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Brief communication

Very low maternal lead level in pregnancy and birth outcomes in an eastern Massachusetts population

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ABSTRACT

Purpose: Maternal lead exposure is associated with poor birth outcomes in populations with moderate to high blood levels. However, no studies have looked at exposure levels commonly experienced by US women.

Methods: We evaluated the relationship between maternal red blood cell (RBC) lead levels in mid-pregnancy and birth outcomes in 949 mother–child pairs in a prebirth cohort. We used multiple linear regression and logistic regression, adjusted for potential confounders including maternal age, race, prepregnancy body mass index, and smoking to relate maternal lead to infant birth size and risk for preterm birth (<37 weeks).

Results: Mean RBC lead level was 1.2 μg/dL (range, 0.0–5.0). Mean (standard deviation) birthweight was 3505 (520) g, birthweight for gestational age z-score 0.22 (0.93), and length of gestation 39.5 (1.7) weeks. Mothers in the highest versus lowest lead quartile did not have higher odds (OR, 1.85; 95% confidence interval [CI], 0.79–4.34) of preterm delivery; after stratifying by child sex, there was an association among males (OR, 5.51; 95% CI, 1.21–25.15) but not females (OR, 0.82; 95% CI, 0.24–2.85). Maternal RBC lead was not associated with any continuous outcomes in combined or sex-stratified analyses.

Conclusions: Maternal lead exposure, even at very low levels, may adversely affect some childbirth outcomes, particularly preterm birth among males.

Introduction

Lead is a ubiquitous environmental toxicant. As studies have accumulated demonstrating the adverse effects of childhood lead exposure on neurodevelopment, recent attention has turned to the effects of prenatal exposure [1,2]. Pregnancy is an especially vulnerable time not only because of the unique sensitivity of the developing fetus to exogenous insults but also because lead previously stored in bones can mobilize with maternal calcium stores and become an endogenous source of exposure [3–5]. Lead readily crosses the placenta and has been measured in fetal brains as early as the first trimester [6].

Higher lead levels during pregnancy have been associated with adverse effects for a range of outcomes, including risks for gestational hypertension, preeclampsia, poor fetal growth, and impaired neurodevelopment [7–12]. However, few studies have examined exposure levels within the range commonly experienced by US women. US guidelines recommend follow-up for pregnant women with a whole blood lead level of 5 μg/dL or more. About 1% of US women of childbearing age (15–44 years) exceed this threshold [6]. Mean lead level among US women is 0.6 μg/dL, and little is known about the effects of prenatal exposure at this level [6,10,13,14].

Our study aimed to determine associations of prenatal lead exposure, at levels commonly experienced by US women, with fetal growth and birth outcomes.

Methods

Study subjects

Study subjects were mother–child pairs in Project Viva, a prospective prebirth cohort designed to study prenatal risk factors on pregnancy and child health outcomes. We recruited women at their

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first prenatal visit from Harvard Vanguard Medical Associates, a large group practice in eastern Massachusetts. Eligibility criteria included English speaking, singleton pregnancy, and less than 22 weeks gestation. Recruitment procedures have been described in detail elsewhere [15]. All women provided written informed consent and the research was approved by the Institutional Review Board at Harvard Pilgrim Health Care.

We recruited 64% of those eligible between 1999 and 2002; 2128 gave birth to a live infant and were enrolled in the cohort. We collected blood samples from 1614 women (76%) at a mean of 27.9 weeks of gestation. Because of funding limitations, we analyzed samples from 950 women for lead. After assay, we excluded from analysis one participant with a red blood cell (RBC) level substantially higher than the rest of the cohort (9.8 μg/dL) as our intention was to study the effect of very low exposure. Overall, participants included were similar in baseline characteristics to those excluded (data not shown). However, participants in this analysis had babies who weighed on average 79 g more and had a mean birthweight for gestational age z-score of 0.09 units higher compared with those not included. Participants in this study were also more likely to be Caucasian (75% vs. 60%).

Measurement of lead

We collected blood in vacutainer tubes containing ethylenediaminetetraacetic acid and put the samples on ice immediately. Within 24 hours, we centrifuged the blood and stored separate aliquots of plasma and erythrocytes. We stored the erythrocytes at −80°C until assay.

