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The association of lead exposure during pregnancy and childhood anthropometry in the Mexican PROGRESS cohort

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ABSTRACT

Lead exposure during pregnancy remains a public health problem with potential lifelong impacts on children's growth and development. Mexico is unique in that stunting and obesity are both major public health concerns in children. This situation might be exacerbated by lead exposure which remains more common in Mexico than in the United States due in part to the use of lead glazed pottery in food preparation and storage. Our objective is to determine how lead exposure during pregnancy is associated with children's growth parameters, including height, weight, body mass index and percentage body fat measured between ages 4–6 years old in a Mexico City pregnancy cohort. Blood lead was collected in the 2nd and 3rd trimester of pregnancy as well as at delivery. Bone lead was assessed in mothers as a long term exposure biomarker. We performed multivariable linear regression analyses to assess the association between each of these lead exposure biomarkers and child anthropometry.

We found a significant negative association between maternal 3rd trimester blood lead concentration and offspring height for age (β−0.10; 95% CI −0.19, −0.01), and a negative association between maternal 3rd trimester blood lead concentration and weight for age (β−0.11; 95% CI −0.22,−0.003). Our results in this Mexican population add to previous findings of an association of lead and decreased stature and weight in early childhood. Ongoing follow-up and longitudinal analyses may help elucidate how this impacts growth trajectory and other children's health outcomes.

1. Introduction

In some developing and middle income countries such as Mexico as well as sporadic episodes in the US, lead exposure is still a concern. In particular, lead exposure remains a public health problem for child-bearing women, their developing fetuses and may have lifelong impacts on children's growth and development. Mexico is unique in that both stunting and obesity are major public health concerns in children (Kroker-Lobos et al., 2014). There are many risk factors for lead exposure, the most common of which are use of traditional lead glazed pottery (the main exposure factor for the general population), pica (the eating of nonfood substances), occupational exposure (directly or indirectly from the inadvertent transfer of lead dust from the workplace on workers' clothing, shoes or bodies), use of alternative remedies or cosmetics, air pollutants and nutritional sources (due to food wrappers and water sources) (Bakhireva et al., 2013; Brown et al., 2000; Meneses-González et al., 2003; Romieu et al., 1994; Ettinger and Wengrovitz, 2010). Recent events in Washington DC and Flint Michigan highlight the importance of water as a source (Bellinger, 2016). Lead is particularly dangerous for the fetus because it crosses

Abbreviations: BMI, body mass index; BlPb, blood lead; CI, confidence interval; ETS, environmental tobacco smoking; FFQ, food frequency questionnaire; HFA, height for age; PBF, percentage body fat; WFA, weight for age

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the placenta and may cause adverse birth outcomes, including low birth weight and preterm birth (Chen et al., 2006 (location: Taiwan; biomarkers: blood; exposure level: mean 10.1 μg/dL, sd 10.4); Gundacker et al., 2010 (Austria; blood, placenta, cord blood, meconium; median: 24.9, 25.8, 13.4, 15.5 μg/dL); Gundacker and Hengstschläger, 2012; Jedrychowsky et al., 2008 (Poland; cord blood; mean 1.42 μg/dL, sd 0.71); Schell et al., 2009 (New York; blood; mean 2.8 μg/dL, sd 2.63); Torres-Sanchèz et al., 1999 (Mexico; cord blood; median 9 μg/dL); Zhu et al., 2010 (New York; blood; median 2 μg/dL)).

There are many ways by which lead might interfere with growth in early life. Lead may alter bone cell function directly (through changes in circulating hormones or by impairing their ability to synthesize or secrete other components of the bone matrix) (Hamilton and O'Flaherty, 1995) or indirectly (by perturbing the ability of bone cells to respond to hormonal regulation, or by effecting or replacing calcium in the active sites of its messenger system) (Pounds et al., 1991). It may induce a reduction of circulating maternal thyroid hormone that impacts overall growth trajectories (Hannigan et al., 1995; Hernández-Avila et al., 2002 (Mexico; tibia, patella; mean 9.83, 14.14 μg/g, sd 8.9, 13.0)). Lead could disrupt heme-mediated generation of critical enzymes involved in metabolism and other metabolic functions such as the synthesis of vitamin D which regulates calcium metabolism (Mushak et al., 1989). Further, lead may impair growth by altering the hypothalamic-pituitary-growth axis function (Fleisch et al., 2013) (Russia; blood; median 3 μg/dL)).

