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Prenatal lead exposure and fetal growth: Smaller infants have heightened susceptibility

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ABSTRACT

Background: As population lead levels decrease, the toxic effects of lead may be distributed to more sensitive populations, such as infants with poor fetal growth.
Objectives: To determine the association of prenatal lead exposure and fetal growth; and to evaluate whether infants with poor fetal growth are more susceptible to lead toxicity than those with normal fetal growth.
Methods: We examined the association of second trimester maternal blood lead levels (BLL) with birthweight-for-gestational age (BWGA) z-score in 944 mother-infant participants of the PROGRESS cohort. We determined the association between maternal BLL and BWGA z-score by using both linear and quantile regression. We estimated odds ratios for small-for-gestational age (SGA) infants between maternal BLL quartiles using logistic regression. Maternal age, body mass index, socioeconomic status, parity, household smoking exposure, hemoglobin levels, and infant sex were included as confounders.
Results: While linear regression showed a negative association between maternal BLL and BWGA z-score ($\beta = -0.06$ z-score units per $\log_2$ BLL increase; 95% CI: −0.13, 0.003; $P = 0.06$), quantile regression revealed larger magnitudes of this association in the <30th percentiles of BWGA z-score (β range [−0.08, −0.13] z-score units per $\log_2$ BLL increase; all P values < 0.05). Mothers in the highest BLL quartile had an odds ratio of 1.62 (95% CI: 0.99–2.65) for having a SGA infant compared to the lowest BLL quartile.
Conclusions: While both linear and quantile regression showed a negative association between prenatal lead exposure and birthweight, quantile regression revealed that smaller infants may represent a more susceptible subpopulation.

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1. Introduction

Poor fetal growth precedes ~60% of neonatal deaths (Black et al., 2008) and leads to adverse fetal growth outcomes such as low birthweight and small-for-gestational age (SGA) (Victora et al., 2008). Low birthweight (<2500 g) and SGA (<10th percentile of the birthweight-for-gestational age distribution) infants, term and preterm, have an increased risk of chronic developmental and cardiometabolic disorders later in life (Lawn et al., 2014), and impose a substantial socioeconomic burden worldwide (Bhutta et al., 2014). The prevalence of low birthweight globally is estimated to be 20 million infants and of SGA about 32 million infants (of whom ~10 million are term low birthweight), with particularly high prevalence in low and middle income countries (Lee et al., 2013). Numerous preventable risk factors have been linked to poor fetal growth, including prenatal lead exposure (Jelliffe-Pawlowski et al., 2006).

Lead is a toxic heavy metal that is widespread in the environment. While exposure to lead has dropped dramatically in the last 30 years, toxic effects are still reported even in populations with blood lead levels (BLL) once believed to be safe (i.e. <5 μg/dL). During pregnancy, maternal lead can cross the placenta and enter the fetal blood circulation (Lin et al., 1998). Due to similar physicochemical properties, lead competes

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with calcium for deposition into the bone, which might lead to impaired fetal growth (Potula and Kaye, 2005). Lead also binds to sulfhydryl groups and inhibits enzymes involved in heme synthesis, which is important for cellular respiration and metabolism, as well as hemoglobin synthesis (Flora et al., 2012). Several epidemiological studies have shown inconsistent associations of prenatal lead exposure and fetal growth (Burris et al., 2011; Cantonwine et al., 2010; Gonzalez-Cossio et al., 1997; Jelliffe-Pawlowski et al., 2006; Nishioka et al., 2014; Wigle et al., 2007; Zhang et al., 2015; Zhu et al., 2010). These studies used traditional regression methods, also known as ordinary least squares (OLS) regression, to estimate the conditional mean response of the association between prenatal lead exposure and fetal growth. Because OLS methods model the mean response of an outcome in relation to the exposure, any differences that occur in the magnitude and direction of the exposure-outcome association (e.g., prenatal lead exposure and birthweight) across different percentiles of the outcome may not be captured (Koenker, 2005).

The value of quantile regression, which allows for effects of the exposure (e.g., lead) to vary across the distribution of the outcome (e.g., birthweight), has been demonstrated previously in lead poisoning with regards to school performance. Burgette et al., showed that childhood lead exposure is predictive of poorer performance on standardized state tests, with more pronounced effects in the lower percentiles of the test score distribution (Burgette et al., 2011). We built upon this research by testing whether prenatal lead exposure predicts lower birthweight more prominently at the lower range of birthweight-for-gestational age distribution. In other words: are infants with poor fetal growth more susceptible to lead toxicity than infants with normal fetal growth? Fetal growth is a complex and dynamic process, with infants at the tails of the outcome (e.g., birthweight) distribution suffering a disproportionate burden of perinatal morbidities (Barker et al., 2002; Barker, 2006; Fabricius-Bjerre et al., 2011). We hypothesized that OLS regression analysis may not capture any differences in the associations between prenatal lead exposure and birthweight-for-gestational age that occur for instance at the tails of the outcome distribution (e.g., small-for-gestational age infants), and that these associations could be revealed by using quantile regression.