Samples were analyzed for lead concentrations at the Trace Metals Laboratory at Harvard School of Public Health in Boston, Massachusetts. To measure lead in RBCs, samples were weighed and digested for 24 hours in 2 mL of concentrated nitric acid and 1 mL of 30% hydrogen peroxide (H_2O_2) per 1 g of RBCs. Samples were subsequently diluted to 10 mL with deionized water. Lead concentrations in RBCs were measured using a dynamic reaction cell-inductively coupled plasma mass spectrometer (Elan DRC II; PerkinElmer, Norwalk, CT).

Quality control measures included analysis of initial and continuous calibration verification standards (National Institute of Standards and Technology Standard Reference Material for trace elements in water [NIST SRM 1643e]), 1 ppb lead standard, procedural blanks, QC standard (NIST SRM 1643d-trace elements in water [NIST SRM955b-lead in blood]). Results given were the average of five replicate measurements. The limit of detection for this procedure is 0.2 ng/mL in RBCs. Recovery of the analysis of QC standard by this procedure is 90%–110% with less than 5% precision.

Ascertainment of birth outcomes

Women reported last menstrual period (LMP) at enrollment. We obtained delivery date from medical records. We calculated gestational age by subtracting LMP date from delivery date or by ultrasound (9.6% of participants) where an ultrasound was available and differed from LMP by more than 10 days [16]. We defined preterm birth as birth before 37 weeks. We obtained birthweight from hospital medical records and calculated birthweight for gestational age z-scores using a US national reference [17]. At the hospital, research assistants measured infant birth length and head circumference for 541 and 596 infants, respectively.

Covariates

We examined covariates that could be associated with maternal lead level or birth outcomes. Through self-administered questionnaires and interviews, we collected maternal demographics including age, income, race, country of birth, marital status, and education level and pregnancy health information including smoking status, diet, and prepregnancy weight and height. We collected parity from medical records. We also considered vitamin D intake, fish intake, iron intake, and anemia status as covariates but did not include them in the final model because they did not change results appreciably.

We calculated gestational weight gain by subtracting reported prepregnancy weight from the last weight recorded before delivery in the medical record. We calculated prepregnancy body mass index (kilogram per square meter) from self-reported prepregnancy weight and height. We calculated gestational age at the time of blood draw by subtracting LMP date or ultrasound date from date of blood draw.

Statistical analyses

We assigned women to quartile of lead exposure based on their continuous blood lead levels with the lowest quartile serving as the reference group. To test for trend across quartiles of exposure in our linear regression models, we assigned the median value to each quartile of maternal RBC lead and included it as a continuous exposure.

We conducted multivariable-adjusted linear regression models to examine the associations between maternal blood lead level and gestational age, birthweight, birthweight for gestational age z-score, birth length, and head circumference. We also conducted multivariable-adjusted logistic regression to examine the association between maternal blood lead level and odds of preterm birth. We assessed effect modification by child sex through stratification [18]. We also performed sensitivity analyses including only women with RBC lead levels less than 3 μg/dL, and defining preterm birth as less than 35 weeks. Results were similar.

We adjusted for covariates identified in the literature and those found to confound the relationship between lead and our outcomes. Using this approach, we identified and adjusted for gestational weight gain, prepregnancy body mass index, race, country of birth, second trimester calcium intake, parity, smoking in pregnancy, maternal age, and child sex. We also adjusted for weight of the blood sample and gestational age at maternal blood draw. Models for birthweight, head circumference, and length were further adjusted for gestational age. Birth length models also adjusted for maternal height.

We used a chained equations approach to multiply impute values for missing covariates and missing birth length and head circumference [19–22]. We generated 50 imputed data sets, and all model results are generated by appropriately combining results [19]. To avoid incorrect imputations, we used all 2128 participants in the imputation process but included only subjects with a valid lead measurement ($n = 949$) in the analysis [20]. The characteristics of the imputed sample were nearly identical to those with complete data (Table 1). We performed data analyses using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Sample characteristics

Seventy-five percent of women were white with 37.9% reporting an annual household income of less than $70,000. The average age of women was 32.4 years and 49.5% were nulliparous. Average gestational age was 39.5 weeks with 6.7% of the deliveries preterm. Mean birthweight was 3505 g, and mean birthweight for