Previous studies have investigated the association between lead exposure and children's growth. The majority of these studies focused on postnatal exposure and found some evidence of associations between lead exposure during childhood and children's growth. In particular, previous investigations identified significant negative correlations between blood lead (BlPb) levels during childhood and child stature and growth over time (Schwartz et al., 1986 (United States; blood; range 5–35 μg/dL); Vivoli et al., 1993 (Italy; blood; mean 7.8 μg/dL); Kafourou et al., 1997 (Greece; blood; mean 12.3 μg/dL, sd 8.9); Ballew et al., 1999 (United States; blood; mean 3.6 μg/dL); Frisancho and Ryan, 1991 (United States; blood; mean 0.5 μmol/L); Cantoral et al., 2015 (Mexico; blood; median 0.17 μmol/L); Dellaire et al., 2014 (Canada; blood; mean 2.7 μg/dL, sd 2.1)). Other studies observed negative associations between lead exposure during pregnancy and children's height and weight (Schell et al., 2009 (New York; blood; mean 2.8 μg/dL, sd 2.63); Afeiche et al., 2011 (Mexico; tibia, patella; mean 8.7 μg/g, 10.4 μg/g, sd 9.7, 11.8); Hong et al., 2014 (South Korea; blood; mean 1.25 μg/dL, sd 1.5)). However, most previous studies focused on postnatal exposures and did not measure exposure to lead during pregnancy. Fetal development is a life state with high plasticity involving a series of delicately regulated processes that can be affected by environmental exposures. Alterations of fetal development may lead to long term consequences with persistent alterations of child phenotype, including growth, in postnatal life.

In the present analysis, we investigated the association of maternal biomarkers of lead exposure during pregnancy with children's anthropometric measures at 4–6 years of age. We examined the association of maternal lead levels with multiple measures related to growth including height, weight, body mass index (BMI) and percentage body fat (PBF).

2. Material and methods

2.1. Recruitment of the study participants

The Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) is an NIH funded ongoing prospective pre-birth cohort in Mexico City. Between July 2007 and February 2011, 1054 pregnant women receiving care through the Mexican Social Security System (IMSS) were enrolled after providing written informed consent. The study protocols were approved by the institutional review boards of the Brigham and Women's Hospital, the Icahn School of Medicine at Mount Sinai and the National Institute of Public Health in Mexico.

Women were considered eligible for enrollment if they were 18 years or older, pregnant at < 20 weeks of gestation, free of heart or kidney disease, did not use steroids or anti-epilepsy drugs, did not consume alcohol on a daily basis, had access to a telephone, and planned to reside in Mexico City for the following three years. The follow-up for this analysis lasted from the 2nd trimester of pregnancy until the children reached 4–6 years old. All measures of interest were gathered during the planned visits at 2nd, 3rd trimester, delivery, one month and around 4 years after delivery. From the initial enrollment of 1054 mothers, 948 live births were assessed. On average ~550 children presented at each postnatal visit and a total of 760 returned for at least 2 postnatal visits. The study subjects for the present analysis were restricted to the 513 mothers and their children who presented to the 4–6 year visit and completed measures of maternal BlPb, maternal bone lead, or cord BlPb, and at least one postnatal growth measurement at the follow-up visit at age 4–6 years and the LeadCare measurement at this stage. We did not find significant differences between the characteristics of the included pairs and the remainder of the cohort for maternal blood and bone lead, age, education, BMI, height, gestational age, parity, environmental tobacco smoking (ETS), delivery mode, breastfeeding, and child's age, sex, LeadCare at 4–6 years, and food frequency questionnaire (FFQ) total dietary intake (all $p > 0.05$).

2.2. Lead measurements in maternal blood and cord blood

Maternal blood was collected at the second and third trimester visit. An additional maternal venous blood sample and an umbilical cord blood sample were collected within 12 h of delivery. All blood specimens were drawn in trace metal free tubes and refrigerated at 2–6 °C until analysis. Lead concentration was measured by external calibration using the Agilent 8800 ICP Triple Quad (ICP-QQQ) in MS/MS mode in the trace metals laboratory at the Icahn School of Medicine at Mount Sinai. The limit of detection was < 0.2 μg/dL and the instrument precision (given as %RSD) was approximately 5%. Blinded quality control samples obtained from the Maternal and Child Health Bureau and the Wisconsin State Laboratory of Hygiene Cooperative Blood Lead Proficiency Testing Program showed good precision and accuracy.

2.3. Bone lead measurements

One month postpartum mothers were recalled for a visit in which tibia (cortical bone) and patella (trabecular bone) lead concentrations were measured using a K-shell X-ray fluorescence instrument (Hu et al.,1991). We estimated lead concentration for 30 min for each leg and the measures were averaged by the inverse of the proportion of the measurement error corresponding to each determination. Bone lead content is thought to provide an indicator of exposure over the span of decades; in particular tibia measurements reflect longer time spans (> 10 years) compared to patella (1–5 years) (Hu et al., 1998). Sometimes negative values are obtained when the true bone lead concentration value is close to 0: the instrument produces a continuous unbiased point estimate that fluctuates around the true bone lead value (Kim et al., 1995). From the epidemiological point of view, useful information would be lost if we set the negative estimates equal to zero or we put them in a single category. Furthermore it was found that results obtained including the negative values or using simulated estimates randomly generated from a normal distribution were very similar (Téllez-Rojo et al., 2004). It is preferable to use all the values to maintain the true shape of the distribution of the measures and to give the relative position of each participant within the study population.