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Decrease in Birth Weight in Relation to Maternal Bone-Lead Burden

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ABSTRACT. *Objectives.* **Birth weight predicts infant survival, growth, and development. Previous research suggests that low levels of fetal lead exposure, as estimated by umbilical cord blood-lead levels at birth, may have an adverse effect on birth weight. This report examines the relationship of lead levels in cord blood and maternal bone to birth weight.**

Methods. **Umbilical cord and maternal venous blood samples and anthropometric and sociodemographic data were obtained at delivery and 1-month postpartum. Blood-lead levels were analyzed by atomic absorption spectrophotometry. Maternal tibia and patella lead levels were determined at 1-month postpartum with use of a spot-source ^{109}Cd K-X-ray fluorescence instrument. The relationship between birth weight and lead burden was evaluated by multiple regression with control of known determinants of size at birth.**

Results. **Data on all variables of interest were obtained for 272 mother-infant pairs. After adjustment for other determinants of birth weight, tibia lead was the only lead biomarker clearly related to birth weight. The decline in birth weight associated to increments in tibia lead was nonlinear and accelerated at the highest tibia lead quartile. In the upper quartile, neonates were on average, 156 grams lighter than those in the lowest quartile. Other significant birth weight predictors included maternal nutritional status, parity, education, gestational age, and smoking during pregnancy.**

Conclusions. **Our results indicate that bone-lead burden is inversely related to birth weight. Taken together with other research indicating that lead can mobilize from bone into plasma without detectable changes in whole blood lead, these findings suggest that bone lead might be a better biomarker than blood lead. Because lead remains in bone for years to decades, mobilization of bone lead during pregnancy may pose a significant fetal exposure with health consequences, long after maternal external lead exposure has declined.** ***Pediatrics*** **1997;100:856–862;** ***bone lead, birth weight, pregnancy, fetus, epidemiology, x-ray fluorescence.***

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ABBREVIATIONS. LBW, low birth weight; K-XRF, K-X-ray fluorescence.

Birth weight is a strong predictor of survival and of developmental outcomes in childhood including growth, morbidity, and cognitive performance.[1–4] High-level occupational lead exposures have been associated with adverse pregnancy outcomes, but studies of lower-level lead exposure on birth weight in community settings have yielded inconsistent findings across the different anthropometric indicators of birth weight.[5–7] Several well-controlled studies failed to show a consistent association of maternal blood-lead levels with preterm delivery, mean gestational age, or birth weight adjusted for gestational age.[7] However, increased risk of low birth weight [(LBW) <2.5 kg] and lower mean birth weights suggest that lead exposure may affect birth weight through intrauterine growth retardation rather than prematurity.

Such inconsistent findings may be explained at least partially by the fact that all previous studies have relied on measurements of lead in whole blood to assess prenatal exposure. More than 95% of lead in a whole blood specimen is bound to red cells.[8] Lead that is available to cross the placenta, however, is derived from lead that is in the free state in plasma.[9] Evidence is beginning to accumulate that plasma-lead levels may fluctuate significantly without a discernible change in whole blood-lead levels; moreover, plasma lead seems to have a positive correlation with levels of lead in bone.[10]

This issue is important because bone lead stores can be retained from years to decades despite a decline in environmental lead exposure and blood-lead levels. Because pregnancy and lactation stimulate increased bone turnover[11] there is concern that mobilization of lead from bone into plasma may constitute a significant threat to the fetus that is not well estimated by measuring lead in whole blood. Although measurement of plasma lead is not feasible for large-scale epidemiologic studies, accurate, in vivo measurements of bone-lead burden can be made with K-X-ray fluorescence (K-XRF).[12]

Mexico City has a history of severe lead exposure related to lead-glazed ceramics used to prepare and serve food, and to leaded gasoline.[13] Because bone lead has a half-life of years to decades, women in their childbearing years who have lived in Mexico City may have a large lead burden that serves as an endogenous source of fetal exposure and may adversely affect fetal growth. This report examines the relationship of blood lead and K-XRF measured maternal bone lead to birth weight, controlling for maternal nutritional status and other determinants of birth weight in a sample of healthy lactating women delivering term infants in Mexico City.

