Effects of Lead Exposure before Pregnancy and Dietary Calcium during Pregnancy on Fetal Development and Lead Accumulation

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Millions of women of child-bearing age have substantial bone lead stores due to lead exposure as children. Dietary calcium ingested simultaneously with lead exposure can reduce lead absorption and accumulation. However, the effects of dietary calcium on previously accumulated maternal lead stores and transfer to the fetus have not been investigated. We studied the effects of lead exposure of female rats at an early age on fetal development during a subsequent pregnancy. We gave 5-week-old female Sprague-Dawley rats lead as the acetate in their drinking water for 5 weeks; controls received equimolar sodium acetate. This was followed by a 1-month period without lead exposure before mating. We randomly assigned pregnant rats (n = 39) to two diets; one with a deficient (0.1%) or normal (0.5%) calcium content during pregnancy. A total of 345 pups were delivered alive. Lead-exposed dams and their pups had significantly higher blood lead concentrations than controls, but the concentrations were in the range of those found in many pregnant women. Pups born to dams fed the calcium-deficient diet during pregnancy had higher blood and organ lead concentrations than pups born to dams fed the 0.5% calcium diet. Pups born to lead-exposed dams had significantly (p < 0.0001) lower mean birth weights and birth lengths than controls. There were significant inverse univariate associations between dam or pup organ lead concentrations and birth weight or length. The 0.5% calcium diet did not increase in utero growth. Stepwise regression analysis demonstrated that greater litter size and male sex were significantly associated with reduced pup birth weight and length. However, lead exposure that ended well before pregnancy was significantly (p < 0.0001) associated with reduced birth weight and length, even after litter size, pup sex, and dam weight gain during pregnancy were included in the regression analysis. The data demonstrate that an increase in dietary calcium during pregnancy can reduce fetal lead accumulation but cannot prevent lead-induced decreases in birth weight and length. The results provide evidence that dietary nutrients can influence the transfer of toxins to the fetus during pregnancy. If these results are applicable to women, an increase in diet calcium during pregnancy could reduce the transfer of lead from prepregnancy maternal exposures to the fetus. Key words: birth weight, calcium, fetus, lead, pregnancy. Environ Health Perspect 108:527–531 (2000). [Online 18 April 2000] http://ehpnet1.niehs.nih.gov/docs/2000/108p527-531hani/abstract.html

Adequate birth weight is a key marker of a successful pregnancy and has a major influence on neonatal mortality. Both maternal nutritional factors and exposure to environmental toxicants can greatly influence fetal growth and development. However, very few studies have addressed interactions among dietary components, environmental toxicants, and fetal development.

There is considerable evidence that a diet low in calcium can enhance gastrointestinal lead absorption and toxicity in humans and experimental animals (1–5). Diets that have adequate amounts of calcium will reduce lead absorption and may provide additional protection against lead toxicity by inhibiting the adverse effects of lead on calcium-mediated cellular functions (6,7).

In a previous investigation (8), we demonstrated that lead exposure of rats during pregnancy can retard fetal growth and development, especially if the maternal diet during pregnancy is low in calcium. However, in humans, most lead exposure in women occurs during childhood, with relatively little additional exposure during pregnancy. Nevertheless, lead exposure as a child and at other ages before pregnancy will result in retention of considerable amounts of lead in the skeleton (5,9,10). Recent evidence demonstrates that maternal skeletal lead stores are mobilized during pregnancy and, in part, are transferred through the bloodstream to the fetus (11,12). One recent study in Mexican women demonstrated an inverse association between maternal bone lead stores and birth weight (13); in this study, maternal nutritional status, assessed by calf circumference, was positively associated with birth weight. However, there was no evaluation of the maternal diet.

The present study is based on the hypothesis that an adequate intake of calcium during pregnancy will prevent or reduce the adverse effects of maternal lead stores on fetal development and lead accumulation in utero. Our primary objective was to determine the influence of deficient and normal calcium intakes in pregnant rats on the effects on the fetus of lead stores from previous maternal lead exposures. Major outcome variables were birth weight, birth length, and fetal blood and organ lead concentrations. A second objective was to assess relationships among the major outcome and other variables to provide insight into mechanisms by which lead and calcium can interact to influence pregnancy and fetal development.

