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Phenols and parabens in relation to reproductive and thyroid hormones in pregnant women

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ABSTRACT

Introduction: Phenols and parabens are ubiquitous environmental contaminants. Evidence from animal studies and limited human data suggest they may be endocrine disruptors. In the current study, we examined associations of phenols and parabens with reproductive and thyroid hormones in 106 pregnant women recruited for the prospective cohort, "Puerto Rico Testsite for Exploring Contamination Threats (PROTECT)".

Methods: Urinary exposure biomarkers (bisphenol A, triclosan, benzophenone-3, 2,4-dichlorophenol, 2,5-dichlorophenol, butyl, methyl and propyl paraben) and serum hormone levels (estradiol, progesterone, sex hormone-binding globulin (SHBG), free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone) were measured at up to two time points during pregnancy (16–20 weeks and 24–28 weeks). We used linear mixed models to assess relationships between exposure biomarkers and hormone levels across pregnancy, controlling for urinary specific gravity, maternal age, BMI and education. In sensitivity analyses, we evaluated cross-sectional relationships between exposure and hormone levels stratified by study visit using linear regression.

Results: An IQR increase in methyl paraben was associated with a 7.70% increase (95% CI 1.50, 13.90) in SHBG. Furthermore, an IQR increase in butyl paraben as associated with an 8.46% decrease (95% CI 16.92, 0.00) in estradiol, as well as a 9.34% decrease (95% CI −18.31, −0.38) in estradiol/progesterone. Conversely, an IQR increase in butyl paraben was associated with a 5.64% increase (95% CI 1.26, 10.02) in FT4. Progesterone was consistently negatively associated with phenols, but none reached statistical significance. After stratification, methyl and propyl paraben were suggestively negatively associated with estradiol at the first time point (16–20 weeks), and suggestively positively associated with estradiol at the second time point (24–28 weeks).

Conclusions: Within this ongoing birth cohort, certain phenols and parabens were associated with altered reproductive and thyroid hormone levels during pregnancy. These changes may contribute to adverse health effects in mothers or their offspring, but additional research is required.

1. Introduction

Phenols and parabens are endocrine disrupting compounds (EDCs) widely used in various consumer products, such as personal care products and plastics. Reports from the National Health and Nutrition Examination Survey (NHANES) show that the majority of the U.S. population have detectable levels of a range of phenols and parabens in their bodies (Centers for Disease Control and Prevention, 2015).

Bisphenol A (BPA) is a high volume chemical used in the manufacture of polycarbonate plastics and epoxy resins in many consumer products. BPA has also been shown to have weakly

Abbreviations: 2,4-DCP, 2,4-dichlorophenol; 2,5-DCP, 2,5-dichlorophenol; BP-3, benzophenone-3; BPA, bisphenol A; BPB, butyl paraben; EDCs, endocrine disrupting compounds; E/P, ratio of estradiol to progesterone; ER, estrogen receptor; Ft4, free thyroxine; FT3, free triiodothyronine; GM, geometric mean; GSD, geometric standard deviation; IQR, interquartile range; LOD, limit of detection; MPB, methyl paraben; NHANES, National Health and Nutrition Examination Survey (NHANES); PPB, propyl paraben; PROTECT, Puerto Rico Testsite for Exploring Contamination Threats; SHBG, sex hormone-binding globulin; SG, specific gravity; TCS, triclosan; TSH, thyroid stimulating hormone

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estrogenic properties (Centers for Disease Control and Prevention, 2015), and has been associated with changes in thyroid and reproductive hormone levels in animals (Peretz et al., 2014), elevated risks of low birth weight, smaller size for gestational age, preterm birth, as well as increases in the levels of leptin and adiponectin among male neonates (Cantonwine et al., 2015; Chou et al., 2011; Huo et al., 2015; Miao et al., 2011).

Benzophenone-3 (BP-3) is a UV-filter used in cosmetics and sunscreens and some plastics (Centers for Disease Control and Prevention, 2015; Krause et al., 2012). Endocrine disruptive properties of BP-3 have been shown in a variety of animals and populations. For example, BP-3 was associated with a decrease in percent fat mass in children after prenatal exposure (Buckley et al., 2016), thyroid receptor agonistic effects in vitro assays (Schmutzler et al., 2007), altered transcription of hormonal receptors in invertebrates (Ozáez et al., 2016), and a decrease in spermatozoa among male fish (Chen et al., 2016). While few studies have assessed the impact of BP-3 exposure specific to reproductive health, it is suggested to be weakly estrogenic and antiandrogenic.

Triclosan (TCS) is an antibacterial and antifungal ingredient added to many consumer products to reduce bacterial contamination. It can be found in personal care products such as, soaps, toothpaste, and deodorants, as well as, toys and kitchenware (Dann and Hontela, 2011). Its chemical structure is similar to that of anthropogenic estrogens, and evidence suggests TCS disrupts hormone metabolism, displaces hormones from receptors and disrupts steroidogenic enzyme activity (Wang and Tian, 2015). There is also evidence from animal and in vitro studies of changes in reproductive hormone levels caused by TCS, albeit the evidence from the studies has varied (Wang and Tian, 2015).

