HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Environ Res. 2015 April ; 138: 453–460. doi:10.1016/j.envres.2015.03.003.

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

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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

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Conflict of interest

The authors have no conflicts of interest to declare.

Competing Financial Interests: The authors have no competing financial interests.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosure: None of these activities are directly related to the present study.

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.

Keywords

Bisphenol A; Thyroid hormones; Thyroid stimulating hormone; Thyroxine; triiodothyronine; Pregnant women; Newborns; Endocrine Disruptors; Epidemiology

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 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 rodent studies report inconsistent effects (Nieminen et al., 2002a; Nieminen et al., 2002b; 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; Wang et al.,

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), >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 1,263 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 (2.7μg/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/√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 7500× 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 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 used multivariable linear regression to estimate the adjusted differences in THs with each 10-fold increase in urinary BPA concentrations. For the analyses of THs in mothers, only urinary BPA collected at 16 weeks was considered because the 26 week urine was collected later in pregnancy than the assessment of THs. For the analyses of THs in newborns, average BPA and the individual measures (16 or 26 week) of maternal urinary BPA were considered. The regression coefficients were used to characterize the percent change in TSH or the mean change in T_3 and T_4 for each 10-fold increase in BPA concentration.

We adjusted for the following variables based on *a priori* knowledge of their potential associations with exposure and/or outcome (Calafat et al., 2008; Chevrier et al., 2007; Chevrier et al., 2013; Herbstman et al., 2008; Meeker et al., 2010): maternal age at delivery, race/ethnicity, parity, serum cotinine concentrations, alcohol consumption, prenatal vitamin use, and $\log_{10}$-transformed maternal serum PCB-153 concentrations. Models examining maternal THs also included adjustment for household income, and gestational week of serum/urine collection. For the analyses of cord THs we also adjusted for maternal education, infant sex, gestational age at delivery, and mode of delivery (Herbstman et al., 2008). Because prior research suggests that sex may modify the association between gestational BPA exposure and THs (Chevrier et al., 2013), we ran additional models that included a product interaction term between maternal urinary BPA and infant sex when analyzing cord serum THs. We considered p-values <0.10 for interaction terms to be indicative of effect modification.

We conducted an exploratory analysis examining effect modification by maternal iodine status. We also created a model including all variables from the final multivariable model plus iodine deficiency (≥150 μg I/g creatinine vs. <150 μg I/g creatinine) and product terms for BPA × infant sex, BPA × iodine deficiency, infant sex × iodine deficiency, and a three-way term for BPA × infant sex × iodine deficiency.

We additionally conducted a series of sensitivity analyses to evaluate the robustness of our results. We assessed for potential confounding by maternal iodine status by adjusting for maternal urinary iodine concentrations. We re-ran the final models using maternal urinary BPA concentrations without creatinine-standardization to determine whether our method for accounting for urine dilution altered our results. We also examined whether compromised thyroid function modifies the association between BPA and THs (Webster et al., 2014). Very few women had clinically significant elevations in thyroid antibody [TPOAb >9.0 IU/mL (n=15); TgAb >2.0 IU/mL (n=5)]. Therefore, we dichotomized TPOAb at the median level and TgAb as detected versus not detected. Product terms of maternal urinary BPA and thyroid antibodies (dichotomous) were added to linear regression models and considered significant if p<0.10. Stata version 13.0 (StataCorp, College Station, TX) and SAS version 9.3 (SAS Institute, Inc., Cary, NC) were used for statistical analyses.

3. Results

3.1 Participant characteristics

The maternal analysis included 181 women who had complete covariate information and both maternal urinary BPA and serum TH concentrations (collected at ~16 weeks gestation). The newborn analysis included 249 infants who had complete covariate information, cord serum TH concentrations, and whose mothers had at least one urinary BPA measurement. One woman provided a urine sample only at 16 weeks, 11 women provided samples only at 26 weeks, and 237 women provided samples at both time points. Mothers in the study were primarily 25–35 years old (65%), non-Hispanic white (67%), and married (73%). Most women had an annual household income from $40,000–80,000 (36%), education equivalent to or greater than a bachelor's degree (56%), and private health insurance (79%). During pregnancy, the majority of women reported that they regularly took prenatal vitamins (88%)

and did not consume alcohol (55%); only 10% of women were active smokers during pregnancy. Fewer than half of the women were nulliparous at enrollment (44%) and most delivered their newborns vaginally (73%) (Table 1).