Materials and Methods

Animal care and treatment. Weanling female Sprague-Dawley (SD) rats (Taconic Farms, Kingston, NY; n = 76) were allowed to acclimate to the research animal facility environment for 1 week. This facility is fully accredited by the Association for Assessment and Accreditation for Laboratory Animal Care. The rats were housed in individual plastic cages in a temperature- and humidity-controlled environment with light/dark cycles of 12 hr each. Beginning at 5 weeks of age, half of the rats were exposed to lead as the acetate in the drinking water (250 mg/L); controls were simultaneously given equimolar sodium acetate in the drinking water. A 5-week period of lead exposure was followed by a 4-week period without lead exposure. During these periods before mating, the rats consumed diets containing 0.5% calcium. At this time, the rats were 14 weeks of age. The female rats were then mated with 14-week-old male SD rats, with 1 male and 3 females caged together. Of the 76 female rats, 39 (51.3%) were impregnated. Lead-exposed and nonexposed pregnant rats were then randomly assigned to either normal (0.5%) or low (0.1%) calcium diets during pregnancy. Nonpregnant animals were also randomly assigned to one of the calcium diets. We used a stratified design based on the blood lead concentration at the time of random assignment. This ensured comparable initial blood lead concentrations in the two lead-exposed treatment groups that were fed either 0.1% or 0.5% calcium. During pregnancy, dam body weights were measured twice each week. In addition, blood samples (150 μL) were drawn from a tail vein once each week.

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Supported in part by grant HL6581 from the National Institutes of Health.

Received 7 September 1999; accepted 14 December 1999.

Environmental Health Perspectives • VOLUME 108 | NUMBER 6 | June 2000
We allowed pregnant rats to carry their litters to term. The 39 pregnant rats delivered a total of 345 live pups; 13 pups were stillborn. Within 3–18 hr of birth, we weighed all pups and measured their lengths (distance from nose to origin of tail) using a micrometer.

We randomly chose two male and two female pups from each litter using a table of random numbers. The pups were anesthetized with methoxyflurane (Metafane; Pittman-Moore, Inc., Mundelin, IL) and euthanized within 18 hr of birth; blood and several organs (brain, kidney, liver) were harvested from each pup. Within 18 hr of delivery, we collected blood from the dams by cardiac puncture; after euthanizing the dams by decapitation under heavy pentobarbital anesthesia, we harvested the following tissues: kidney, liver, brain, femur, and spinal column bone.

The modified calcium diets used were prepared by Research Diets Inc. (New Brunswick, NJ) and have been previously described (1,8). The above procedures were approved by the Institutional Animal Care and Use Committee of the New Jersey Medical School.

**Laboratory analyses.** We used electrothermal atomic absorption spectrophotometry to determine whole blood lead concentrations (14). We used a quality control sample (Bio-Rad whole blood control level 3; Bio-Rad, Anaheim, CA) to monitor the accuracy of these analyses. Concentrations determined for this sample were within 8% of the certified value.

We ashed the organs with a 3:1 mixture of double-distilled nitric and perchloric acids (GFS Chemicals, Columbus, OH); the residue was quantitatively transferred to a 10- or 25-mL volumetric flask and diluted with distilled, deionized water. Further dilutions were necessary for some organs. We determined lead concentrations of the ashed samples by electrothermal atomic absorption spectrophotometry. Calculations of concentrations were based on wet tissue weight. We used National Institute of Standards and Technology bovine liver (NIST 1577b; Gaithersburg, MD) as a quality control sample. Assays of this sample in our laboratory gave results within 5% of certified values.

