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A nested case-control study of the association between exposure to polybrominated diphenyl ethers and the risk of gestational diabetes mellitus

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is rapidly increasing worldwide. Exposure to endocrine-disrupting chemicals such as polybrominated diphenyl ethers (PBDEs) is thought to be a contributor to GDM, independent of diet and physical activity.

Objective: The prospective association between PBDEs body burden in early pregnancy and GDM risk was investigated.

Methods: A nested case-control study of 439 pregnant women was conducted between 2013 and 2015 in Beijing, China. Seven predominant PBDE congeners were measured in first trimester maternal serum by gas chromatography-high resolution mass spectrometry. Pregnant women were screened for GDM at 24–28 weeks of gestation using the oral glucose tolerance test. GDM was defined based on the diagnostic criteria set by China Ministry of Health. Conditional logistic and linear regression were used to estimate the association between PBDEs exposure and GDM risk, and PBDEs exposure and glucose level, respectively.

Results: A total of 77 (17.5%) women developed GDM in this study. Median concentrations of PBDEs were higher in women with GDM. Analyses parameterizing PBDE concentrations as continuous variables suggested significant associations between BDE-153, -154, -183 and GDM risk with an estimated odds ratio of 4.04 (95%CI: 1.92, 8.52), 1.88 (95%CI: 1.15, 3.09) and 1.91 (95%CI: 1.31, 2.08), respectively. In the quartile analyses, a significant increase in the odds ratio of GDM was associated with the highest levels of BDE-153 (OR = 3.42 95%CI: 1.49, 7.89) and BDE-183 (OR = 3.70, 95%CI: 1.58, 8.65), whereas, BDE-154 demonstrated an inverted U-shaped association with GDM. In addition, BDE-153 and -154 were significantly positively associated with fasting glucose, and both 1 h and 2 h glucose level ($p < 0.05$).

Conclusions: These results suggest that exposure to PBDEs disturbs maternal glucose homeostasis and increases the risk of GDM. These findings should be replicated in future studies with a larger population and wider range of exposure.

1. Introduction

Polybrominated diphenyl ethers (PBDEs) are flame retardant chemicals and have been used as additives to retard fire in a variety of commercial and household products since the 1960s (Siddiqi et al., 2003). PBDEs have entered the environment via emissions from manufacturing processes, volatilization from various furniture products and leachate from waste disposal sites (Rahman et al., 2001), which has resulted in human exposure. China is one of the major PBDE manufacturing countries and has an increasing annual market demand due to rapid economic growth in recent decades. The amendments of the Stockholm Convention that list the components of the penta- and octa-BDE commercial mixtures as persistent organic pollutants (POPs) were ratified by China, and the production, circulation, use and import of PBDEs have all been prohibited since 2014 (Zhang et al., 2017). However, products containing PBDEs (e.g., furniture, textiles and electronics) are still in use in many households, and human exposure will likely continue for some time. Concerns have been widely

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expressed with regard to the possible adverse health effects of exposure to PBDEs.

Gestational diabetes mellitus (GDM), a common medical complication in pregnancy, is rapidly increasing worldwide. According to the latest diagnostic criteria established by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in 2010, GDM prevalence was estimated to be 9.8–25.5% worldwide (Sacks et al., 2012). This high prevalence is of great concern as GDM is significantly associated with an increased risk of type 2 diabetes (T2D) and leads to several health complications for both mother and child (Bellamy et al., 2009; Osgood et al., 2011). The consensus on risk factors for GDM (e.g. maternal age, overweight/obesity, family history of diabetes) fails to fully account for the large and rapid increase in prevalence. Attention is now focused on environmental factors as increasing evidence supports the plausible contribution of specific environmental chemicals, including PBDEs, in the etiology of diabetes (Magliano et al., 2014; Taylor et al., 2013). In animal studies, PBDEs have been demonstrated to have diabetogenic effects, such as disturbing glucose and lipid metabolism (Hoppe and Carey, 2007; Nash et al., 2013), inducing hyperglycemia (Zhang et al., 2013; Zhang et al., 2016), and influencing insulin production and sensitivity (Karandrea et al., 2017; Nash et al., 2013). A more recent epidemiological study in two independent communities found that BDE-47 significantly increased the risk of diabetes (Zhang et al., 2016). In addition, using the data from the U.S. National Health and Nutrition Examination Survey (NHANES), Lim et al. found that BDE-153 was significantly associated with both T2D and metabolic syndrome (Lim et al., 2008). These studies have provided the impetus to examine the contribution of PBDEs in GDM risk, while evidence regarding an association between PBDEs exposure and GDM risk is still very limited.

Pregnancy may be a window of susceptibility where researchers can examine the role environmental chemicals play in the etiology of GDM and subsequently T2D (Robledo et al., 2016). Although several previous studies have assessed the association between many flame retardants including PBDEs and increased risk of T2D or GDM, most of these studies were cross-sectional and measured PBDEs exposure and outcome at one point in time (Lim et al., 2008; Smarr et al., 2016; Turyk et al., 2009a, 2009b; Zhang et al., 2016). Therefore, causal evidence on PBDEs exposure and diabetes risk is scarce. In the present study, we addressed the issues of PBDEs exposure and outcomes, and performed a nested case-control study in a prospective cohort to investigate the association between PBDEs exposure in early pregnancy and GDM risk as well as the status of glucose homeostasis (Thomas, 2009).