2,4-dichlorophenol (2,4-DCP) is a metabolite of the widely used herbicide 2,4-dichlorophenoxyacetic acid, and 2,5-dichlorophenol (2,5-DCP) is a metabolite of 1,4-dichlorobenzene, a compound used in mothballs and room deodorizers (Centers for Disease Control and Prevention, 2015). 2,4-DCP and 2,5-DCP exposure in-utero has been linked to decreased birthweight in humans (Philippat et al., 2012). 2,5-DCP was also associated with earlier breast development in young girls (Wolff et al., 2015), and greater percent fat mass in children (Buckley et al., 2016), and was theorized to be a thyroid agonist (Wolff et al., 2015).

Due to their antimicrobial properties, parabens are found in personal care products, pharmaceuticals, and food products (Błędzka et al., 2014). While parabens have low binding affinity to estrogen receptors, they have been documented to have full agonist properties, particularly with longer exposure durations (Darbre and Harvey, 2008). In animal and human studies, methyl paraben (MPB) and butyl paraben (BPB) have been linked to various adverse health effects, including increased birthweight (Philippat et al., 2014), decreased odds of live births (Dodge et al., 2015), increases in dam uterine weights (indicating estrogenic effects) (Taxvig et al., 2008), and changes in various reproductive hormone levels (Taxvig et al., 2008; Zhang et al., 2014).

To our best knowledge, there have been no reports of repeated measure studies aimed to explore the effects of phenols and parabens on reproductive and thyroid hormones during pregnancy. The Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) Program is an ongoing prospective birth cohort in Northern Puerto Rico that was initiated in order to explore the impact of environmental contaminants, including phenols, parabens, and other EDCs, on reproductive health. We previously observed higher urinary concentrations of TCS, BP-3, 2,4-DCP and 2,5-DCP, and similar concentrations of BPA, 2,4-DCP and parabens in the PROTECT cohort compared to U. S. women of reproductive age (Meeker et al., 2013); therefore, this cohort provides an opportunity to study relationships between phenol and paraben exposure and hormone levels during pregnancy. In the present study, we assessed associations among a range of phenols and parabens, and reproductive and thyroid hormones within a sample of the PROTECT cohort.

2. Methods

2.1. Study participants

The present study included participants from an ongoing prospective cohort of pregnant women in Puerto Rico, and was designed to explore associations between environmental contaminants and adverse birth outcomes. Details on the recruitment and inclusion criteria have been described previously (Cantonwine et al., 2014; Meeker et al., 2013). In brief, the study participants included in the present analysis were recruited from 2010 to 2012 at 14 ± 2 weeks gestation from two hospitals and five affiliated prenatal clinics in Northern Puerto Rico, and were aged 18–40 years. Women who lived outside the region, had multiple gestations, used oral contraceptives within three months prior to getting pregnant, got pregnant using in vitro fertilization, or had known medical health conditions (diabetes, hypertension, etc.) were excluded from the study. Demographic information was collected via questionnaires at the initial study visit. Spot urine samples and blood samples were collected at three separate study visits (Visit 1: 16–20; Visit 2: 20–24; Visit 3: 24–28 gestation weeks), and blood samples were collected during the first and third visits. The timing of the visits were aimed to coincide with periods of rapid fetal growth and routine clinical visits.

This preliminary analysis includes the first 106 women recruited into the study for whom both total phenol/paraben concentrations and hormone measurements from at least one study visit were available. This study was approved by the research and ethics committees of the University of Michigan School of Public Health, University of Puerto Rico, Northeastern University, and participating hospitals and clinics. All study participants provided full informed consent prior to participation.

2.2. Urinary phenol and paraben measurement

After collection, spot urine samples were divided into aliquots and frozen at -80 °C until they were shipped overnight to the CDC for phenol and paraben analysis. Urine samples were analyzed for five phenols (BPA, TCS, BP-3, 2,4-DCP, and 2,5-DCP) and three parabens (BPB, MBP and propyl paraben (PPB)) using online solid phase extraction-high-performance liquid chromatography-isotope dilution tandem mass spectrometry (Watkins et al., 2015; Ye et al., 2006, 2005). Concentrations below the limit of detection (LOD) were assigned a value of the LOD divided by $\sqrt{2}$. Urinary specific gravity (SG) was used to account for urinary dilution, and was measured using a digital handheld refractometer (AtagoCo., Ltd., Tokyo, Japan). Exposure biomarkers were corrected for SG using the following formula:

$$P_c = M\left[\left(SG_m - 1\right)/\left(SG_i - 1\right)\right] \quad (1)$$

Equation 1: Specific gravity correction of exposure biomarker.

where P_c is the SG-corrected exposure concentration (ng/mL), M is the measured exposure concentration, SG_m is the study population median urinary specific gravity (1.0196), and SG_i is the individual's urinary specific gravity.

2.3. Reproductive hormone measurement

Estradiol, progesterone, and sex hormone-binding globulin (SHBG) were measured in serum samples using a