower weight gains. The estimated weight gain arrest from birth to 1 month of age was 15.1 g per μg/dL of blood lead (95% confidence interval [CI]: 1.8–28.3). Compared with infants who had blood lead levels below 10 μg/dL, those with higher levels ($n = 26$) had a 142-g lower weight gain from birth to 1 month (95% CI: −7.5–287; $P = .06$). The 2 associations mentioned above remained unchanged even when other lead biomarkers were included in the model.

We observed that maternal patella lead levels significantly modified the effect of exclusive breastfeeding on weight gain. When we included the interaction term between maternal patella lead levels and

TABLE 1. Comparison of Participants With Complete Information and Those Excluded Because of Missing Information in One Key Variable

	Percent With Complete Information	Eligible Women Who Agreed to Participate		Eligible Women Who Did Not Agree to Participate
		Included in the Analyses $n = 329$	Excluded From the Analyses $n = 276$	Nonparticipants $n = 765$
Infant lead biomarkers				
Blood lead at birth (umbilical cord) (μg/dL)	82.6	6.8 (3.9)†	6.3 (3.00)	6.5 (3.6)
Blood lead at 1 mo of age (μg/dL)	75.5	5.7 (3.0)	5.5 (3.3)	
Maternal lead biomarkers				
Patella lead level (μg of lead/g of mineral bone)	92.7	15.2 (15.2)	14.2 (17.3)	
Tibia lead level (μg of lead/g of mineral bone)	97.3	10.1 (10.3)	9.75 (10.3)	
Blood lead level at 1 mo postpartum (μg/dL)	100	9.7 (5.2)*	8.8 (3.9)	
Infant characteristics				
Age (d)	96.8	31.6 (5.75)	32.9 (6.8)	
Gender (percent male)	99.8	52	52	52
Birth weight (g)	100	3136 (402)	3132 (438)	3139 (407)
Weight at 1 mo of age		4187 (544)	4178 (624)	
Weight gain (g)	94.6	1051 (418)	1067 (426)	
Exclusively breast fed (%)	99.8	50.7	49.7	
Sick, made hospital visit (%)	100	4.0	9.3	
Maternal characteristics				
Mother's age (y)	100	24.4 (5.1)	24.5 (5.1)	24.2 (4.9)
Height (cm)	96.3	153 (5.4)	153 (5.4)	
Calf circumference (cm)	100	33.8 (3.1)	34.2 (3.5)	
Years in school (y)	100	9.2 (3.2)	9.5 (2.8)	9.2 (3.1)
% with elementary school	100	24.0	19.9	23.3
place of recruitment (% from Social Security hospitals)	100	87.5	91.0	88.3
First pregnancy	100	39.5*	47	44.5

* Differences with sample included in the analysis significant at $P < .05$.
† Mean (SD).

TABLE 2. Mothers' and Infants' Lead Biomarkers Correlations*

	Umbilical Cord Blood	Infant Blood (1 Month)	Maternal Blood (1 Month pp)	Maternal Patella (1 Month pp)
Infant blood (1 mo)	0.60			
Maternal blood (1 mo pp)	0.62	0.75		
Maternal patella (1 mo pp)	0.27	0.25	0.30	
Maternal tibia (1 mo pp)	0.17	0.12	0.13	0.33

pp indicates postpartum. All correlations were significant at $P < .05$.
* $n = 239$ mother–infant pairs.

