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Exposure to chromium during pregnancy and longitudinally assessed fetal growth: Findings from a prospective cohort

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ABSTRACT

Background: Prenatal exposure to chromium may be associated with reduced birth weight; however, critical windows of such exposure for fetal growth are unclear.

Objective: Our study was aimed to assess trimester-specific associations of chromium exposure with fetal growth parameters measured repeatedly by ultrasound and birth size, and to see whether these associations were modified by fetal sex.

Methods: We conducted a prospective cohort of 3041 women in Wuhan, China, from 2013 to 2016. Chromium concentrations were measured in maternal urine samples collected in the 1st, 2nd, and 3rd trimesters using an inductively coupled plasma mass spectrometry. We calculated standard deviation scores for ultrasound measured head circumference, abdominal circumference (AC), femur length, and estimated fetal weight (EFW) at 16, 24, and 31 weeks of gestation. Linear regressions with generalized estimating equations were used to estimate the associations of specific gravity-adjusted urinary chromium concentrations in each trimester with fetal growth parameters and birth weight, birth length, and ponderal index.

Results: Inverse associations of chromium exposure in the 1st trimester with fetal growth parameters at 31 weeks of gestation were observed, resulting in significant reductions in AC of −5.4% (95% confidence interval [CI]: −9.6%, −1.2%) and EFW of −5.6% (95% CI: −9.8%, −1.4%) per unit increase in natural logarithm transformed urinary chromium concentration. Urinary chromium concentration in the 2nd trimester was also associated with reductions in AC of −7.0% (95% CI: −12.5%, −1.4%) and in EFW of −5.0% (95% CI: −10.6%, 0.6%) at 31 weeks, and these inverse associations were evident in boys (reduction in AC of −13.9% [95% CI: −21.1%, −6.7%]; EFW of −9.5% [95% CI: −16.9%, −2.0%]) but not in girls (increase in AC of 2.9% [95% CI: −5.7%, 11.5%]; EFW of 1.5% [95% CI: −6.8%, 9.8%]) (both $p_{\text{ineraction}} < 0.05$). Moreover, one-unit increase in urinary chromium concentrations in the 1st and 2nd trimesters were both associated with significant reductions in ponderal index of $-0.11\ \text{kg/m}^3$ (95% CI: -0.19, $-0.03\ \text{kg/m}^3$) and $-0.15\ \text{kg/m}^3$ (95% CI: -0.27, $-0.03\ \text{kg/m}^3$), respectively.

Conclusion: Our findings suggest that chromium may be a toxic metal for fetal growth. Early and mid-pregnancy seem to be the most vulnerable period for fetal exposure to chromium, but these results need further confirmation.

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1. Introduction

Chromium, a naturally occurring element in the earth's crust, is released into the environment from natural and anthropogenic sources, with the largest contribution from industrial activities, such as electroplating, leather tanning, textile production, and the manufacture of chromium-based products (ATSDR, 2012). Due to the increasing use of chromium in industries, its levels in the atmosphere are rising constantly (Cheng et al., 2014; Pellerin and Booker, 2000; Sutton, 2010), resulting in widespread exposure to chromium in the general population via diet, drinking water, and air (ATSDR, 2012; Sutton, 2010). Chromium is able to cross placental barrier and concentrate in fetal tissues (Saxena et al., 1990), and has been related with impaired fetal development in rodents (Bailey et al., 2006; Elbetieha and Al-Hamood, 1997; Junaid et al., 1996). However, evidence from human studies is limited and inconsistent. Only two studies related prenatal exposure to chromium with an increased risk of low birth weight (Berry and Bove, 1997; Xia et al., 2016), but such association was not observed in other studies (Cabrera-Rodríguez et al., 2018; Guo et al., 2010; McDermott et al., 2014).

The fetal period is considered a highly sensitive stage to environmental toxicants (Barker, 2007). Prenatal exposure to environmental toxicants could result in reduced fetal growth and an increased risk of low birth weight (Zheng et al., 2016), which have been associated with not only neonatal mortality (Lawn et al., 2005) but also a variety of adverse outcomes during childhood and even adulthood (Gluckman et al., 2008; Johnson and Schoeni, 2011). Environmental exposures during critical windows of vulnerability had stronger effects on impaired fetal growth (Harari et al., 2015; Kippler et al., 2012). However, whether there are critical windows of vulnerability to chromium for fetal growth remains unclear.

In this prospective cohort study of 3041 women enrolled in Wuhan, China, we assessed the trimester-specific associations of exposure to chromium in the 1st, 2nd, and 3rd trimesters with ultrasound measures of fetal growth and birth size. We also investigated whether these associations were modified by fetal sex, because our previous studies suggested sex-based differences in the associations of prenatal exposure to chromium with increased risks of adverse birth outcomes (Huang et al., 2017; Pan et al., 2017; Xia et al., 2016).