Women included in the final analyses were more likely to be >25 years old, non-Hispanic white, married, highly educated (>bachelor's degree), overweight at enrollment (>25 kg/m^2), taking prenatal vitamins, or have a household income >$20,000/year (Supplemental Material, Table S2).The geometric mean of 16 week urinary BPA was similar for women excluded from and included (1.9 vs. 2.1 μg/g creatinine) in the maternal analyses. Among newborns excluded from and included in the final analyses, the geometric mean of their mothers' average maternal urinary BPA concentrations was also similar (2.5 vs. 2.4 μg/g creatinine).

3.2 Maternal urinary BPA concentrations and maternal and newborn thyroid hormones

Median maternal urinary BPA concentrations were relatively similar at 16 and 26 weeks gestation (Table 2). Very few mothers (n=13, 7.2%) had TSH serum levels suggestive of subclinical or clinical hypothyroidism (>3.0 mIU/L) (Shields et al., 2013); likewise, few newborns (n=11, 4.4%) had cord blood TSH levels indicative of insufficient thyroid function (>20 mIU/L) (Manglik et al., 2005).

In adjusted analyses, we did not observe any significant associations between maternal urinary BPA and serum TH concentrations at 16 weeks gestation (Table 3). Likewise, we did not identify any notable associations between maternal urinary BPA concentrations (average, 16 week, or 26 week) and newborn THs when both sexes were combined (Table 3). In contrast, we observed inverse associations between BPA and TSH and suggestive positive relations between BPA and TT_3 among female newborns for both average and 26 week urinary BPA (Table 3). Among female newborns, each 10-fold increase in average maternal urinary BPA was associated with decreased cord TSH (percent change=−36.0%; 95% confidence interval [CI]: −58.4, −1.7%) (Table 3); no association was observed among males (7.8%; 95% CI: −28.5, 62.7%; p for effect modification=0.09) (Table 3). In analyses of individual BPA measures, maternal urinary BPA concentrations at 16 weeks were not associated with TSH (Table 3). However, 26 week maternal urinary BPA was associated with reduced TSH in female (−42.9%; 95% CI:−59.9, −18.5%), but not male newborns (7.6%; 95% CI:−17.3, 40.2%; p for effect modification=0.005) (Table 3). Unadjusted analyses yielded a similar pattern of results (Supplemental Material, Table S3).

In our exploratory analysis, we observed no evidence of effect modification of the relations between BPA and THs by iodine status among mothers or all newborns (Supplemental Material, Table S4). There was some suggestion that the inverse relation between BPA and TSH was strongest among female newborns with iodine deficient mothers (p-for-effect modification=0.11 of the BPA-TSH relation by iodine deficiency among girls) (Figure 1, Supplemental Material, Table S5).

3.3 Sensitivity analyses

In general, estimates obtained in the sensitivity analyses were similar to those described above. Adjustment for iodine deficiency did not substantially alter the observed pattern of

associations (Supplemental Material, Table S6). Our results were similar when we used non-creatinine standardized BPA measurements (Supplemental Material, Table S7). Thyroid antibody status did not modify the associations between maternal urinary BPA and maternal serum THs at 16 weeks or average maternal urinary BPA and cord serum THs (Supplemental Material, Table S8 & Table S9).

4. Discussion

In the present study, we observed an inverse association between prenatal BPA exposure and TSH among female newborns, but not males. The association among female newborns was stronger for the more temporally proximal maternal urinary BPA concentration from 26 weeks gestation. We did not observe notable associations between prenatal BPA measures and maternal serum TH concentrations or with cord serum concentrations of T_4 or T_3.

In contrast with our study results, a prior study of pregnant women enrolled in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort observed an inverse association between urinary BPA and maternal TT_4 serum levels during pregnancy (Chevrier et al., 2013). Results from studies of BPA and THs in non-pregnant adults have been inconsistent, with some observing elevated FT_3 and FT_4 and lowered TSH (Wang et al., 2012; Wang et al., 2013), and others observing reductions in TT_4 (Meeker and Ferguson, 2011), or no association (Meeker et al., 2010).

In the only prior study of prenatal BPA exposure and newborn TSH, Chevrier et al. observed an inverse association between urinary BPA and TSH among male newborns (Chevrier et al., 2013), whereas we only observed an inverse association among female newborns. For each doubling of average maternal urinary BPA (across 1st, 2nd, and 3rd trimester urine samples), Chevrier et al. observed a ~10% reduction in TSH among male but not female newborns (Chevrier et al., 2013). Discrepant results between these studies could be due to differences in the racial, ethnic, or socioeconomic makeup of participants, BPA levels [median maternal urinary BPA (IQR) – CHAMACOS: 1.2 μg/g creatinine (0.8–1.9) versus HOME Study 2.2 μg/g creatinine (1.5–3.4)], co-exposures such as pesticides, or timing and method of outcome measurements (i.e., heel stick blood spot at a median of 21 hours in CHAMACOS versus cord blood in the current study).

