Environmental Research 165 (2018) 379–386

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Associations of maternal exposure to triclosan, parabens, and other phenols with prenatal maternal and neonatal thyroid hormone levels

Kimberly Berger[a], Robert B. Gunier[a], Jonathan Chevrier[a], Antonia M. Calafat[b], Xiaoyun Ye[b], Brenda Eskenazi[a], Kim G. Harley[a,*]

[a] Center for Environmental Research and Children's Health (CERCH), School of Public Health, University of California, Berkeley, 1995 University Avenue, Berkeley, CA 94704, USA

[b] Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, 4770 Buford Hwy, Atlanta, GA 30341, USA

ARTICLE INFO

Keywords:
Triclosan
Parabens
Phenols
Thyroid hormone
in utero exposure

ABSTRACT

Environmental phenols and parabens are commonly used in personal care products and other consumer products and human exposure to these chemicals is widespread. Although human and animal studies suggest an association between exposure to phenols and parabens and thyroid hormone levels, few studies have investigated the association of *in utero* exposure to these chemicals and thyroid hormones in pregnant women and their neonates. We measured four environmental phenols (triclosan, benzophenone-3, and 2,4- and 2,5-dichlorophenol), and three parabens (methyl-, propyl-, and butyl paraben) in urine collected from mothers at two time points during pregnancy as part of the CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) study. We measured free thyroxine (T4), total T4, and thyroid-stimulating hormone (TSH) in serum of the pregnant women (N = 454) and TSH in their neonates (N = 365). We examined potential confounding by a large number of additional chemical exposures and used Bayesian Model Averaging (BMA) to select the most influential chemicals to include in regression models. We observed negative associations of prenatal urinary concentrations of propyl paraben and maternal TSH (β for two-fold increase = −3.26%, 95% CI: −5.55, −0.90) and negative associations of 2,4-dichlorophenol and maternal free T4 (β for two-fold increase = −0.05, 95% CI: −0.08, −0.02), after controlling for other chemical exposures. We observed negative associations of triclosan with maternal total T4 after controlling for demographic variables, but this association became non-significant after controlling for other chemicals (β for two-fold increase = −0.05, 95% CI: −0.11, 0.00). We found evidence that environmental phenols and parabens are associated with lower TSH and free T4 in pregnant women after controlling for related chemical exposures.

1. Introduction

Environmental phenols and parabens, chemicals commonly used in personal care products and other consumer items, have shown endocrine disrupting properties and may impact thyroid hormone regulation and homeostasis (Boberg et al., 2010; Witorsch and Thomas, 2010). Thyroid hormone balance is essential during pregnancy for fetal neurodevelopment (Ghassabian et al., 2014; Haddow et al., 1999; Julvez et al., 2013). Low levels of thyroxine (T4), especially in early pregnancy, can lead to neurological disabilities and underdevelopment of the cortex (De Escobar et al., 2004). Thyroid hormones work in a feedback loop, with low blood levels of triiodothyronine (T3) and T4 leading to increased release of thyroid-stimulating hormone (TSH) (Dietrich et al., 2012).

Particular attention has been paid to the potential thyroid-hormone disrupting properties of triclosan, a chemical used as an antibacterial agent in certain toothpastes, personal care products, and antimicrobial fabrics (Dann and Hontela, 2011). Triclosan was also widely used in antibacterial hand soaps until it was banned by the FDA in 2016 (United States Food and Drug Administration, 2013). Triclosan is structurally similar to T3 and T4 and has been shown to decrease T4 in rodent studies (Crofton et al., 2007; Paul et al., 2012, 2010; Rodriguez and Sanchez, 2010; Zorrilla et al., 2009), although studies in humans have been less consistent (Aker et al., 2018, 2016; Allmyr et al., 2009; Braun et al., 2017; Cullinan et al., 2012; Geens et al., 2015; Koeppe et al., 2013; Ley et al., 2017; Wang et al., 2017)

Benzophenone-3, a chemical that absorbs ultraviolet rays A and B, is used in sunscreens and other products for skin protection, and in

* Correspondence to: Center for Environmental Research and Children's Health (CERCH), School of Public Health, University of California, Berkeley, 1995 University Ave Suite 265, Berkeley, CA 94704, USA.

E-mail address: kharley@berkeley.edu (K.G. Harley).

https://doi.org/10.1016/j.envres.2018.05.005
Received 8 March 2018; Received in revised form 24 April 2018; Accepted 7 May 2018

cosmetics such as lipsticks, hairsprays, shampoos and skin lotions to prolong the products' durability (Han et al., 2016). Among 106 pregnant Puerto Rican women, urinary benzophenone-3 concentrations were associated with decreased free T3, but no associations were seen with free T4 and TSH (Aker et al., 2016). However, maternal urinary benzophenone-3 was not associated with maternal serum free or total T3 or T4 in 183 pregnant women in Denmark. (Krause et al., 2018)

Other environmental phenols include 2,4-dichlorophenol, a photodegradation product of triclosan that is also an intermediate in the manufacturing of the herbicide 2,4-dichlorophenoxyacetic acid (Latch et al., 2005), and 2,5-dichlorophenol, a metabolite of p-dichlorobenzene which is used in moth balls and room and toilet deodorizers (Wei et al., 2014; Ye et al., 2014). A cross-sectional study of 1889 Flemish adolescents found that 2,5-dichlorophenol was positively associated with TSH and negatively associated with free T4 (Croes et al., 2015). In a study of 618 adolescents in the National Health and Nutrition Examination Survey (NHANES), urinary concentrations of 2,5-dichlorophenol, but not 2,4-dichlorophenol, were associated with increased levels of TSH and thyroglobulin and unchanged levels of free T4 and free T3 (Wei and Zhu, 2016).

