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Cadmium body burden and pregnancy-induced hypertension

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ABSTRACT

Previous studies provided a strong evidence of the association between environmental exposure to cadmium (Cd) and hypertension in the general population. However, the role of Cd in pregnancy-induced hypertension (PIH) remains unclear. A total of 5429 pregnant women was selected from a birth cohort in Wuhan, China to investigate the association between Cd exposure and risk of PIH. Among them, 199 (3.7%) women were diagnosed with PIH. The Cd concentrations in maternal urine collected at delivery were measured by inductively coupled plasma mass spectrometry. Multivariable logistic regression was performed on Cd concentrations as a continuous variable (natural logarithm transformed) or as a categorical variable (tertiles). For about 3-fold increase in urinary Cd concentrations, there was 75% increase in the odds of PIH after adjusting for potential confounders (odds ratio (OR) = 1.75; 95% confidence interval (CI): 1.45, 2.11). Women in the highest tertile of urinary Cd had 2.2-fold increased OR of PIH, compared with women in the lowest tertile (2.24; 95% CI: 1.47, 3.41). Furthermore, we found a significant interaction between Cd exposure and maternal socioeconomic status on PIH (*P* for interaction = 0.04). Our findings indicate that higher Cd exposure might increase the risk of PIH, and the association might be modified by socioeconomic status.

1. Introduction

Pregnancy-induced hypertension (PIH), including gestational hypertension and preeclampsia, is a major pregnancy complication and considered one of the leading cause of maternal and neonatal mortality and severe morbidity (Say et al., 2014). It increases lifetime risk for developing hypertension and cardiovascular disease in mothers and children (Alsnes et al., 2017; Mol et al., 2016; Veerbeek et al., 2015), as well as leads to many long-term consequences, such as increasing risk of type 2 diabetes in adult offspring (Kajantie et al., 2017). Although the etiology of PIH has not been well-understood, increasing evidence has suggested that its association with environmental factors (Pedersen et al., 2014; Yazbeck et al., 2009).

Cadmium (Cd), a ubiquitous natural and toxic heavy metal, can be released into the environment through industrial processing and agricultural activities, such as metal mining and refining, disposal of batteries and plastics, manufacturing and household waste (ATSDR, 2012). Human absorbs Cd into the body through diet, tobacco smoking, drinking water, and air (ATSDR, 2012). With a long biological half-life of 10–30 years and low excretion rate, Cd can be accumulated in the human body, and stored in liver, kidneys, and bones for years, leading to cardiovascular, neurological, renal and reproductive disorders (Pant, 2014). The absorption of Cd increases when there is iron deficiency, therefore pregnant women tend to absorb more Cd due to high iron demand during gestation (Akesson et al., 2002; Nishijo et al., 2004).

In previous studies, Cd exposure has been associated with elevated blood pressure or hypertension in non-pregnant women (Eum et al., 2008; Lee et al., 2011; Satarug et al., 2003; Tellez-Plaza et al., 2008). In general, women are at high risk of developing hypertension during pregnancy due to endocrine changes, placenta releasing pressor substances and elevated stress level during pregnancy (Bjelica, 2004; Gluhovschi et al., 2012; Hu et al., 2017). Some animal studies reported that Cd exposure in pregnant rats could lead to high blood pressure (Nwokocha et al., 2013; Yoopan et al., 2008), due to possible mechanisms such as renal dysfunction, immune system abnormalities, and placental oxidative stress (Jacquillet et al., 2007; Zhang. et al., 2016;

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Xiaojie et al., 2016). However, human studies are still limited and inconsistent concerning the relationship between Cd exposure and risk of hypertension during pregnancy. For example, Kosanovic et al. (2002) studied 60 pregnant women and found a positive relationship between Cd exposure and PIH. While Yazbeck et al. (2009) studied 971 pregnant women and found no association. Maduray et al. (2017) observed no relationship between Cd in hair and nail of 66 pregnant women and preeclampsia. We believe that more epidemiological studies are needed to clarify the role of Cd in the onset of PIH, especially among Chinese women as they have a relatively higher Cd status than in other developed countries (Nie et al., 2016).

People of low socioeconomic status (SES) are generally vulnerable to at a higher exposure risk to toxic chemicals and environmental pollutants because of poor living conditions, or proximity to heavy traffic or industrial facilities which called environmental injustice (Friedrich, 2000). Environmental injustice wildly exist in developed and developing counties, including Korea (Choi et al., 2016), Canada (Chan et al., 2015), America (Morello-Frosch et al., 2002), India (Saha et al., 2011), as well as China (Ji et al., 2015). Thus SES is considered an important determinant of health and potential modifier of the effects of environmental contaminants (Chan et al., 2015). Therefore, exposure to Cd might be associated with SES. The National Health and Nutrition Examination Survey (NHANES) cross the U.S. observed that exposure to environmental contaminants exposures was different among different SES groups, and higher Cd burden was found in lower SES individuals (Tyrrell et al., 2013). Lower SES individuals also tend to have a higher risk of adverse health problems, including hypertension (Leng et al., 2015).

In this study, we investigated the association between Cd exposure and the risk of PIH in 5429 pregnant women selected from a birth cohort in Wuhan, China; and the role of SES as an effect-modifier of the Cd-PIH relationship.