TABLE 3. Relationship of Maternal and Infant Characteristics† to Infant Growth

	Weight Gain (Grams) Birth to 1 Month of Age (95% CI)	*P* Value	Attained Weight (Grams) at 1 Month of Age (95% CI)	*P* Value
Age (d)	32.8* (25.7 to 39.8)	<.01	28.7* (18.8 to 38.4)	<.01
Maternal height (cm)	3.1 (−4.3 to 10.50)	.41	18.9* (8.83 to 29.4)	<.01
Calf circumference (cm)	1.68 (12.6 to 15.9)	.23	32.9* (14.8 to 51.2)	<.01
Infant gender (male = 1)	130.3* (40.2 to 220.3)	<.01	137.1* (19.3 to 254.8)	.01
First pregnancy	−50.5 (−133.3 to 32.3)	.28	−198.2* (−312.3 to −85.4)	<.01
Breast feeding (exclusive = 1)	77.7* (−13.8 to 189.3)	.09	47.8 (−79.9 to 175.6)	.46
Hospital visit because of infant sickness (yes = 1)	−193.6* (−401.2 to 13.7)	.07	−110.7* (−413.8 to 192.4)	.47
Place of recruitment (IMSS = 1)	−72.9 (−210.2 to 64.3)	.29	−52.9 (−231.8 to 125.8)	.56
Complete elementary school (yes = 1)	47.5 (−47.41 to 142.38)	.32	112.3* (−19.21 to 243.9)	.09

IMSS indicates Instituto Mexicano del Seguro Social (Mexican Institute of Social Security).
* Indicates the variables that were selected in backward stepwise regression procedure.
† Adjusted for infant age (except infant age).

type of breastfeeding, the association between exclusive breastfeeding and growth became apparent (Table 5). This association was progressively less apparent among infants of women with increasing patella lead levels. Exclusively breastfed infants had 6 g lower weight gains per μg increase of their mothers patella lead burden. A similar relationship was observed when we conducted a stratified analysis according to terciles of maternal patella lead (Fig 1). This analysis shows that the larger weight gain of exclusive breastfeeding was only apparent among those infants whose mothers had the lowest tercile of patella lead concentrations.

We observed an inverse association between maternal patella lead burden and attained weight at 1 month, adjusting for the infant's age and gender and maternal characteristics (Table 5). Regression analysis predicted a 3.6-g decrease in attained weight per μg of lead/g of bone mineral increase in maternal patella lead. When patella lead was used as a categorical variable, we observed a mean difference in weight of 66 g, comparing infants whose mothers had patella lead levels in the first quartile with those in the fourth quartile (equivalent to 34 μg of lead/g of bone mineral difference). We also tested for an interaction between type of breastfeeding and patella lead. Inclusion of the interaction term in the model did not improve the fit. In stratified analysis by tercile of patella lead, the positive association of exclusive breastfeeding to weight attained at 1 month of age decreased from 143.0 g (95% CI: −91.3–377.1; $P = .22$) among participants whose mother had a bone lead value in the lower tercile, to −47.8 g (95% CI: −272.3–176.8; $P = .67$) for those with values in the upper tercile.

DISCUSSION

Our findings suggest that lead exposure during the early postnatal period has an adverse effect on early weight gain among healthy breastfed infants. We observed that those infants with a blood lead concentration above 10 μg/dL experienced a 142-g lower weight gain from birth to the first month of life compared with infants with lower blood lead levels. The magnitude of this growth arrest corresponds to a reduction of 16% in weight gain from birth to 1 month of age.[17] We also found an important positive association between exclusive breastfeeding and early growth. Infants who received only their mother's milk in their first month of life gained ~77 g more than did those who were only partially breastfed. This growth benefit has been repeatedly observed in many developing countries.[19,20] However, our data suggest that a high maternal bone lead burden inhibits this benefit, because this growth improvement was only apparent among infants of women with lower lead burden. The benefit of being exclusively breastfed in terms of early weight gain

TABLE 4. Relationship† Between Different Biomarkers of Lead Burden and Infant Growth

