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Maternal urinary phthalate metabolites during pregnancy and thyroid hormone concentrations in maternal and cord sera: The HOME Study

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ABSTRACT

Background: Phthalates, endocrine-disrupting chemicals that are commonly found in consumer products, may adversely affect thyroid hormones, but findings from prior epidemiologic studies are inconsistent.

Objectives: In a prospective cohort study, we investigated whether maternal urinary phthalate metabolite concentrations and phthalate mixtures measured during pregnancy were associated with thyroid hormones among pregnant women and newborns.

Methods: We measured nine phthalate metabolites [monoethyl phthalate (MEP), mono-*n*-butyl phthalate, mono-isobutyl phthalate, monobenzyl phthalate (MBzP), and four monoesthers of di(2-ethylhexyl) phthalate] in urine collected at approximately 16 and 26 weeks' gestation among women in the Health Outcomes and Measures of the Environment Study (2003–2006, Cincinnati, Ohio). Thyroid stimulating hormone (TSH) and free and total thyroxine and triiodothyronine were measured in maternal serum at 16 weeks' gestation (n = 202) and cord serum at delivery (n = 276). We used multivariable linear regression to assess associations between individual urinary phthalate metabolites and concentrations of maternal or cord serum thyroid hormones. We used weighted quantile sum regression (WQS) to create a phthalate index describing combined concentrations of phthalate metabolites and to investigate associations of the phthalate index with individual thyroid hormones.

Results: With each 10-fold increase in 16-week maternal urinary MEP, maternal serum total thyroxine (TT_4) decreased by 0.52 μg/dL (95% CI: −1.01, −0.03). For each 10-fold increase in average (16- and 26-week) maternal urinary MBzP, cord serum TSH decreased by 19% (95% CI: −33.1, −1.9). Among mothers, the phthalate index was inversely associated with maternal serum TT_4 (WQS beta = −0.60; 95% CI: −1.01, −0.18). Among newborns, the phthalate index was inversely associated with both cord serum TSH (WQS beta = −0.11; 95% CI: −0.20, −0.03) and TT_4 (WQS beta = −0.53; 95% CI: −0.90, −0.16).

Conclusion: Our results suggest that co-exposure to multiple phthalates was inversely associated with certain thyroid hormones (TT_4 in pregnant women and newborns, and TSH in newborns) in this birth cohort. These findings highlight the need to study chemical mixtures in environmental epidemiology.

Abbreviations: BPA, bisphenol A; CCHMC, Cincinnati Children's Hospital Medical Center; CDC, The Centers for Disease Control and Prevention; CV, coefficient of variation; ΣDEHP, molar sum of urinary monoesther di(2-ethylhexyl) phthalate metabolites; EMM, effect measure modification; FT_3, free triiodothyronine; FT_4, free thyroxine; HOME, Health Outcomes and Measures of the Environment; HPT, hypothalamic-pituitary-thyroid; IQR, interquartile range; LOD, limit of detection; MBzP, monobenzyl phthalate; MCPP, mono-3-carboxylpropyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-*n*-butyl phthalate; TSH, thyroid stimulating; TT_3, total triiodothyronine; TT_4, total thyroxine; PCBs, polychlorinated biphenyls; PBDEs, polybrominated diphenyl ethers; QC, quality control; QCL, low-concentration quality control; WQS, Weighted quantile sum

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1. Introduction

Phthalates are synthetic chemicals frequently used as plasticizers in polyvinyl chloride, fragrance retainers in personal care products, and excipients in pharmaceuticals and dietary supplements (Braun et al., 2014; Hauser and Calafat, 2005; Kelley et al., 2012; Koo and Lee, 2004). Phthalate exposure is common among the general population, including pregnant women, because phthalate diesters, which are metabolized to phthalate monoesters and other secondary metabolites in the human body, have many uses in consumer products (Braun et al., 2014; Braun et al., 2012; Koo and Lee, 2004; Philippat et al., 2012; Silva et al., 2004). Experimental evidence suggests that maternal-fetal transfer of phthalates occurs during gestation (Singh et al., 1975), and animal and *in vitro* studies suggest that phthalate exposure may adversely influence thyroid hormone levels and thyroid homeostasis (Breous et al., 2005; Ghisari and Bonefeld-Jorgensen, 2009; O'Connor et al., 2002; Shimada and Yamauchi, 2004). Collectively, the epidemiologic literature suggests that phthalates may adversely affect thyroid hormones among adolescents and adults (Meeker and Ferguson, 2011), pregnant women (Huang et al., 2007; Huang et al., 2016; Johns et al., 2016; Johns et al., 2015b; Kuo et al., 2015), and newborns or children (Kuo et al., 2015; Morgenstern et al., 2017; Weng et al., 2017; Yao et al., 2016). However, the direction and magnitude of these associations, as well as the implicated phthalates, have been inconsistent across studies.

