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Cumulative risk assessment of phthalates associated with birth outcomes in pregnant Chinese women: A prospective cohort study☆

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ABSTRACT

A prospective cohort study of a Chinese population of mother–neonate pairs (n = 3103) was conducted to investigate the relationship between the cumulative hazard index (HI) of combined diethyl phthalate (DEP), dibutyl phthalate (DBP), dibenzyl phthalate (BBzP) and di(2-ethylhexyl) phthalate (DEHP) exposure and birth outcomes. The estimated HI for phthalates was based on phthalate metabolite concentrations in urine collected between 5th and 14th gestational weeks. The median HI values according to the European Food Safety Authority tolerable daily intake (HI_{TDI}) and U.S. Environmental Protection Agency reference dose (HI_{RfD}) were 0.358 and 0.187, respectively. A total of 16.3% and 1.9% of the women exhibited HI_{TDI} and HI_{RfD} exceeding the value of one, respectively. In unadjusted models, the categories (low < P_{25}, median P_{25}–P_{50}, high > P_{75}) of HI_{TDI} were associated with decreased birth weight ($\beta = -26.34$ g, $p = 0.021$) and head circumference ($\beta = -0.09$ cm, $p = 0.029$), whereas those for HI_{RfD} were negatively associated with birth weight ($\beta = -31.74$ g, $p = 0.005$), birth length ($\beta = -0.11$ cm, $p = 0.032$), head circumference ($\beta = -0.13$ cm, $p = 0.003$) and chest circumference ($\beta = -0.10$ cm, $p = 0.021$) in all neonates. Adjustment for potential confounders revealed that HI_{RfD} was inversely associated with head circumference ($\beta = -0.10$ cm, $p = 0.020$). Stratification by gender indicated that HI_{RfD} was associated with decreased birth length ($\beta = -0.17$ cm, $p = 0.041$) in infant boys and HI_{TDI} was associated with decreased birth weight ($\beta = -33.12$ g, $p = 0.036$) and head circumference ($\beta = -0.13$ cm, $p = 0.027$) in girls. This is the first study on the cumulative risk assessment of phthalate exposures in pregnant Chinese women. We found that the HI values of multiple phthalate co-exposure were sex-specifically related to birth outcomes.

1. Introduction

Phthalates are a group of ubiquitous environmental pollutants that have similar structures to each other and cause adverse health effects (Ejaredar et al., 2015; Gray et al., 2000; Howdeshell et al., 2008; Miodovnik et al., 2014). Ample evidences show simultaneous exposure to multiple phthalates with extremely high detection rates among populations (Ferguson et al., 2014a; Kim et al., 2016; Meeker and Ferguson, 2014; Zhao et al., 2015). Therefore, the U.S. Environmental Protection Agency (EPA) requested the National Research Council to investigate the health risks of phthalates and conduct a cumulative risk assessment (CRA) (U.S. NRC, 2008). A CRA is defined as a science policy tool for organizing and analyzing relevant scientific information to examine, characterize and quantify the combined adverse effects of exposure to a combination of environmental stressors on human health (U.S. EPA, 2003). Hazard quotient (HQ) and hazard index (HI) are used as CRA indicators for phthalates. The two values focus on the most critical outcome, namely ‘phthalate syndrome’, which entails disrupted male reproductive development (U.S. NRC, 2008). A HQ is calculated as the ratio of an estimated exposure level to a reference

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value (RfV) for a phthalate-affected person. The RfV includes the U.S. EPA reference dose (RfD) and the European Food Safety Authority (EFSA) tolerable daily intake (TDI) (Christensen et al., 2014). The HQs are then summed up to estimate an overall HI. Previous studies have demonstrated this methodology well (Dewalque et al., 2014; Frederiksen et al., 2011; Gao et al., 2016; Hartmann et al., 2015; Koch et al., 2011; Kortenkamp and Faust, 2010; Pan et al., 2011; Soeborg et al., 2012; Tefre de Renzy-Martin et al., 2014; U.S. NRC, 2008; Wang et al., 2015a).

On the basis of EFSA TDI, research findings suggested that the median HI values of the child population were approximately 0.18–0.84, whereas those of the adult population were approximately 0.12–0.90 (Dewalque et al., 2014; Frederiksen et al., 2011; Gao et al., 2016; Hartmann et al., 2015; Koch et al., 2011; Soeborg et al., 2012; Wang et al., 2015a). In addition, a survey revealed that the median HI value in pregnant Danish women (8–30 gestational weeks) was 0.06 (Tefre de Renzy-Martin et al., 2014).