**Statistics.** We performed data reduction and analysis by using dBASE III+ (Ashton-Tate, Torrance, CA) and the Statistical Analysis System (SAS Institute, Cary, NC). We used analysis of variance (ANOVA; SAS General Linear Models, SAS Institute) to evaluate the effects of treatment on blood and organ lead concentrations, birth weights, birth lengths, and other variables. If ANOVA indicated statistically significant (p < 0.05) differences among groups for a specific variable, we then made pair-wise comparisons using Duncan’s multiple range test at α = 0.05. Kidney lead concentrations are known to vary considerably among individual animals, even for rats in the same treatment group (1,8,14). Therefore, kidney lead concentrations were log transformed before evaluation by ANOVA.

We assessed univariate associations between variables by calculating Pearson correlation coefficients. In addition, we performed stepwise multiple regression analyses to assess the possibility that other factors besides lead exposure or dietary calcium might influence the effect of these variables on birth weight or birth length. In these analyses, birth weight or birth length was the dependent variable, and the independent variables were lead exposure status, dietary calcium intake during pregnancy, litter size, pup sex, dam weight gain during pregnancy, and dam body weight before pregnancy and after delivery.

**Results**

**Lead dosing and dam growth.** The mean (± SE) daily intakes of drinking water during the 5-week period of lead exposure were 22.4 ± 0.9 mL/day for control rats and 20.9 ± 0.6 mL/day for rats given lead in the drinking water. These values do not differ significantly (t-test, p > 0.05).

Figure 1 shows growth curves for rats before mating and after random assignment to 0.1% or 0.5% calcium diets during pregnancy. Mated females that did not become pregnant are also included in Figure 1. Growth of lead-exposed and nonexposed rats was comparable before and after mating, and was not influenced by the dietary calcium content subsequent to mating. Pregnant rats developed substantially higher body weights than the nonpregnant rats (~100 g greater), but their body weights did not differ significantly among the four treatment groups (ANOVA, p > 0.05).

**Fetal development.** Figures 2 and 3 show birth weights and lengths of the 345 pups (163 males and 182 females) that were delivered alive by the 39 pregnant dams. Female pups had lower body weights and lengths than male pups; therefore, males and females in the various treatment groups are compared separately. Lead exposure reduced birth weight and length for both the males and the females. The dietary calcium intake of the dams during pregnancy generally did not influence pups at birth, but dams fed the 0.5% Ca diet had larger pups (Figure 2).

![Figure 1. Growth curves of female rats before, during, and after pregnancy. Abbreviations: NP, not pregnant; P, pregnant. n = 39 pregnant rats and 37 nonpregnant rats.](image)

![Figure 2. Birth weights (mean ± SE) of pups within 3–18 hr of delivery. Pups delivered by dams with previous lead exposure had significantly lower birth weights than those delivered by nonexposed dams (ANOVA, p < 0.0001) for males, females, and both sexes combined. n = 31–43 male pups, 32–64 female pups, and 63–107 pups for both sexes combined per treatment group. Bars not marked by the same letter (A, B, or C) are significantly different (Duncan’s test, p < 0.05).](image)
not influence fetal growth. However, the higher diet calcium intake increased birth weight for the male pups not exposed to lead. In addition, we observed reduced birth length in the male and female pups whose lead-exposed mothers were fed the 0.5% calcium diet.

**Blood and organ lead concentrations.** Figure 4 shows blood lead concentrations of the dams before pregnancy and for days 9, 16, and 21 of gestation. Blood lead concentrations were much higher in dams previously exposed to lead than in those not given lead in the drinking water. Blood lead concentrations of the lead-exposed dams declined during pregnancy, as expected, because lead exposure was terminated 1 month before pregnancy. For both the lead-exposed and unexposed dams, blood lead concentrations on days 9, 16, and 21 of gestation were lower in rats fed the 0.5% calcium diet during pregnancy than in those receiving the 0.1% calcium diet. However, the differences were only significant for day 21 of gestation for the lead-exposed rats.

Organ lead concentrations of the dams are shown in Table 1; lead-exposed dams had significantly higher lead concentrations than unexposed dams in each of the five organs assessed. Lead-exposed dams fed the normal calcium diet during pregnancy had lower lead concentrations in brain, femur, kidney, liver, and spinal column bone than those fed the low calcium diet. Of these, the brain and kidney lead concentrations were significantly lower ($p < 0.05$).