METHODS AND POPULATION

This article presents baseline data of a randomized double-blind calcium supplementation trial to lactating women to test the hypothesis that maternal-to-infant lead mobilization decreases as calcium intake increases. Data collection of such study started at the end of pregnancy and the intervention began at 1-month postpartum.

Sample Selection

We collected data at delivery and 1-month postpartum from women attending any of three hospitals in Mexico City (Mexican Social Security Institute, Manuel Gea González Hospital, and National Institute of Perinatology) that serve a low-to-moderate income population. Baseline information on health status and on social and demographic characteristics was collected from all eligible participants. Anthropometric data from the mother and newborn, and umbilical cord and maternal blood-lead levels were gathered within ±12 hours of delivery. Information on estimated gestational age, based on date of last menstrual period, and characteristics of the birth and newborn were extracted from the medical records. Interviewers explained the study to, and obtained written consent from, eligible women willing to participate.

Exclusion criteria included factors that could interfere with maternal calcium metabolism, medical conditions that could cause LBW, and logistic reasons that would interfere with data collection, which included living in a household outside the metropolitan area; intention not to breastfeed; delivered a premature neonate (<37 weeks); physician's diagnosis of multiple fetuses; preeclampsia, 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; ingestion of corticoids, or blood pressure >140 mm Hg systolic or >90 mm Hg diastolic. One month after delivery (±5 days) each mother-infant pair attended the research center for an evaluation that included measurement of maternal bone lead using a spot-source ^{109}Cd K-XRF instrument.

The research protocol was approved by the Human Subjects Committee of the National Institute of Public Health of Mexico and the participant hospitals. All participant mothers received a detailed explanation of the study and its procedures used, as well as counseling on reduction of lead exposure.

Questionnaires

An interview questionnaire was used to assess social and demographic characteristics, reproductive history, maternal and infant perinatal health, infant feeding practices, as well as information on known risk factors for high blood lead documented in our previous studies.[13]

Anthropometry

Anthropometry was used to assess the nutritional status of mothers and infants.[14] Nude newborns were weighed within the first 12 hours of delivery by experienced obstetric nurses using calibrated beam scales (Oken, Model TD16, Naucalpan, México) read to the nearest 10 grams. Maternal anthropometric measures were collected by our trained[15] project personnel and standardized according to the technique described by Habicht.[16] Maternal height was measured at 1-month postpartum with professional scales (PAME, Puebla, Puebla) read to the nearest mm. Arm and calf circumferences were measured with plastic-covered fabric measuring tapes read to the nearest mm. Standardization exercises were performed until the project staff reached imprecision errors equal to or below those reported by Lohman and coworkers.[15] Accepted technical errors were 0.3 cm for arm and calf circumferences and 0.22 cm for height.

Lead Measurements

Blood samples were analyzed using an atomic absorption spectrophotometry instrument (Perkin-Elmer 3000, Chelmsford, MA) at the metals laboratory of the American British Cowdray Hospital in Mexico City. Analysis of external blinded quality control samples were provided throughout the study period by the Maternal & Child Health Bureau (MCHB) and the Wisconsin State Laboratory of Hygiene (WSLH) Cooperative Blood Lead Proficiency Testing Program (PBPTP), which demonstrated good precision and accuracy of the American British Cowdray Hospital determinations, with a correlation coefficient of 0.99 and mean difference of 0.17 μg/dL compared with MCHB and WSLH PBPTP blanks and spikes.