Foetuses are an especially sensitive population. Therefore, phthalate exposure during pregnancy is of particular concern. Rodent and human data suggest adverse effects of phthalates on foetal growth, including low birth weight, preterm birth, reduced gestational age and decreased birth length. However, results are inconsistent across studies (Huang et al., 2009; Latini et al., 2003; Meeker et al., 2009; Philippat et al., 2012; Wolff et al., 2008; Zhang et al., 2009). The apparent heterogeneity of the findings seems to have several causes. First, studies have been designed with small sample size and with different concerned populations. Second, concentrations of phthalates from maternal urine and blood in the third trimester of pregnancy and from umbilical cord blood and meconium have been measured, indicating the exposure level around the perinatal period. However, the associations between early pregnancy exposure to phthalates and offspring's outcomes are poorly understood, with conflicting findings (Watkins et al., 2016; Sathyanarayana et al., 2016). Furthermore, using repeated measures across pregnancy, Ferguson et al. (2014b) found that the average mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-carboxypentyl) phthalate and total di(2-ethylhexyl) phthalate (DEHP) levels in urine collected at three visits (approximately 10, 18 and 26 weeks of gestation) were associated with increased odds of preterm birth. Shoaff et al. (2016) observed no association between average phthalate metabolite concentrations in urine samples that were collected at approximately 16 and 26 weeks of gestation and birth size or gestational duration in adjusted model. Third, Tefre de Renzy-Martin et al. (2014) argued that human health risk assessments that have not accounted for the combined effects of phthalate exposure have potentially underestimated their true cumulative risks to the developing foetus.

The present study is the first investigation of the risk of cumulative phthalate exposure to pregnant Chinese women during early pregnancy. In addition, we estimated the associations between HIs and neonate sizes at birth.

2. Materials and methods

2.1. Study population and sample collection

Our participants were from the Ma'anshan-Anhui Birth Cohort (MABC) in China (05/2013–09/2014). Detailed procedures of pregnant women recruitment and of urine sampling are described elsewhere (Ge et al., 2016). The MABC consisted of 3474 eligible pregnant women. Of these women, 371 participants were excluded because of miscarriage ($n = 120$), stillbirth ($n = 10$), therapeutic abortion ($n = 30$), ectopic pregnancy ($n = 2$), multiple pregnancy ($n = 39$), unavailability of urine samples ($n = 162$) and unavailability of birth outcome data ($n = 8$). Ultimately, 3103 mother–infant pairs were enrolled in the present study. When participants accepted the first antenatal visit ($\leq$14 gestational weeks), they were asked to provide the first morning spot urine at the Ma'anshan Maternal and Child Health Center. All urine specimens were immediately frozen and transported on ice packs to the Anhui Provincial Key Laboratory of Population Health & Aristogenics (Hefei City, Anhui, China) within 3 h for analysis. All women provided informed consent. All protocols including recruitment, subsequent follow-up and the urinary analysis of phthalates were approved by the ethical committee of Anhui Medical University.

2.2. Questionnaire

On the first visit, women completed a questionnaire, providing data regarding demographic information (maternal age, pre-pregnancy weight, height, residence, occupation, and educational level), maternal characteristics (cigarette and alcohol assumption during pregnancy), monthly household income per capita, gestational weeks and seasons when urine samples were collected. Pre-pregnancy body mass index (BMI) was calculated as self-reported pre-pregnancy weight (kg) divided by height (m) squared. The gestational weeks were calculated using the last menstrual period data or that determined by ultrasound if menstruation was irregular (Carey et al., 2000). The sampling seasons were defined as follows: spring, March–May; summer, June–August; autumn, September–November; and winter, December–February (Riala et al., 2009).

2.3. Measures of birth outcomes

We obtained neonates' birth weight, length, gestational age, head and chest circumferences, and gender from medical records. The birth weight, body length, and head and chest circumferences were measured by trained midwives within 1 h after birth.

2.4. Phthalate metabolite analyses

Seven urinary phthalate metabolites, namely monomethyl phthalate (MMP), monoethyl phthalate (MEP), monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), MEHP, mono(2-ethyl-5-hydroxyl) phthalate (MEHHP) and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), were measured with solid phase extraction followed by high performance liquid chromatography–tandem mass spectrometry analysis. The phthalate metabolites in urine were measured according to a previous methodology with modifications (Wang et al., 2013). The detailed experimental procedure in the present study was described in our previous study (Gao et al., 2015). The recovery from urine spiked at three concentration levels (5, 50 and 200 ng/mL) was in the range of 88.8–108.9%. The inter- and intra-day precision for analysis were in the range of 0.19–8.75% and 1.16–9.85%, respectively, except for MBzP, in which the intra-day precision for the urine spiked at 5 ng/ml was at 17.5%. The metabolite concentration below limits of detection (LOD) was replaced by $LOD/\sqrt{2}$ for statistical analyses.

2.5. Daily intake estimation

We estimated the daily intake (DI) of phthalates using the following equation: