Effect of Maternal Bone Lead on Length and Head Circumference of Newborns and 1-Month-Old Infants

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ABSTRACT. The authors evaluated the effects that maternal bone lead stores have in anthropometry at birth in 223 mother-infant pairs. The participants were recruited between April and November 1994. Anthropometric data were collected within the first 12 hr following delivery. Maternal information was obtained 1 mo after delivery occurred. Bone lead burden was determined with in-vivo K-x-ray fluorescence of the tibia (cortical bone) and the patella (trabecular bone). The authors transformed anthropometric measurements to an ordinal 5-category scale, and the association of measurements with other factors was evaluated with ordinal logistic-regression models. Mean bone lead levels were 9.8 µg/gm bone mineral and 14.4 µg/gm bone mineral for the tibia and patella, respectively. Birth length of newborns decreased as tibia lead levels increased. Compared with women in the lower quintiles of the distribution of tibia lead, those in the upper quintile had a 79% increase in risk of having a lower birth length newborn (odds ratio = 1.79; 95% confidence interval = 1.10, 3.22). The authors adjusted by birth weight, and the effect was attenuated—but nonetheless significant. Patella lead was positively and significantly related to the risk of a low head circumference score; this score remained unaffected by inclusion of birth weight. The authors estimated the increased risk to be 1.02 per µg lead/gm bone mineral (95% confidence interval = 1.01, 1.04 per µg lead/gm bone mineral). Odds ratios did not vary substantially after the authors adjusted for birth weight and other important determinants of head circumference.

<Key words: birth anthropometry, bone lead, pregnancy, reproductive outcomes, smoking>

also reanalyzed our data, excluding these observations or recoding them as zero. Both of these approaches produced results that were essentially unchanged.

We excluded 12 individuals who had questionable values that resulted from either the movement of the limb being measured or the extreme thickness of overlying tissue—resulting in estimates of uncertainty greater than 10 µg lead/gm bone mineral for the tibia, or 15 µg lead/gm bone mineral for the patella. One participant who had a very high and influential tibia lead reading (i.e., > 70 µg lead/gm bone mineral; 3 *SD*s above the mean) was also excluded.

Statistical analyses. Univariate and bivariate statistics, tabulations, and distribution plots were examined for all variables. Plots of newborn length and head circumference demonstrated a digit preference bias; 60% of head circumference measurements and 64% of length measurements were recorded as integers. To account for this bias, we transformed the outcome variables to an ordinal scale with 5 categories. To define the initial cutoff point for each variable, we used the integer value closest to the 5th percentile; other cutoff points were defined in such a way that the preference integer digits were located as midpoints of the interval. The following categories were used for length at birth: 5 = 44.0–47.5 cm, 4 = 47.6–49.5 cm, 3 = 49.6–50.5 cm, 2 = 50.6–51.5 cm, and 1 = 51.6–55.0 cm. The categories for head circumference were as follows: 5 = 30.0–31.5 cm, 4 = 31.6–32.5 cm, 3 = 32.6–33.5 cm, 2 = 33.6–34.5 cm, and 1 = 34.6–37.0. Lead biomarkers were modeled as continuous and as categorical variables. For this last approach, we used the cutoff point of 10 µg/dl for venous and umbilical cord blood lead levels and 20.5 µg lead/gm bone mineral and 30.9 µg/gm bone mineral for tibia and patella lead, respectively. These last cutoff points corresponded to the lower limit of the top quintile.

To assess the relationship of lead biomarkers to length and head circumference, we used the Cumulative Odds Model.[15,16] With this model, covariate coefficients are interpreted simply. The coefficient represents the odds ratio (OR) of having a lower value in birth length or head circumference per unit of change of the lead biomarker.

Selection of potential confounders was on the basis of known predictors of size at birth,[17] and they included the following maternal variables: height, calf circumference, smoking during pregnancy, parity, prior history of poor reproductive outcomes, age and education (yr), hospital of delivery, infant gender, and gestational age (wk). We included all potential confounders in the models for length and head circumference. We then dropped covariates, one-by-one, that did not improve the overall fit of the model or that changed the effect estimates associated with the different lead biomarkers. In particular, we explored the hypothesis of residual effect of bone lead levels on head circumference or birth length—after we adjusted for maternal and umbilical cord blood lead levels and other important predictors.

In a previous report,[9] we showed that maternal tibia lead was associated with a lower-than-normal birth weight. As an indicator of overall size at delivery, birth weight is an important predictor of head circumference and birth length.[16] To test the hypothesis that the effect of bone lead on head circumference or birth length is independent of its effect on birth weight, we included birth weight in the regression models. We performed all analyses with Stata software (Stata Statistical Software, release 5.0; Stata Corporation [College Station, Texas]).

