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Associations between maternal phenol and paraben urinary biomarkers and maternal hormones during pregnancy: A repeated measures study

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ABSTRACT

Background: A number of phenols and parabens are added to consumer products for a variety of functions, and have been found at detectable levels in the majority of the U.S. population. Among other functions, thyroid hormones are essential in fetal neurodevelopment, and could be impacted by the endocrine disrupting effects of phenols and parabens. The present study investigated the association between ten maternal urinary phenol and paraben biomarkers (bisphenol S, triclosan, triclocarban, benzophenone-3, 2,4-dichlorophenol, 2,5-dichlorophenol, and ethyl, butyl, methyl and propyl paraben) and four plasma thyroid hormones in 439 pregnant women in a case–control sample nested within a cohort study based in Boston, MA. Methods: Urine and blood samples were collected from up to four visits during pregnancy (median weeks of gestation at each visit: Visit 1: 9.64, Visit 2: 17.9, Visit 3: 26.0, Visit 4: 35.1). Linear mixed models were constructed to take into account the repeated measures jointly, followed by multivariate linear regression models stratified by gestational age to explore potential windows of susceptibility. Results: We observed decreased total triiodothyronine (T3) in relation to an IQR increase in benzophenone-3 (percent change [%Δ] = −2.07; 95% confidence interval [CI] = −4.16, 0.01), butyl paraben (%Δ = −2.76; 95% CI = −5.25, −0.26) and triclosan (%Δ = −2.53; 95% CI = −4.75, −0.30), and triclocarban at levels above the LOD (%Δ = −5.71; 95% CI = −10.45, −0.97). A 2.41% increase in T3 was associated with an IQR increase in methyl paraben (95% CI = 0.58, 4.24). We also detected a negative association between free thyroxine (FT4) and propyl paraben (%Δ = −3.14; 95% CI = −6.12, −0.06), and a suggestive positive association between total thyroxine (T4) and methyl paraben (%Δ = 1.19; 95% CI = −0.10, 2.47). Gestational age-specific multivariate regression analyses showed that the magnitude and direction of some of the observed associations were dependent on the timing of exposure. Conclusion: Certain phenols and parabens were associated with altered thyroid hormone levels during pregnancy, and the timing of exposure influenced the association between phenol and paraben, and hormone concentrations. These changes may contribute to downstream maternal and fetal health outcomes. Additional research is required to replicate the associations, and determine the potential biological mechanisms underlying the observed associations.

1. Introduction

There are thousands of chemicals found in personal care products (PCP) and household items to which humans could potentially be exposed (Egeghy et al., 2012; Guo and Kannan, 2013). Usage of PCPs continues during pregnancy, and this may have unique effects on the mother and/or her developing fetus (Braun et al., 2014; Lang et al., 2016).

Phenols and parabens are among the chemicals used in PCPs, and are regularly found at detectable levels in the U.S. population (Centers for Disease Control and Prevention, 2017). Phenols regularly detected in exposure biomonitoring studies include triclosan (TCS), triclocarban (TCB), benzophenone-3 (BP-3), bisphenol-A (BPA), bisphenol-S (BPS), 2,4-dichlorophenol (2,4-DCP) and 2,5-dichlorophenol (2,5-DCP). Parabens, TCS and TCB are used in PCPs such as soaps and makeup for their anti-microbial properties (Centers for Disease Control and

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Prevention, 2017). The phenol BP-3 is a UV-filter, and is used in sunscreen, cosmetics and some plastic products (Centers for Disease Control and Prevention, 2017). BPS is a common alternative to BPA, and is found in foods, plastics and paper products (Rochester and Bolden, 2015). 2,4-DCP and 2,5-DCP are biomarkers of a compound used in mothballs and room deodorizers; 2,4-DCP is also a metabolite of a herbicide used as a weed killer (Centers for Disease Control and Prevention, 2017).

Although results have been conflicting, in vitro, animal and human studies have linked a range of phenols and parabens with changes in thyroid hormones (Andrianou et al., 2016; Guignard et al., 2017; Kim et al., 2017; Koeppe et al., 2013; Lee et al., 2017; Wang et al., 2017a; Wang et al., 2017b; Zhang et al., 2017). Studies have also linked these exposures to a series of adverse health effects that could potentially be mediated through the thyroid hormone system, including changes in pubertal development (Wolff et al., 2015), adverse birth outcomes (Philippat et al., 2012; Tang et al., 2013), male infertility (Den Hond et al., 2015), diminished female fecundity (Vélez et al., 2015), increases in oxidative stress (Watkins et al., 2015), and childhood adiposity (Buckley et al., 2016), among other health effects.

Thyroid hormones, triiodothyronin (T3) and thyroxine (T4), are produced in the thyroid gland, and their levels are negatively controlled by thyroid stimulating hormone (TSH) from the pituitary gland via the hypothalamic–pituitary-thyroid axis (Tingi et al., 2016). The fetal thyroid only begins to produce hormones at 10–12 weeks gestation, and is completely dependent on maternal thyroid hormones for neurodevelopment in its first weeks of life, particularly T4 (Mastorakos et al., 2007; Williams, 2008; Zoeller et al., 2002). Additionally, thyroid hormones (maternal and fetal) are essential to the development of fetal tissues, and fetal growth promotion (Forhead and Fowden, 2014). Given this, and the complexity in the hypothalamic–pituitary–thyroid axis, even slight alterations in thyroid hormones could lead to adverse effects in the child (Alemu et al., 2016; Mead, 2004). In fact, subclinical maternal thyroid dysfunction has been associated with low birth weight, low Apgar scores, and neurological disabilities (Braun, 2017; Chen et al., 2014; Saki et al., 2014). It is, therefore, important to understand the effects of in-utero exposure to chemicals such as phenols and parabens on maternal thyroid hormones.

