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Changes in low levels of lead over the course of pregnancy and the association with birth outcomes

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ABSTRACT

Data are lacking on the effect of low level prenatal lead exposure. We examined the change in blood lead from the second trimester until delivery and the association between maternal and cord blood lead and birth outcomes in 98 participants of the CANDLE birth cohort study. Mixed effects models were constructed to assess blood lead change over pregnancy and regression models were used to explore the relationship with cord blood lead, characteristics effecting maternal lead, birth weight and gestational age. Overall, the geometric mean maternal blood level was 0.43 μg/dL. Maternal blood lead at each time point was predictive of cord blood lead level. A 0.1 μg/dL increase in second trimester lead was associated with lower birth weight and pre-term birth. Maternal blood lead below 1 μg/dL behaves in a manner similar to lead at higher levels and is associated with a small decrease in birth weight and gestational age.

1. Introduction

Maternal blood lead readily crosses the placenta creating a pathway of exposure to the developing fetus. The biokinetics of blood lead throughout pregnancy and the adverse effect of prenatal lead exposure have been examined in numerous studies where maternal lead is well above general population levels; however, data are lacking on both the pattern of lead and its effect on the developing fetus when maternal lead is at levels typically found in the general population.

In women with elevated blood lead levels, lead follows a U-shaped pattern over the course of pregnancy. There is a significant drop from the first trimester to the second and then a gradual increase until delivery [1–3]. This rise is thought to occur because of the increased demand for calcium during the latter months of pregnancy and the subsequent mobilization of lead from maternal bone stores into the blood stream [4,5]. Approximately 90% of lead is stored in bone creating an important endogenous source of fetal exposure [6]. Maternal blood lead level and infant blood lead are highly correlated [7] with umbilical cord lead estimated to be approximately 85% of the maternal lead level [8,9].

Prenatal lead exposure affects embryonic development and is associated with negative outcomes for children from birth into adulthood including reduced neurocognitive development [10,11] spontaneous abortion [12], elevated blood pressure [13] and reduced genomic DNA methylation [14]. Adverse birth outcomes, including pre-term delivery and lower birth weight, have also been associated with exposure to lead in utero [15–19]. Knowledge of lead's effects on birth outcomes is based on populations with moderate to high levels where study cohorts typically include either women in developing countries where current exposure to environmental lead is much greater than in the U.S. or lower income women living in the inner-city of the U.S., a demographic with higher average blood lead due to the well-established disparity in exposure during childhood [2,10,17,20]. Two factors make the study of general population levels of maternal blood lead of importance. First, there is growing evidence that the adverse effects of lead are without a threshold and second, resorption from bone is the primary exposure pathway so women of childbearing age today, despite currently low blood lead levels, likely have

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substantial bone lead burden due to their exposure during childhood. The geometric mean blood lead level in pregnant women in the U.S. is 0.64 μg/dL [21]. Whether maternal blood lead at this low level fluctuates randomly throughout pregnancy, or follows the pattern seen in populations with moderate to high levels, has yet to be explored. Furthermore, the relationship between maternal blood lead level and umbilical cord level and birth outcomes has not been fully examined at the low levels typically found in pregnant women in the U.S. today.

The goals of this study were: (1) to examine the change in blood lead from the second trimester of pregnancy until delivery; (2) to investigate the association between maternal blood lead level and umbilical cord lead; (3) to explore the characteristics associated with incremental changes in maternal blood lead; and (4) to examine the relationship between maternal blood lead and birth weight and gestational age in a cohort of pregnant women with blood lead levels typical of the general population of pregnant women in the U.S. today.

2. Materials and methods

2.1. Study population

Subjects were selected from women participating in the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study. CANDLE is a birth cohort study examining the factors during pregnancy and early childhood that impact child development and learning. From 2008 to 2011, the CANDLE study recruited 1,503 healthy pregnant women between their 16th and 28th week of gestation from private obstetrics and gynecology clinics and the community at large via media campaigns. Eligibility criteria included being a healthy pregnant woman between the ages of 16 and 40 years, carrying a single fetus with the intent to deliver the fetus, residence within Shelby County, Tennessee, and having the intent to deliver at one of three area-based hospitals (Methodist Healthcare, Baptist Memorial Hospital for Women, or St. Francis Hospital). Women with health issues beyond those expected for a singleton pregnancy (e.g. insulin dependent diabetes, renal or cardiopulmonary disease, hepatitis, HIV) and women unable to speak English were ineligible for inclusion in the study. From 2009 to 2011, a convenience sample of 98 women were invited to participate in the lead sub-study at the time they were recruited into CANDLE, the parent study. Women in the sub-study were recruited from all CANDLE sites. Women agreeing to participate signed an informed consent for both the lead sub-study and for the larger CANDLE study. Institutional Review Board (IRB) approval was obtained from Tulane University Health Sciences Center, the University of Tennessee Health Sciences Center, and from all participating recruitment hospitals.