Results

We found no significant differences between nonparticipants and those in the analytical sample with respect to maternal anthropometry, age, education, parity, infant anthropometry and gestational age, or to lead levels in umbilical cord or maternal venous blood (Table 1). The mean maternal age of study participants was 24.4 yr,

Table 1.—Maternal and Newborn Characteristics and Anthropometry at Birth

Characteristic	Participants (n = 223) Mean	*SD*	Nonparticipants (n = 494) Mean	*SD*
Infant characteristics				
Gender (% female)	50.0		51.2	
Gestational age (wk)	39.5	1.2	39.0	2.0
Birth weight (gm)	3,168	404	3,119	396
Birth length	50.4	1.9	50.3	2.4
Head circumference (cm)	33.8	1.5	33.9	1.8
Delivered by cesarean section (%)	19.2		17.7	
Maternal characteristics				
Age (yr)	24.4	5.4	24.2	5.4
Education (yr)	9.1	3.3	9.0	3.3
Height (m)	1.53	5.6	1.53	5.5
Calf circumference (cm)	33.9	2.9	34.0	3.2
History of adverse reproductive outcomes (% yes)	22.0	2.4	*NA*	
Smoked during pregnancy (% yes)	4.4		*NA*	
First pregnancy (% yes)	45.1		43.6	
Age ≤ 16 (% yes)	2.1		3.1	
Lead biomarkers				
Maternal blood lead (µg/dl)	8.82	4.0	8.47	4.19
Umbilical cord lead (µg/dl)	7.01	3.5	6.75	3.50
Tibia lead (µg/gm bone)	9.83	8.9	*NA*	
Tibia corrected	10.70	7.58	*NA*	
Patella lead (µg/gm bone)	14.14	13.0	*NA*	
Patella corrected	15.39	11.18	*NA*	

Notes: Correction made, assuming a limit of detection of 5 µg/gm bone. *NA* = information not available in baseline questionnaire.

and 2.1% were 16 yr of age or less at the time of delivery (Table 1). Approximately 45% (n = 123) were primiparous, 4.4% (n = 12) reported smoking during pregnancy, and 22% had a prior history of poor reproductive outcomes (i.e., low birth weight, prematurity, stillbirth, or spontaneous abortion). Means and *SD*s for newborn anthropometry were 3,168 gm (*SD* = 404 gm) for birth weight, 33.8 (*SD* = 1.5 cm) for head circumference, and 50.4 cm (*SD* = 1.9 cm) for birth length.

Maternal blood lead levels ranged from 1.8 to 23.5 µg/dl (mean = 8.8 µg/dl [Table 1]). Fifteen percent of cord blood lead levels exceeded 10 µg/dl (range = 1.9–21.6 µg/dl). Mean bone lead concentrations were 9.8 µg lead/gm of bone mineral (i.e., 10.7 corrected for values below the limit of detection) for patella bone. Maternal bone lead levels were associated positively with maternal and umbilical cord blood lead levels. Maternal blood lead levels increased linearly by 0.096/µg of tibia lead (95% confidence interval [CI] = 0.041, 0.149) and by 0.078/µg of patella lead (95% CI = 0.041, 0.115). Umbilical cord blood lead levels increased by 0.111/µg tibia lead (95% CI = 0.064, 0.159) and by 0.061/µg of patella lead (95% CI = 0.027, 0.096).

Birth length. We observed that maternal calf circumference, gender, gestational age, parity, and history of adverse reproductive outcomes were all important predictors of birth length (Table 2). In the multivariate models, umbilical cord blood lead level was associated positively with the risk of having a lower-than-normal birth-length score (OR = 1.04/µg · dl of umbilical cord blood lead [95% CI = 0.97, 1.12]). We observed an increase in the risk of a lower birth length value with increasing tibia lead levels (OR = 1.03/µg lead · gm bone mineral [95% CI = 1.01, 1.06]). When we compared women who were in the upper quintile of the tibia lead distribution with the remainder of the sample, those in the higher quintile had a 79% increase in risk of having a lower birth-length score (OR = 1.79 [95% CI = 1.01, 3.22]); this association was independent of umbilical or maternal blood lead levels. The association with patella lead was weaker than with tibia lead (Table 2). However, when we compared women who had high lead levels in both the tibia (> 16.6 µg/gm bone mineral) and patella (> 24.7 µg/gm bone mineral) with the remainder of the population, those with higher values had a larger risk of having a lower score (OR = 3.06 [95% CI = 1.31, 7.09]). When we included birth weight in the models, the effect attenuated, but it remained significant for women who had higher levels of lead in both the tibia and patella (Table 2).