Further, assessment of maternal dietary iodine using a questionnaire to assess did not appear to modify the associations between BPA and either maternal or newborn THs in prior work (Chevrier et al., 2013). We did not see evidence of effect modification by maternal iodine status among mothers or newborns with both sexes combined. However, our exploratory analysis suggested that gestational BPA exposure might have the greatest adverse influence among female newborns with iodine deficient mothers. A relatively small number of female newborns had mothers with iodine deficiency in our analytic sample (n=24), and thus our statistical power was substantially reduced when analyzing this subgroup.

Because excess levels of TT_3 may influence the negative feedback loop of the hypothalamic-pituitary-thyroid axis, resulting in less production of TSH (Melmed and Williams, 2011), the pattern of reduced TSH among female newborns with greater prenatal

BPA exposure in our study is consistent with the observed positive association between maternal urinary BPA and TT_3 concentrations among female newborns. In general, women have a higher prevalence of thyroid disorders than men (Fortunato et al., 2014). Although the responsible underlying mechanisms are not well understood, it is hypothesized that disruption of gonadal hormones, particularly estrogen, and gender-related differences in the thyroid redox environment may be involved in the pathogenesis of thyroid disorders among women (Fortunato et al., 2014). Purported differences in regulation of oxidative stress for the male versus female thyroid have some support in animal models (Fortunato et al., 2013). We speculate that such differences, if further elucidated, may extend to the female fetal thyroid and account for sexually dimorphic sensitivity of the thyroid to environmental chemicals. However, rodent studies specifically assessing the effect of prenatal BPA exposure on thyroid hormones have been inconsistent, with one study suggesting that BPA affects thyroid hormones among male pups only (Xu et al., 2007), another reporting similar thyroid hormone responses to BPA in both male and female pups (Zoeller et al., 2005), and another observing no effect of BPA on thyroid function for male or female pups (Kobayashi et al., 2005).

Similar to the associations observed by Chevrier et al. (2013), the relation observed in our study between BPA and newborn THs was stronger when the most temporally proximal exposure measurement (26 week BPA) was used in the models. Chevrier et al. (2013) observed that the association between BPA and newborn TSH levels among male newborns was strongest when maternal urinary BPA concentration was measured in the third trimester versus the second, or first trimester. The stronger relation between 26-week BPA compared to 16 week BPA in the present study lends additional support to the possibility that BPA exposure later in gestation has greater influence on newborn TSH. Alternatively, rather than suggesting a window of susceptibility, this may reflect a transient effect of BPA on the thyroid axis, made more apparent by the shorter period of time between BPA measurements near 26 weeks gestation and cord blood THs at delivery (Chevrier et al., 2013).

At birth, a surge of TSH occurs, which subsequently leads to increased T_4 and T_3 production (Melmed and Williams, 2011). It is unknown whether the lower levels of TSH that we observed among female newborns with greater prenatal BPA exposure translates into meaningful reductions in subsequent T_4 or leads to clinical or subclinical hypothyroidism. However, we previously observed a suggestive association between BPA concentrations in our population and infant hypotonia (Yolton et al., 2011), which is a symptom of hypothyroidism (Rastogi and LaFranchi, 2010). In addition, we previously observed that increasing prenatal urinary BPA concentrations were associated with more anxious and hyperactive behaviors among 2–3 year old girls, but not boys (Braun et al., 2011b; Braun et al., 2009). A prior rodent study found that gestational hypothyroidism induced learning deficits and hyperactivity in females, but not males (Friedhoff et al., 2000). This suggests that TH disruption is a potential mediator of the BPA-behavior associations we previously observed that appear to be specific to girls. Interestingly, the CHAMACOS study observed that higher prenatal exposure to BPA was associate with increased anxiety among male children at age 7 (Harley et al., 2013), echoing the same potential relation between lower neonatal TSH and health later in childhood. Further research is necessary to confirm this hypothesis.

