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Association of prenatal and childhood PBDE exposure with timing of puberty in boys and girls

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ABSTRACT

Background: Polybrominated diphenyl ether (PBDE) flame retardants are endocrine-disrupting chemicals that exhibit estrogenic and androgenic properties and may affect pubertal timing.
Methods: Study subjects were participants between 1999 and 2013 in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a longitudinal cohort study of predominantly Mexican origin families in Northern California. We measured serum concentrations of four PBDEs (BDE-47, -99, -100, -153) in blood collected from mothers during pregnancy ($N = 263$) and their children at age 9 years ($N = 522$). We determined timing of pubertal onset in 309 boys and 314 girls using clinical Tanner staging every 9 months between 9 and 13 years of age, and timing of menarche by self-report. We used Poisson regression for relative risk (RR) of earlier puberty and parametric survival analysis for time ratios (TR) of pubertal milestones.
Results: Prenatal concentrations of all 4 congeners and ΣPBDEs were associated with later menarche in girls ($RR_{earlier\ menarche} = 0.5$, 95% confidence interval (CI): 0.3, 0.9 for ΣPBDEs) but earlier pubic hair development in boys ($RR_{earlier\ pubarche} = 2.0$, 95% CI: 1.3, 3.3 for ΣPBDEs). No associations were seen between prenatal exposure and girls' breast or pubic hair development or boys' genital development. Childhood PBDE exposure was not associated with any measure of pubertal timing, except for an association of BDE-153 with later menarche.
Conclusions: We found that prenatal PBDE exposure was associated with later menarche in girls but earlier pubarche in boys, suggesting opposite pubertal effects in girls and boys.

1. Introduction

Age at onset of puberty among girls, defined as first breast development (thelarche), has been decreasing over recent decades (Biro et al., 2013; Euling et al., 2008; Herman-Giddens et al., 1997), potentially placing girls at increased risk of reproductive cancers (Kelsey et al., 1993; Riman et al., 1998), psychiatric disorders (Graber et al., 2004; Hayward et al., 1997), and behavior problems (Flannery et al., 1993; Lanza and Collins, 2002; Phinney et al., 1990; Udry and Cliquet, 1982). Recent evidence suggests that age of onset of puberty in boys, defined by testicular enlargement (gonadarche) and the appearance of pubic hair (pubarche), may also be decreasing (Herman-Giddens, 2006; Herman-Giddens et al., 2001). The reasons for the downward shifts in timing of puberty are unclear, but one hypothesis is that exposure to endocrine disruptors – chemicals that mimic, block, or interfere with the body's natural hormones – may impact pubertal timing in children (Chiabotto et al., 2006; Massart et al., 2006).

Polybrominated diphenyl ethers (PBDEs) are a class of brominated chemicals used for many years as flame retardants in consumer products such as furniture, textiles, and electronics (U.S. DHHS, 2004). The pentaBDE mixture, which includes the congeners BDE-47, -99, -100, and -153, was widely used in furniture and other household products containing polyurethane foam until its use was discontinued in 2004. Exposure to the pentaBDE mixture is widespread, with >93% of Americans having detectable levels of BDE-47, -100, and -153 in their blood (Sjödin et al., 2008b). Although use of PBDE flame retardants has stopped, exposure continues because they are present in existing furniture, electronics, and other large items in the home, are not chemically bound and can leach out into house dust (Sjödin et al., 2008a), and are persistent in the environment and the body (Geyer et al., 2004; Hale et al., 2003; Sjodin et al., 2003).

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Several studies have shown that PBDEs (Hamers et al., 2006; Harju et al., 2007; Stoker et al., 2005) and their hydroxylated PBDE (OH-PBDE) metabolites (Hamers et al., 2008; Meerts et al., 2000) have endocrine-disrupting properties, which may differ by congener. In estrogen receptor binding assays, lowerbrominated PBDEs and OH-PBDEs (e.g. BDE-28, -47 and -100) exhibit estrogenic activity (Dang et al., 2007; Meerts et al., 2001), while higher-brominated congeners (e.g. BDE-153 and -190) display anti-estrogenic properties (Meerts et al., 2001). The pentaBDE mixture also exhibits anti-androgenic activity in androgen receptor binding assays (Harju et al., 2007; Stoker et al., 2005).

A small number of animal studies suggest that PBDE exposure may impact timing of puberty. In female rats, gestational (Lilienthal et al., 2006; Kodavanti et al., 2010) and peripubertal (Stoker et al., 2004) exposure to pentaBDE and BDE-99 have been associated with significant delays in puberty as measured by age at vaginal opening or mammary gland development. In two studies of male rats, gestational (Kodavanti et al., 2010) and peripubertal (Stoker et al., 2004) exposure to the pentaBDE mixture were associated with later puberty, assessed by age at preputial separation, although gestational exposure to BDE-99 was non-significantly associated with earlier preputial separation in another study (Lilienthal et al., 2006).