Head circumference. Maternal calf circumference, smoking during pregnancy, and parity were important predictors of head circumference (Table 3). With the exception of patella lead, the inclusion of lead biomarkers did not substantially modify the predictive ability of the model. Smoking during pregnancy increased the risk of having a low head circumference score (OR = 4.17 [95% CI = 1.19, 12.2]). Patella lead was related positively to the risk of having a low head-circumference score (Table 3). We estimated from the multivariate models an increase of 1.02/µg lead · gm bone mineral in the risk of having a lower head circumference score (95% CI = 1.01, 1.04). When we compared women in the higher quintile with the remainder of participants, those in the highest quintile had more than a 2-fold increase in risk of having a lower head-circumference score (OR = 2.13 [95% CI = 1.14, 3.97]). When we adjusted for birth weight, the effect of patella lead remained unchanged (Table 3).

Table 2.—Coefficients and Odds Ratios (ORs) Estimated by Cumulative Odds Models for Birth Length of Newborns

Variable	Multivariate model 1				Estimates adjusted by birth weight	
	Beta	*SE*	OR	95% CI	OR	95% CI
Calf circumference (cm)	–0.142	0.042	0.87	0.80, 0.94		NE
Gestational age	–0.300	0.114	0.74	0.59, 0.93		NE
Gender	0.756	0.247	2.13	1.31, 3.46		NE
Parity (primiparous vs. other)	0.653	0.272	1.92	1.13, 3.28		NE
History of adverse reproductive outcome	0.785	0.335	2.19	1.14, 4.22		NE
Umbilical cord blood lead (µg/dl)	0.042	0.035	1.04	0.97, 1.12		NE
Patella lead (µg/gm bone)	0.008	0.009	1.01	0.99, 1.03	1.01	0.99, 1.02
Patella lead > 24.7 µg/gm bone	0.210	0.315	1.23	0.67, 2.29	1.34	0.71, 2.52
Tibia lead (µg/gm bone)	0.030	0.014	1.03	1.00, 1.06	1.02	0.99, 1.05
Tibia lead > 16.6 µg/gm bone	0.584	0.299	1.79	1.10, 3.22	1.26	0.69, 2.29
Patella lead > 24.7 µg/gm bone and tibia lead > 16.6 µg/gm bone	1.12	0.431	3.06	1.31, 7.09	2.38	1.06, 5.36

Notes: The following variables were included in the models: calf circumference (cm), gestational age (wk), gender (1 = female), parity, history of adverse reproductive outcomes, and umbilical cord lead levels (µg/dl). Indicators of bone lead burden were included, 1 at a time. NE = not estimated, *SE* = standard error, OR = odds ratio, and CI = confidence interval.

Table 3.—Coefficients and Odds Ratios (ORs) Estimated by Cumulative Odds Models for Head Circumference at Birth

Variable	Multivariate model 1				Estimates adjusted by birth weight	
	Beta	*SE*	OR	95% CI	OR	95% CI
Calf circumference (cm)	-0.100	0.042	0.90	0.83, 0.98		NE
Smoked during pregnancy	1.427	0.548	4.17	1.42, 12.21		NE
Parity (primiparous vs. other)	0.665	0.252	1.94	1.19, 3.19		NE
Umbilical cord blood lead (μg/dl)	-0.035	0.036	0.97	0.90, 1.04		NE
Patella lead (μg/gm bone)	0.020	0.010	1.02	1.01, 1.04	1.02	1.00, 1.04
Patella lead > 24.7	0.756	0.318	2.13	1.14, 3.97	2.35	1.26, 4.40
Tibia lead (μg/gm bone)	0.024	0.014	1.02	1.00, 1.05	1.02	0.99, 1.05
Tibia lead > 16.6 μg/gm bone	0.429	0.299	1.54	0.86, 2.76	1.31	0.72, 2.38
Patella lead > 24.7 μg/gm bone and tibia lead > 16.6 μg/gm bone	1.004	0.448	2.73	1.14, 6.56	2.21	0.94, 5.20

Notes: The following variables were included in the models: calf circumference (cm), gestational age (wk), gender (1 = female), parity, history of adverse reproductive outcomes, and umbilical cord lead levels (μg/dl). Indicators of bone lead burden were included, 1 at a time. NE = not estimated, *SE* = standard error, OR = odds ratio, and CI = confidence interval.