The short half-lives of phthalates in the human body (Fisher et al., 2015) create challenges for exposure assessment and the investigation of health effects related to phthalate exposures (Johns et al., 2015a). Most prior studies among pregnant women have relied on a single spot urine sample to measure urinary phthalate metabolites which were collected at varying points during pregnancy to quantify phthalate exposure (Huang et al., 2007; Huang et al., 2016; Kuo et al., 2015; Yao et al., 2016). Relatively little prior research has explored the potential influence of phthalates on newborn thyroid hormones, though other endocrine-disrupting chemicals have been associated with changes in newborn thyroid hormones (Chevrier et al., 2007; Chevrier et al., 2013; Kuo et al., 2015; Romano et al., 2015). Moreover, no prior studies have examined the impact of phthalate mixtures on thyroid hormones, to our knowledge; this is of particular importance given that pregnant women are exposed to several phthalates simultaneously, and individual phthalates may share a common mechanism of action (Braun et al., 2016). Because maternal thyroid insufficiency during pregnancy may have adverse consequences for fetal neurodevelopment and physical growth (Ajmani et al., 2014; Gilbert et al., 2012; Medici et al., 2013; Saki et al., 2014; Shields et al., 2011), preventing exposure to thyrotoxic chemicals during pregnancy and gestation is of public health importance.

To address this knowledge gap, we sought to determine if maternal urinary phthalate metabolite concentrations or phthalate metabolite mixtures during pregnancy were associated with thyroid hormones in women during pregnancy or their newborns.

2. Materials and methods

2.1. Study participants

The Health Outcomes and Measures of the Environment (HOME) Study is a prospective pregnancy and birth cohort based in the greater Cincinnati, Ohio metropolitan area and designed to evaluate the influence of common environmental chemical exposures on children's health (Braun et al., 2017). Women were eligible to participate if at baseline they were pregnant (16 ± 3 weeks gestation), ≥18 years old, English speakers, living in a home built before 1978, intending to continue prenatal care and deliver at a HOME Study-affiliated obstetric practice, and had no history of HIV infection. Women were not eligible to participate if they were taking medication for seizure or thyroid disorders. Women were enrolled in the study between March 2003 and January 2006. Of 1263 eligible women, 468 (37%) were enrolled; 389 (83%) enrolled women were followed through live birth of a singleton infant. The Institutional Review Boards of Cincinnati Children's Hospital Medical Center (CCHMC), and all delivery hospitals approved the study protocol. The Centers for Disease Control and Prevention (CDC) deferred to CCHMC IRB as the IRB of record since the role of CDC was primarily technical oversight of the phthalate assays. All mothers provided written informed consent before enrollment in the study.

2.2. Phthalate metabolites in maternal urine

Mothers provided two spot urine samples at approximately 16 (range: 10–23) and 26 (range: 19–35) weeks' gestation. Urine was collected into polypropylene specimen cups, refrigerated until processing, and stored at ≤ −20 °C. After thawing, nine phthalate monoesther metabolites [monoethyl phthalate (MEP), mono-*n*-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono-3-carboxylpropyl phthalate (MCPP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)], reflecting exposure to at least six parent phthalates, including diethyl phthalate, di-*n*-butyl phthalate, di-isobutyl phthalate, benzylbutyl phthalate, di-*n*-octylphthalate, and di(2-ethylhexyl) phthalate (DEHP), were measured in maternal urine at the CDC Environmental Health Laboratories, using previously described methods (Silva et al., 2007). The limits of detection (LOD) ranged from 0.2–1.2 ng/mL; concentrations below the LOD were given a value of LOD/√2 (Hornung and Reed, 1990). Two low and two high concentration quality control (QC) samples were analyzed in each analytic run. Depending on the analyte, the coefficients of variation (CVs) generally ranged from 4.4–9.0% for the low-concentration QC (QCL) samples, and 3.1–7.9% for the high-concentration QC samples in a period of 15 months. For MBzP, the CV for the QCL was 16% and for MCPP, both CVs were ~18.5% for the same time period. Urinary creatinine concentrations were measured using enzymatic methods. Phthalate metabolite concentrations were creatinine-standardized to account for urine dilution and $\log_{10}$-transformed to decrease the influence of extreme values on effect estimates. We also calculated the average of the $\log_{10}$-transformed creatinine-standardized values from the 16- and 26-week samples. We created a molar sum of metabolites of DEHP (ΣDEHP) standardized to the molecular weight of MECPP, incorporating the four measured DEHP metabolites [MEHP, MEHHP, MEOHP, and MECPP] by dividing the urinary concentration of each metabolite by its molecular weight, summing the metabolite concentrations, and multiplying by the molecular weight of MECPP (308 g/mol). For the maternal analysis, only urinary phthalate metabolites collected at 16 weeks were considered, because the 26 week urine was collected later in pregnancy than the maternal assessment of thyroid hormones. For the newborn analyses, average maternal urinary phthalates were used to better represent exposure over the course of gestation.

2.3. Serum thyroid hormone concentrations

Maternal blood was collected at approximately 16 weeks' gestation, and venous cord blood was collected at delivery. Serum was separated from clotted blood for both maternal and cord blood samples and stored at −80 °C until analysis for thyroid stimulating hormone (TSH), total and free thyroxine (TT_4 and FT_4) and triiodothyronine (TT_3 and FT_3) at the Department of Laboratory Medicine at the University of Washington clinical chemistry laboratories using an Access2 automated clinical immunoassay analyzer (Beckman Coulter Inc., Fullerton, CA). The CV for the thyroid hormone assays ranged from < 1.0% to 10%.

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