	Weight Gain From Birth to 1 Month of Age		Attained Weight at 1 Month of Age	
	Age-Adjusted	Multivariate-Adjusted	Age-Adjusted	Multivariate-Adjusted
Patella lead‡	−0.61 (−3.27 to 2.1)	−0.31 (−2.94 to 2.30)	−2.80 (−6.49 to 0.88)	−3.69* (−7.21 to −0.16)
Patella lead (1st vs 4th quartile)	−37.2 (−154.6 to 80.2)	−22.6 (−138.4 to 93.1)	−39.0 (−202.2 to 124.1)	−66.2 (−222.3 to 89.9)
Tibia lead (μg/g bone mineral)	0.26 (−3.68 to 4.2)	−0.24 (−4.13 to 3.6)	−3.61 (−9.32 to 1.61)	−4.84 (−10.1 to 0.36)
Tibia lead (1st vs 4th quartile)	−20.6 (−134.4 to 93.1)	−39.7 (−152.2 to 72.6)	−89.9 (−248.5 to 68.5)	−131.1 (−282.6 to 20.50)
Lead umbilical cord§	−6.5 (−16.9 to 3.9)	−5.6 (−15.9 to 4.7)	−5.6 (−20.2 to 8.9)	−6.67 (−20.63 to 7.1)
Lead umbilical cord	−111.6 (−228.2 to 4.8)	−96.0 (−211.2 to 18.5)	−118.2 (−280.5 to 44.1)	−132.2 (−286.8 to 22.17)
Infant blood lead	−15.9* (−29.3 to −2.4)	−15.1* (−28.3 to −1.8)	−6.0 (−24.9 to 12.8)	−8.2 (−26.1 to 9.7)
Infant blood lead	−132.8 (−29.3 to −2.4)	−140.2 (−287.8 to 7.5)	−106.5 (−315.8 to 102.9)	−109.1 (−308.3 to 90.0)
Maternal blood lead	0.62 (10.2 to −11.4)	−4.9 (−12.6 to 2.6)	0.6 (−10.2 to 11.4)	−1.0 (−11.3 to 9.3)
Maternal blood lead level (>10 μg/dL)	−54.6 (139.4 to 30.2)	−66.5 (−150.0 to 16.9)	21.7 (−96.6 to 139.8)	−9.8 (−122.9 to 103.3)

* $P < .05$.
† Ordinary least-squares multiple regression models adjusted as follows: variables in the model for weight gain: infant's age (days), gender, sick and made hospital visit, and exclusively breastfed. Variables for weight at 1 month: infant's age, maternal education, first pregnancy, gender, hospital visit, maternal height, and calf circumference.
‡ Bone measurement units are μg of lead/g of bone mineral.
§ Blood measurement units are μg/dL.

TABLE 5. Maternal and Infant Predictors of Early Growth*

Variable	[β]	95% CI	*P* Value
Weight gain from birth to 1 mo (r^2 = 26%)			
Infant age (d)	31.3	(21.6 to 41.0)	<.01
Gender (male = 1)	102.5	(23.6 to 181.3)	.01
Sick, made visit to hospital (yes = 1)	−200.5	(−377.0 to −23.9)	.02
Exclusive breastfeeding (yes = 1)	180.2	(30.6 to 329.6)	.01
Infant blood lead (1 mo of age, μg/dL)	−15.6	(−27.9 to −3.34)	.01
Patella lead level (μg Pb/g bone mineral)	1.77	(−1.34 to 4.90)	.26
Patella breastfeeding interaction term	−7.77	(−15.3 to −0.17)	.04
Model for weight attained at 1 mo (r^2 = 19%)			
Infant age (d)	26.29	(16.9 to 35.7)	<.01
Education level	107.9	(−22.5 to 238.8)	.10
Primiparous (yes = 1)	−224.4	(−336.6 to −112.4)	<.01
Gender (male = 1)	110.41	(2.1 to 218.7)	.04
Sick, made visit to hospital (yes = 1)	−234.7	(−509 to 40.3)	0.09
Maternal calf circumference (cm)	21.4	(4.0 to 38.7)	0.01
Maternal height (cm)	14.5	(4.2 to 24.8)	0.006
Patella lead (μg of lead/g of bone mineral)	−3.65	(−7.21 to −0.16)	0.040

* Ordinary least-squares multiple regression models.

was not apparent at increasing levels of lead in maternal bone. The mechanism for this effect might be through the exposure to lead through breast milk. Lead isotopes studies suggest that there is an important mobilization of bone lead during lactation, and a small fraction of this lead appears in breast milk.[5] The strong health benefits of breastfeeding clearly outweigh the negative association of lead burden in growth at this age, and our data must not be taken as a recommendation against exclusive breastfeeding.

