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Does exposure to flame retardants increase the risk for preterm birth?

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ABSTRACT

During the past 40 years, polybrominated diphenyl ethers (PBDEs) have been widely used as flame retardants and nearly all women have some level of exposure. PBDEs have been isolated from amniotic fluid and cord plasma indicating vertical transmission; however, their effects on pregnancy outcome are largely unknown. Therefore, we quantified PBDE-47, the most common congener in maternal plasma samples collected at the time of labor from women who subsequently had term or preterm birth (PTB). Women were then scored based on whether or not they had very low, low, medium, high or very high peripheral plasma concentrations of PBDE-47. Probit regression analysis suggested that women in the PTB group had a greater chance of scoring higher on this scale ($P < 0.001$). Women with high (OR = 3.8, CI: 1.6, 9.7; $P = 0.003$) or very high PBDE-47 concentrations were at greater odds (OR = 5.6, CI: 2.2, 15.2; $P < 0.001$) for PTB than women with very low levels of PBDE-47. Results became even more significant after adjustment for maternal race, age, and marital status. These findings suggest that high levels of maternal exposure to PBDEs might increase the risk for PTB.

1. Introduction

Polybrominated diphenyl ethers (PBDEs) have been in widespread use as flame retardants in home construction, furniture, clothing, and electronic appliances for decades. They save lives and reduce injury by giving occupants valuable time to extinguish or escape from a spreading fire. However, they are not covalently bound to materials that they are used in. With time, they leach into the environment and have become one of the most prevalent of the persistent organic pollutants (POPs).

Polybrominated diphenyl ethers most commonly enter the body through inhalation or ingestion of PBDE-contaminated dust where they bioaccumulate in lipophilic tissues (Costa and Giordano, 2007; Costa et al., 2008). Their concentrations have been increasing in human tissues since their introduction into consumer products in the 1970s (Schecter et al., 2005; Thomsen et al., 2002; Fängström et al., 2008). Breast-milk and blood concentrations of PBDEs are 10- to 100-fold higher in the United States than in other countries (Costa and Giordano, 2007; Costa et al., 2008), reflecting greater usage, which is often for compliance with strict fire codes (Trudel et al., 2011).

Polybrominated diphenyl ethers may affect human health as endocrine disruptors because of their structural

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similarity to triiodothyronine (T_3) and thyroxine (T_4). Site-directed mutagenesis and bioassay studies indicate that PBDEs interfere with the ligand-binding domain of the thyroid hormone receptor (TR) to inhibit the transcription of TR-dependent genes and their biological effects (Ibhazehiebo et al., 2011). Developmental exposure to PBDEs causes hypothyroid-like conditions in pregnancy and increased hyperactivity and learning and memory deficits in the offspring (Branchi et al., 2003; Costa and Giordano, 2007).

Polybrominated diphenyl ethers have been detected in amniotic fluid (Miller et al., 2012), umbilical cord plasma (Vizcaino et al., 2011; Frederiksen et al., 2010, 2009b; Kim et al., 2009; Kawashiro et al., 2008; Gómara et al., 2007; Herbstman et al., 2007; Jaraczewska et al., 2006), umbilical cord tissue (Kawashiro et al., 2008), placental tissues (Frederiksen et al., 2009a; Qing Zhang et al., 2008; Gómara et al., 2007; Main et al., 2007), and fetal membranes (Miller et al., 2009). Maternal plasma levels have recently been found to correlate with higher thyroid-stimulating hormone (TSH) levels (Zota et al., 2011). TSH is negatively regulated by T_3 and T_4, suggesting the reduced bioactivity of these hormones. Overt and subclinical hypothyroidism increase the risk for preterm birth (PTB) (Vissenberg et al., 2012; Stagnaro-Green, 2011). Therefore, we hypothesized that increased exposure to PBDEs might increase the risk of spontaneous PTB.