Bone lead measurements were taken of each mother's mid-tibia shaft (cortical) and patella (trabecular bone) with a spot-source ^{109}Cd K-XRF instrument constructed at Harvard University and installed in a research facility at the American British Cowdray Hospital. The physical principles, technical specifications, and validation of this and other similar K-XRF instruments have been described in detail elsewhere.[17] Briefly, this instrument uses a spot ^{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. The net lead signal is determined after subtraction of the Compton background counts by a linear least-squares algorithm. The lead fluorescent signal is then normalized to the elastic or coherently scattered γ-ray signal, which arises predominantly from the calcium and phosphorous present in bone mineral. Because the instrument provides a continuous unbiased point estimate that oscillates around the true bone lead value, negative point estimates are sometimes produced when true bone lead values are close to zero. The instrument also provides an estimate of the uncertainty associated with each measurement, derived from a goodness-of-fit calculation of the spectrum curves that is equivalent to a single standard deviation. Although a minimal detectable limit calculation of twice this value has been proposed for interpreting an individual's bone lead estimate, statistical experiments have shown that retention of all point estimates makes better use of the data in epidemiologic studies.[12] For the present study, 30-minute measurements were taken at the mid-shaft of the left tibia and at the left patella. Analysis of means and standard deviations of phantom-calibrated measurements did not disclose any significant shift in accuracy or precision.

Statistical Analyses

We examined the relationship between birth weight and known determinants of size at birth, as well as potential confounders of the lead-birth size relationship. Measured variables included umbilical cord and maternal venous blood lead and tibia and patella lead as biomarkers of fetal lead exposure. Information on maternal height, arm and calf circumferences at delivery (cm), smoking (current, past, or never), parity (1 vs 2+ prior deliveries), history of poor reproductive outcomes (yes/no), age and education (yr), site of delivery (Mexican Social Security Institute/not-Mexican Social Security Institute), infant gender, and gestational age (wk) was also collected.

Univariate and bivariate statistics, tabulations, and distribution plots were examined for all variables. Analyses were conducted using STATA[18] and SAS-PC Version 6.04[19] software. An ordinary least-squares multiple regression procedure was used to estimate the adjusted association of lead to birth weight. Specification of our initial saturated model, based on a biologic paradigm of known determinants of birth weight,[20] included all the variables mentioned above. We dropped covariates, one by one, with an associated two-tailed P value of $>.05$. Our final model included only those variables with a statistically significant association ($P <$ .05) with birth weight. Independent variables were included in their original values, without categorization. Smoothed plots indicated that birth weight did not decrease linearly with increasing lead burden. Thus, we analyzed the association of the lead biomarkers first with the variables as continuous variables and then with the variables divided into four groups (often quartiles), with the lowest group as the reference category.

RESULTS

Eleven hundred sixty-two (59%) of the 1959 pregnant women interviewed were not eligible, mostly because they lived outside the metropolitan area or did not intend to breastfeed their infants. Of the 797 eligible women, 315 (40%) completed the 1-month postpartum evaluations. A final sample of 272 mother-infant pairs (34% of the originally eligible women and 86% of those who returned for the study at 1 month) had complete data for all variables of interest. Among the eligible women, there were no significant differences between participants and nonparticipants in maternal nutritional status, age, education, parity, or infant birth weight or gestational age, or in lead levels in maternal or umbilical cord blood.

Mean, median, and standard deviation of lead levels were as follows: maternal blood, 8.9, 8.1, and 4.1 μg/dL, respectively; umbilical cord blood, 7.1, 6.2, and 3.5 μg/dL; maternal tibia, 9.8, 9.1, and 8.9 μg Pb/g bone mineral; patella, 14.2, 13.8, and 13.2 μg Pb/g bone mineral. The numbers of point estimates that were below 0 μg Pb/g bone mineral were 28 (10%) and 36 (13%) for the tibia and patella, respectively.

Mean (standard deviation) birth weight was 3168 ($\pm$404) grams, and 11 infants (4%) had LBW. Because all newborns had a gestational age of $\geq$37 weeks, these 11 neonates were intrauterine growth retarded. Birth weight tended to be higher for neonates of mothers who did not smoke during pregnancy and significantly higher in the group of multiparous women. Birth weight was 3182 ($\pm$408) grams and 3155 ($\pm$402) grams for boys and girls, respectively ($P > .05$). Data on maternal characteristics and their unadjusted associations with birth weight are presented in Table 1. These crude analyses suggest an inverse association between tibia lead and size at birth. Other lead burden biomarkers were unrelated to the study outcome in a bivariate fashion. Maternal nutritional status, gestational age, and parity were strongly associated with size at birth.