Our results confirm the previously reported finding that maternal lead burden is an important determinant of infant lead levels at birth and at 1 month of age.[21] However, although maternal blood lead was strongly associated with infant blood lead levels, both at birth and at 1 month of age, it failed to predict adverse effects in attained weight or on weight gain from birth to 1 month of age. In contrast, maternal patella lead levels, which in comparison to maternal blood lead levels had a lower association with infant blood lead level, predicted significantly an adverse effect in anthropometry at 1 month of age. This observation adds to the recent accumulating evidence suggesting that maternal blood lead may not be a good indicator of exposure in the maternal–infant unit during pregnancy or lactation, especially because this biomarker fails to adequately reflect endogenous exposure resulting from bone lead mobi-

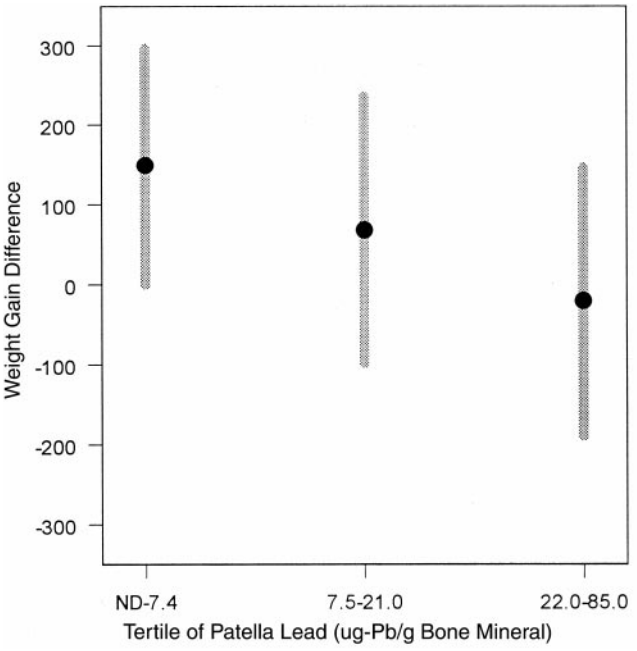

Fig 1. Estimated weight gain differences (mean ± standard error) between exclusively and nonexclusively breastfed infants according to their mother's patella lead levels. (The difference between exclusively and nonexclusively breastfed infants in the lowest tercile of patella lead was significant at $P = .04$.) ND indicates nondetectable.

lization.[22] This limitation of maternal blood lead levels may explain previous discrepancies in studies that evaluated lead effects in anthropometry at birth or the early postnatal period using maternal blood or umbilical cord lead levels.[23]

To the best of our knowledge, this is the first report of a deleterious effect of an endogenous lead source (as bone lead), evaluated directly, on functional outcomes in a free-living population. The population that we studied is in transition from a period of high to low environmental lead exposure. Because of the recent phase-out of leaded gasoline in Mexico, blood lead levels have show an important decline.[9] Because the half-life of lead in bone is 10 to 15 years,[24] bone lead levels have remained elevated despite these important declines in blood lead. Therefore, the mothers of the children studied in this cohort entered into pregnancy and lactation with a relatively high endogenous lead burden and a low environmental exposure (air lead), which determined our ability to study the health effects of endogenous sources.

Our results cannot be explained by other important determinants of early growth, such as infant's age, gender, and morbidity. We have considered these factors, statistically or by design. Thus, our findings of the negative association between lead exposure and early growth cannot be explained by confounding factors. Actually, predictors of weight gain and weight at 1 month of age were similar to those reported in other populations.

Exposure to lead is also associated with a variety of socioeconomic circumstances that may include poor nutrition, childhood illness, and other related factors that influence growth. We controlled for these factors by studying only breastfed infants from a homogenous population. We also included in our regression models socioeconomic information and history of disease. As expected, all these variables were important determinants of weight gain but did not modify the observed associations between lead exposure and weight gain. Therefore, it is unlikely that confounding by important determinants of growth, or selection bias, could explain our findings. Furthermore, our observation that lead level in trabecular bone (as represented by patella) as opposed to cortical bone (by tibia) was an important predictor of attained weight at 1 month of age, agrees with evidence resulting from bone resorption studies that suggest that trabecular bone is importantly mobilized during lactation.[10,25,26]

Bone lead measurements are subject to error, especially when the concentration of lead in bone approaches the limit of detection of the Kx-radiograph fluorescence instrument. However, lead measurement errors are expected to occur at random in relation to anthropometry, resulting in an underestimation of the true association. To evaluate the magnitude of this potential bias, we excluded measurements with negative values and applied more stringent criteria for accepting bone lead measurements as admissible (imprecision for patella lead <11). As expected, when we applied these conditions, the observed associations became more apparent (results not shown). For example, more stringent imprecision criteria substantially increased the inverse association between patella lead and attained weight from -3.6 g to -5.8 g per μg of patella lead.