Parabens, including methyl paraben, propyl paraben, and butyl paraben, are commonly used as preservatives in cosmetics as well as in food, pharmaceuticals, and paper products (Cao et al., 2013; Guo and Kannan, 2013; Liao and Kannan, 2014). A study of 439 pregnant women in Boston found negative associations of urinary propyl paraben concentrations and maternal free T4 during pregnancy, but found positive associations of methyl paraben and maternal total T4 (Aker et al., 2018). Butyl paraben was positively associated with levels of free T4 among 106 pregnant women in Puerto Rico, and no associations were seen with methyl or propyl paraben or with free T3 or TSH (Aker et al., 2016).

Exposure to environmental phenols and parabens is widespread (CDC, 2018). Although thyroid hormone homeostasis is vital to fetal brain development, few studies have examined the association of environmental phenol and paraben exposure during pregnancy on thyroid hormone levels of pregnant women and their children. We have previously reported an association between bisphenol A (BPA) and lower maternal total T4 and lower male neonatal TSH. (Chevrier J et al., 2013). In the present study, we examined the association of urinary concentrations of other phenols and parabens in pregnant women with thyroid hormones levels in the women during pregnancy and their neonates at birth.

2. Methods

2.1. Participants

Participants were part of the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a longitudinal birth cohort study of environmental exposures and health among pregnant women and children living in an agricultural region in Northern California. Pregnant women were recruited from prenatal clinics serving the region's largely Latino farmworker community between October 1999 and October 2000. Women were eligible to participate in this study if they spoke Spanish or English, were ≥ 18 years old, were < 20 weeks gestation, qualified for California's low-income health insurance program (MediCal), and planned to deliver at the county hospital. A total of 601 women were enrolled. Losses were due to miscarriages (N = 20, 3.3%), stillbirths (N = 3, 0.5%), neonatal death (N = 2, 0.3%) and loss to follow-up during pregnancy (N = 40, 6.9%), leaving 536 women followed through a live delivery. We additionally excluded women taking the medication Levothyroixine that could affect thyroid hormone levels (N = 1, 0.2%), women with no urinary biomarker measurements during pregnancy (N = 17, 3.2%), and twins (N = 5, 1.0%), leaving 513 women and 508 infants. For the analysis of maternal thyroid hormones, we excluded women missing thyroid hormone measurements due to insufficient serum volume (n = 175, 34.1%), leaving a final sample of 338 mothers. For the analyses of neonatal TSH, we excluded neonates with missing TSH measures (n = 144, 28.1%), leaving a total of 364 infants. Written informed consent was obtained from all mothers and all research was approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley prior to the study's conduct. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The Centers for Disease Control and Prevention (CDC) deferred to the University of California, Berkeley institutional review board (IRB) as the IRB of record.

2.2. Interviews

We interviewed mothers near the end of the first trimester (mean: 14.1 weeks gestation, range: 5.3–28.5) and second trimester (mean: 26.9 weeks gestation, range: 21.1–39.5) of pregnancy using structured questionnaires in English or Spanish to collect demographic information including maternal age, education, country of birth, and family income.

2.3. Measurement of thyroid hormones

Maternal blood was collected by venipuncture at the time of the second interview and stored at −80 °C until shipment to Quest Diagnostics' Nichols Institute (San Juan Capistrano, CA) for analysis. Free T4 was measured in maternal serum using direct equilibrium dialysis followed by radioimmunoassay (Nelson and Tomei, 1988) which provides accurate measurements despite pregnancy-induced elevations in T4-bound proteins (Nelson et al., 1994). Total T4 and TSH were measured in maternal serum using solid-phase immunochemiluminometric assays (Bayer ADVIA Centaur system; Siemens Healthcare Diagnostics, Deerfield, IL). The limits of detection (LODs) were 0.1 ng/dL (free T4), 0.1 μg/dL (total T4), and 0.01 mIU/L (TSH).

Neonatal TSH was measured by the California Department of Health Services Genetic Diseases Branch (Richmond, CA) as part of the state's routine Newborn Screening Program. Blood spots on filter paper were collected shortly after birth [median = 21 h; interquartile range (IQR) = 17–26 h] by heel stick and were analyzed using a solid-phase, time-resolved sandwich fluoroimmunoassay (AutoDELFIA; PerkinElmer, Wellesley, MA). The LOD was 2 mIU/L. Neonatal TSH and age (in hours) at the time of heel stick were abstracted from medical records. Neonatal TSH levels were abstracted from medical records for comparison with maternal prenatal exposures.

2.4. Measurement of phenols and parabens

Spot urine samples were collected from participants in sterile, polypropylene urine cups at each of the two pregnancy interviews. Samples were stored at −80 °C until shipment on dry ice to the CDC in Atlanta, GA. Environmental phenols (including BPA which was used as a covariate in this analysis) and parabens were quantified using an on-line solid phase extraction-high performance liquid chromatography-isotope dilution tandem mass spectrometry approach, as previously described (Ye et al., 2006, 2005). The LODs were 2.3 ng/mL (triclosan), 0.4 ng/mL (benzophenone-3), 0.2 ng/mL (2,4-dichlorophenol, 2,5-dichlorophenol, propyl paraben, butyl paraben), and 1.0 ng/mL (methyl paraben). For concentrations below the LOD, we used instrument-generated values when available; if no signal was detected, we substituted a random value < LOD based on a log-normal probability distribution whose parameters were determined by maximum likelihood estimation (Lubin et al., 2004). Several samples had biomarkers with concentrations above the highest calibration standard (methyl paraben: 39 measurements [23 at baseline, 16 at 26 weeks]; propyl paraben: 41