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Maternal phthalate exposure during the first trimester and serum thyroid hormones in pregnant women and their newborns

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HIGHLIGHTS

- We assessed seven phthalate metabolites level of urine samples in pregnancy women.
- We measured thyroid hormone (TH) concentrations in maternal and cord serum.
- The study had a prospective design and large sample size.
- It is the largest study examing THs change on phthalates exposure in pregnancy.
- Phthalates exposure during the first trimester may disrupt maternal THs levels.

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ABSTRACT

Animal and human studies have suggested that phthalate alters thyroid hormone concentrations. This study investigated the associations between phthalate exposure during the first trimester and thyroid hormones in pregnant women and their newborns. Pregnant women were enrolled from the prospective Ma'anshan Birth Cohort study in China. A standard questionnaire was completed by the women at the first antenatal visit. Seven phthalate metabolites were measured in one-spot urine at enrolment (10.0 ± 2.1 gestational weeks), as were thyroid hormone levels in maternal and cord sera. Multivariable linear regression showed that 1-standard deviation (SD) increase in natural log (ln)-transformed mono(2-ethylhexyl) phthalate (MEHP) and mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) was associated with 0.163 μg/dL ($p = 0.001$) and 0.173 μg/dL ($p = 0.001$) decreases in maternal total thyroxine (TT_4). Both MEHP and MEHHP were negatively associated with maternal free thyroxine (FT_4; β: −0.013, $p < 0.001$ and β: −0.011, $p = 0.001$, respectively) and positively associated with maternal thyroid-stimulating hormone (β: 0.101, $p < 0.001$; β: 0.132, $p < 0.001$, respectively). An inverse association was observed between monobenzyl phthalate and maternal TT_4 and FT_4. A 1-SD increase in ln-transformed monoethyl phthalate was inversely associated with maternal TT_4 (β: −0.151, $p = 0.002$). By contrast, the concentrations of phthalate metabolites in urine were not associated with those of thyroid hormone in cord serum. Our analysis suggested that phthalate exposure during the first trimester disrupts maternal thyroid hormone levels.

1. Introduction

Phthalates are a group of synthetic chemicals, several million tonnes of which are reported to be consumed globally every year (Mankidy et al., 2013). Phthalates are mainly used as plasticisers to increase the flexibility of commercial products such as building materials, medical devices, and children's toys (Chou and Wright,

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2006; Schettler, 2006). They are also applied in cosmetics as a vehicle for fragrance (Chou and Wright, 2006; Schettler, 2006). Because phthalates are not covalently bound to a polyvinyl chloride polymer, they are easily released into the environment resulting in human exposure increasing (Hankett et al., 2014; Wormuth et al., 2006). General populations are mainly exposed to phthalates through inhalation, ingestion, dermal contact, and medical treatments (Chou and Wright, 2006; Rudel et al., 2003). Measurements in urine samples showed that people worldwide are widely exposed to phthalates including pregnant women (Arbuckle et al., 2014; Casas et al., 2011; Suzuki et al., 2009; Zeman et al., 2013; Zhu et al., 2016). Notably, several phthalates and their metabolites can cross the placenta barrier to reach the foetus, potentially affecting foetal growth and development in early life (Wittassek et al., 2009).

Considering the widespread use and ubiquitous exposure to phthalates, their adverse impact on human health including neurodevelopment and reproductive toxicity have aroused public concern (de Cock et al., 2016; Ejaredar et al., 2015; Hannon and Flaws, 2015). Ample evidence from animal and *in vitro* studies has revealed that the thyroid is vulnerable to the endocrine-disrupting effects of phthalates, which can selectively disrupt thyroid hormone (TH) signalling and affect the biosynthesis, biotransport, biotransformation, and metabolism of THs, resulting in a the disruption of thyroid homeostasis (Boas et al., 2012; Breous et al., 2005; Ishihara et al., 2003a, 2003b; Jugan et al., 2010; Liu et al., 2015; Zoeller, 2005). THs are involved in numerous physiological processes of growth regulation, metabolic promotion and energy homeostasis (Jugan et al., 2010). Even subtle changes in TH homeostasis may severely affect human health (Berbel et al., 2009; Hollowell et al., 1999). Hypothyroidism during pregnancy can cause adverse birth outcomes such as preterm birth and low birth weight, impair postnatal mental development, and even result in cretinism in infants (Engel et al., 2010; Nazarpour et al., 2015). Because the foetal thyroid is nonfunctional before 12 gestational weeks and entirely relies on the transplacental delivery of maternal THs (de Escobar et al., 2004), maternal TH levels play a major role in foetal development and growth, particularly during early life stages.