2.2. Gestational age

Gestational age was determined using criteria from the National Institutes of Health Maternal Fetal Medicine Units Network. Upon enrollment, women were asked their expected due date (EDD) and whether it was determined via ultrasound. They were then asked to report the first day of their last menstrual period (LMP). If they were sure of their LMP, that date and the associated EDD were used to calculate gestational age. If the LMP date was unsure, but the EDD was based on early ultrasound, this date was used to determine gestational age. If both LMP and the EDD were unknown, medical records were reviewed for most accurate EDD based on early ultrasound which was then used to calculate gestational age. The second trimester was defined as occurring between weeks 16 and 26 of pregnancy. The third trimester was defined as weeks 27 through 42. In models exploring the effect of low levels of maternal lead on length of gestation, gestational age was categorized as pre-term birth (<37 weeks), early term birth (37–39 weeks), or full term birth (≥39 weeks).

2.3. Blood lead measurements

Venous blood was obtained from participants during the second and third trimester of pregnancy, and at delivery. Cord blood was collected at the time of delivery. Blood samples were collected into 3-mL purple-top Vacutainer tubes (Becton Dickinson) containing K_2EDTA that were certified as trace-metal free by the analyzing laboratory for blood lead measurements. Immediately following collection the tubes were inverted several times to mix blood with the K_2EDTA anticoagulant, a particularly important step when analyzing cord blood. After inversion, blood samples were refrigerated until they were shipped overnight to the Trace Elements Section of the Laboratory of Inorganic and Nuclear Chemistry, at the Wadsworth Center, New York State Department of Health (NYS DOH), Albany NY for analysis. The laboratory serves as New York State's principal reference laboratory for blood lead and is both state and CLIA-certified for blood lead. Blood samples were analyzed for lead content by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) using a method developed specifically to support low level measurements for biomonitoring studies [22]. The method was recently re-validated for low-level work and measurements have been demonstrated to be traceable to international standards [23]. In the laboratory, blood samples are processed in a Class 2 Biosafety Cabinet that has been certified as meeting a Class 100 environment. Reagents, calibrators and other materials are prepared in a Class 100 clean room, which is specifically used for low-level trace element analyses. Both the Biosafety Cabinet and the Clean Room are monitored routinely using a Laser Particle counter to ensure Class 100 conditions are maintained. Complete details of the analytical method are given elsewhere [24]. In brief, blood samples were diluted 1 + 49 with 0.5% (v/v) double-distilled HNO_3, 0.005% (v/v) Triton X-100 and 25 μg/L iridium as the internal standard for lead. A PE Sciex ELAN DRC Plus ICP-MS (PerkinElmer Life and Analytical Sciences, Shelton, CT, USA) was used for all analyses. The instrument was calibrated with matrix-matched lead standards traceable to the National Institute of Standards and Technology (NIST) and, given the variation in isotopic ratio of lead in nature, the three most abundant naturally occurring lead isotopes, ^{206}Pb, ^{207}Pb, and ^{208}Pb, were monitored and their ion signals summed for analytical purposes. Blood lead method performance at concentrations below 1 μg/dL was previously investigated using NIST SRM 955c Toxic Metals in Caprine Blood [23] Level 1, which has a certified blood lead value of 0.424 (±0.011) μg/dL. In the 2009 study, the ICP-MS biomonitoring method reported a blood lead concentration of 0.4125 μg/dL, the method standard uncertainty (u_c) was 0.0092 μg/dL, yielding an expanded uncertainty (U, k = 2 for 95% coverage) of ±0.018 μg/dL, which is equivalent to 2.0% RSD [23]. During the period of the study, the LOD was calculated as 0.038 μg/dL, based the IUPAC/ISO harmonized guidelines for establishing the LOD - essentially 3 SD (n = 10 independent runs) of a base caprine blood that is used for matrix matching. The LOD value, which includes a dilution factor as well as imprecision from the blood matrix, varies between 0.03 and 0.04 and, given the uncertainty, can be rounded to 0.04 μg/dL.

2.4. Covariables

During the second trimester clinic visit, maternal sociodemographic data, medical history, and lifestyle factors including smoking status and alcohol consumption were obtained using standardized questionnaires by CANDLE staff trained in survey data