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Adverse associations between maternal and neonatal cadmium exposure and birth outcomes

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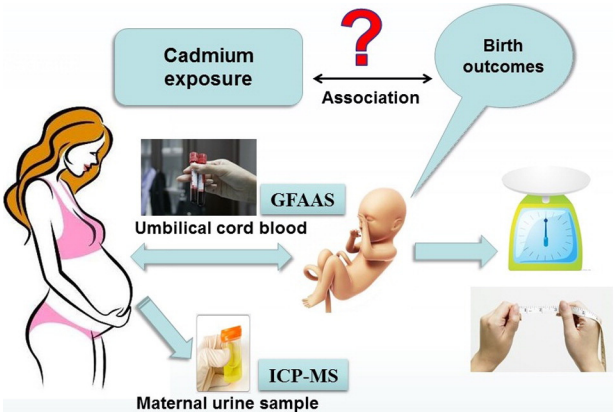
HIGHLIGHTS

- Cd concentrations were determined in both umbilical cord blood and maternal urine.
- Associations between Cd exposure and birth outcomes were explored in 1073 mother-newborn pairs.
- Cord blood Cd concentrations were negatively associated with ponderal index of neonates.
- Adverse effects of Cd exposure on birth outcomes differed by neonatal sex.

GRAPHICAL ABSTRACT



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ABSTRACT

Effects of low-level cadmium (Cd) exposure during early life on fetal growth remain unclear. Our aim was to evaluate whether Cd exposure in maternal urine and umbilical cord blood was associated with birth size parameters. A birth cohort study including 1073 mother-newborn pairs was conducted from 2009 to 2010 in an agricultural population in China. Cd concentrations were analyzed in both cord blood and maternal urine. Generalized linear models were performed to determine associations between maternal and neonatal exposure to Cd and birth indicators, including birth weight, length, head circumference and ponderal index. The median (25th to 75th percentile) value of Cd concentration in maternal urine and umbilical cord blood was 0.19 (0.08, 1.00) μg/L and 0.40 (<LOD ~ 0.62) μg/L, respectively. After adjusting for potential confounders, Cd concentration in cord blood was significantly negatively associated with ponderal index at birth [$\beta = -0.06$ g/cm^3, 95% confidence interval (CI): −0.11, −0.02; $p < 0.01$]. Considering sex difference, significant reduction in ponderal index was only observed in males ($\beta = -0.06$ g/cm^3, 95%CI: −0.11, −0.02; $p < 0.01$), but not in females ($\beta = -0.03$ g/cm^3, 95%CI: −0.07, 0.01; $p = 0.18$) (p for interaction term = 0.24). Additionally, no significant associations were

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Urine
Newborns

observed between maternal urinary Cd levels and birth outcomes. Our findings suggest that adverse effects of neonatal exposure to Cd on fetal growth are of considerable public health importance.

1. Introduction

Cadmium (Cd) is a toxic heavy metal and has long been considered as a hazardous material to human health. Due to its high volume use from industrial and agricultural sources, Cd was extensively distributed in soil, water, air and even food (Järup and Åkesson, 2009). Environmental contamination by Cd posed a potential threat to human health because of Cd-induced toxicity. Recently, exposure to Cd has attracted growing public concern because Cd has also been suspected to disrupt the endocrine function and may thereby affect reproduction and development in human (Gollenberg et al., 2010). Particularly, pregnant women were highly susceptible due to increased uptake of Cd with low iron status (Akesson et al., 2002). Furthermore, Cd can transfer from mother to fetus through placenta, thus for the developing embryo and fetus in utero, fetal growth could be affected during pregnancy (Di Sant'Agnese et al., 1983). Cd has been detected in several types of biological sample, including maternal blood, maternal urine, placenta, cord tissue, cord blood as well as breast milk (Olszowski et al., 2016; Sakamoto et al., 2013).

Given evidence of relationships between Cd exposure during early life and potential health effects are emerging. In rodent animals, increasing evidence demonstrated that Cd was an embryotoxic and teratogenic metal, namely, offspring malformations and fetal growth restriction could be induced by maternal Cd exposure during gestation (Ji et al., 2011; Paniagua-Castro et al., 2007; Scott et al., 2005). Though several epidemiological studies have suggested that exposure to Cd during pregancy were associated with decrease in birth outcome measures, including birth weight and length, head circumference, ponderal index (PI), chest circumference and small for gestational age (SGA) (Al-Saleh et al., 2014; Kippler et al., 2012a; Llanos and Ronco, 2009; Romano et al., 2016; Wang et al., 2016), the results are still controversial. While some studies observed no associations (Odland et al., 2004; Osman et al., 2000; Tang et al., 2016), either others found positive associations (Bloom et al., 2015), or inverted U-shaped associations (Kippler et al., 2012b). Limited studies are available looking at maternal and fetal Cd exposure in large sample size of mother-newborn pairs.