In multivariate regression models, lead was always negatively associated with decreased size at birth, although not all biomarkers with statistical significance. Of the four biomarkers of lead burden, with adjustment for other important determinants of birth weight, only tibia lead level had a statistically significant relationship to birth weight ($P < .005$; Table 2). The final regression model is presented in the upper panel of Table 2. An increase of 10 μg Pb/g bone mineral in tibia is associated with a decrease in birth weight of 73 grams, this estimate increased modestly to 75 grams after correction for measurement uncertainty.[12] Other significant independent predictors of birth weight include current maternal nutritional status (as estimated by calf circumference), parity, smoking during pregnancy, education, and newborn gestational age. In the lower panel of Table 2, we present the adjusted change in birth weight associated with quartiles of tibia lead, as described above. The Figure presents a smoothed curve of the adjusted relationship of these two study variables.

The association between birth weight and the other three biomarkers of lead burden, adjusted for the same variables in the regression model, was also analyzed. Results show that, although all other maternal lead burden indicators were also inversely related to birth weight (Table 3), these relationships were not statistically significant.

DISCUSSION

The results of this study suggest that lead in bone (as represented by the tibia) is inversely associated with birth weight. This is the first study to evaluate the association between maternal bone-lead burden and birth weight. Using cord blood lead as the biologic marker of intrauterine lead burden, other studies in this area have reported an association between blood lead and LBW adjusted for gestational age.[21] Their results are in the same direction as ours; ie, birth weight decreases as blood lead increases with an apparent threshold relationship at around 15 μg/dL. However, other studies have failed to find this association[22,23] or have found an association in the opposite direction.[24]

Probably the best explanations for the lack of positive findings in the latter studies may be the type of measurement and control for independent causes of size at birth considered, their statistical power, or the use of blood (as opposed to bone) lead as the biomarker to assess lead burden. We collected information on the most relevant predictors of birth weight, and controlled for this information either by design or by statistical modeling. Furthermore, our use of maternal bone lead as well as blood lead as biomarkers for fetal lead exposure is a sizable improvement over previous methods because bone lead is an indicator of cumulative rather than recent lead exposure. In addition, as noted above, bone lead might be a better biomarker of plasma lead.

Our data suggest an inverse relationship between tibia lead and birth weight (see Figure). In the upper quartile of tibia lead burden, neonates were on average 156 grams lighter than those in the lowest quartile. We selected healthy women for our study so probably the association of lead on birth weight may be larger. Public health problems of this magnitude are seldom as strong, possibly only surpassed by maternal malnutrition, which may explain the more than 50% incidence of LBW in developing countries.[20] The impact on birth weight of most supplementation trials to pregnant women at high nutritional risk have had similar or smaller effects.[25–30] Only when food supplements were consumed in most stressful conditions[31–32] or during current and previous reproductive cycles,[33] is a larger effect on birth weight observed.

Inferring causality in the path of lead burden and birth weight from a cross-sectional observational study such as ours is always problematic, even if there are no obvious biases or confounders. Nevertheless, in support of the biologic plausibility of this relationship there is evidence in the literature of a biologic link of low-lead burden and impaired growth, particularly in studies of lead exposure and childhood stature from birth to 7 years,[5–7,34–38] although not in all studies.[39–40] A recent review of epidemiologic studies suggest this link.[7] The assumed link may be similar in both cases; lead may