Reverse causality may be a problem in our study because infant weight at 1 month of age and blood lead levels were measured concurrently. Larger infants could incorporate more lead in bone, thereby lowering blood lead levels in the infant and creating a spurious negative association between blood lead and weight gain. To address this issue, we included length at 1 month of age and length change between birth and 1 month of age in the analysis and observed that the association between infant blood lead and weight gain remained unchanged.

With our study design, we are not able to draw causal inferences relative to the association between lead exposure and weight gain. However, our findings are consistent with animal models that have extensively documented this inverse association in the rat.[27–29] Some epidemiologic studies have documented similar findings looking at anthropometry at birth[23]; however, no single investigation has looked at both the effects of maternal bone and blood lead levels so as to allow a direct comparison with our results. The mechanisms behind lead effects on growth seem to involve actions at different sites. Lead may interfere with vitamin D metabolism[30] or with calcium's role as a cellular messenger in its endocrine functions,[31] or it may act as a depressant of food intake.[32]

The public health significance of our findings is notable because early growth problems have health and social consequences. It has been shown that early impaired growth is associated with decreased intellectual and physical performance, such that

work capacity, school achievement, and human capital in a broader sense are compromised.[33,34] Unfortunately the growth deficit most often observed in developing countries occurs early in infancy before the age of 2 years, and often this retardation begins during the first 3 months of life, or even as early as in the first month, as has been demonstrated in this study. The earlier that the nutritional or environmental insult occurs, the larger the damage will be. Nutritional interventions aimed at infants younger than 3 years of age have shown to be beneficial at improving linear growth, as well as the short- and long-term health consequences.[33,34] In this context, it is important to mention that the deleterious association of lead and infant weight observed in this study parallels in magnitude that of successful nutrition interventions in young infants. Infants with better growth have a greater opportunity to fulfill their intellectual potential and have a greater work capacity as young adults than do infants and children whose growth falters early in life.[33,34]

Prevention of fetal and postnatal lead exposure of breastfed infants requires identification and control of sources of environmental lead exposure for pregnant and lactating women. With the removal of lead from gasoline, food contaminated by cooking or storage in low-temperature lead-glazed ceramics has risen in prominence as the major pathway for environmental lead exposure and needs urgent action for its elimination.[35,36] However, our results also indicate that prevention of lead exposure during pregnancy and lactation will also require the control of endogenous maternal bone lead stores. Studies are needed to evaluate intervention measures to reduce bone resorption during pregnancy and lactation. Because bone lead has a half-life of years to decades, our results suggest that lead can remain a significant threat to the fetus long after cessation of external lead exposure to women who are pregnant or who are going to become pregnant.

Lead concentrations in breast milk are low and must not be a reason to discourage breastfeeding. A critical analysis of the known health benefits of breastfeeding versus lead exposure must be performed, but present knowledge strongly suggests that breastfeeding should be encouraged and that other interventions to reduce early lead exposures must be studied intensely.

ACKNOWLEDGMENTS

This work was supported by US National Institute of Environmental Health Sciences P42-ES05947 Project 3, National Institute of Environmental Health Sciences R01ES07821, and National Institute of Environmental Health Sciences Center Grant 2 P30 ES 00002; by Consejo Nacional de Ciencia y Tecnología Grant 1233P-M; and by Consejo de Estudios para la Restauración y Valoración Ambiental, Department of the Federal District, Mexico.