Our study had several strengths, including a prospective design, rich covariate data, exclusion of women who had thyroid disorders or were taking any thyroid medication and up to two measures of urinary BPA concentrations during the latter two-thirds of pregnancy. Due to the short biological half-life of BPA, the average of multiple spot urine samples may be a better reflection of BPA exposure over time than a single sample (Braun et al., 2011a). Likewise, our study has limitations worth noting. Although we were able to account for exposure to PCBs, we did not adjust for all known environmental thyroid disruptors (e.g., perchlorate). Furthermore, we may also have residual bias due to exposure misclassification of BPA, which is a non-persistent compound with episodic exposures. If present, such exposure misclassification is likely to be non-differential and would attenuate the observed associations towards the null, suggesting that we may have missed associations and that the true associations between BPA and THs may be stronger than those reported in our study. Similarly, physiologic changes during late pregnancy can increase renal clearance of chemicals (Costantine, 2014) such that urinary levels of BPA may have been overestimated at 26 weeks gestation in our study. However, exposure measurement error due to pharmacokinetic changes in the elimination of BPA in later pregnancy is also unlikely to be differentially associated with cord serum TH concentrations. Day-to-day variability in urinary iodine concentrations may have resulted in some misclassification of women's iodine status (Busnardo et al., 2006). Also, our statistical power was reduced when we examined for effect modification by child sex and maternal iodine deficiency, and by the smaller sample size for the analysis of maternal THs (n=181). Finally, the clinical implications of small reductions in TSH at birth are not certain. However, over 10% of US children are affected by learning disabilities, autism spectrum disorders, affective disorders, and ADHD (Boyle et al., 2011; CDC, 2012; Costello et al., 2003), and disruption of prenatal THs may play a role in their etiology (Gilbert et al., 2012). These disorders have profound impacts on the health and well-being of children and their families and carry substantial financial costs (Leibson et al., 2001), making the identification of modifiable environmental risk factors for thyroid dysfunction a critical research priority.

5. Conclusions

We observed an inverse relation between maternal urinary BPA concentration and cord blood TSH concentrations among female but not male newborns. The association between maternal urinary BPA and cord blood TSH among female newborns was strongest in BPA measures collected later in pregnancy, which may suggest a window of susceptibility or a transient effect of BPA on TH function. Our findings raise the possibility that disturbance of the thyroid axis may be a mechanism by which BPA could be related to child neurobehavioral outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was supported by R00-ES020346, R01-ES020349, P01-ES11261, P01ES022832-02, and RD-83544201. The authors thank the HOME Study personnel for their skillful assistance and acknowledge the

Centers for Disease Control and Prevention (CDC) laboratory staff who performed the measurements of BPA, creatinine, PCBs, and cotinine

Dr. Lanphear has served as an expert witness and a consultant to the California Attorney General's Office for the plaintiffs in a public nuisance case related to childhood lead poisoning, but he has not personally received any compensation for these services. Dr. Lanphear has also served as a paid consultant on a US Environmental Protection Agency research study related to childhood lead poisoning. Dr. Braun received financial compensation for conducting a re-analysis of a study of child lead exposure for the plaintiffs in a public nuisance case related to childhood lead poisoning.

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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Highlights

- Examined associations of BPA with thyroid hormones in pregnant women and newborns
- Assessed effect modification of BPA-thyroid hormone associations by newborn sex
- Greater BPA related to decreased thyroid stimulating hormone in girls' cord serum
- Results may suggest window of susceptibility to BPA in later gestation
- BPA potentially has greatest adverse effect on girls with iodine deficient mothers