TABLE 1. Birth Weight in Relation to Maternal Lead Burden, Health, and Sociodemographic Characteristics Among Postpartum Mexican Women

	n	Mean ± SD
Tibia Lead*		
≤4.50	68	3191 ± 363
4.51–9.59	69	3241 ± 421
9.60–15.14	65	3138 ± 421
≥15.15	70	3103 ± 406
Patella lead*		
≤4.84	66	3178 ± 385
4.85–13.75	67	3184 ± 433
13.76–23.34	66	3146 ± 387
≥23.35	64	3177 ± 437
Maternal blood lead†		
≤5.8	68	3221 ± 382
5.9–8.0	66	3084 ± 365
8.1–11.0	66	3187 ± 444
≥11.1	70	3177 ± 414
Umbilical cord blood lead†		
≤4.6	61	3139 ± 372
4.7–6.1	57	3181 ± 394
6.2–8.5	60	3140 ± 422
≥8.6	60	3158 ± 438
Maternal age (y)		
14–18	31	3113 ± 433
19–24	118	3123 ± 359
25–35	114	3218 ± 444
≥36	9	3322 ± 250
Maternal education (y)		
≤6	71	3208 ± 472
7–9	104	3089 ± 367
≥10	97	3224 ± 379
Maternal height (cm)		
≤150	72	3061 ± 453
150.1–154	73	3148 ± 316
154.1–157	56	3191 ± 451
>157	64	3288 ± 380§‖
Arm circumference (cm)		
≤24.6	71	2996 ± 347
24.7–26.5	74	3161 ± 381
26.6–28.5	64	3221 ± 399
>28.5	63	3318 ± 432§‖
Calf circumference (cm)		
≤32	73	2986 ± 352
32.1–34	74	3167 ± 385
34.1–35.5	53	3150 ± 385
≥35.6	72	3368 ± 403§‖
History of poor reproductive outcome‡		
Yes	61	3177 ± 449
No	211	3166 ± 392
Cigarette smoking		
Never	149	3157 ± 402
In the past	111	3199 ± 410
During this pregnancy	12	3018 ± 366
Gestational age (wk)		
37–38	49	3011 ± 349
59–40	187	3170 ± 396
≥41	36	3374 ± 432§‖
Hospital delivery		
Mexican Social Security Institute	223	3177 ± 414
Other	49	3127 ± 361
Parity		
1	123	3065 ± 374
2+	149	3253 ± 410§

* μg Pb/g bone mineral.
† μg/dL.
‡ Prior birth weight <2.5 kg, gestational age <37 weeks, stillbirth, or spontaneous abortion.
§ $P < .05$, Scheffè.
‖ Test for trend, $P < .01$.

impair birth weight through an effect on prenatal bone growth itself in such a way that attained weight at birth may be negatively affected.

TABLE 2. Regression of Maternal Tibia Lead on Birth Weight Controlling for Maternal Health and Sociodemographic Characteristics Among Postpartum Mexican Women (n = 272)

Variables in the Model*	Regression Coefficient	Standard Error	*P* values
Tibia lead†	−7.29	2.45	0.003
Calf circumference (cm)	40.42	7.81	<0.001
Parity (1 = 1, 2 = 2+)	205.87	44.24	<0.001
Education (y)	17.01	6.98	0.016
Gestational age (wk)	75.49	18.72	<0.001
Current smokers	−239.61	104.73	0.023
Constant	−1576.02	733.59	0.033
Adjusted effect of tibia lead† by quartiles, on birth weight‡			
Second quartile >4.46−≤9.59	−7.57	60.98	0.901
Third quartile >9.59−≤15.14	−50.86	62.03	0.413
Fourth quartile >15.14	−155.55	61.18	0.012

* Model adjusted $R^2 = 23.8$.
† μg Pb/g bone mineral.
‡ First quartile is the reference category.

On the other hand, evidence that lead deposited in bone serves as a source of blood lead is rapidly growing.[41] Ninety-five percent or more of adult's lead is stored in bone[42] and it is now recognized that bone, rather than blood, acts as a sink for lead, and that it is a metabolically active depot from which lead moves in and out at a rate determined by factors affecting bone remodeling.[43]

Neither hospital staff, study personnel, nor study participants were aware of the hypothesis being tested. This prevented that participation in the study or completeness of follow-up were differentially affected by birth weight or lead levels. Birth weight data was not directly measured by our project staff, but by trained hospital personnel. However, variability associated with birth weight in our study was low compared with most,[25–27,44] although not all[29] similar reports of hospital deliveries of well-controlled nutritional supplementation trials with birth weight as the critical study outcome. This serves as an indication of the adequacy of our birth weight data. Furthermore, measurement imprecision was most likely random, and the potential bias would attenuate the observed association. Thus, it is likely that ours is probably an underestimation of the true association between lead burden and size at birth.