We used data from the Programming Research in Obesity, Growth Environment and Social Stress (PROGRESS) prospective cohort study of 946 mother-infant pairs in Mexico City to determine the association between prenatal lead exposure at second trimester and fetal growth as measured by birthweight-for-gestational age and risk of SGA. Lead exposure is still a major public health problem in Mexico (Caravanos et al., 2014) and the prevalence of both low birthweight and SGA, which are measures of poor fetal growth, is relatively high (~10%) in the Mexican population (Lee et al., 2013).

2. Material and methods

2.1. Study population

Study participants were enrolled as part of the PROGRESS *birth cohort project* in Mexico City, Mexico, between 2007 and 2011. Details of the cohort's profile and enrollment are described in previous publications (Braun et al., 2014; Burris et al., 2013). In brief, pregnant women who attended the *Mexican Social Security Institute* (Instituto Mexicano del Seguro Social) *clinics for their prenatal care were enrolled*. Eligibility criteria for participation in the study were singleton pregnancy, gestational age <20 weeks, maternal age of ≥18 years, expectation to live in Mexico City for the following three years, and have access to a telephone. Exclusion criteria at screening were chronic medical conditions such as heart or kidney disease; use of steroids or anti-epilepsy drugs; drug addiction; and daily consumption of alcoholic beverages due to its association with adverse fetal outcomes. We screened 3898 women who presented to the IMSS clinics during this time, and we enrolled 1054 who agreed to participate by providing written informed consent and who met the eligibility criteria. All eligible participants were Hispanic. Of these, 946 gave birth to a live infant; this represents our base population. Two participants had missing blood lead measurements and were excluded, resulting in 944 participants included in the statistical analysis. The study was approved by the Institutional Review Boards of Brigham and Women's Hospital (#14265-101; #14706-101; #2006-P-001416; #2006-P-001792) and the National Institute of Public Health in Mexico (#560) according to the Declaration of Helsinki.

2.2. Data collection

Baseline information on demographics, anthropometric characteristics, and health status was collected from all participants at first visit (<20 weeks of gestation), and at every subsequent visit until delivery. We calculated gestational age at enrollment using the date of last menstrual period (LMP) and at birth using a standardized physical examination assessment (Capurro et al., 1978). In cases where the estimated gestational age from the two methods differed by more than three weeks ($n = 40$), the physical examination assessment data were used. Second trimester (<20 weeks of gestation) maternal BLL were used, which was the earliest time point lead was measured. Pre-pregnancy body mass index (BMI) was calculated using self-reported maternal body weight. Because we noticed that there was some error associated with self-reported body weight data, we decided to use the second trimester body weight to calculate BMI, as measured by professional staff at enrollment. Pearson correlation between pre-pregnancy and second trimester BMI was $rho = 0.88$. Infants' birthweight was adjusted for gestational age at delivery, and percentiles and z-scores were calculated according to the international infant growth charts developed by Fenton et al. (2013). We defined infants with a birthweight-for-gestational age z-score <10th percentile as SGA. Socioeconomic status (SES) was calculated based on an index created by the Mexican Association of Market and Public opinion Research Agencies (Spanish acronym AMAI) using the following 13 variables derived from questionnaire results: (1) education of the head of household, (2) number of rooms, (3) number of bathrooms with showers, (4) type of floor, (5) number of light bulbs, ownership of: (6) car, (7) hot water heater, (8) automatic washing machine, (9) videocassette recorder, (10) toaster, (11) vacuum cleaner, (12) microwave oven, and (13) personal computer (Carrasco, 2002). Other lifestyle information such as alcohol consumption, maternal smoking, and household smoking exposure was also attained from the validated in-person questionnaire at first visit. We defined household smoking exposure as the reported cases of indoor smoking by the participants' spouse and/or other household members based on relevant questions from the questionnaire administered at enrollment.

2.3. Measurement of maternal blood lead levels

Blood samples were collected from participants at enrollment in trace metal-free tubes and stored at -20° C. Upon thaw on ice, blood samples (1 mL) were weighed, digested in 2 mL of ultra-pure concentrated HNO_3 acid (1 mL) for 48 h, and diluted to 10 mL with deionized water after the addition 0.5 mL of 30% hydrogen peroxide. Samples were handled in ISO Class 5 laminar flow clean hood in an ISO Class 6 clean room. Digested samples were analyzed using external calibration with seven calibration points using an Agilent 8800 ICP Triple Quad (ICP-QQQ) instrument (Agilent technologies, Inc., Delaware, USA) in MS/MS mode with Lutetium as the internal standard. Quality control and quality assurance procedures included analyses of calibration verification standards and continuous calibration verification standards (CCVS) [1 ng/mL and 5 ng/mL standards, National Institute of Standard and Technology Standard Reference Material (NIST SRM) 1640a (trace elements in natural water, Gaithersburg, MD)], procedural blanks, duplicates, spiked samples, NIST SRM 955c (Toxic metals in Caprine blood), Seronorm, Trace Elements Whole Blood L-3 (SERO, Billingstad,

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