Environmental Research 138 (2015) 453–460

Contents lists available at ScienceDirect

Environmental Research

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

Gestational urinary bisphenol A and maternal and newborn thyroid hormone concentrations: The HOME Study

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ARTICLE INFO

Article history:
Received 1 December 2014
Received in revised form
14 February 2015
Accepted 8 March 2015
Available online 17 March 2015

Keywords:
Bisphenol A
Thyroid hormones
Thyroid stimulating hormone
Thyroxine
Triiodothyronine
Pregnant women
Newborns
Endocrine disruptors
Epidemiology

ABSTRACT

Bisphenol A (BPA), an endocrine disruptor used in consumer products, may perturb thyroid function. Prenatal BPA exposure may have sex-specific effects on thyroid hormones (THs). Our objectives were to investigate whether maternal urinary BPA concentrations during pregnancy were associated with THs in maternal or cord serum, and whether these associations differed by newborn sex or maternal iodine status. We measured urinary BPA concentrations at 16 and 26 weeks gestation among pregnant women in the HOME Study (2003–2006, Cincinnati, Ohio). Thyroid stimulating hormone (TSH) and free and total thyroxine (T_4) and triiodothyronine (T_3) were measured in maternal serum at 16 weeks ($n=181$) and cord serum at delivery ($n=249$). Associations between BPA concentrations and maternal or cord serum TH levels were estimated by multivariable linear regression. Mean maternal urinary BPA was not associated with cord THs in all newborns, but a 10-fold increase in mean BPA was associated with lower cord TSH in girls (percent change = −36.0%; 95% confidence interval (CI): −58.4, −1.7%), but not boys (7.8%; 95% CI: −28.5, 62.7%; *p*-for-effect modification = 0.09). We observed no significant associations between 16-week BPA and THs in maternal or cord serum, but 26-week maternal BPA was inversely associated with TSH in girls (−42.9%; 95% CI: −59.9, −18.5%), but not boys (7.6%; 95% CI: −17.3, 40.2%; *p*-for-effect modification = 0.005) at birth. The inverse BPA–TSH relation among girls was stronger, but less precise, among iodine deficient versus sufficient mothers. Prenatal BPA exposure may reduce TSH among newborn girls, particularly when exposure occurs later in gestation.

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1. Introduction

Bisphenol A (BPA) is a synthetic chemical used as a monomer in polycarbonate plastics and epoxy resins. Virtually every pregnant woman and child in the United States (US) is exposed to BPA (Calafat et al., 2008; Woodruff et al., 2011). Interference of BPA with the action of thyroid hormones (THs) during critical developmental stages may adversely affect neurobehavioral outcomes (Boas et al., 2012; Henrichs et al., 2013). BPA may interfere with TH action by interacting directly with the TH receptor, affecting the normal delivery of TH to target cells, or altering the metabolism of THs, including thyroid stimulating hormone (TSH), free and total

Abbreviations: BMI, body mass index; BPA, bisphenol A; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; Cr, creatinine; CV, coefficient of variation; FT_3, free triiodothyronine; FT_4, free thyroxine; GM, geometric mean; HOME, Health Outcomes and Measures of the Environment; I, iodine; ICP-MS, inductively coupled plasma-mass spectrometer; IQR, interquartile range; LOD, limit of detection; PCB, polychlorinated biphenyl; QC, quality control; TgAb, thyroglobulin antibody; TH, thyroid hormone TPOAb, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; TT_3, total triiodothyronine; TT_4, total thyroxine; US, United States

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http://dx.doi.org/10.1016/j.envres.2015.03.003
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thyroxine (FT_4, TT_4), or free and total triiodothyronine (FT_3, TT_3). Prenatal THs are essential for normal brain development. Shifts in the distribution of maternal or newborn TH levels that are not associated with acute clinical sequelae could have population-level impacts on child neurodevelopment. A number of studies have shown that variations in maternal T_4 or TSH levels during gestation are associated with reduced cognitive abilities and increased risk of behavior problems in children (Ghassabian et al., 2011; Henrichs et al., 2013; Julvez et al., 2013).

Few experimental or epidemiological studies have examined the effect of BPA exposure on the thyroid axis. *In vitro* and animal studies report inconsistent effects (Nieminen et al., 2002a,b; Xu et al., 2007; Zoeller et al., 2005) and epidemiological studies, which have predominately been cross-sectional, have also been equivocal. Two studies from China reported that occupational exposure to BPA exposure was associated with elevated FT_3 and FT_4 and reduced TSH concentrations (Wang et al., 2012, 2013). A study in US adult men found no associations with FT_3, FT_4, and TSH (Meeker et al., 2010), whereas, a nationally representative cross-sectional study in the US reported that BPA concentrations were associated with lower TT_4 (Meeker and Ferguson, 2011). Prenatal urinary BPA concentrations were associated with lower TT_4 in pregnant women and reduced TSH in their male newborns in a pregnancy cohort study from California (Chevrier et al., 2013). To address this knowledge gap, we sought to determine if maternal urinary BPA concentrations during pregnancy were associated with thyroid hormones in women or their newborns, and to assess whether newborn sex modified these associations. Additionally, we explored whether maternal iodine status was an effect modifier of these associations.

