Environment International 120 (2018) 464–471

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Prenatal lead exposure modifies the effect of shorter gestation on increased blood pressure in children

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ARTICLE INFO

Handling Editor: Olga-Ioanna Kalantzi

Keywords:
Lead
Gestational age
Preterm birth
Blood pressure
Systolic
Diastolic
Childhood

ABSTRACT

Background: High blood pressure (BP) in childhood is frequently renal in origin and a risk factor for adult hypertension and cardiovascular disease. Shorter gestations are a known risk factor for increased BP in adults and children, due in part to a nephron deficit in children born preterm. As nephrogenesis is incomplete until 36 weeks gestation, prenatal lead exposure occurring during a susceptible period of renal development may contribute to programming for later life renal disease. The relationship between shorter gestation and children's BP has not yet been explored to identify i) critical windows using nonlinear piecewise models or ii) combined with other early life risk factors such as prenatal lead exposure.

Objectives: (1) To evaluate the nonlinear relationship between lower gestational age and childhood BP measured at 4–6 years of age, and (2) to investigate modification by prenatal lead exposure.

Methods: In a prospective longitudinal birth cohort, we assessed 565 children between 4 and 6 years of age (mean: 4.8 years) in the PROGRESS cohort in Mexico City, Mexico. Gestational age at delivery was calculated using maternal report of last menstrual period (LMP) and confirmed with Capurro physical examination at birth. We measured pregnant women's blood lead levels (BLLs) in the second trimester via inductively coupled plasma-mass spectrometry and children's BP using an automated device. We performed both linear and nonlinear piecewise regression analyses to examine associations of gestational age with children's BP adjusting for children's age, sex, height, prenatal exposure to smoke, and maternal socioeconomic status. We stratified to assess modification by prenatal lead exposure, and used a data-adaptive approach to identify a lead cutpoint.

Results: Maternal second trimester BLLs ranged from 0.7 to 17.8 μg/dL with 112 (20%) women above the CDC guideline level of 5 μg/dL. In adjusted linear regression models, a one week reduction in gestational age was associated with a 0.5 mm Hg (95%CI: 0.2, 0.8) increase in SBP and a 0.4 mm Hg (95%CI 0.1, 0.6) increase in DBP. Our nonlinear models suggested evidence for different magnitude estimates on either side of an estimated join-point at 35.9 weeks' gestation, but did not reach statistical significance. However, when stratified by prenatal lead exposure, we identified a cutpoint lead level of concern of 2.5 μg/dL that suggested an interaction between gestational age and blood lead. Specifically, for BLLs ≥ 2.5 μg/dL, SBP was 1.6 (95%CI: 0.3, 2.9) mm Hg higher per each week reduction in gestational age among children born before 37.0 weeks; and among

Abbreviations: BLL, blood lead level; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; LMP, last menstrual period; NHANES, National Health and Nutrition Examination Survey; PROGRESS, Programming Research in Obesity, GRowth, Environment, and Social Stress; SBP, systolic blood pressure

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https://doi.org/10.1016/j.envint.2018.08.038
Received 27 April 2018; Received in revised form 15 August 2018; Accepted 15 August 2018

children born after 37.0 weeks, this relationship was attenuated yet remained significant [β: 0.9, 95%CI (0.2, 1.6)]. At BLLs below 2.5 μg/dL, there was no appreciable association between lower gestational age and SBP.
Conclusions: Our findings suggest that shorter gestation combined with higher prenatal lead exposure contributes to a higher risk of increased SBP at 4–6 years of age, particularly among infants born < 37 weeks gestation. Our results underscore the importance of preventing prenatal lead exposure - even levels as low as 2.5 μg/dL - especially among pregnant women at risk for preterm birth. Given that high BP in childhood is a risk factor for adult hypertension and cardiovascular disease later in life, these results may have implications that extend across the life span.

1. Introduction

High blood pressure (BP) in childhood can lead to adult hypertension (Belsha et al., 1998; Berenson et al., 1998; Chen and Wang, 2008; Hanevold et al., 2004; Sorof et al., 2003). Elevated BP in childhood, in the absence of congenital heart disease, is nearly always renal in origin (Boubred et al., 2013). While some studies have examined the effect of environmental nephrotoxic exposures during susceptible windows of renal development on elevated childhood BP, none has examined the effect of environmental exposure as a modifier of the effect of shorter gestation.