2. Methods

2.1. Study population

This was a cross-sectional study of a prospective Healthy Baby Cohort (HBC), studying the impact of environmental pollutants on pregnancy disorders, and prenatal exposure to environmental factors on fetal growth, and neurodevelopment in children later in life. The study was conducted in Wuhan Medical and Health Center for Women and Children, a major maternity hospital in the area. The details of the study have been described elsewhere (Jie et al., 2016). Briefly, women who were able to speak and read Chinese, delivered a singleton live baby at the study hospital, and plan to live in Wuhan for the foreseeable future were asked to join in the cohort. The study protocols were approved by both the ethics committees of the hospital under this study and Tongji Medical College, Huazhong University of Science and Technology. All participating individuals provided their signed informed written consents.

Between September 2012 and October 2014, a total of 11311 women were enrolled in the HBC study. In the present study, we only selected to participants who had provided urine samples before delivery (n = 7359). We only included the first delivery record for three women who had two separate deliveries. A total of 302 women were excluded because they had either amniorrhea or blood in urine before they come to the hospital. The presence of blood cells and amniotic fluid in the urine samples may cause biased the results of heavy metals. Moreover, we excluded women with health conditions before pregnancy such as preexisting hypertension (n = 9), renal disease (n = 4), and cardiovascular disease (n = 11), who consumed alcohol during pregnancy (n = 2), and those with either diluted (< 0.3 g/l) or concentrated (> 3 g/l) urinary creatinine, according to WHO guidelines (n = 1901) (WHO, 1996). A total of 5429 pregnant women were included in this study.

2.2. Urine sampling and analysis

Immediately after admission to the hospital and before delivery, midstream urine samples were collected from each pregnant woman into polyethylene containers promptly aliquoted into 3–5 mL in 5 mL polypropylene tubes and stored at −20 °C until analyses. Urinary Cd and lead (Pb) was quantified using inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7700, Agilent Technologies, Waldbronn, Germany) as described previously (Jie et al., 2016). The recovery of spiked urine samples was 103%. To assess the method performance, we used the Standard Reference Material Human Urine (SRM2670a Toxic Elements in Urine, National Institute of Standards and Technology, USA) as an external quality control in each batch. The low and high concentrations of the certified reference materials (μg/L) were respectively 0.059 ± 0.0034, and 5.16 ± 0.11 for Cd; and 0.49 ± 0.16, and 249.90 ± 4.30 for Pb. Our results fit well within the 5% the certified range recommended by the manufacturer. The intra-day and inter-day coefficient of variation were 1.32-1.75% and 1.15-2.69%, respectively. The limit of detection for of Cd and Pb was 0.003 and 0.051 μg/L, respectively. We measured urinary creatinine to adjust for variation in urine dilution, using a creatinine kit based on the sarcosine oxidase assays (Mindray CREA Kit, Sarcosine Oxidase Method, Shenzhen, China).

2.3. Outcomes and covariates

The outcome of this study was PIH, also called preeclampsia or gestational hypertension based on the physician diagnosis (Lin et al., 2016). Information about doctor-diagnosed preeclampsia or gestational hypertension was obtained from medical records at delivery. Women's medical and reproductive histories, the date of last menstrual period and body weight at delivery and pregnancy, were also retrieved from medical records of their first antenatal care appointment at the hospital. The information on demographic and socioeconomic characteristics (age, height, annual household income, education, and occupation), lifestyle behaviors during pregnancy (alcohol consumption, and smoking tobacco), and supplements intake (iron, calcium, and multivitamins) were obtained from face-to-face interviews by trained nurses. Passive smoking was defined as nonsmoking women exposed to tobacco smoke during pregnancy from her spouse or other family member living in the same household or the workplace (Zairina, 2016). Self-reported body weight and height were used to calculate prepregnancy body mass index (Pre-pregnancy BMI) since medical record for pregnant women in this city usually opens at 12–16 weeks of gestation. Prepregnancy BMI (kg/m^2) was computed as the ratio of body weight (kg) divided by the height squared (m^2). Gestational weight gain was calculated by subtracting prepregnancy weight from the weight before delivery. Gestational age was calculated in weeks from the first day of last menstrual period (LMP) until the date of delivery. Women whose menstrual cycles were irregular or unsure of their LMP, gestational age was corrected based on their first-trimester ultrasound examination. Women's SES categorized according to annual household income: lower SES (< 50,000 yuan per year) and higher SES groups (≥50,000 yuan per year). The 50,000 yuan cut-off was chosen based on the Statistical Communique on National Economic and Social Development of Hubei province in 2013 and published by Hubei Provincial Bureau of Statistics (Hubei Provincial Bureau of Statistics, 2014).

2.4. Statistical analysis

Urinary Cd levels were natural logarithm transformed (ln-Cd) because of skewed distributions. Continuous variables, such as age, prepregnancy BMI, gestational age, and urinary creatinine were presented as mean ± SD. The geometric means (GMs) of Cd concentrations, lead (Pb) concentrations and creatinine-adjusted Cd concentrations were calculated. The distributions of relevant characteristics between PIH