2. Materials and methods

2.1. Study setting

The Health Outcomes and Measures of the Environment (HOME) Study is a prospective pregnancy and birth cohort in the greater Cincinnati, Ohio metropolitan area that was designed to investigate the impact of exposures to common environmental chemicals on child health and development. At baseline, women were eligible to participate if they were pregnant (16 ± 3 weeks gestation), $\geq$18 years old, English speakers, living in a home built before 1978, intending to continue prenatal care and deliver at a HOME Study-affiliated obstetric practice, and had no history of HIV infection. Women taking medication for seizure or thyroid disorders were not eligible to participate. Women were enrolled in the study between March 2003 and January 2006. Of 1263 eligible women, 37% enrolled ($n=468$) and 83% ($n=389$) were followed through live birth of a singleton infant. We excluded one mother–newborn pair in which the woman had a urinary BPA concentration of 583 μg/g creatinine (Sathyanarayana et al., 2011), orders of magnitude higher than the median (2.7 μg/g creatinine) among these participants. The Institutional Review Boards of Cincinnati Children's Hospital Medical Center, the Centers for Disease Control and Prevention (CDC), and all delivery hospitals approved the study protocol. All mothers provided written informed consent before enrollment in the study.

2.2. BPA assessment in maternal urine

Women provided two spot urine samples directly into polypropylene specimen cups at an average of 16.0 (range=13.0–20.9) and 26.5 (range=23.1–34.6) weeks of gestation. Urine was stored at or below −20 °C until samples were analyzed for total BPA (conjugated plus free) using online solid phase extraction coupled to high performance liquid chromatography-isotope dilution tandem mass spectrometry (Ye et al., 2005). Four quality control (QC) samples were analyzed in each analytic run. For 31 analytical batches analyzed in a period of one year, the coefficients of variation were 6.9–9.2% for the low-concentration QC samples (~2.8 μg/L), and 3.4–7.6% for the high-concentration QC samples (~9.7 μg/L). The limit of detection (LOD) was 0.4 μg/L; concentrations below the LOD were given a value of LOD/$\sqrt{2}$. All study protocols included appropriate measures to prevent BPA contamination during collection, storage, and analysis of urine. Urinary creatinine concentrations were measured using enzymatic methods and urinary BPA concentrations were creatinine-standardized (μg/g creatinine) to account for individual variability in urine dilution. The creatinine-standardized BPA concentrations were $\log_{10}$-transformed, and the mean of the $\log_{10}$-transformed BPA concentrations from the urine collected at 16 and 26 weeks gestation was calculated.

2.3. Serum thyroid hormone and antibody concentrations

Maternal blood was collected at approximately 16 weeks gestation, and venous cord blood was collected at delivery. Serum was separated from clotted blood and stored at −80 °C until analysis. THs (TSH, TT_4, TT_3, FT_4, and FT_3), and thyroid antibodies [thyroid peroxidase (TPOAb) and thyroglobulin antibodies (TgAb)] were measured in maternal and cord sera 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 coefficient of variation (CV) for the thyroid hormone assays ranged from <1.0% to 10% (Supplemental material, Table S1).

2.4. Covariate data

During the second trimester, demographic, socioeconomic, perinatal, and behavioral factors, as well as reproductive and medical histories, were collected using a computer-assisted questionnaire administered by trained research staff. Delivery method and newborn sex were abstracted from neonatal medical records. To account for previously observed associations between polychlorinated biphenyls (PCBs) and THs (Chevrier et al., 2007), we measured PCB-153 concentrations in maternal serum samples collected at 16 weeks gestation (Sjodin et al., 2014). Tobacco smoke exposure at 16 weeks was assessed using serum cotinine, a sensitive and specific biomarker of secondhand and active tobacco smoke exposure, using previously described methods (Bernert et al., 2009). Urinary iodine was measured in maternal urine collected at 26 ($n=228$) or 16 weeks ($n=8$) with an Agilent 7500x Inductively Coupled Plasma-Mass Spectrometer (ICP-MS) (Caldwell et al., 2003). The LOD was 0.5 μg I/L, and the average CV for all QC specimens was ≤10%. Maternal urinary iodine was creatinine-standardized and and women were categorized as iodine sufficient (≥150 μg I/g creatinine) or deficient (<150 μg I/g creatinine) (Ghassabian et al., 2014).

2.5. Statistical analysis

We examined the distribution of average maternal urinary BPA, maternal serum TSH, and newborn cord serum TSH concentrations across categories of maternal sociodemographic, behavioral, and perinatal factors. TSH was natural log-transformed because its distribution was right-skewed. T_4 and T_3 were expressed on the arithmetic scale. We fit 3-knot, restricted-cubic splines to assess model linearity assumptions for linear regression (Desquilbet and Mariotti, 2010). We observed approximately linear relationships between $\log_{10}$-transformed BPA and THs (data not shown). We

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