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Birth outcome measures and prenatal exposure to 4-tert-octylphenol☆

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ABSTRACT

Exposure to 4-tert-octylphenol (tOP) has been linked with adverse health outcomes in animals and humans, while epidemiological studies about associations between prenatal exposure to tOP and fetal growth are extremely limited. We measured urinary tOP concentrations in 1100 pregnant women before their delivery, and examined whether tOP levels were associated with birth outcomes, including weight, length, head circumference and ponderal index at birth. tOP could be detected in all samples, and the median uncorrected and creatinine-corrected tOP concentrations were 0.90 μg/L (range from 0.25 to 20.05 μg/L) and 1.33 μg/g creatinine (range from 0.15 to 42.49 μg/g creatinine), respectively. Maternal urinary log-transformed tOP concentrations were significantly negatively associated with adjusted birth weight [β (g) = −126; 95% confidence interval (CI): −197, −55], birth length [β (cm) = −0.53; 95% CI:−0.93, −0.14], and head circumference [β (cm) = −0.30; 95% CI: −0.54, −0.07], respectively. Additionally, considering sex difference, these significant negative associations were also found among male neonates, while only higher maternal tOP concentrations were associated with a significant decrease in birth weight among female neonates. This study suggested significant negative associations between maternal urinary tOP concentrations and neonatal sizes at birth, and they differed by neonatal sex. Further epidemiological studies are required to more fully elaborate the associations between prenatal tOP exposure and birth outcomes.

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1. Introduction

4-tert-octylphenol (tOP, one of isoforms of octylphenol) is known as intermediate material and main degradation product of octylphenol polyethoxylates, which are non-ionic surfactants extensively used as components of plastics, detergents, paints and pesticides (Ying et al. 2002). Considering that tOP is a significant environmental endocrine disrupting chemical (EDC) (White et al. 1994), it was included in the list of priority hazardous substances by European Commission (Commission Directive 2000/60/EC, 2000). However, it is still commonly used in Asian countries and widely dispersed in various environment compartments, such as wastewaters, river sediments, fish tissue and drinking water (Wang et al., 2005; Yang et al., 2014; Ying et al. 2002). Furthermore, tOP can be detected in several types of human biological samples, including urine, cord blood, plasma and breast milk (Chen et al. 2005, 2010; Tan and Ali, 2003).

Exposure to EDC may adversely affect growth, development and reproduction (Meeker, 2012). Several studies focusing on aquatic species and laboratory animals suggested that estrogenic activity of tOP had been associated with adverse health outcomes (Aydogan and Barlas, 2006; Bian et al. 2006; Segner et al. 2003), such as developmental and reproductive alterations in fish, avian, and mammalian cells (White et al. 1994). Recently, epidemiological studies found exposure to 4-t-OP, but not 4-n-octylphenol (4-n-OP), was associated with idiopathic male infertility in Chinese men

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(Chen et al., 2013; Qin et al., 2013). It was found that tOP could freely cross the placental barrier and rapid access to the fetus after exposure of pregnant rats (Haavisto et al. 2003; Hong et al. 2003). Prenatal exposure is especially of concern because the developing fetus is the most vulnerable to endocrine disruption during critical periods of early development. It was reported exposure to tOP during pregnancy might be related to anomalies of fetal development in animal studies, such as reducing body weight, inhibiting the periosteal bone formation, delaying the development (Hong and Zhang, 2010; Kamei et al. 2008; Kim et al. 2015), and arising dysfunctions in later life (Aydogan and Barlas, 2006; Barlas and Aydogan, 2009; Goktekin and Barlas, 2008). A recent epidemiological study by Jung et al. (2013) found exposure to tOP might be related to congenital hypothyroidism in infants.

Information on tOP exposure levels in population, especially in pregnant women, is important for evaluating the potential health risk on humans. It was found that urinary tOP was present 57% of 2517 participants ≥6 years of age in USA and the median concentration was 0.3 μg/L (0.3 μg/g creatinine), with concentrations ranging from 0.2 μg/L to 20.6 μg/L (Calafat et al., 2008). Recently, a study assessed phenols concentrations in 200 samples from Denmark pregnant women showed that the urinary tOP was undetectable in all samples due to high limit of detection (LOD, 0.87 μg/L) (Tefre et al. 2014). Until now, limited epidemiological studies have evaluated the degree of tOP exposure among pregnant women and the possible associations between prenatal tOP exposure and birth outcomes of neonates.

In spite of its demonstrated animal toxicity and the high potential for endocrine disruption effect on human body, the interpretation related to the low-dose effects of tOP on human health remains unclear. Therefore, in the present study, our aim was to investigate prenatal exposure to tOP in a cohort in an agricultural area of Jiangsu Province, China, and to examine its potential associations with birth outcomes.

