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Maternal urinary cadmium concentrations in relation to preterm birth in the Healthy Baby Cohort Study in China

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ABSTRACT

Background: Prenatal cadmium (Cd) exposure has been associated with adverse birth outcomes, but the findings of previous studies are inconsistent. The aim of this study was to evaluate the association between prenatal Cd exposure and birth outcomes.

Methods: This study was conducted in 5364 pregnant women with a live singleton birth, who were recruited between September 2012 and October 2014 in the Healthy Baby Cohort (HBC) in Wuhan, China. Gestational age (in days) was estimated using both the woman's last menstrual period (LMP) and ultrasound data. All the birth outcomes including birth weight and birth length were measured in the hospital within one hour after birth through standardized procedures. Cd was measured in maternal urine collected before delivery with inductively coupled plasma mass spectrometry.

Results: The geometric mean of Cd concentration in maternal urine was 0.55 (range 0.01–2.85) μg/g creatinine. We found each ln-unit increase in Cd concentration (μg/g creatinine) in maternal urine was associated with decreased gestational age [adjusted $\beta = -0.77$ day; 95% confidence interval (CI): −1.15, −0.39 for all infants; −0.77; 95% CI: −1.29, −0.25 for boys; and −0.80; 95% CI: −1.35, −0.25 for girls]. Increased likelihood of preterm birth (PTB) was associated with ln-unit increase in urinary Cd (μg/g creatinine) [adjusted odds ratio (OR) = 1.78; 95% CI: 1.45, 2.19 for all infants; 1.97; 95% CI: 1.46, 2.65 for boys; and 1.67; 95% CI: 1.24, 2.25 for girls]. Maternal urinary Cd was not significantly associated with low birth weight (LBW) and small for gestational age (SGA).

Conclusions: Maternal exposure to Cd during pregnancy was associated with decreased gestational age and increased likelihood of PTB.

1. Introduction

Cadmium (Cd) is a toxic heavy metal that is ubiquitous in the environment (ATSDR, 2012). Cd mainly enters the human body through ingestion of food and smoking (Jarup and Akesson, 2009). In addition, people may be exposed via ambient air in areas with industrial emissions or mining, burning of coal, and household wastes, particularly when Cd is used in commercial products, including batteries, pigments, and plastics (ATSDR, 2012). Cd exposure has been linked to adverse effects on the kidney (Hellstrom et al., 2001), bone (Engstrom et al., 2012), cardiovascular disease (Tellez-Plaza et al., 2013), and fetal growth in human beings (Y. Wang et al., 2016; Zhang et al., 2004).

Generally, women have higher body burden of Cd than men, and pregnant women appear to accumulate more Cd than nonpregnant women (Vilahur et al., 2015). Cd is largely retained in the placenta (Vilahur et al., 2015), and there is growing interest in studying the effects Cd toxicity on fetal development. Previous studies examining the association between prenatal exposure to Cd and adverse birth outcomes have yielded inconsistent results. Several previous studies have reported significant associations between prenatal Cd exposure and increased risk of preterm birth (Fagher et al., 1993; Nishijo et al., 2002), small for gestational age (Johnston et al., 2014), or decreased birth weight (Galicia-Garcia et al., 1997; Kippler et al., 2012; Llanos and Ronco, 2009; Salpietro et al., 2002). However, some studies have showed no such association (Odland et al., 1999; Osman et al., 2000;

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Thomas et al., 2015; Zhang et al., 2004). The inconsistent results from previous studies may be caused by the differences in environmental exposures, study design, sample size, and the nutritional status of study population. Further studies are needed to clarify the adverse effects of Cd on birth outcomes.

China is a developing country, and many environmental pollution issues have emerged due to the fast industrialization (Fu et al., 2008). Cd pollution has become a major health concern in China owing to the industrial emissions and the mass consumption of plant-derived food such as rice which contained high levels of Cd transferred from soil (Du et al., 2013; Uraguchi and Fujiwara, 2012). However, few data are available on the effects of prenatal exposure to Cd on birth outcomes in Chinese populations (Hu et al., 2015; Lin et al., 2011; Sun et al., 2014; Zheng et al., 2014). Given this background, we took advantage of our large prospective mother-child cohort to assess the effects of maternal Cd exposure on birth outcomes in 5364 Chinese pregnant women. We measured Cd concentrations in maternal urine, and evaluated the associations between maternal urinary Cd and birth outcomes, including the birth weight, birth length, and gestational age, as well as the likelihood of LBW, PTB and SGA.

2. Materials and methods

2.1. Study population

The present study was a part of the prospective Healthy Baby Cohort (HBC), which was conducted to explore the effects of environmental factors on health and development. This cohort enrolled participants at three maternity hospital in Wuhan, Ezhou, and Macheng, where located in Hubei Province in central China. The eligibility criteria for pregnant women participating in this cohort were as follows: 1) residence in the study area at the time of the recruitment period with an expectation to reside continually in this area for the foreseeable future; 2) with a single gestation and live birth; and 3) ability to comprehend the Chinese language and complete the questionnaire. The participants in this study were selected from the pregnant women who were enrolled in Wuhan during September 2012 and October 2014 (n = 11,311). In the present study, we excluded participants without urine samples available for analysis (n = 3947), and those who gave birth to an infant with a birth defect (n = 62). Also, for the women whose both first baby and second baby were enrolled in this cohort, we excluded the samples of the second baby (n = 3). Then, we excluded the women who reported smoking (n = 7) and alcohol consumption (n = 2) during pregnancy. The women who quit smoking during pregnancy but smoked before pregnancy ($n = 52$) were also excluded. In order to provide valid estimates of the concentration of the urinary Cd, we excluded participants with urinary creatinine <0.3 g/L and >3 g/L (n = 1864) according to World Health Organization guidelines (WHO, 1996), which suggested that creatinine concentration may be used to identify spot urine samples that are too concentrated or too dilute. In addition, we also excluded the participants who had renal disease or dysfunction (n = 10). In total, 5364 women were included in the final study. In this study, all participants provided written informed consent at enrollment and the research protocol was approved by the Ethics Committee of the School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, and Women and Children Medical and Healthcare Center of Wuhan.

2.2. Outcomes and covariates

This cohort recruited women who gave birth at the study hospital. Birth weight, birth length, and gestational age were retrieved from medical records. The measurements of birth weight and birth length in the hospital were conducted within one hour after birth by experienced obstetric nurses using standardized procedures. In detail, birth weight was measured by an electronic scale with precision of 10 g. Length was measured in the recumbent position by using a calibrated lengthboard that had a fixed headpiece and a moveable footpiece which was perpendicular to the surface of the table. Headpiece was against the crown of baby's head, keeping baby's two ears at the same level. The legs were held flat (knees down) and the movable footpiece was pressed gently against the balls of the feet. Then, the trained nurse read the inner value of the slide plate when the two sides of the scale reading were consistent. Gestational age (in days) was estimated using both the woman's last menstrual period (LMP) and ultrasound data. The date of LMP was obtained from medical records. If the two methods differed more than 7 days, then gestational age was determined using ultrasound data due to concerns over the reliability of the recalled LMP estimate. Births were dichotomized into low birth weight (LBW; <2500 g) and preterm birth (PTB; <37 weeks gestational age). PTB were further classified as preterm premature rupture of membranes (pPROM). In this study, we have detail information about preterm birth following premature rupture of membranes for over 12 h (pPROM). Small gestational age (SGA) is defined as a birth weight below the 10th percentile for the gestational age by infant sex based on all the newborns in the HBC from Wuhan (Mikolajczyk et al., 2011).

All participants were interviewed by specially trained nurses after delivery to collect covariate data including demographic (e.g., maternal age at delivery), socioeconomic (e.g., education, occupation, household income), and lifestyle factors (alcohol and tobacco exposure). Maternal pre-pregnancy body mass index (BMI, weight in kilograms divided by height in meters squared) was calculated based on self-reported pre-pregnancy weight and height, which was measured using a stadiometer.

2.3. Urine sample collection and exposure assessment

The mid-stream urine samples were collected from pregnant women immediately after they admitted to the hospital awaiting for delivery (within 3 days before delivery). All of the urine samples were directly collected in polypropylene tubes and then stored at −20 degrees Celsius (°C) until further analysis. Urinary Cd concentrations have been reported to be fairly stable at multiple points per day, indicating spot time urine sample could reflect Cd exposure (Y.X. Wang et al., 2016). Cd, total arsenic and lead in urine were simultaneously measured with inductively coupled plasma mass spectrometry (ICP-MS; Agilent 7700, Agilent Technologies, Waldbronn, Germany). The ICP-MS was operated in helium mode and 111Cd, 75As, and 108Pb were monitored. Before the instrumental analysis, urine samples were thawed at room temperature, and then 1 mL of urine from the supernatant and 4 mL of 3% HNO_3 were introduced in 15 mL Kirgen polypropylene conical centrifuge tubes for overnight nitrification. The resulting sample was digested by ultrasound at 40 °C for 1 h. The operating parameters for ICP-MS were presented in Supplemental material, Table S1. The standard Reference Material Human Urine (SRM2670a Toxic Elements in Urine, National Institute of Standards and Technology, USA) was used as an external quality control in each batch to assess the instrument performance. Certifies mass concentration values (μg/L) were as follows: Cd low level: 0.059 ± 0.0034, high level: 5.16 ± 0.11; As low level: none, high level: 220 ± 10; Pb low level: 0.49 ± 0.16, high level: 249.9 ± 4.3. The concentrations of quality controls were measured within the certified range recommended by the manufacturer (5%). LOQ was calculated by $10 * LOD/3$. LOD was determined from $LOD = 3RSD_b \times C/SBR$, where RSD_b is the relative standard deviation of the background intensity of 10 measurements, C is the concentration of the element in solution, and SBR is the signal-to-background ratio (Boumans et al., 1991). The average LOQs for Cd, As and Pb were 0.01 μg/L, 0.01 μg/L and 0.17 μg/L, respectively. The intra-day coefficient of variation was 1.32%–1.75%, and the inter-day CV was 1.15%–2.69%, and no sample was below the LOQ. We also performed field and procedure blanks, and found Cd was not detected in the containers and storage tubes for urine.