2. Materials and methods

2.1. Patients and sampling

Samples for this study were collected as a part of a larger study that investigated genetic biomarkers for PTB. The parent study was approved by the Western institutional review board and the Tristar Nashville institutional review board. Written consent was acquired from all patients to use their samples for the original study and to deposit them into a biobank for use in future research projects that would include the current study. All subjects were recruited at Centennial Women's Hospital in Nashville, TN, USA, between September 2008 and December 2011. Pregnant women between the ages of 18 and 40 were eligible and enrollment occurred at the time of admission for delivery. All subjects had regular uterine contractions at a minimum frequency of two contractions every 10 min. Gestational age was determined by last menstrual period dating and verified by ultrasound dating.

Maternal blood samples were collected in EDTA tubes at the time of admission for preterm or term labor and transported to the blood on ice. Blood samples were then centrifuged at $1500 \times g$. Plasma was then separated, aliquoted, and stored at $-80\,^{\circ}C$ until assay. Samples from patients whose pregnancies ended in spontaneous PTB without pPROM were randomly selected for the present study as cases. The distribution of gestational age at delivery was: quartile 1, 23–32.6 weeks; quartile 2, 32.6–35.1 weeks; quartile 3, 35.1–36 weeks; quartile 4, 36–37 weeks. Samples from women with term labor and delivery (37 weeks), intact membranes, and no pregnancy-related complications were randomly selected for this study to use as controls (without any matching criteria).

2.2. Immunoassays

Polybrominated diphenyl ether(s) exist as 209 different congeners that are usually quantified by high-resolution mass-spectroscopy; however, PBDE-47 is the most abundant congener in the environment. It is well-studied in pregnant and nonpregnant women and concentrations of this particular congener correlate well with total PBDE exposure (Frederiksen et al., 2010). To reduce the cost of performing studies where PBDEs must be quantified, immunoassays have been developed and found to be useful for quantifying PBDE-47 in biological and environmental samples that correlate well with data from mass spectroscopy of the same samples (Shelver et al., 2008; Xu et al., 2009). We used a commercially available version of this immunoassay (Abraxis, Warminster, PA, USA) to quantify PBDE-47 equivalents 25–1000 pg/ml in maternal plasma samples for this project. In this assay, PBDE-47 in the samples competes with horseradish peroxidase-conjugated PBDE for binding sites onto an antibody attached to magnetic beads. Beads are then separated and washed with buffer, incubated in substrate, and color development is monitored by absorbance at 450 nm. Sample concentrations are estimated from a standard curve of 0–1000 pg/ml PBDE-47. PBDE concentrations below the sensitivity of the assay (25 pg/ml) were set equal to the sensitivity of the assay for analysis.

2.3. Statistical analyses

All statistical analyses were performed using the R programming language (www.r-project.org). Comparisons of patient characteristics between groups were made using χ^2 or Wilcoxon rank-based tests. When evaluating PBDE-47 levels, a significant number of samples fell above the standard curve (1000 pg/ml), and there was insufficient sample to re-assay them at a lower dilution. Therefore, patient samples were ranked on an ordinal scale of 1–5 based on having very low (135 pg/ml), low (136–199 pg/ml), moderate (200–321 pg/ml), high (322–1000 pg/ml) or very high (>1000 pg/ml) maternal plasma concentrations of PBDE-47. These cutoffs were based on quartiles for PBDE-47 concentrations in a subset of patients from the control group whose PBDE-47 levels were <1000 pg/ml. Ordinal scale values of patients with high PBDEs and low PBDEs were compared using probit regression, as previously described (Faraway, 2006). Logistic regression methods were used to compare the potential association of level of PBDE with the risk of PTB. All models were checked for lack-of fit by analysis of deviance (Faraway, 2006) and the analysis was restricted to patients for whom there were complete data. Results are presented as proportions and odds ratios with 95% CI.

3. Results

Basic patient demographics are shown in Table 1. Although both outcome groups were similar with regard