REFERENCES

1. Gulson BL, Mahaffey KR, Jameson CW, et al. Mobilization of lead from the skeleton during the postnatal period is larger than during pregnancy. *J Lab Clin Med*. 1998;131:324–329
2. Lagerkvist BJ, Ekersydh S, Englyst V, Nordberg GF, Soderberg H, Wiklund DE. Increase blood lead and decreased calcium levels during pregnancy: a prospective study of Swedish women living near a smelter. *Am J Public Health*. 1996;86:1247–1252
3. Gulson BL, Jameson CW, Mahaffey KR, Mizon KJ, Korsh MJ, Vimpani G. Pregnancy increases mobilization of lead from maternal skeleton. *J Clin Lab Med*. 1997;130:51–62
4. Goyer RA. Transplacental transport of lead. *Environ Health Perspect*. 1990;89:101–105
5. Gulson BL, Jameson CW, Mahaffey KR, et al. Relationships of lead in breast milk to lead in blood, urine, and diet of the infant and mother. *Environ Health Perspect*. 1998;106:667–674
6. Romieu I, Palazuelos E, Hernandez-Avila M, et al. Sources of lead exposure in Mexico City. *Environ Health Perspect*. 1994;102:384–389
7. Montoya-Cabrera MA, Maldonado-Torres L, Landazuri-Laris P, Montes-Allende F, Escobar-Marquez R, Margain-Compean JC. Lead determinations in the blood of the umbilical cord of normal neonates. *Arch Invest Med*. 1981;12:457–462
8. Hernandez-Avila M, Sanin LH, Romieu I, et al. Higher milk intake during pregnancy is associated with lower maternal and umbilical cord lead levels in postpartum women. *Environ Res*. 1997;74:116–121
9. Rothenberg SJ, Schnaas L, Perroni E, Hernandez RM, Karchmer S. Secular trend in blood lead levels in a cohort of Mexico City children. *Arch Environ Health*. 1998;53:231–235
10. Sowers MF, Corton G, Shapiro B, et al. Changes in bone density with lactation. *JAMA*. 1993;269:3130–3135
11. Holmberg-Marttila D, Sievanen H. Prevalence of bone mineral changes during postpartum amenorrhea and after resumption of menstruation. *Am J Obstet Gynecol*. 1999;180:537–538
12. Gonzalez-Cossio T, Peterson KE, Sanin LH, et al. Decrease in birth weight in relation to maternal bone lead burden. *Pediatrics*. 1997;100:856–862
13. Hernadez-Avila M, Gonzalez de Cossio T, Hernandez-Avila JE, et al. Randomized placebo-controlled trial of dietary calcium supplements to lower blood lead levels in lactating women. In press
14. Habicht JP. Estandarización de métodos epidemiológicos cuantitativos sobre el terreno. *Bol Officina Sanit Panam*. 1974;76:375–384
15. Aro ACA, Todd AC, Amarasiriwardena C, Hu H. Improvement in the calibration of ^{103}CD K X-ray fluorescence systems for measuring bone lead in vivo. *Phys Med Biol*. 1994;39:2263–2271
16. Hu H, Aro A, Roknitzky A. Bone lead measured by X-ray fluorescence: epidemiological methods and a new biomarker. *Environ Health Perpect*. 1995;103(suppl 1):105–110
17. World Health Organization. *Measuring Change in Nutritional Status*. Geneva, Switzerland: World Health Organization; 1983
18. Zar JH. *Biostatistical Analysis*. 2nd ed. Englewood Cliffs, NJ: Prentice-Hall; 1984
19. Cohen RJ, Brown KH, Canahuati JM, Rivera L, Dewey KG. Determinants of growth from birth to 12 months among breast-fed Honduran infants in relation to age of introduction of complementary foods. *Pediatrics*. 1995;96:504–510
20. Dewey KG, Peerson JM, Brown KH, et al. Growth of breast-fed infants deviates from current reference data: a pooled analysis of US, Canadian, and European data sets. *Pediatrics*. 1995;96:495–503
21. Rothenberg SJ, Karchmer S, Schnaas L, et al. Maternal influences on cord blood lead levels. *J Exp Analysis Environ Epidemiol*. 1996;6:211–227
22. Hu H. Bone lead as a new biologic marker of lead dose: recent findings and implications for public health. *Environ Health Perspect*. 1998;106(suppl 4):961–967
23. Andrews KW, Savitz DA, Hertz-Picciotto I. Prenatal lead exposure in relation to gestational age and birth weight: a review of epidemiological studies. *Am J Ind Med*. 1994;26:13–31
24. Hu H, Milder F, Burger D. X-Ray Fluorescence: issues surrounding the application of a new tool for measuring lead burden. *Environ Res*. 1989;49:295–317
25. Sowers M, Randolph L, Shapiro B, Jannaush M. A prospective study of bone density and pregnancy after an extended period of lactation with bone loss. *Obstet Gynaecol*. 1995;85:285–289
26. Krebs NK, Reidinger CJ, Robertson AD, Brenner M. Bone mineral density changes during lactation: maternal, dietary and biochemical correlates. *Am J Clin Nutr*. 1997;65:1738–1746
27. Ronis MJ, Badger TM, Shema SJ, Roberson PK, Shaikh F. Reproductive toxicity and growth in rats exposed to lead at different periods during development. *Toxicol Appl Pharmacol*. 1996;136:361–771
28. Grant LD, Kimmel CA, West GL, Martinez-Vargas CM, Howard JL. Chronic low level toxicity in the rat: effects on postnatal physical and behavioral development. *Toxicol Appl Pharmacol*. 1980;56:42–47