Our study may be limited by measurement of bone lead at 1-month postpartum and not during pregnancy. We did not measure bone lead during pregnancy because current Mexican human subjects guidelines for medical research prohibit the use of any research procedure that involves radiation in pregnant women, even if the dose delivered is insignificant and well below current accepted criteria for all ages of life.[45] There are two lines of evidence which suggest that bone lead measurements at 1-month postpartum may adequately reflect those at the beginning of pregnancy: 1) lead in cortical bone (such as the tibia) has a half-life of decades,[46] and 2) we observed in our data that both patella and tibia lead estimates were correlated to maternal ($r = 0.24$ and 0.20) as well as to umbilical ($r = 0.25$ and 0.26) cord blood-lead levels, respectively.

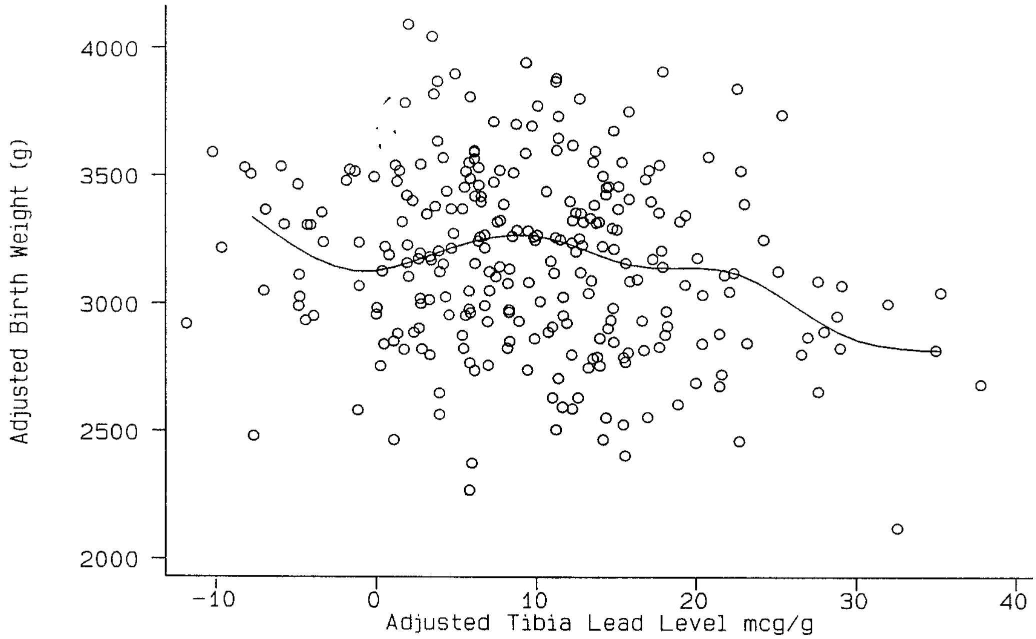

Figure. Adjusted relation between birth weight and tibia-lead levels* (smooth). Adjusted by gestational age, parity, smoking status, calf circumference, and education (year).

