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Prenatal exposure to lead in relation to risk of preterm low birth weight: A matched case–control study in China

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ABSTRACT

We investigated the association between prenatal exposure to lead (Pb) and the risk of preterm low birth weight (PLBW). Pb concentrations in maternal urine collected at birth from 408 subjects (102 cases and 306 matched controls) were analyzed and adjusted by creatinine. The median Pb concentration in the PLBW cases (10.60 μg Pb/g creatinine) was higher than that of the controls (7.28 μg Pb/g creatinine). An adjusted odds ratio (OR) of 2.96 (95% CI = 1.49–5.87) for PLBW was observed when the highest tertile was compared to the lowest tertile of Pb levels. The association was more pronounced among female infants (adjusted OR = 3.67 for the highest tertile; 95% CI = 1.35–9.93) than male infants (adjusted OR = 1.91 for the highest tertile; 95% CI = 0.74–4.95). Our study suggests that prenatal exposure to levels of Pb encountered today in China is associated with an elevated risk of PLBW.

1. Introduction

About 15 million infants each year are born preterm (infants born alive prior to 37 completed weeks of pregnancy) worldwide, which equates to more than 1 in 10 born infants [1]. Moreover, infants born preterm account for about two-thirds of all low birth weight infants (<2500 g) [2], in which case it is referred to as preterm delivery of low-birth-weight (PLBW). It is known that PLBW infants face a higher risk of serious health problems. Specifically, PLBW infants have a 40-fold greater risk of dying during the neonatal period and a 50 percent greater risk of having serious childhood development problems compared to normal weight infants [3]. To identify and analyze the factors affecting PLBW may help to prevent preterm labor and its associated adverse outcomes.

During the past decades, epidemiological studies have suggested the importance of environmental exposures as risk factors for preterm birth, particularly exposure to heavy metals. Lead (Pb), a widespread heavy metal, can easily across the placenta and affect the fetus [4]. Findings from studies evaluating prenatal exposure to Pb at community levels and preterm birth have been inconsistent. Some studies have showed a significant association with an increased risk of a preterm birth or a decreased total days of gestation [5–10], while other studies have observed no such association [11–16]. So far, no study has been conducted to investigate prenatal Pb exposure and risk of PLBW infants in Chinese women.

With the unprecedented economic development, China has become not only the largest producer of raw and refined Pb, but also the largest consumer [17]. As a result, Pb exposure and its associated health effects remain a serious public health issue [18], though Pb petrol has been forbidden in China since 2000. Given this background, we conducted a pair-matched case–control study in Hubei province, China, involving 408 pregnant women, including 102 cases that gave birth to PLBW infants and 306 matched controls,

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to investigate the relationship between prenatal Pb exposure and the risk of delivering PLBW infants.

2. Materials and methods

2.1. Study population

This study was designed as a pair-matched case–control study. The subjects in the present study were derived from the prospective Hubei-Tongji birth cohort, which enrolled participants at the three hospitals in Wuhan, Ezhou, and Macheng cities, which are located in Hubei province, the central of People's Republic of China. Pregnant women, who came for their first examination in the first trimester or gave birth at one of the three hospitals, have been asked to participate in the study. Participants were invited to provide blood and urine samples and to participate in a face-to-face interview. Between November 2012 and April 2014, 16,293 women with a live singleton infant were recruited from the three study hospitals (9209 from Wuhan, 4550 from Ezhou and 2534 from Macheng). All participants in this study provided a written informed consent form at enrollment. The research protocol was reviewed and approved by the ethical committee of Tongji Medical College, Huazhong University of Science and Technology and the three study hospitals.

In this study, cases were mothers who delivered a live singleton infant with a gestational age <37 weeks and weighing <2500 g (PLBW) in the obstetrics departments of the three hospitals. Three controls were matched to each case and included mothers who delivered a single live newborn with gestational age $\geq$37 weeks and weighing between $\geq$2500 g and <4000 g. Potential cases and controls were excluded if they had multiple pregnancies, a stillborn infant, or an infant with a birth defect. Women without urine samples available for analysis were also excluded. Each case and control set had the same maternal age at conception (within 1-year interval), delivery of an infant of the same gender, and the same delivery hospital. A total of 102 cases and 306 controls were included in the analysis.