29. Hallen IP, Jorhem L, Oskarsson A. Placental and lactational transfer of lead in rats: a study on the lactational process and effects on offspring. *Arch Toxicol*. 1995;69:596–602
30. Rosen JF, Chensey FW, Hamstra AJ, DeLuca HF, Mahaffey KR. Circulating calcitrol concentrations in health and disease. *J Pediatr*. 1983; 103:1–7
31. Habermann E, Crowell K, Janmicki P. Lead and other metals can substitute for Ca^{++} in calmodulin. *Arch Toxicol*. 1983;54:61–70
32. Minnema DJ, Hammond PB. Effects of lead exposure on patterns of food intake in weanling rats. *Neurotoxicol Teratol*. 1994;16:623–629
33. Martorell R. Results and implications of the INCAP follow-up study. *J Nutr*. 1995;125(suppl):1127S–1138S
34. Pollit E, Gorman KS, Engle PL, Rivera JA, Martorell R. Nutrition in early life and the fulfillment of intellectual potential. *J Nutr*. 1995;125(suppl): 1111S–1118S
35. Hernández Avila M, Romieu L, Ríos C, et al. Lead glazed ceramics as major determinants of blood lead levels in Mexican women. *Environ Health Perspect*. 1991;94:117–120
36. Rothenberg SJ, Pérez IA, Perroni E, et al. Fuentes de plomo en embarazadas de la Cuenca de México. *Salud Pública Mex*. 1990;32:632–643

NEW ARMY CAMPAIGN

After 20 years, the Army is dropping its famous recruiting slogan . . . the new slogan is "An Army of one," an odd contradiction in terms, and it may be too mystifying to make anyone dash to the nearest enlistment center. But the Army has a problem. It missed its recruiting goals in 3 of the past 6 years and barely met them in the other 3.

The economic boom is a factor, draining off many potential recruits. But the real difficulty is the mind-set of the 18- to 24-year-olds targeted for enlistment ads. They think of soldiers as "nameless, faceless people in green uniforms crawling through mud," said an Army public relations man. The Army churned up a lot of research on young adults by the Rand Corporation, Yankelovich Partners Incorporated, and McKinsey & Company. On the basis of the findings, many of them already well-known, the Army apparently concluded that the current generation of young people is so individualistic, so resistant to authority and rules, that it has to market military life as the natural home of the freewheeling, unfettered spirit. . .

Leo J. On society. *US News & World Report*. January 22, 2001

Noted by JFL, MD

Effect of Maternal Lead Burden on Infant Weight and Weight Gain at One Month of Age Among Breastfed Infants

Luz Helena Sanín, Teresa González-Cossío, Isabelle Romieu, Karen Eileen Peterson, Silvia Ruíz, Eduardo Palazuelos, Mauricio Hernández-Avila and Howard Hu

Pediatrics 2001;107;1016-1023
DOI: 10.1542/peds.107.5.1016