Several epidemiological studies have investigated the associations between phthalate exposure and TH levels in adults, adolescents, and children (Boas et al., 2010; Huang et al., 2007; Kuo et al., 2015; Meeker et al., 2007; Meeker and Ferguson, 2011). Although these studies have reported the associations of phthalates with one TH or more, the results are inconsistent. Moreover, few human health studies have reported the effects of phthalate exposure during pregnancy on maternal and neonatal thyroid function. In a cross-sectional study of Taiwanese women ($n = 76$) in the second trimester, Huang et al. (2007) reported that urinary concentrations of mono-n-butyl phthalate (MBP), the metabolite of dibutyl phthalate (DBP), were inversely associated with both total and free thyroxine (TT_4 and FT_4, respectively). Furthermore, in a prospective birth cohort study in Taiwan examining the associations of phthalate exposure during the third trimester with serum THs in women ($n = 148$) and their newborns, an inverse association between maternal mono-benzyl phthalate (MBzP) level and thyroid-stimulating hormone (TSH) in cord serum was observed. However, both studies analysed a small sample and did not measure the TH levels before complete functioning of the foetal thyroid axis.

Because of the crucial role in early pregnancy of THs on the foetus and the inconsistent results of studies concerning the relationship between phthalates and THs, we performed a large cohort study to examine the associations between prenatal phthalate exposure during the first trimester and TH levels in maternal and cord sera.

2. Methods

2.1. Study population

We enrolled participants from the Ma'anshan Birth Cohort (MABC) study conducted in the Maternal and Child Health (MCH) Center in Ma'anshan city, Anhui Province, China. In total, 3474 pregnant women were enrolled in this prospective study and provided informed consent. A standard questionnaire was completed for the eligible women to acquire information on social demographic characteristics, lifestyle (tobacco consumption, alcohol use) and a detailed medical history when they first visited the MCH center for antenatal care. Meanwhile, one-spot urine was collected at the first prenatal visit to measure phthalate metabolites, and maternal serum samples at enrolment and cord serum samples at delivery were collected to measure TH levels. The present study selected 2521 women from the pregnant women with single live birth neonate ($n = 3273$) after excluding 752 women because of a history of thyroid disease ($n = 67$); the unavailability of maternal urine ($n = 159$), serum ($n = 86$), or cord serum ($n = 440$).

Study protocols were approved by the Ethical Committee of Anhui Medical University. All participants provided written informed consent before study enrolment.

2.2. Measurement of phthalate metabolites in urine samples

The urinary samples of the pregnant women were provided at approximately 10 gestational weeks. To avoid the contamination of urine by external phthalates in the environment, maternal urine samples were collected in polypropylene tubes (Kuo et al., 2015) and stored at −80 °C until analysis. We collected urine samples from women in their first trimester for measuring seven phthalate metabolites: mono-methyl phthalate (MMP), mono-ethyl phthalate (MEP), MBP, MBzP, mono-(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP). Among these metabolites, five were phthalate monoesters (MMP, MEP, MBP, MBzP, and MEHP) of parent chemicals dimethyl phthalate, diethyl phthalate, DBP, butylbenzyl phthalate, and di(2-ethylhexyl) phthalate (DEHP), respectively, and two (MEHHP and MEOHP) were secondary metabolites of DEHP. The high-performance liquid chromatography (HPLC) electrospray ionisation-tandem mass spectrometry (MS/MS) method was used according to the procedure of Wang et al., 2013. In brief, maternal urine samples underwent enzymatic deconjugation, solid-phase extraction, separation through HPLC, and subsequent detection through MS. Calibration standards, field blanks, and quality control samples of low and high concentrations were included in every batch analysed to confirm the quality and reproducibility of the measurements. To consider urine dilution, urinary creatinine was determined using a creatinine assay kit (picric acid method, Jiancheng Bioengineering Institute, Nanjing, China) for analyzing the Jaffe reaction. Phthalate metabolites were expressed as μg/g creatinine after corrected by creatinine, and the value less than the limit of detection (LOD) was replaced with LOD/$\sqrt{2}$ for statistical analysis.

2.3. Measurement of serum thyroid profiles

Maternal serum specimens were collected from the women at their first antenatal visit, and umbilical cord samples were collected at delivery. Serum samples were aliquoted and stored at −80 °C until analysis. Serum TH profile, including TSH, TT_4, FT_4, and total triiodothyronine (TT_3) were quantified through electrochemiluminescence by using the Cobas e411 immunoassay analyser (Roche Diagnostics GmbH, Mannheim, Germany). Two levels of