2. Materials and methods

2.1. Study design and population

A nested case-control study was designed to determine the exposure of a non-occupational population to PBDEs and the risk of GDM. Primipara healthy pregnant women at first trimester were recruited between August 2013 and June 2015 at Xicheng Maternal & Child Health Hospital in Beijing, China. Women receiving prenatal care and planning on delivering at this site were eligible to participate if they had no previous or family history of diabetes. The whole study was approved by the Ethics Committee of China National Center for Food Safety Risk Assessment, and all participants were aware of the purpose of this study and signed the informed consent.

Participants were screened for GDM using a 75-g oral glucose tolerance test (OGTT) at 24–28 weeks of gestation. During the study period, a total of 439 women were included in the cohort and provided blood samples. Of these women, 77 developed GDM and were included as case subjects in the analysis. For each GDM subject, two controls were selected from those in the cohort who did not develop GDM. Controls were matched to cases based on age within 2 years. The final sample size for analyses was 231 women (77 GDM cases and 154 controls).

2.2. Blood collection and exposure assessment

Maternal overnight fasting venous blood specimens (10-mL) were collected by nurses from pregnant women at the first trimester in the study hospital. The samples were immediately centrifuged and the liquid supernatant was stored at −40 °C for subsequent analysis of PBDEs and blood lipid parameters.

The sources and timing of PBDEs exposure were unknown, and given that PBDEs are persistent chemicals in the body with a long half-life, PBDEs levels in first trimester maternal serum were measured to evaluate accumulative exposure before pregnancy and the variations in exposure during pregnancy. Under the study design, selected PBDE congeners were measured in all study cases and pair-matched control serum samples. An aliquot (2 mL) of serum was spiked with ^{13}C-labeled surrogate standards (BDE-MXG, Wellington Laboratories Inc., Breslau, Ontario, Canada) and then mixed with 15 g diatomite. The mixture was extracted by ASE 350 (ThermoScientific, Sunnyvale, CA, USA). Anhydrous sodium sulfate (10 g) was added to the extract to remove the water. The extract was then concentrated to almost 1 mL, and subsequently purified by the tandem columns of acid silica gel and carbon (CAPE Technologies, South Portland, ME, USA). The fractions containing PBDEs were concentrated to near dryness and then re-dissolved in approximately 40 μL nonane. A ^{13}C-labeled injection standard (BDE-ISS, Wellington Laboratories Inc., Breslau, Ontario, Canada) was spiked prior to instrumental analysis. Identification and quantification were completed by gas chromatography-high resolution mass spectrometry (GC-HRMS, DFS, ThermoScientific, Bremen, Germany). The extracts (1 μL) were injected and separated on a DB-5 MS capillary column (15 m × 0.25 mm i.d. × 0.1 μm) with GC programmed at 120 °C and held for 2 min followed by 15 °C/min raised to 230 °C, 5 °C/min to 270 °C, and 9 °C/min to 325 °C and held for 2 min. Mass spectrometry resolution was set at > 8000 for measurements. Serum total cholesterol and triglycerides were analyzed by a TBA-120FR automatic biochemical analyzer (Toshiba Medical System, Tokyo, Japan).

Seven PBDE congeners (BDE-28, -47, -99, -100, -153, -154, -183) of primary interest were measured in maternal serum. The total PBDE concentration was calculated by summing the concentrations of all seven individual PBDE congeners. PBDEs concentrations were expressed as pg/g wet weight serum. The method detection limit (MDL) was 0.01–0.03 pg/g. BDE-28, -49, -99, -100, and -153 were detected in all serum samples. BDE-154 and -183 were not detectable in only one or two serum samples and the value was assigned as MDL/2 for further data analysis.

All serum samples were measured by a laboratory analyst without any knowledge of exposure and outcome status. Samples were analyzed using standard laboratory QA/QC protocols: each analytical batch of 10 serum samples was accompanied by a procedure blank and a standard reference material (Organic Contaminants in Non-Fortified Human Serum, SRM1957) purchased from the U.S. National Institute of Standards and Technology. The average amount in blank samples was subtracted from the amount in the samples. The precision and accuracy of PBDEs from SRM1957 were within the certified reference ranges recommended by the manufacturer. Recovery of the ^{13}C-labeled internal standard in all samples was in the criteria range of 25–150% established by the U.S. EPA (EPA 1614 draft).

2.3. GDM diagnosis

The diagnosis of GDM was made following the Diagnostic Criteria for Gestational Diabetes Mellitus (WS311-2011) released by the Ministry of Health of China (Yang, 2012), which coincided with the recommendations by the International Association of Diabetes and Pregnancy Study Groups (IADPSG). Briefly, the subjects were tested in the morning after an overnight fast of at least 8 h. The first blood