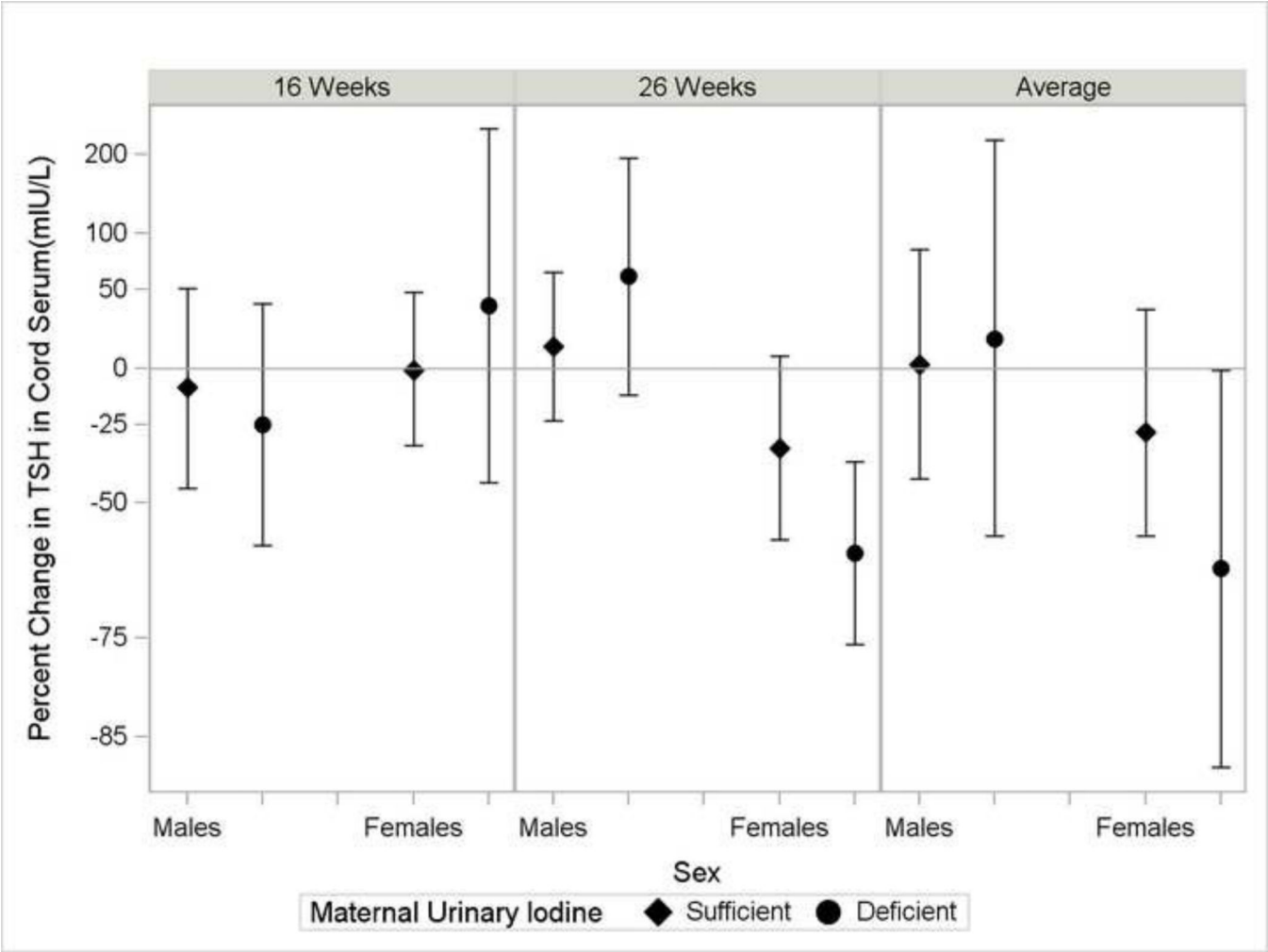

Figure 1.

Percent change in thyroid stimulating hormone concentrations in cord serum (n=193) with 10-fold increase in maternal urinary BPA in the Health Outcomes and Measures of the Environment Study by newborn sex and iodine deficiency. Sufficient iodine was defined by maternal urinary iodine ≥150 μg/g creatinine (diamond marker) and deficient iodine as maternal urinary iodine <150 μg/g creatinine (circle marker). Percent change calculated as $e^{\beta}-1\times100$, where β=coefficient from a multivariable linear regression model including adjustment for maternal age, race, education, alcohol consumption, smoking, parity, prenatal vitamin use, Log_{10}-polychlorinated biphenyl 153, delivery by Cesarean section, gestational week at delivery, newborn sex, iodine insufficiency, and product terms for bisphenol A by newborn sex, bisphenol A × iodine deficiency, newborn sex × iodine deficiency, and a bisphenol A × newborn sex × iodine deficiency. From left to right, the panels represent estimates from log_{10}-transformed creatinine-standardized bisphenol A in maternal urine at 16 weeks, 26 weeks, and the average of the log_{10}-transformed creatinine-standardized bisphenol A from maternal urine collected at the 16 and 26 week visits urine

Table 1

Maternal and newborn characteristics of participants in the Health Outcomes and Measures of the Environment Study, Cincinnati, Ohio, 2003–2006