Discussion

Although we did not collect direct data for the assessment of bone lead mobilization during pregnancy, we observed 2 lines of evidence that indicated that bone lead may be mobilized and may have a negative impact in anthropometry at birth. First, we observed that bone-lead biomarkers were associated positively and significantly with maternal and umbilical cord blood lead. Second, we observed that maternal bone lead burden was associated inversely with head circumference and birth length, and this association was independent of maternal venous blood lead levels, umbilical cord lead levels, and other important predictors of size at birth, including birth weight.

The full-term human fetus contains approximately 30 gm of calcium, all of which must originate from maternal sources. Recent studies suggest that maternal bone is the main source of calcium in utero.[18-20] This source is important, because women who have a large bone lead burden may release significant quantities of lead, as well as calcium, into plasma.[5,6,21-23] Recent data by Gulson et al. show that bone-derived lead may increase venous blood lead levels up to 30% by the end of pregnancy.[21] Rothenberg et al.[22] reported that maternal trabecular bone lead levels were directly associated with prenatal and postnatal lead levels. Similarly, in a small cohort study in which bone lead levels were measured during and after pregnancy, Markowitz et al.[23] observed that a declining bone lead concentration was associated with an increase in blood lead.

Animal experiments[24] and epidemiologic studies suggest that both in utero and postnatal lead exposure may have an adverse effect on growth. However, results relating head circumference or birth length to prenatal lead exposure have been inconsistent. Among 185 women with a mean blood lead level of 6.5 μg/dl, Greene[26] reported weak, inverse associations between prenatal blood lead levels and head circumference (–0.03 cm/μg lead) and birth length (–4.88% of *SD*/μg lead). Similar estimates were reported by McMichael et al.[27] for newborns (N = 831 women) who had a mean blood lead level of 10.6 μg/dl. Recently, Rothenberg et al.[31] reported that prenatal maternal blood lead at 36 wk was associated inversely with head circumference at 6 mo.

Some of the limitations of our study require consideration. We evaluated bone-lead burden cross-sectionally at 1-mo postpartum; therefore, we did not collect direct evidence to evaluate mobilization of bone-lead stores during pregnancy. Evaluation of prepregnancy bone lead levels impose important logistic constraints. Alternatively, a determination in early pregnancy could have represented a more timely evaluation of exposure. However, because current regulations prohibit the use of any research procedure that involves radiation in pregnant women for research purposes (even if the dose is well below accepted criteria for all ages of life), this determination was impossible. Evidence suggests that bone lead measurements at 1-mo postpartum may adequately reflect the bone-lead burden at the beginning of pregnancy. First, lead in cortical bone has a long half-life of 5–10 yr, indicating that changes during pregnancy may not substantially alter bone-lead concentrations. Also, bone-lead biomarkers were significant predictors of umbilical cord and maternal blood lead levels at delivery. Finally, in a small sample of women (n = 16) in which we measured trabecular bone lead levels before and after pregnancy, we observed a high correlation between measurements (r = .66, p < .01).

The mechanism by which lead may reduce a newborn's size is unknown. Birth weight is an indicator of overall size, the variance of which is explained independently by length and weight-for-length[17]; head circumference will reflect overall skeletal growth and will be protected to a greater degree from toxic exposures

than proportionality (weight-for-length) per se.[17] Controlling for birth weight attenuates the association of variables related to the variance in overall size, including maternal and umbilical cord lead levels and tibia lead, suggesting that mobilization of patella lead may predict skeletal growth, reflected in birth-weight-adjusted effects observed for head circumference. These observations indicate the possibility that bone-lead effects may be mediated by 2 mechanisms (Fig. 1): (1) a systemic mechanism that may reduce global size (reflected in the effect on birth weight), and (2) a local mechanism that may affect various tissues, including bone (reflected in the residual effect after adjusting for birth weight). Lead may reduce size at birth by reducing circulating levels of thyroid hormones. Even within normal ranges of variation, serum thyroxin is an important predictor of birth weight, gestational age, and fetal growth.[32] The results of animal studies suggest that lead exposure is associated with lower serum concentrations of triiodothyronine and thyroxin.[33] In humans, different studies have shown that lead exposure may depress the release of thyrotropin-stimulating hormones.[34–36] No information is available about the relationship between thyroid function and prenatal exposure to lead; therefore, more data are needed if this hypothesis is to be confirmed. Lead may also reduce size at birth by a direct toxic effect in calcified tissue. Data from experiments in nonhuman primates indicate that lead is deposited in fetal bone at even higher concentrations than it is in adult bone, suggesting the possibility that there is a direct effect of lead on bone growth.[37]

Our results indicate 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. Although the magnitude of effects was small, such effects are indicative that a continuous exposure during pregnancy affects overall growth in size and, possibly, skeletal maturation. The effects of lead on head circumference may reflect disruption of early brain growth[31] and raises concerns about the potential effects of increased lead exposure resulting from maternal bone-lead mobilization on the developing fetus.

