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Maternal urinary paraben levels and offspring size at birth from a Chinese birth cohort

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HIGHLIGHTS

- This is the first study to assess paraben exposure in Chinese pregnant women.
- Parabens were detected in the majority of urine samples in Chinese pregnant women.
- The association of maternal urinary parabens with infants' birth size was examined.
- Maternal urinary levels of MeP were positively associated with birth length in boys.

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ABSTRACT

Background: Parabens are suspected to impair fetal growth because of their endocrine disrupting effects. Epidemiological studies regarding the effects of prenatal exposure to parabens on birth outcomes are limited.
Objectives: Our aim was to evaluate the association between prenatal paraben exposure and size of infants at birth.
Methods: Within the longitudinal Healthy Baby Cohort (HBC) in Hubei Province, China, we randomly selected 1006 mother-infant pairs recruited in Wuhan City in 2014. Concentrations of parabens were measured in maternal urine collected before delivery. General linear models were used to analyze the associations of maternal parabens exposure levels with birth weight and birth length.
Results: The specific gravity adjusted geometric means for urinary concentrations of methyl paraben (MeP), ethyl paraben (EtP), and propyl paraben (PrP) were 5.41, 0.11, and 0.94 ng/mL, respectively. Maternal urinary concentrations of parabens tended to be positively associated with birth weight in boys, while opposite trends were found in girls, though these associations were not significant. Higher maternal urinary levels of MeP were positively associated with birth length in boys ($\beta = 0.30$, 95% CI: 0.01, 0.58 for the medium tertile, and $\beta = 0.30$, 95% CI: 0.01, 0.58 for the highest tertile compared to the lowest tertile); however, no significant associations with birth length were observed in girls.
Conclusions: Maternal urinary levels of MeP were positively associated with length at birth in boys. Besides, we did not find strong associations of the current exposure levels of parabens in Chinese pregnant women with size of infants at birth.

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1. Introduction

Parabens, also named as esters of parahydroxybenzoic acid, are widely used as antimicrobial preservatives in the cosmetic and pharmaceutical industry, and several parabens are often used in combination (Golden et al., 2005; Calafat et al., 2010). The chemicals can be found in multiple products, including personal care products (such as cosmetics, lotions, and hair care productions), foods and beverages (Andersen, 2008; Crinnion, 2010). Exposure to parabens in the general population may occur through ingestion, inhalation, or dermal absorption (Mortensen et al., 2014). As the chemicals with short half-lives of less than 24 h in the human body, parabens are rapidly metabolized and are mainly eliminated through urine (Janjua et al., 2008). The levels of total form of the parent compounds and some new metabolites found in urine can be valid biomarkers for recent paraben exposure (Ye et al., 2006; Moos et al., 2016).

Although parabens have been extensively used as preservatives for a long time, several concerns have been raised over the past twenty years about the safety of parabens due to their potential endocrine disrupting effects (SCCP, 2005; Darbre and Harvey, 2008; Diamanti-Kandarakis et al., 2009). Prenatal exposure is of particular concern due to the potential health effects on the vulnerable embryos, in which exposure may cause lifetime adverse health impacts. Some animal studies have showed that maternal exposure to several parabens impaired growth, hormone balance, neurodevelopment, learning ability and behavior of the offspring (Kang et al., 2002; Boberg et al., 2008; Kawaguchi et al., 2009).

Human data are sparse regarding the effects of prenatal exposure to parabens on fetal growth. A study conducted in 191 French male newborns reported no associations between maternal urinary levels of parabens and offspring size (Philippat et al., 2012). However, after enlarging the sample size to 520 male newborns, they came to the conclusion that maternal urinary levels of methyl paraben (MeP), ethyl paraben (EtP), propyl paraben (PrP) and butyl paraben (BuP) tended to be positively associated with weight at birth (Philippat et al., 2014). On the contrary, another study conducted among only 34 newborns from immigrant population in Brooklyn, New York, demonstrated that PrP in cord blood plasma was associated with decreased length at birth (Geer et al., 2017).