Covariate	n(%)	Urinary BPA[a] Median(IQR)	Newborn TSH[b] Median(IQR)	n(%)	Maternal TSH[c] Median(IQR)
Overall	249(100)	2.2(1.5–3.4)	7.1(5.1–10.1)	181(100)	1.3(0.9–2.0)
Maternal age (years)					
<25	45(18)	2.7(1.7–3.7)	6.4(4.9–8.3)	33(18)	1.1(0.7–1.8)
25–35	161(65)	2.2(1.5–3.4)	7.5(5.4–10.7)	112(62)	1.3(0.8–2.0)
>35	43(17)	2.0(1.6–3.0)	6.5(4.4–7.6)	36(20)	1.5(1.3–2.2)
Race/ethnicity					
Non-Hispanic White	166(67)	2.1(1.6–3.5)	7.4(5.4–10.7)	116(64)	1.4(0.9–2.1)
Black	66(27)	2.3(1.5–3.2)	6.4(4.4–7.9)	49(27)	1.2(0.8–1.7)
Other	17(7)	2.6(1.4–4.0)	7.4(4.4–9.3)	16(9)	1.6(0.8–2.3)
Marital Status					
Married	182(73)	2.1(1.5–3.4)	7.3(5.3–10.3)	128(71)	1.4(0.9–2.1)
Unmarried, cohabiting	25(10)	2.7(1.6–3.8)	7.4(5.9–9.9)	20(11)	1.4(0.9–1.8)
Unmarried, living alone	42(17)	2.3(1.7–3.2)	5.8(4.1–7.7)	33(18)	1.1(0.6–1.6)
Household Income ($/year)					
<20,000	43(17)	2.7(1.7–3.8)	6.4(4.1–9.7)	37(20)	1.1(0.7–1.6)
20–<40,000	40(16)	2.3(1.8–3.3)	6.5(5.3–8.9)	28(16)	1.6(1.0–2.0)
40–80,000	89(36)	2.1(1.5–3.2)	7.4(5.8–10.1)	62(34)	1.3(0.8–2.1)
>80,000	77(31)	2.0(1.4–3.4)	7.6(5.3–11.6)	54(30)	1.5(1.0–2.3)
Education					
Less than high school	22(9)	3.1(1.7–3.9)	7.0(4.2–10.3)	20(11)	1.2(0.6–1.7)
High school or some college	88(35)	2.2(1.6–3.3)	6.9(5.1–8.4)	55(30)	1.3(0.8–1.9)
Bachelors or more	139(56)	2.1(1.5–3.4)	7.4(5.3–11.3)	106(59)	1.4(0.9–2.2)
Insurance					
Private	196(79)	2.1(1.5–3.4)	7.4(5.5–10.6)	138(76)	1.4(0.9–2.1)
Public/uninsured	53(21)	2.7(1.7–3.8)	6.4(4.1–7.8)	43(24)	1.1(0.7–1.6)
Prenatal vitamins[d]					
Regular use	218(88)	2.2(1.5–3.4)	7.3(5.4–10.1)	158(87)	1.3(0.9–2.0)
Never/infrequent use	31(12)	2.2(1.7–3.5)	5.5(4.2–7.6)	23(13)	1.3(1.0–2.0)

Covariate	n(%)	Urinary BPA[a] Median(IQR)	Newborn TSH[b] Median(IQR)	n(%)	Maternal TSH[c] Median(IQR)
Alcohol consumption[e]					
Any	112(45)	2.1(1.5–3.4)	7.5(5.4–11.1)	80(44)	1.5(1.0–2.1)
None	137(55)	2.2(1.6–3.4)	7.0(5.1–9.8)	101(56)	1.3(0.8–2.0)
Serum cotinine (ng/mL)[f]					
<0.015 (Unexposed)	77(31)	2.0(1.4–3.0)	7.6(5.6–10.9)	57(32)	1.5(1.1–2.3)
0.015–3 (Secondhand)	148(59)	2.3(1.7–3.7)	7.1(5.0–10.1)	104(57)	1.2(0.8–1.9)
>3 (Active smoker)	24(10)	2.5(1.5–3.5)	6.0(4.3–7.2)	20(11)	1.4(0.7–1.7)
Maternal BMI (kg/m^2)[g]					
<24.9 (Underweight-normal)	102(41)	2.3(1.6–3.4)	6.5(5.2–9.4)	82(45)	1.5(1.0–2.1)
25.0–29.9 (Overweight)	82(33)	2.0(1.5–3.4)	7.8(5.5–12.5)	39(22)	1.6(1.2–2.3)
≥30 (Obese)	56(22)	2.2(1.4–3.3)	7.2(4.6–9.1)	52(29)	1.0(0.6–1.7)
Mode of delivery					
Vaginal delivery	182(73)	2.3(1.6–3.5)	7.2(4.9–10.3)	127(70)	1.3(0.9–2.0)
Cesarean section	67(27)	2.0(1.4–3.1)	7.1(5.6–9.0)	54(30)	1.3(0.9–2.1)
Parity					
Nulliparous	110(44)	2.2(1.5–3.5)	7.5(5.4–11.6)	87(48)	1.6(1.0–2.1)
Primiparous	78(31)	2.1(1.6–2.8)	7.2(5.0–10.2)	55(30)	1.3(0.9–2.2)
Multiparous	61(25)	2.3(1.5–3.5)	6.5(4.7–7.7)	39(22)	1.1(0.7–1.5)
Newborn Sex					
Female	135(54)	2.2(1.5–3.5)	6.7(4.4–9.9)	98(54)	1.3(0.9–2.1)
Male	114(46)	2.2(1.5–3.4)	7.5(5.8–10.1)	83(46)	1.3(0.9–2.0)
Polychlorinated Biphenyl-153					
Low(<9.2 ng/g lipid)	82(33)	2.2(1.5–3.5)	7.5(5.2–10.3)	51(28)	1.5(1.0–2.1)
Middle (9.2–14.0 ng/g lipid)	80(32)	2.2(1.4–3.5)	7.0(5.0–10.0)	59(32)	1.3(0.7–2.1)
High (>14.0 ng/g lipid)	87(35)	2.2(1.7–3.4)	7.0(5.3–10.1)	72(40)	1.3(0.8–2.0)
Maternal urinary iodine[h]					
Sufficient (≥150 μg/g Cr)	137(55)	2.2(1.5–3.5)	7.2(5.3–11.0)	101(56)	1.4(0.9–2.0)
Deficient (<150 μg/g Cr)	56(22)	2.2(1.6–2.8)	7.2(5.1–8.4)	48(27)	1.2(0.7–2.0)