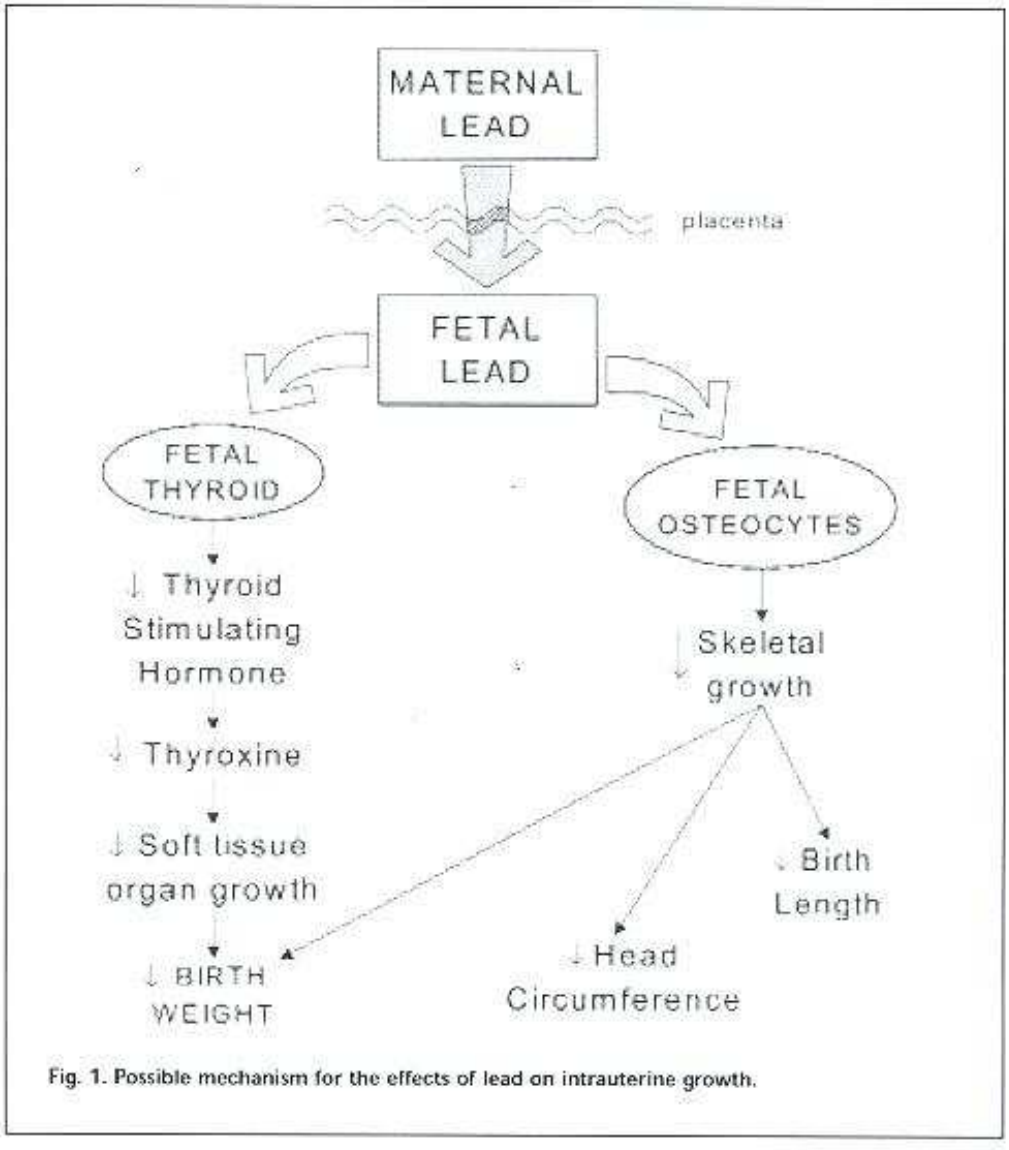

Fig. 1. Possible mechanism for the effects of lead on intrauterine growth.

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