Once absorbed, Cd can be accumulated in the human body with a half-life of 10–30 years, especially in the kidneys (Järup and Åkesson, 2009). Urinary Cd is a well-documented biomarker of chronic exposure that reflects long-term body burden (Åkesson et al., 2014), while cord blood Cd concentration represents neonatal exposure effectively (Järup et al., 1998). In the present study, Cd exposure in maternal urine and cord blood were evaluated and their associations with birth size measures were explored in a birth cohort from a population living in an agricultural region, China.

2. Materials and methods

2.1. Study subjects

From June 2009 through January 2010, a prospective birth cohort originally recruited 1303 pregnant women in an agricultural region in Jiangsu Province, China. The aim of the cohort study was to explore associations between prenatal and postnatal exposure to environmental chemicals and children's health. As described previously (Guo et al., 2016; Qi et al., 2012), information on sociodemographic characteristics, lifestyle factors, medical history and maternal anthropometry were collected by trained interviewers, and birth outcomes of neonates were extracted from medical records. Written informed consents were obtained from all the particpants, and the research protocol was approved by the Ethics Committees of School of Public Health, Fudan University, China.

Of the 1303 participants, we excluded 23 women without cord blood samples and 113 women without adequate or missing urinary samples for exposure assessment. Furthermore, 94 pregnant women were also excluded due to <18 years old (5), stillbirth (1), congenital anomalies (8), twin births (9), serious diseases during pregnancy (16), as well as missing information on important factors (55). A total of 1073 mother-newborn pairs were eligible for this analysis. Women in the current study did not differ from the original birth cohort in terms of demographics and other key covariates (data not shown).

2.2. Samples collection and analysis

Umbilical cord blood samples were collected by professional midwives using standard protocols. 5 mL blood samples were collected in sterile centrifuge tubes containing anticoagulant EDTA and frozen at −80 °C until analysis. Cd levels in umbilical cord blood were measured using graphite furnace atomic absorption spectrometry (GFAAS, Perkin Elmer AA 800, USA). Briefly, cord blood samples were mixed with 1:9 (v/v) of 0.1% nitric acid. The accuracy of measuring method was ensured using certified reference material (Seronorm, BATCH NO.905). The external quality-control program did not show any time trend in the accuracy of the Cd measurement. The recovery of cord blood Cd was 97.8% ~ 100.8% and relative standard deviation (RSD) was <4.3%. The limit of detection (LOD) was 0.25 μg/L (Li, 2001).

Urine samples were collected on the delivery day, then transferred to the high-density polypropylene centrifuge tubes. After shaken, 1 mL urine was acidified with 69% HNO_3 (5 μL). All biological samples were immediately stored at −20 °C, then shipped to the laboratory and kept frozen at −80 °C until analysis. Cd concentrations in urine samples were measured using inductively coupled plasma mass spectrometry with standard mode (ICP-MS, NexION 300X, Perkin Elmer, USA). Briefly, urine samples were thawed at room temperature before analysis and mixed with 10-fold dilution with 3% nitric acid. Strict quality control measures were implemented to ensure the accuracy of the analytical results (Seronorm Trace Elements Urine, Billingstad, Norway). Both the intra-day and inter-day RSD were <5.0%. The LOD for urinary Cd was 0.06 μg/L. Moreover, urinary creatinine was measured to correct for variability in urinary dilution and using a spectrophotometric method on a visible spectrometer (wavelength 325–1000 nm, UNICO 2000, USA) (Qi et al., 2012).

2.3. Measurement of birth outcomes

Sex, birth date, parity and birth anthropometric measures of the neonates were extracted from medical records. Birth outcomes were measured by midwives immediately after delivery in the hospital. In brief, birth weight was measured using a digital scale and rounded to 0.05 kg. Birth length and head circumference were measured using measuring tape and rounded to 0.1 cm (Guo et al., 2016). PI, a measure used to quantify asymmetric fetal growth restriction (Landmann et al., 2006) and obesity risk (Loaiza et al., 2011) in newborns, was calculated as (birth weight in grams)/(birth length in centimeters)^3 × 100.

2.4. Statistical analysis

Associations between Cd exposure and birth outcomes were analyzed using generalized linear regression models. We also modeled Cd

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