BMI=Body Mass Index, BPA=Bisphenol A, Cr=Creatinine, IQR=Interquartile range, and TSH=thyroid stimulating hormone

[a]Median level of the average of maternal urinary creatinine-standardized bisphenol A collected at 16 and 26 gestational weeks (μg/g Cr)

[b] Concentration of thyroid stimulating hormone (mIU/L) in cord serum collected at delivery for newborns included in the final multivariate analysis

[c] Concentration of thyroid stimulating hormone (mIU/L) in maternal serum collected at 16 weeks gestation for women included in the final multivariate analysis

[d] Use of prenatal vitamins at least weekly during pregnancy versus less frequent use

[e] Serum cotinine at 16 weeks gestation estimated tobacco smoke exposure during pregnancy

[f] Self-reported maternal consumption of alcohol during pregnancy

[g] Maternal body mass index at 16 weeks gestation, (n=9 (4%) missing from newborn analytic sample; n=8 (4%) missing from maternal analytic sample)

[h] Maternal urinary iodine, (n=56 (22%) missing from newborn analytic sample; n=32 (17%) missing from maternal analytic sample)

Table 2

Maternal urinary bisphenol A and maternal and cord sera thyroid hormone concentrations in the Health Outcomes and Measures of the Environment Study, Cincinnati, Ohio, 2003–2006

Biomarker	Maternal Analysis GM (95% CI) Mean ± SD n		Newborn Analysis GM (95% CI) Mean ± SD n	
Average BPA (μg/g Cr)[a]		---	249	2.4(2.2, 2.6)
16 week BPA (μg/g Cr)[b]	181	2.1(1.8, 2.4)	248	2.0(1.8, 2.2)
26 week BPA (μg/g Cr)[b]		---	238	2.3(2.1, 2.5)
TSH (mIU/L)	181	1.2(1.1, 1.4)	249	7.2(6.7, 7.8)
TT_4 (μg/dL)	181	10.3 ± 1.9	245	9.6 ± 1.8
TT_3 (ng/dL)	181	160 ± 24	249	52 ± 19
FT_4 (ng/dL)	181	0.7 ± 0.1	249	1.0 ± 0.2
FT_3 (pg/mL)	181	3.2 ± 0.3	247	1.7 ± 0.3

BPA=Bisphenol A, CI=Confidence interval, Cr=creatinine FT3=free triiodothyronine, FT4=free thyroxine, GM=geometric mean, TSH=thyroid stimulating hormone, TT3=total triiodothyronine, and TT4=total thyroxine

[a] The average of the creatinine-standardized bisphenol A from maternal urine collected at the 16 and 26 week visits

[b] Creatinine-standardized bisphenol A in maternal urine

Table 3

Difference or percent change in thyroid hormone concentrations in maternal (n=181) and cord sera (n=249) with 10-fold increase in maternal urinary BPA in the Health Outcomes and Measures of the Environment Study

