Environment International 85 (2015) 244–253

Contents lists available at ScienceDirect

Environment International

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

Associations of birth outcomes with maternal polybrominated diphenyl ethers and thyroid hormones during pregnancy

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ARTICLE INFO

Article history:
Received 30 January 2015
Received in revised form 10 September 2015
Accepted 11 September 2015
Available online xxxx

Keywords:
Birth outcomes
Birth weight
Head circumference
Infant length
Polybrominated diphenyl ethers
Thyroid hormone

ABSTRACT

Background: Previous research has linked polybrominated diphenyl ether (PBDE) exposure to poor birth outcomes and altered thyroid hormone levels.
Objectives: We examined whether maternal PBDE serum levels were associated with infant birth weight (g), head circumference (cm), birth length (cm), and birth weight percentile for gestational age. We explored the potential for a mediating role of thyroid hormone levels.
Methods: During 2008–2010, we recruited 140 pregnant women in their third trimester as part of a larger clinical obstetrics study known as Healthy Pregnancy, Healthy Baby. Blood samples were collected during a routine prenatal clinic visit. Serum was analyzed for PBDEs, phenolic metabolites, and thyroid hormones. Birth outcome information was abstracted from medical records.
Results: In unadjusted models, a two-fold increase in maternal BDE 153 was associated with an average decrease in head circumference of 0.32 cm (95% CI: −0.53, −0.12); however, this association was attenuated after control for maternal risk factors. BDE 47 and 99 were similarly negatively associated but with 95% confidence intervals crossing the null. Associations were unchanged in the presence of thyroid hormones.
Conclusions: Our data suggest a potential deleterious association between maternal PBDE levels and infant head circumference; however, confirmatory studies are needed in larger sample sizes. A mediating role of thyroid hormones was not apparent.

1. Introduction

Polybrominated diphenyl ethers (PBDEs) are a class of chemicals that have historically been used to decrease the flammability of consumer products. As additives, these chemicals are not chemically bound to consumer products and ultimately leach out over time, contaminating the environment. Due to their high volume use over the past several decades, PBDEs are now ubiquitous contaminants in most environments, especially in the United States (Hale et al., 2003; Law et al., 2006a; de Wit et al., 2006). In addition, due to their physicochemical properties, PBDEs are persistent in the environment, and several PBDEs are highly bioaccumulative. In the United States, it is estimated that more than 97% of the general population has PBDEs circulating in their bloodstream (Sjodin et al., 2008), and infants and toddlers have higher concentrations than adults (Rose et al., 2010; Stapleton et al., 2012a). Commercial production of two of the three PBDE mixtures ceased in 2005 in the United States following a voluntary phase-out by manufacturers (Tullo, 2003), and the third commercial mixture was phased-out in 2013 (EU-Commission, 2008). Despite these phase-outs, products containing PBDEs are still found in homes; (Stapleton et al., 2011a; Stapleton et al., 2012b) therefore, exposure among the general population is likely to continue for some time.

Fetuses are believed to be particularly vulnerable to the effects of environmental pollutants because of their relatively immature organs, which are in sensitive developmental stages, and because they have less well developed detoxification systems (Barr et al., 2007). PBDEs are known to cross the placenta, and maternal exposures can therefore lead to fetal exposure as evidenced by measurements of PBDEs in fetal cord serum (Foster et al., 2011; Kim et al., 2009; Vizcaino et al., 2011). Over the past few years, human health studies have found associations between PBDE body burdens and adverse health outcomes including reduced fecundity in women, failed embryo implantation (Johnson et al.,

Abbreviations: BMI, body mass index; FT4, free thyroxine; FT3, free triiodothyronine; HPHB, Healthy Pregnancy, Healthy Baby; PBDE, polybrominated diphenyl ether; OH-BDE, polybrominated diphenyl ether metabolite; TSH, thyroid stimulating hormone; T4, thyroxine; TT4, total thyroxine; TT3, total triiodothyronine; T3, triiodothyronine.

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http://dx.doi.org/10.1016/j.envint.2015.09.015
0160-4120/

2012), reductions in infant birth weight and length, decreased neurodevelopmental scores in children, and changes in circulating thyroid hormone levels in pregnant women (Herbstman et al., 2010; Chevrier et al., 2010; Roze et al., 2009; Harley et al., 2010; Stapleton et al., 2011b; Turyk et al., 2008). PBDEs in maternal breast milk were also associated with the incidence of cryptorchidism in newborn boys (Main et al., 2007). In a Taiwanese cohort study of 20 women, Chao et al. (2007) found that increased PBDEs in breast milk were related to decreased birth weight and birth length, chest circumference, and Quetelet's index of infants, following adjustment for maternal age, pre-pregnancy body mass index (BMI), and parity (Chao et al., 2007). In an e-waste recycling region in China, significant differences in PBDEs in umbilical cord blood were found between samples from normal births and those with adverse birth outcomes including premature delivery, low birth weight, and still birth, whereby median PBDE levels in the adverse birth outcome group were significantly higher than those in the normal birth group (Wu et al., 2010). While some studies have found associations between PBDEs and birth outcomes, other studies have not (Tan et al., 2009). In addition to small sample numbers, multiple chemical exposures, both to other contaminants and different mixtures of PBDEs, could explain some of the differences across these studies.