Lower gestational age is a well-established risk factor for increased systolic blood pressure (SBP) in early life (Johansson et al., 2005; Keijzer-Veen et al., 2010) and even among adults (Raju et al., 2017). For example, a meta-analysis of 10 studies of former low birth weight or preterm infants compared to term controls found a pooled estimate of 2.5 mm Hg (95% CI: 1.7, 3.3) higher SBP later in life (average age = 17.1 years) (de Jong et al., 2012). Infants born prior to 36 weeks' gestation, the time by which nephrogenesis (the formation of new nephrons) is complete (Benz and Amann, 2010; Solhaug et al., 2004), represent a particularly susceptible population for altered renal function. Based on the timing of in utero nephron development, we hypothesize that a nonlinear model would more appropriately examine critical windows of renal development. By comparing associations before and after 36 weeks, we hypothesize that there would be a stronger association with increased children's BP among shorter gestations since this is coupled with renal immaturity.

Moreover, we speculate that nephrotoxic exposures during perinatal life in combination with shorter gestation could alter kidney growth/developmental trajectories and program adult diseases of renal origin. Gestation and early childhood are potential susceptibility windows for nephrotoxic metals, as these life stages are associated with development of glomerular filtration and maturation of tubular function (e.g. absorption and secretion) (Gubhaju et al., 2014; Luyckx et al., 2013; Sutherland et al., 2014). Relatively minor insults can offset the normal developmental trajectory towards a hypertensive phenotype in later life, as BP will increase with age. Lead is a common nephrotoxicant in adults (Chiu and Yang, 2005; Hellstrom et al., 2001; Loghman-Adham, 1997; Sommar et al., 2013). Specifically, in the US, lead accounts for 5% of the population attributable risk for hypertension in adults participating in National Health and Nutrition Examination Survey (NHANES) from 2009 to 2012 (Shiue and Hristova, 2014). Previously, we have shown sex-specific associations between prenatal lead levels and elevated BP in children in Mexico City (Zhang et al., 2012). Other studies have shown links between lead and children's elevated SBP or diastolic blood pressure (DBP) (Gump et al., 2005; Gump et al., 2007; Hawkesworth et al., 2013; Sorensen et al., 1999). However no studies to-date have examined the interaction of prenatal lead exposure in combination with shorter gestation on childhood BP.

We sought to understand whether the association between shorter gestation and increased childhood BP was modified by prenatal lead exposure, selected a priori as a prevalent nephrotoxic metal. To assess effects on BP at 4–6 years of age in a prospective cohort of 565 mother-child dyads, we examined the relationship between gestational age and BP using linear and nonlinear piecewise models. To investigate the modification effect of lead exposure, we used a data driven approach to assess 1) a change point in gestational age associated with SBP; and 2) a cutpoint level of 'high' or 'low' lead that might exacerbate developmental nephrotoxic exposure. This study expands our understanding of the early origins of adult cardiovascular disease, a leading cause of mortality and morbidity in the US (Heron, 2013), and provides suggestive evidence for the role of prenatal lead exposure in the developmental programming childhood BP.

2. Methods

2.1. Study design

This study was conducted using mother-child pairs participating in the longitudinal cohort study called Programming Research in Obesity, GRowth, Environment, and Social Stress (PROGRESS) based in Mexico City. Full details of enrollment for the parent cohort are published elsewhere (Burris et al., 2013; Renzetti et al., 2017; Sanders et al., 2015). Briefly, women in their second trimester were recruited between 2007 and 2011 through the Mexican Social Security System (Instituto Mexicano del Seguro Social), which is the second largest health provider in the country. Women were considered eligible for enrollment if they were over 18 years of age, at fewer than 20 weeks gestation, free of heart and kidney disease, did not use anti-epilepsy drugs or steroids, and did not consume alcohol daily (Burris et al., 2013). There were 948 women who delivered a live-born infant into the cohort. For this analysis, we included pairs who had maternal blood lead measured in the 2nd trimester, delivery before 42 weeks of gestation, and child BP measured at 4–6 years of age (n = 565 out of 609 children with follow-up at this stage). No children were excluded from the analysis based on existing renal or cardiovascular conditions. We performed a sensitivity analyses to ensure that including the 10 infants < 34 weeks of gestation did not affect our results. The IRBs of the participating institutions approved this study: Icahn School of Medicine human subjects management #12-00751 and Instituto Nacional de Salud Pública project #560.

2.2. Participant data collection

Demographics and medical data were collected as part of the parent study including maternal age and socioeconomic status (SES), as well as gestational age at delivery, birth weight, age at BP measurement, as well as height and sex. Gestational age was calculated in units of days starting with the maternally reported last menstrual period (LMP) to the date of delivery. The Capurro method (i.e. an infant physical exam) was used as a secondary confirmatory estimate of gestational age and in instances where the gestational age estimated from the LMP differed by more than three weeks from the Capurro method, the Capurro method-derived estimate was used (n = 19) (Sanders et al., 2015). Capurro method estimates were converted from weeks into days, by using week gestation × 7 days/week + 3.5 days (imputed days mid-week). Staff conducted in-person interviews, which included a question about household smoke exposure. Household environmental tobacco smoke exposure was dichotomized as yes/no based on the mother's report that at least one household member smoked during the pregnancy. Very few