BPA Measurement	Mothers Estimate (95% CI)[a]	All Newborns Estimate (95% CI)[b]	Female Newborns Estimate (95% CI)[c]	Male Newborns Estimate (95% CI)[c]	p-value[d]
Average[e]					
% Change in TSH[f]	---	−19.4 (−40.3, 8.9)	−36.0 (−58.4, −1.7) **	7.8 (−28.5, 62.7)	0.09 *
TT_4 (μg/dL)	---	0.12 (−0.82, 1.05)	0.51 (−0.62, 1.64)	−0.36 (−1.90, 1.16)	0.37
TT_3 (ng/dL)	---	3.97 (−6.52, 14.45)	11.89 (−1.08, 24.87) *	−6.13 (−23.37, 11.12)	0.11
FT_4 (ng/dL)	---	−0.03 (−0.11, 0.04)	−0.06 (−0.17, 0.05)	0.002 (−0.11, 0.12)	0.44
FT_3 (pg/mL)	---	−0.06 (−0.23, 0.10)	0.04 (−0.15, 0.22)	−0.18 (−0.46, 0.11)	0.24
16 weeks[g]					
% Change in TSH[f]	5.6 (−19.1, 37.9)	−4.6 (−24.4, 20.5)	−7.9 (−32.3, 25.2)	0.6 (−30.6, 46.0)	0.72
TT_4 (μg/dL)	−0.14 (−1.00, 0.71)	−0.31 (−0.91, 0.29)	−0.004 (−0.71, 0.70)	−0.77 (−1.79, 0.25)	0.23
TT_3 (ng/dL)	2.74 (−7.14, 12.62)	−1.39 (−8.63, 5.84)	2.69 (−5.89, 11.27)	−7.39 (−19.75, 4.97)	0.20
FT_4 (ng/dL)	−0.001 (−0.03, 0.03)	−0.03 (−0.08, 0.02)	−0.04 (−0.10, 0.03)	−0.02 (−0.10, 0.06)	0.75
FT_3 (pg/mL)	0.02 (−0.10, 0.15)	−0.06 (−0.18, 0.06)	0.002 (−0.13, 0.13)	−0.14 (−0.35, 0.06)	0.24
26 weeks[g]					
% Change in TSH[f]	---	−19.9 (−36.6, 1.2) *	−42.9 (−59.9, −18.5) **	7.6 (−17.3, 40.2)	0.005**
TT_4 (μg/dL)	---	0.51 (−0.27, 1.28)	0.73 (−0.43, 1.89)	0.33 (−0.67, 1.33)	0.60
TT_3 (ng/dL)	---	6.25 (−1.80, 14.29)	12.79 (−0.41, 26.00) *	0.41 (−9.14, 9.99)	0.14
FT_4 (ng/dL)	---	−0.003 (−0.07, 0.06)	−0.03 (−0.14, 0.08)	0.02 (−0.05, 0.09)	0.46
FT_3 (pg/mL)	---	−0.004 (−0.13, 0.12)	0.05 (−0.14, 0.24)	−0.05 (−0.22, 0.12)	0.46

BPA=bisphenol A, CI=Confidence interval, FT_4=free thyroxine, TSH=thyroid stimulating hormone, TT_3=total triiodothyronine, and TT_4=total thyroxine

* p<0.10

** p<0.05

[a] Adjusted for maternal age, race, income, alcohol consumption, serum cotinine at 16 weeks gestation, parity, prenatal vitamin use, Log_{10}-PCB 153, and gestational week at urine/serum collection

[b] Adjusted for maternal age, race, education, alcohol consumption, serum cotinine at 16 weeks gestation, parity, prenatal vitamin use, Log_{10}-PCB 153, delivery by Cesarean section, gestational week at delivery, and newborn sex

[c] Adjusted for maternal age, race, education, alcohol consumption, serum cotinine at 16 weeks gestation, parity, prenatal vitamin use, Log_{10}-PCB 153, delivery by Cesarean section, gestational week at delivery, and newborn sex, and including an interaction term for maternal bisphenol A and newborn sex in the model

[d] p-value for the maternal bisphenol A and newborn sex interaction term

[e] The average of the log_{10}-transformed creatinine-standardized bisphenol A from maternal urine collected at the 16 and 26 week visits

[f] Percent change calculated as $e^{\beta}-1\times100$, where β=coefficient from the multivariable model

[g] Log_{10}-transformed creatinine-standardized bisphenol A in maternal urine