The blood and organ lead concentrations for the rat pups are shown in Table 2. Pups born to lead-exposed dams had significantly higher lead concentrations than pups born to unexposed dams for blood, kidney, liver, and carcass, but not for brain. Pups delivered by dams fed the normal calcium diet had lower lead concentrations than those delivered by dams fed the low calcium diet. Of these, the blood, liver, and carcass concentrations were significantly lower.

**Relationships between birth weight, birth length, and other variables.** Univariate associations between birth weight, birth length, and other measured variables are presented in Table 3. Birth weight and length were significantly and negatively associated with litter size, dam brain lead, dam kidney lead, dam femur lead, and dam spinal column lead. Birth weight was also significantly associated with pup kidney lead. There was also a significant positive association between birth weight and birth length. Birth length but not weight was significantly associated with weight gain during pregnancy and pre-pregnancy dam weight.

Table 4 presents regression models of birth weight and length on other measured variables. In these models, birth weight or length is the dependent variable, and litter size, pup sex, pregnancy weight gain, dam weight before pregnancy and after delivery, lead exposure status, and dietary calcium status during pregnancy are the independent variables. Lead exposure remained a significant ($p = 0.0001$) predictor of birth weight and length even after inclusion of the other variables in the model. Together, litter size, lead exposure, pup sex, and dam weight gain during pregnancy explained 32.5% of the variability in birth weight and 33.5% of the variability in birth length.

### Discussion

The present study demonstrates that lead exposure which ends well before pregnancy can nevertheless cause decreases in birth weight and length in the rat. This observation is relevant to human pregnancy because most women are likely to have limited exposure to lead during pregnancy, but may have considerable body lead burdens from a history of lead exposure, including exposure during childhood. This may be especially true for older women and those who are nulliparous, factors that are associated with greater bone lead stores. Bone lead is considered the dominant source of blood lead if environmental exposures are low, especially during pregnancy and lactation, conditions that tend

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**Figure 3.** Birth lengths (mean ± SE) of pups within 3–18 hr of delivery. Pups delivered by dams with previous lead exposure had significantly (ANOVA, $p < 0.0001$) lower birth lengths than those delivered by nonexposed dams. $n = 31–43$ male pups, 32–64 female pups, and 63–107 for both sexes combined per treatment group. Bars not marked by the same letter (A, B, or C) are significantly different (Duncan’s test, $p < 0.05$).

**Figure 4.** Blood lead concentrations of pregnant rats with or without lead exposure. Both exposed and nonexposed rats fed the low calcium (0.1%) diet developed higher blood lead concentrations than those fed the normal (0.5%) calcium diet during gestation, but the difference was significant only for the lead-exposed rats on day 21 (study day 86) of gestation. $p < 0.0001$. $n = 10$ lead-exposed and 8 nonexposed rats fed the 0.1% Ca diet and 12 lead-exposed and 9 nonexposed rats fed the 0.5% Ca diet. To convert blood lead concentrations to μg/dL, multiply μmol/L by 20.7.

### Table 1. Organ lead concentrations of dams.

|                  | Not lead-exposed | Lead-exposed |
|------------------|------------------|--------------|
|                  | Low calcium diet | Normal calcium diet | Low calcium diet | Normal calcium diet |
| Brain            | 0.22 ± 0.10 C    | 0.16 ± 0.06 C   | 2.37 ± 0.25 A    | 1.70 ± 0.14 B      |
| Femur            | 6.98 ± 1.86 B    | 3.93 ± 1.29 B   | 884 ± 104 A      | 757 ± 62 A         |
| Kidney           | 2.74 ± 0.59 C    | 1.34 ± 0.40 D   | 138 ± 37 A       | 96 ± 12 B          |
| Liver            | 0.14 ± 0.05 B    | 0.46 ± 0.33 B   | 4.00 ± 0.74 A    | 2.94 ± 0.41 A      |
| Spinal column bone | 6.59 ± 1.63 B   | 3.15 ± 0.94 B   | 763 ± 95 A       | 696 ± 70 A         |

Data shown are mean ± SE (nmol/g); $n = 8–12$. Kidney concentrations were log transformed before ANOVA analysis. Values in the same row that are not marked with the same letter are significantly different ($p < 0.05$; ANOVA with Duncan’s test).