In human studies, prenatal PBDE exposure has been associated with reduced fertility (Harley et al., 2010), altered thyroid hormone and sex hormone levels (Chevrier et al., 2011; Chevrier et al., 2008; Eskenazi et al., 2016; Herbstman et al., 2008; Lin et al., 2011; Stapleton et al., 2011), lower infant birth weight (Harley et al., 2011), and impaired childhood neurodevelopment and behavior (Chevrier et al., 2013; Eskenazi et al., 2013; Herbstman et al., 2010; Sagiv et al., 2015), but only two studies have examined timing of puberty. Among 271 adolescent girls participating in the National Health and Examination Survey (NHANES), higher serum PBDE concentrations between ages 12 and 19 years was associated with early menarche (<12 years of age) (Chen et al., 2011). However, among 645 girls participating in the Breast Cancer and the Environment Research Program, higher exposure to several individual PBDE congeners between ages 6 and 8 years was associated with older age at onset of breast and pubic hair development (Windham et al., 2015). No epidemiologic studies have examined the association of PBDEs and puberty in boys or have examined the association of in utero exposure and puberty in boys or girls.

In the present prospective study, we examined the association of prenatal and childhood exposure to four components of the pentaBDE flame retardant mixture on timing of puberty in girls and boys.

2. Methods

2.1. Study population

Participants were children in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a longitudinal cohort study examining the effects of environmental exposures on children's growth and development in a largely Latino region of California. Participants were enrolled in the study in two waves: in the first wave (CHAM1), 601 pregnant mothers were recruited from prenatal care clinics in 1999–2000, and 529 mothers stayed in the study through the birth of a live born infant. The CHAM1 children were assessed at multiple time points throughout childhood, with 326 children (54.2%) continuing to participate in the study at age 9 years. In the second wave of enrollment in 2009–2011, 305 additional mothers and their 9-year-old children were recruited through community outreach (CHAM2). Eligibility requirements were the same for both waves: the children were born between 2000 and 2002 in the Salinas Valley to Spanish- or English-speaking mothers who, at the time of pregnancy, were at least 18 years of age and were eligible for low income health insurance (Medicaid). Pubertal timing was assessed in 641 children between 9 and 13 years of age. We excluded 18 participants who did not provide serum samples for PBDE measurements, for a total of 623 children (309 boys and 314 girls). This study was approved by the Institutional Review Board at the University of California, Berkeley. Informed consent was obtained from mothers and assent was obtained from children for all activities.

2.2. Physical exam and pubertal assessment

At 7 years of age, we used Tanner stage diagrams (Tanner, 1986) to obtain mothers' report of their daughters' pubertal stages. Between the ages 9 and 13 years, five trained research assistants assessed timing of puberty using clinical Tanner staging conducted at 9 month intervals. We assessed girls' stages of breast development (B1–B5) using palpation and pubic hair development (PH1–PH5) using visual inspection. Menarche status was asked at each visit and age at menarche was ascertained at the first post-menarchal visit. We visually assessed boys' stages of genital (G1–G5) and pubic hair development (PH1–PH5) and measured testicular volume (TV) by comparison with orchidometer beads. A boy was not considered to be in stage G2 unless his TV was >3 cm^3. Research assistants were trained and supervised by two pediatric endocrinologists (R.L. and L.G.). Kappas for inter-rater reliability were 0.70 for breast and 0.79 for pubic hair development in girls, and 0.75 for genital and 0.86 for pubic hair development in boys. The examiners' assessments agreed with those of the pediatric endocrinologists 90%, 92%, 92%, and 100% of the time for girls' breast and pubic hair stage and boys' genital and pubic hair stage, respectively, with regard to whether the child was in stage 1 versus stage 2 +.

At each visit, we measured weight (Tanita TBF 300A bioimpedence scale) and height (Seca 222 stadiometer). Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and classified as underweight, normal weight, overweight, or obese according to CDC age- and sex-specific percentiles (National Center for Health Statistics, 2005). Child's birth weight was obtained from medical records. Maternal pre-pregnancy BMI was based on measured height and either self-reported (CHAM1) or medical record (CHAM2) pre-pregnancy weight.

2.3. PBDE exposure assessment

PDBE concentrations were measured in serum collected from 263 CHAM1 mothers during pregnancy ($N = 203$; mean: 25.7 weeks gestation) or at delivery ($N = 60$) and 522 CHAM1 and CHAM2 children at age 9. Serum was stored at −80 °C until shipment to the Centers for Disease Control and Prevention in Atlanta, GA, where specimens were analyzed for 10 PBDE congeners (BDE-17, -28, -47, -66, -85, -99, -100, -153, -154, and -183) by gas-chromatography isotope-dilution high-resolution mass spectrometry (Sjödin et al., 2004). Each analytical run included laboratory blanks and spikes.

PBDE concentrations are expressed on a serum lipid basis (ng/g lipid) (Phillips et al., 1989). Limits of detection ranged from 0.8–2.6 ng/g for BDE-47 and 0.2–0.7 ng/g for other congeners. For concentrations below the limit of detection (LOD), the machine-read value was used if available or a value <LOD was imputed based on a log-normal probability distribution if not (Lubin et al., 2004). Of the 10 congeners analyzed, 6 were detected in <55% of samples and were not included in this analysis. The four components of the pentaBDE commercial mixture (BDE-47, −99, −100, and −153) were detected in 97% of samples. These four congeners were examined individually and summed to generate a ΣPBDE variable.

2.4. Covariates

Information on potential confounders was collected using structured interviews conducted in the mother's language of choice (English or Spanish) during pregnancy and/or at the 9-year visit. Potential confounders were selected a priori using directed acyclic graphs (Supplemental Figs. S1 & S2). All models controlled for mother's education and years of residence in the United States at time of pregnancy, child's