Given the absence of data concerning the levels of paraben exposure in Chinese pregnant women, in this study, we analyzed urinary concentrations of five commonly used varieties of parabens, including MeP, EtP, PrP, BuP, and benzyl paraben (BzP) in 1006 pregnant women in Wuhan city, China to fill the gap of the biological monitoring data. As many previous studies suggested that endocrine-disrupting chemicals can have adverse effects at low doses (Melnick et al., 2002; Vandenberg et al., 2012), we also aimed to find out whether the current exposure levels of parabens could affect fetal growth by evaluating their relationships with weight and length of infants at birth.

2. Materials and methods

2.1. Study population

The Healthy Baby Cohort (HBC) study, a longitudinal prospective birth cohort in Hubei Province, China, is committed to investigate the associations between environmental exposures and children's health. Details of the cohort study have been described previously (Yang et al., 2016). The population in this present study was selected from participants in Wuhan city, which enrolled 11,311 pregnant women from September 2012 through October 2014.

The present study restricted to a subset of women with paraben measurements in urine samples collected before delivery ($n = 1016$). These urine samples were randomly chosen from the participants who were enrolled in Wuhan during January to October 2014. Ineligible women who gave birth to infant with birth defects ($n = 7$), or had missing medical record data ($n = 3$) were excluded, leaving 1006 mother-infant pairs for analyses. None of the participants reported smoking or drinking during pregnancy. The women included in the present study did not significantly differ in the basic characteristics or the characteristics of their infants (sex, birth weight, gestational age) with the parent cohort.

All participants in this study provided written informed consent before enrollment. The research protocol received the approvals of the ethics committee of Tongji Medical College, Huazhong University of Science and Technology, and the study hospital.

2.2. Birth outcomes and covariates

At the time of delivery, routine anthropometric measurements including birth weight (g) and length (cm) were measured by trained nurses with standardized procedures. Information concerning history of gestation (parity), maternal age, education level, weight at delivery, and birth outcomes (infant's birth date, sex, gestational age at birth, birth weight, and birth length) were obtained from electronic medical records. Gestational age (in days) was calculated based on the date of last menstrual period (LMP) or assessed by ultrasound data if it differed from the LMP-based estimation by over 7 d due to the concerns over the reliability of the self-reported LMP estimation. Questionnaire information regarding maternal demographic characteristics and lifestyle factors (smoking, drinking, etc.) was collected by a face to face interview after delivery by specially trained nurses in the hospital. The pre-pregnancy body mass index (BMI) was calculated by self-reported pre-pregnancy weight and height.

2.3. Urine sample collection and paraben exposure assessments

The urine samples were collected immediately after the pregnant women admitted to the hospital for delivery (within 3 d before delivery), and divided into aliquots storing in the 5-mL polypropylene cryovials at −20 °C until further analysis.

Ultra performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) was used to analyze the urinary paraben concentrations, as previously reported by Wang et al. (2013) with some modifications. In brief, 1 mL urine sample was added with 25 μL isotope-labeled internal standard solution which contained $^{13}C_6$-MeP, $^{13}C_6$-EtP, $^{13}C_6$-n-PrP, and $^{13}C_6$-n-BuP (10 ng each), and then the mixture was incubated with 10 μL of β-glucuronidase/sulfatase at 37 °C overnight. The digested samples were further extracted for three times with 3 mL methyl *tert*-butyl ether (MTBE). The total supernatant organic layer was collected and concentrated to near-dryness at room temperature under a gentle stream of nitrogen gas. Finally, a 500-μL acetonitrile-water (6:4) was added, vortexed, and filtered into a vial for UPLC-MS/MS analysis.

Chromatographic separation and detection of target analytes were accomplished using Waters Acquity UPLC system (Waters Corporation, Maple Street Milford, MA, USA), interfaced with a Waters TQD triple quadrupole tandem mass spectrometer, negative-ion electrospray ionization mass spectrometry (ESI-MS/MS) and multiple reaction monitoring mode (Waters Corporation). Five μL of the extract was injected onto an analytical column (Betasil C18, 100 × 2.1 mm column; Thermo Electron Corporation, Waltham, MA), which was connected serially to a guard column (Betasil C18, 20 × 2.1 mm column; Thermo Electron Corporation, Waltham, MA, USA). The mobile phase comprised methanol and ultrapure water. All samples were coded anonymously during the measurement. Each batch of analytical run included calibration