### Table 2. Blood and organ lead concentrations of pups.

|                  | Not lead-exposed | Lead-exposed |
|------------------|------------------|--------------|
|                  | Low calcium diet | Normal calcium diet | Low calcium diet | Normal calcium diet |
| Blood            | 0.137 ± 0.030 C  | 0.032 ± 0.003 C | 1.160 ± 0.053 A | 0.771 ± 0.050 B    |
| Brain            | 0.05 ± 0.02 A    | 0.05 ± 0.02 A  | 0.11 ± 0.02 A   | 0.07 ± 0.03 A      |
| Kidney           | 0.77 ± 0.52 B    | 0.21 ± 0.09 B  | 1.93 ± 0.39 A   | 1.16 ± 0.25 A      |
| Liver            | 0.40 ± 0.15 C    | 0.38 ± 0.07 C  | 2.16 ± 0.19 A   | 1.27 ± 0.12 B      |
| Carcass          | 0.14 ± 0.07 C    | 0.05 ± 0.03 C  | 1.39 ± 0.31 A   | 0.53 ± 0.08 B      |

Data shown are mean ± SE, $n = 6–12$. Units are μmol/L for blood and nmol/g for organs and carcass. Kidney concentrations were log transformed before ANOVA analysis. To convert blood lead concentrations to μg/dL, multiply μmol/L by 20.7. Values in the same row that are not marked by the same letter are significantly different ($p < 0.05$; ANOVA with Duncan’s test).
to mobilize skeletal lead stores (12). In the present study, an increase in dietary calcium during pregnancy reduced fetal lead accumulation, but did not prevent the adverse effects of lead on birth weight and length.

Paradoxically, the diet with higher calcium reduced birth length (but not birth weight) in male pups with in utero lead exposure. This effect is likely due to effects on birth length of other variables (litter size, pup sex, pregnancy weight gain, and organ lead concentrations) because the impact of diet calcium does not remain after consideration of these variables (Tables 3 and 4).

The decrease in blood lead concentrations during pregnancy is probably due to the gradual increase in time since the end of lead exposure, despite the expected mobilization of skeletal lead during pregnancy. Dams fed the low-calcium diet had higher lead concentrations at the end of the third trimester than dams fed the normal calcium diet; this suggests suppression of bone lead mobilization by the normal calcium diet.

Studies in humans have not consistently demonstrated an inverse relationship between lead exposure and birth weight (16-21). This may in part be related to the numerous factors that can influence birth weight and to a limited ability to accurately assess maternal lead exposure and other relevant factors. An advantage of studying the effects of lead and dietary calcium on fetal development in experimental animals is the ability to regulate lead exposure and dietary calcium intake, this permits a more precise assessment of effects on other variables. The present study demonstrates that the lead exposure before pregnancy was a significant predictor of reduced birth weight and length, even after adjustment for other factors such as pup sex, litter size, and maternal weight gain during pregnancy.

**Table 3. Univariate associations between birth weight, or birth length, and other variables.**

| Birth weight | Birth length |
|--------------|-------------|
| Pup birth length | 0.73 0.0001 | 0.26 0.0001 |
| Litter size | -0.43 0.0001 | -0.12 0.0001 |
| Lead exposure | -0.31 0.0001 | -0.24 0.0001 |
| Dietary calcium | -0.01 NS | -0.08 NS |
| Pup sex | 0.28 0.0001 | 0.35 0.0001 |
| Pregnancy weight gain | -0.02 NS | -0.11 0.049 |
| Dam weight before pregnancy | -0.02 NS | 0.11 0.040 |
| Dam brain lead | -0.26 0.0001 | -0.23 0.0001 |
| Dam liver lead | 0.01 NS | 0.01 NS |
| Dam kidney lead | -0.26 0.0001 | -0.17 0.0015 |
| Dam femur lead | -0.24 0.0001 | -0.21 0.0001 |
| Dam spinal column bone lead | -0.20 0.0002 | -0.21 0.0001 |
| Pup kidney lead | -0.40 0.0001 | -0.18 NS |