TABLE 3. Adjusted* Estimates of the Association† of Maternal Venous Blood, Patella, and Umbilical Cord Blood Lead on Birth Weight Among Postpartum Mexican Women

	Regression coefficient	Standard Error	*P* Values
Model 1 patella lead‡			
(Adjusted R^2 = 24.3, n = 269)	−2.70	1.65	.104
Model 2 patella lead‖			
Second quartile 4.7–13.8	26.34	61.40	.668
Third quartile 13.9–23.3	−39.35	61.90	.526
Fourth quartile >23.3	−57.37	63.22	.365
Model 3 umbilical cord blood lead§			
(Adjusted R^2 = 22.9, n = 246)	−4.07	6.55	.535
Model 4 umbilical cord blood lead‖			
Second quartile 4.6–6.1	13.87	64.51	.830
Third quartile 6.2–8.5	−53.15	63.85	.406
Fourth quartile >8.5	−41.84	64.04	.514
Model 5 venous blood level§			
(Adjusted R^2 = 23.0, n = 278)	−6.20	5.27	.241
Model 6 venous blood lead‖			
Second quartile 5.8–8.0	−152.21	58.91	.010
Third quartile 8.1–11.0	−34.85	60.10	.562
Fourth quartile >11.0	−98.30	59.55	.100

* Adjusted for the independent variables of model in Table 2.
† By quartiles of available observations.
‡ μg Pb/g bone mineral.
§ μg/dL.
‖ First quartile is the reference category.

Tibia and patella lead were both inversely related to birth weight, but this association was significant only for tibia lead. The difference in our observed associations between the two bone lead markers could be attributed to the error measurement associated with patella lead determination. On one side is the fact that patella-lead levels varies faster probably because of its trabecular nature.[46–47] It is also likely that in response to the important calcium demand that women experience during pregnancy and lactation —preferentially affecting trabecular bone—biologic variability may have increased, conditioning an increase in error measurement at this site. On the other side, trabecular bone lead measurement is also measured with a higher degree of error, because of the low mineral content of this bone type. The combination of these factors may explain the observed lack of a statistically significant association between patella lead and birth weight.

Because bone lead has a half-life of years to decades, our results suggest that blood-lead levels cannot be used to fully predict risk of associated fetal toxicity. Lead can remain a significant threat to the fetus long after cessation of external lead exposure to women who are pregnant or who will become pregnant. Bone-lead levels in our study population were three times higher than median postpartum bone levels of women who gave birth in a Boston hospital in 1990 to 1992 (tibia median, 4; patella median, 5 μg Pb/g).[48] This finding has significant public health implications. Moreover, current regulations governing occupational exposure to lead do not offer any protection to women who might become pregnant in the future.

The finding of neurotoxic effects at increasingly lower lead concentrations[21] suggests that a fetotoxic effect may still occur among women who have relatively low blood-lead levels but that retain high bone-lead burdens. We explored the association of tibia lead burden and birth weight at three levels of cord and maternal blood-lead values (<5, 5 to 10, and <10 μg/dL; data not shown) and observed that the negative association persisted at the middle level ($P < .02$ and .07, respectively).

Our data show a negative association between lead burden and birth weight, the latter being one of the strongest predictors of neonatal survival and future health status, growth, and cognitive and school performance. Future research should be directed at confirming this finding, and, if confirmed, at developing strategies to prevent the mobilization of lead from bone during conditions of rapid bone turnover such as pregnancy and lactation. Governments and society have been remarkably slow to recognize the lead burden problem and respond with appropriate lead-abatement programs. In many countries, leaded gasoline continues to be in use, and control over other important sources such as lead-glazed ceramics to prepare and serve food is almost nonexistent or not enforced. Research in this area provides information needed to be transferred to decision makers to implement measures to effectively eliminate lead from the environment, protecting future generations from its deleterious effects.

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'Déjà vu' all over again?

"As I once before remarked, the desire to take medicine is one feature which distinguishes man, the animal, from his fellow creatures. It is really one of the most serious difficulties with which we [physicians] have to contend. Even in minor ailments, which would yield to dieting or to simple home remedies, the doctor's visit is not thought to be complete without the prescription. And now that the pharmacists have cloaked even the most nauseous remedies, the temptation is to use medicine on every occasion, and I fear we may return to that state of polypharmacy, the emancipation of which has been the sole gift of Hahnemann and his followers to the race. As the public becomes more enlightened, and as we get more sense, dosing will be recognized as a very minor function in the practice of medicine in comparison with the old measures of Asclepiades."