2. Materials and methods

2.1. Study subjects

From June 2009 to January 2010, the participants recruited in the present study were healthy pregnant women who delivered their babies in a maternity hospital in Sheyang County, Jiangsu Province, China. The study protocol was approved by the Ethics Committees of School of Public Health, Fudan University, Shanghai, China, and written informed consent was obtained from each participant.

Detailed descriptions for the study were published in our previous report (Qi et al., 2012). Eligible subjects included the women who had their spot urinary tOP levels measured during pregnancy and recorded questionnaire information about sociodemographic characteristics. Additionally, we excluded multiple births (9), congenital anomalies (9), and stillbirths (1), as well as cases with an incomplete data for the requirements of the study (30). Finally, a total of 1100 mother-neonate pairs were included in the cohort.

2.2. Birth outcome measures

Information on birth outcomes, such as birth weight, length, head circumference, gestational age and neonatal sex, was retrieved from the medical records. The ponderal index (PI), known to be a good indicator of fetal nutrition and a measure of proportionality to reflect adiposity in infants, was calculated as the ratio of birth weight in grams to length in centimeters cubed.

2.3. Urinary tOP analysis

Maternal spot urine samples were collected on parturition day, and transferred to the high-density polypropylene centrifuge tubes (Corning Incorporated, USA). All samples were immediately stored at −20 °C, then shipped in a frozen state to the laboratory and kept frozen at −80 °C until analysis. These samples were measured for creatinine (Qi et al., 2012). The urinary tOP concentration was detected by large-volume-injection gas chromatography-tandem mass spectrometry (LVI-GC–MS/MS) (Lu et al. 2015). Briefly, the urine samples were prepared by hydrochloric acid (HCl) hydrolysis, liquid–liquid extraction (LLE), K_2CO_3-treated-silica-gel solid-phase extraction (SPE), and derivatization. Three quality control (QC) samples were included in each batch of the unknown samples and it was spiked in the pooled urine with a mixture of tOP standard. The LOD of tOP was 0.01 μg/L.

2.4. Statistical analysis

All statistical analyses were carried out using IBM SPSS Statistical software (19.0 version). The 0.05 level of probability was used as the criterion of significance. The tOP creatinine-corrected concentrations were used as variables to normalize for urine dilution. The sociodemographic characteristics of the study subjects were expressed as a number (%) or mean ± standard deviation (SD), with the geometric mean (GM) for the tOP creatinine-corrected concentrations. The associations between the maternal tOP levels and mother-infant couple characteristics were examined by Wilcoxon rank-sum test or Kruskal–Wallis rank sum test. Wilcoxon rank-sum test was used to examine the difference of tOP levels between the subjects with missing value and the others.

Generalized linear model (GLM) was performed to examine the associations between the tOP levels and birth weight, length, head circumference and PI. In order to determine an appropriate hierarchy of covariates, we identified the factors associated with fetal growth according to previous literature, and observed the change of regression coefficients for tOP exposure when factors were added to the crude model (Kramer, 1987; Philippat et al., 2012; Ugwa, 2015; Wolff et al., 2008). The final model included gestational duration (continuous), maternal age (continuous), prepregnancy body mass index (BMI, continuous), pregnancy weight gain (continuous), prenatal smoking [including active smoking (0.4%) and passive smoking] (yes or not), annual family income (<30,000 RMB or more), education level (<High school or greater), parity (0 or more), and neonatal sex (male or female). Furthermore, mode of delivery (cesarean section or eutocia) was included in models for head circumference (Philippat et al. 2012). To assess the linearity of the effects, associations with exposure represented as a continuous (log-transformed) variable, and quartiles of tOP creatinine-corrected concentrations were examined separately in statistical models. Recognizing that tOP is hormonally active, we explored the possibility that associations differed by neonatal sex by adding an interaction term (neonatal sex*log−tOP), and analyzed our models separately for different sex of neonates.

In sensitivity analyses, urinary uncorrected tOP concentrations in log-transformed were explored. Additionally, we reanalyzed our models controlling separately for three important prenatal exposures in this population: non-persistent phenolic compounds [using prenatal urinary concentrations, including bisphenol A (BPA), parabens (methyl paraben, ethyl paraben, propyl paraben, and butyl paraben), triclosan (TCS), and benzophenone-3 (BP-3)], pyrethroid pesticides (using prenatal urinary metabolites of pyrethroid pesticides), and heavy metals (using cord serum concentrations of lead and cadmium). Timing of urine collection may reflect differences in use of products that cause exposure to

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