**Table 4. Multiple regression models of birth weight and birth length on other measured variables.**

| Birth weight | Birth length |
|--------------|-------------|
| Partial $R^2$ | Parameter estimate | $p$ | Partial $R^2$ | Parameter estimate | $p$ |
| Pup birth length | 0.724 | 7.284 | 0.0001 | NS | 53.771 |
| Litter size | 0.185 | -0.126 | 0.0001 | 0.178 | 0.180 | 0.0001 |
| Lead exposure | 0.074 | -0.002 | 0.0001 | 0.037 | 0.0001 |
| Pup sex | 0.056 | 0.356 | 0.0001 | 0.089 | 0.134 | 0.0001 |
| Dam weight gain during pregnancy | 0.010 | 0.006 | 0.03 | 0.021 | -0.032 | 0.001 |
| Dietary calcium | NS | NS | NS | NS | NS |
| Dam weight before delivery | - | - | NS | 0.012 | 0.072 | 0.016 |
| Dam weight after delivery | - | - | NS | 0.024 | -0.059 | 0.0004 |

NS, not significant ($p > 0.05$).

$R^2$ Pearson correlation coefficient. *Female = 0 and male = 1.

$R^2$ = 0.325 for the birth weight model, and $R^2$ = 0.37 for the birth length model. Data are from stepwise multiple regression analyses with entry and exclusion criteria of $R^2 > 0.05, n = 344$. Dam and pup weights were measured in grams and pup length was measured in millimeters. For birth length, $R^2 = 0.335$ if dam weights before and after delivery are not included in the model.
high-precision measurements of lead isotopes in maternal blood and urine and in environmental samples to confirm the increases in lead mobilization from the maternal skeleton that occur during human pregnancy. Because skeletal mobilization of calcium and lead occurs primarily in the third trimester, the ability of increased diet calcium to alter fetal lead accumulation but not fetal growth suggests that the adverse effects of lead on fetal growth may occur primarily in the first and/or second trimesters.

In the United States, African-American women have a greater risk of delivering low birth weight neonates than white women (27,28). Although there are likely numerous variables that may contribute to this higher risk, a largely unexplored factor could be the higher skeletal lead stores of some African-American women due to childhood lead exposures while living in inner cities.

In a recent study, Ballwe et al. (29) evaluated relationships between blood lead concentrations and anthropometric measurements in over 4,000 children 1–7 years of age. Significant negative associations between blood lead concentrations and height or head circumference were found. Their regression models predicted a reduction in height of 1.57 cm for each 10 μg/dL (0.48 μmol/L) increase in the blood lead concentration. In this study (29), calcium intake from supplements was a significant predictor of increased height and head circumference. In contrast, we found in the present study that increased maternal diet calcium did not increase birth weight and length. The mechanisms by which calcium–lead interactions influence growth in utero may differ from those that are operative after birth.

Events in utero can influence health for many years after birth; the term “fetal programming” has been used to describe this process. For example, several studies found associations between low birth weight and the development of hypertension as an adult (30–32). Other studies found associations between hypertension and bone or blood lead concentrations in adults (33–35). Skeletal lead, whether accumulated in utero or after birth, is in equilibrium with blood lead. It is possible that in utero lead exposure could cause both reduced birth weight, as suggested by the present study, and hypertension many years later. If this possibility is supported by additional studies, then the association between low birth weight and hypertension as an adult could be due in part to in utero lead exposure.

In summary, the results of this study demonstrate that lead exposure which ends well before pregnancy can reduce birth weight and birth length and that an increase in dietary calcium intake during pregnancy can reduce fetal lead accumulation in pregnant rats with a history of previous lead exposure. The results provide evidence that the composition of the diet can influence the transfer of an environmental toxicant to the fetus during pregnancy.

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