Due to these observations in human epidemiological studies, and animal exposure studies demonstrating effects both on thyroid hormone regulation and neurodevelopment, researchers have started questioning whether the observed associations between PBDE body burdens and adverse birth outcomes and neurodevelopment may be mediated through thyroid hormone dysregulation (Dingemans et al., 2011). A number of animal exposure studies using different animal models have demonstrated that exposure to PBDEs can result in reductions in the circulating levels of thyroxine (T4), and sometimes triiodothyronine (T3) (Zhou et al., 2002; Fernie et al., 2005; Law et al., 2006b). However, in human epidemiological studies, one using the same cohort reported on here and two using additional cohorts, both positive and negative associations between serum PBDEs and T4 have been observed (Stapleton et al., 2011b; Turyk et al., 2008; Vuong et al., 2015; Zota et al., 2011). One study found positive associations between PBDEs and thyroid stimulating hormone (TSH) among pregnant women (Chevrier et al., 2010). The specific pathways by which PBDEs alter circulating levels of T4 and T3 are currently unclear (Harley et al., 2011), and may vary depending on the age, sex, and developmental stage of the exposed individual. An in vitro study using human liver tissues demonstrated that PBDE metabolites (OH-BDEs) can inhibit thyroid deiodinase (dio) activity (Butt et al., 2011), which may influence the circulating levels of thyroid hormones. Another study further demonstrated that OH-BDEs can competitively bind to serum proteins that transport thyroid hormones (Meerts et al., 2000), while another study found that PBDEs can lead to upregulation of hepatic enzymes that metabolize and clear thyroid hormones from the body (Szabo et al., 2009). Regardless of the mechanism and direction of change, alterations in thyroid hormone regulation during pregnancy can impact developing fetuses (Hulbert, 2000). Therefore, examining the potential for interaction of PBDEs and thyroid hormone levels on birth outcomes is important.

In the current study, we build on our previous research (Stapleton et al., 2011b) that examined the relationships between PBDE exposure during pregnancy and maternal circulating thyroid hormone levels. We previously reported positive associations between maternal serum PBDEs and free and total thyroxine (T4) during the third trimester of pregnancy in a cohort of predominantly low-income, non-Hispanic black women in Durham County, North Carolina (Stapleton et al., 2011b). Using the same PBDE and thyroid hormone data set collected from pregnant women from the Healthy Pregnancy, Healthy Baby (HPHB) cohort, we extend this research by conducting an exploratory analysis of our hypothesis that PBDEs may interfere with fetal growth regulation either directly or by disrupting thyroid hormone levels or thyroid hormone homeostasis. We first examine whether maternal PBDE serum levels are adversely associated with infant birth weight, head circumference, birth length, and birth weight percentile for gestational age in this cohort. We then explore the potential mediating role of thyroid hormones in the association of birth outcomes with PBDEs/OH-BDEs. We examine: a) how observed PBDE/OH-BDE-birth outcome associations change in the presence of thyroid hormone levels; and b) the potential for interaction between PBDEs and thyroid hormone

Table 1
Maternal and infant characteristics of pregnancy cohort, Durham, North Carolina (N = 137).

Covariate	Descriptive statistic		
	No. missing	Mean (SD)	IQR
Continuous variables			
Birth weight, g	4	3261 (418)	3005–3570
Birth length, cm	17	49 (2)	48–51
Head circumference, cm	15	34 (1)	33–35
Birth weight percentile for gestational age	4	40 (25)	19–59
Maternal age, years	0	23 (4)	20–25

Covariate	Descriptive statistic		
	No. missing	n	%
Categorical variables			
Male infant sex	2	63	47
First birth	0	69	50
Maternal race			
Non-Hispanic white	0	12	9
Non-Hispanic black	0	109	80
Hispanic	0	13	9
Other race/ethnicity	0	3	2
Maternal educational attainment			
Less than high school	0	20	15
High school diploma	0	73	53
More than high school	0	44	32
No private insurance	0	137	100
Smoking status			
Non-smoker	0	89	65
Smoker	0	20	15
Quit smoking	0	28	20

Abbreviations: IQR, interquartile range.

Table 2
PBDE and metabolite concentrations (nanograms per gram lipid) and thyroid hormone measurements in serum from pregnancy cohort, Durham, North Carolina (N = 137).

	N	MDL	% > MDL	Percentile			
				25	50	75	95
PBDEs							
BDE 28	137	1.2–3.0	38.69	<DL	<DL	2.58	4.9
BDE 47	137	2.0–4.5	94.89	8.98	18.87	30.64	111.36
BDE 66	137	1.2	2.19	<DL	<DL	<DL	<DL
BDE 99	137	2.0–4.5	64.23	<DL	5.5	12.59	46.33
BDE 100	137	1.2	89.05	2.27	4.61	7.2	21.33
BDE 85, 155	137	1.2	16.06	<DL	<DL	<DL	3.35
BDE 153	137	1.2	96.35	3.82	5.65	9.82	31.97
BDE 154	137	1.2	48.18	<DL	<DL	2.4	6.99
Phenolic metabolites							
246 TBP	55	1.4–2.5	38.18	<DL	<DL	14.94	101.67
4′-OH-BDE-49	57	0.01–0.03	71.93	<DL	0.12	0.27	2.04
6′-OH-BDE-47	57	0.01–0.03	66.67	<DL	0.19	0.57	4.9
Thyroid hormones							
TSH (μIU/mL)	136		100	0.89	1.28	1.75	2.88
TT4 (μg/dL)	136	0.5	98.53	5.18	6.9	8.5	10.33
FT4 (ng/dL)	136		100	0.59	0.66	0.75	0.89
TT3 (ng/dL)	136		100	165.25	187.5	220.25	324.25
FT3 (pg/dL)	136		100	2.47	2.71	2.97	3.35

Abbreviations MDL, method detection limit; TSH, thyroid stimulating hormone; TT4, total thyroxine; FT4, free thyroxine; TT3, total triiodothyronine; FT3, free triiodothyronine.