2.2. Data and sample collection

Standardized face-to-face interviews were conducted with the participants after delivery by specially trained nurses in the three hospitals. The interview collected a variety of information, including socioeconomic data (e.g., maternal age, education, reproductive history, occupation, and household income) and lifestyle factors during pregnancy (e.g., smoking, passive smoking, alcohol consumption, and multivitamin supplement use). The body mass index of mothers was calculated using the self-reported weight before pregnancy, as obtained from the interview, and height, which was measured using a stadiometer. Information about the mothers' history of pregnancy outcomes, disease, and information concerning the infants' birth date, gender, gestational age at birth, birth weight, and any apparent congenital malformations were retrieved from medical records. Gestational age was estimated using the date of the last menstrual period. Birth weight of nude infants was measured within one hour after birth by experienced obstetric nurses using standardized procedures.

The maternal urine samples were obtained during admission to the hospital as part of the preparation for delivery (within 3 days before delivery). All of the urine samples were collected in 50 mL polypropylene tubes, and frozen at −20 degrees Celsius (°C) until further processing.

2.3. Instrumental analysis

Pb concentrations in urine samples were measured by inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7700, Agilent Technologies, Santa Clara, CA, USA). Prior to the instrumental analysis, urine samples were thawed at room temperature, and then 1 mL of urine from the supernatant was introduced in 15 mL Kirgen polypropylene conical centrifuge tubes together with 3% HNO_3 to a final volume of 5 mL for overnight nitrification. The resulting sample was digested by ultrasound at 40 °C for 1 h. The operating parameters for ICP-MS were as follows: RF power, 1550 w; auxiliary gas flow, 0.9 L/min; carrier gas flow, 0.25 L/min; plasma gas flow, 15.00 L/min; resolution (peak high 10%), 0.65–0.80 amu; improve quantity of samples, 0.4 mL/min; unimodal residence time, 0.1 s; repetitions, 3 times; analysis of the time, 5 min.

To ensure the accuracy of the analytical methods and results, we applied stringent laboratory quality controls. Each sample was measured in triplicate. An external quality control sample (SRM2670a Toxic Elements in Urine, a standard reference material of National Institute of Standards and Technology, Gaithersburg, MD, USA) was analyzed in each batch to check for accuracy, and the concentrations measured were within the certified range (5%). A 3% HNO_3 blank was processed in each batch of samples to control for possible contamination. The samples were analyzed with an external calibration method, using eight standard concentrations ranging from 0 to 5 μg/L. The limit of detection (LOD) of the urine Pb analysis in this study was 0.05 μg/L. The recovery of the quality control standard using this procedure was 99%. The intra-day coefficient of variation was 0.76% and the inter-day CV was 2.99%. Field blanks were also included for quality control and the levels of Pb in the field blanks were <LOD. Pb measurements below the LOD were given values of 1/2 LOD.

Urine creatinine concentrations were measured by a creatinine kit (Mindray BS-200 CREA Kit, Shenzhen, China). Pb concentrations in urine (μg/L) were adjusted for creatinine, in order to account for variations in urine dilution in spot urine specimens, and results were expressed as μg Pb/g Creatinine.

Estradiol (E2), an important hormone for fetal development, was also measured in maternal urine by liquid chromatography–tandem mass spectrometry (ACQUITY UPLC H-Class System-TQD, Milford, MA) as previously described [19].

2.4. Statistical analysis

The distributions of Pb concentrations were tested by the Shapiro–Wilk normality test. The differences of Pb concentrations in maternal urine between cases and controls were evaluated using the Wilcoxon matched pairs signed rank test. Conditional logistic regression analyses were used to estimate the associations between the risk of PLBW and maternal urinary Pb levels by calculating matched odds ratios (OR) and 95% confidence intervals (CI). Models were fit using Pb measurements as categorical variables (the tertile distribution of urinary Pb concentrations in controls) and the lowest tertile was assigned as the referent group. Univariate analyses were carried out by computing crude ORs and 95% CIs. We tested for linear trends by modeling the median values of tertiles of Pb as a continuous variable and evaluated the statistical significance of this predictor using the Wald test. In this study, we selected household income to represent socioeconomic status, because inclusion of income, education, and occupation into the model did not produce significantly different results from addition of each individual variable into the model, and adjustment by income showed a larger impact on the estimate than the other two variables. In the final model, we adjusted for potential confounding factors, including household income ($\geq$50,000, <50,000 yuan per year), pre-pregnancy body mass index (<18.5, 18.5–23.9, $\geq$24), parity (1, $\geq$2), passive smoking (No, Yes), and hypertension during pregnancy (No, Yes). Additional adjustment for diabetes, heart disease, multivitamin supplement use during pregnancy, and delivery