2. Methods

2.1. Study population

Women of the present study were selected from our ongoing prospective cohort study, which is conducted at the Wuhan Maternal and Child Healthcare Hospital, a major maternity hospital in Wuhan, China. Women were eligible for participation if they fulfilled the following criteria: 1) < 16 weeks of gestation at the time of enrollment, 2) carrying a singleton fetus, 3) a resident of Wuhan city who comprehended the Chinese language, 4) agreed to have in-person interviews, take ultrasound examinations, and provide blood and urine samples at routine prenatal care visits, 5) planning to deliver at the study hospital. From October 2013 to October 2016, 3057 women who took at least one ultrasound examination and gave birth to live singletons without any birth defect were included. We excluded those women who smoked during pregnancy (n = 2), and who had only one ultrasound measurement of fetal crown-rump length in the 1st trimester (n = 14), leaving 3041 participants in the present study. The study protocol was reviewed and approved by the ethics committees of the Tongji Medical College, Huazhong University of Science and Technology, and the Wuhan Maternal and Child Healthcare Hospital. All participants provided written informed consents at enrollment.

2.2. Urine collection and chromium measurement

Maternal urine samples were collected during prenatal care visits in the 1st (mean ± standard deviation [SD]: 13.0 ± 1.0 weeks of gestation; 81.2% of urine samples were collected at or prior to 13 weeks of gestation), 2nd (23.3 ± 2.3 weeks of gestation), and 3rd (37.8 ± 1.8 weeks of gestation) trimesters. Among the 3041 women in the present study, 824 (27.1%) donated one urine samples, 1351 (44.4%) donated two urine samples, and 866 (28.5%) donated three urine samples. All urine samples were stored in polypropylene tubes at $-20\,^{\circ}\mathrm{C}$ until laboratory analysis.

The urinary chromium concentrations were measured using an inductively coupled plasma mass spectrometry (ICP-MS; Agilent 7700, Agilent Technologies, Santa Clara, CA, USA). Urinary concentrations of vanadium, arsenic, cadmium, and lead were also measured simultaneously, as they were related with restricted fetal growth (Cheng et al., 2017; Hu et al., 2017; Kippler et al., 2012; Rabito et al., 2014). The methods of assessment and quality control have been described in detail in our previous study (Cheng et al., 2017). Briefly, urine samples were thawed at room temperature and then nitrated overnight using 3% HNO_3. After this, the samples were sonicated by ultrasound at 40 °C for 1 h. The ICP-MS was operated in helium mode and these metals were monitored. The urinary chromium concentrations of 80 (1.3%) samples were below the detection limit of quantification (LOQ; 0.03 μg/L). The detection rates of vanadium, arsenic, cadmium, and lead were all higher than 99%. Urinary specific gravity (SG) was measured using a digital handheld refractometer (Atago PAL-3, Atago, Tokyo, Japan) as an indicator of urine dilution.

2.3. Fetal growth measurements and birth outcomes

Fetal ultrasound examinations were scheduled at approximately 16, 24, and 31 weeks of gestation by professional sonographers at the study hospital. Based on the frequencies of ultrasound measurement across time (see Supplementary, Fig. S1), we chose these 3 time points to achieve as much ultrasound data as possible. The fetal growth parameters (in mm) included head circumference (HC), abdominal circumference (AC), and femur length (FL). Estimated fetal weight (EFW) was calculated using Hadlock's formula of HC, AC and FL (Hadlock et al., 1985). Birth weight (in g) and birth length (in cm) were retrieved from medical records. Ponderal index (in $\mathrm{kg/m^3}$) was calculated as $(\text{birth weight} / \text{birth length}^3) \times 1000$. Gestational age was determined by the self-reported last menstrual period (LMP) if it agreed with the ultrasound estimation within 7 days; otherwise, the ultrasound estimation was used. The self-reported or ultrasound corrected LMP was used as the start point for calculating the gestational age of ultrasound examination and birth.

2.4. Covariates

Information on maternal age, height (in m), pre-pregnancy weight (in kg), education, active smoking, passive smoking, alcohol use, folic acid supplement use, and paternal height (in m) and weight (in kg) were obtained in the face-to-face interviews using standardized and structured questionnaires. Maternal pre-pregnancy and paternal body mass index (BMI, in $\mathrm{kg/m^2}$) were calculated as $\text{weight} / \text{height}^2$. Information on parity, infant sex, and pregnancy complications (hypertensive disorders in pregnancy and gestational diabetes mellitus) were retrieved from medical records.

2.5. Statistical analysis

Urinary concentrations of chromium and other toxic metals below the LOQs were imputed as LOQs divided by $\sqrt{2}$. SG-adjusted metals concentrations were utilized through the following formula: $P_c = P \times [(1.011 - 1) / (SG - 1)]$, where P_c is the SG-adjusted