Our group recently reported associations between phenols and parabens and maternal thyroid hormones in pregnancy in a small prospective cohort study in Puerto Rico (Aker et al., 2016). The present study aimed to test these relationships in a larger study of pregnant women recruited in Boston, USA. We published a study on the effects of BPA on thyroid hormones in this same cohort since BPA was initially the only phenol measured in our samples (Aung et al., 2017); the analytical method was recently expanded to include additional phenols and parabens, which are the focus of this study.

2. Methods

2.1. Study population

The study population includes pregnant women who were participants in a case–control study nested within the longitudinal birth cohort study in Boston, MA, Lifecodes (Ferguson et al., 2014, 2015). Lifecodes enrolled 1600 women from 2006 to 2008, of whom 1181 were followed until delivery to live singletons. Women ages ≥18 years old were recruited early in pregnancy (< 15 weeks of gestation) between 2006 and 2008 and were eligible for participation if they were carrying a singleton, non-anomalous fetus and planned to deliver at Brigham and Women's Hospital. Additional information regarding recruitment and eligibility criteria are described in detail elsewhere (Ferguson et al., 2014; McElrath et al., 2012). Women were followed through the duration of their pregnancy and relevant health information as well as urine and blood samples were collected at initial study visit (Visit 1: median 9.64 weeks of gestation [range = 5.43–19.1 weeks]) as well as three subsequent visits: Visit 2 (median = 17.9 weeks of gestation [range = 14.9–32.1 weeks]), Visit 3 (median = 26.0 weeks of gestation [range = 22.9–36.3 weeks]), and Visit 4 (median = 35.1 weeks of gestation [range = 33.1–38.3]). The study protocols were approved by the ethics and research committees of the participating institutions, and all study participants provided written informed consent.

From the parent birth cohort, 130 women who delivered preterm (< 37 weeks gestation) and 352 randomly selected women who delivered after a full term pregnancy (≥37 week gestation) were included in the case–control study. From these, we excluded participants who had pre-existing thyroid conditions such as thyroid cancer, Graves' disease, and hyper- or hypothyroidism (N = 41), and excluded those who did not provide any blood samples at any visit (N = 2). Our final study population (N = 439) included 116 preterm birth cases and 323 controls.

2.2. Phenol and paraben measurement

Spot urine samples were collected at each of the four visits. After collection, spot urine samples were divided into aliquots and frozen at −80 °C until they were shipped overnight. The samples were analyzed at NSF International (Ann Arbor, MI) for six phenols (2,4-DCP, 2,5-DCP, BP-3, BPS, TCS, and TCB) and four parabens (ethyl- (EPB), methyl- (MPB), butyl- (BPB), and propyl- (PPB) paraben) using isotope dilution-liquid chromatography–tandem mass spectrometry (ID-LC-MS/MS). The analytical method was a modification of a method developed by the Centers for Disease Control and Prevention (CDC), as described previously (Lewis et al., 2013; Ye et al., 2005, 2006). Samples below the limit of detection (LOD) were assigned a value of LOD/√2 (Hornung and Reed, 1990). Urinary specific gravity (SG) was used to account for urinary dilution, and was measured using a digital handheld refractometer (AtagoCo., Ltd., Tokyo, Japan). For descriptive, univariate data analysis, phenol and paraben concentrations were corrected for SG as follows: $Pc = M\ [(SGm - 1) / (SGi - 1)]$, where Pc is the SG-corrected exposure concentration (ng/mL), M is the measured exposure concentration, SGm is the study population median urinary specific gravity (1.0196), and SGi is the individual's urinary specific gravity. For bivariate and multivariate analysis, urinary specific gravity was included as a covariate in all models.

To minimize measurement error from the variability in urine dilution, we applied the method developed by O'Brien et al., 2016. In brief, we ran a linear mixed model (LMM) regressing SG on maternal age, extracted the predicted values of SG from that regression, calculated the ratio of SG and the predicted SG, and used this ratio to standardize the phenol and paraben measurements.

2.3. Thyroid hormone measurement

Blood samples were collected at each of the four visits. The samples were frozen at −80 °C until shipped overnight on dry ice to the analytical laboratory. Blood plasma was analyzed for free thyroxine (FT4), total thyroxine (T4), total triiodothyronine (T3), and thyroid stimulating hormone (TSH) at the Clinical Ligand Assay Service Satellite (CLASS) lab at the University of Michigan (Ann Arbor, MI). TSH, T3 and T4 were measured using an automated chemiluminescence immunoassay (Bayer ADVIA Centaur, Siemens Health Care Diagnostics, Inc.), and FT4 was measured using direct equilibrium dialysis followed by radioimmunoassay (IVD Technologies). Thyroid hormones were highly detected in the study population (Johns et al., 2017). TSH samples below the LOD (N = 5) were assigned a level at the LOD level (0.01 μIU/mL). Given that the LOD for FT4 is not biologically feasible, samples < LOD for FT4 were regarded as missing values in our statistical analyses. The inter-assay coefficients of variation (CV) for all hormones ranged from 2.3% (for T3) to 10.4% (for FT4). The intra-assay CVs ranged from 1.2% (for T3) to 12.3% (for FT4). Volume limitations in some of the samples resulted in differences in the number of samples.