Original Article

Concentrations of Polybrominated Diphenyl Ethers in Maternal Blood, Placental Size, and Risk for Fetal Growth Restriction: A Nested Case-control Study*

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Abstract

Objective To explore the effects of prenatal exposure to polybrominated diphenyl ethers (PBDEs) on placental size and birth outcomes.

Methods Based on the perspective Wenzhou Birth Cohort, this nested case-control study included 101 fetal growth restriction (FGR) and 101 healthy newborns. Maternal serum samples were collected during the third trimester and measured for PBDEs by gas chromatography tandem mass spectrometry. The basic information of mother-newborn pairs was collected from questionnaires, whereas the placental size and birth outcomes of newborns were obtained from hospital records.

Results A total of 19 brominated diphenyle ether (BDE) congeners were detected in maternal serum samples. Higher concentrations of BDE-207, -208, -209, and $\sum_{19}$PBDEs were detected in FGR cases than in controls. Increased BDE-207, -208, -209, and $\sum_{19}$PBDEs levels in maternal serum were related to decreased placental length, breadth, surface area, birth weight, birth length, gestational age, and Quetelet index of newborns. After adjusting for confounders, BDE-207 and $\sum_{19}$PBDE concentrations in maternal serum were significantly associated with an increased risk of FGR.

Conclusion A negative association was found between PBDE levels in maternal serum and placental size and birth outcomes. Prenatal PBDE exposure may be associated with elevated risk of the incidence of FGR birth.

Key words: Polybrominated diphenyl ethers; Fetal growth restriction; Maternal serum; Birth outcome

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INTRODUCTION

Polybrominated diphenyl ethers (PBDEs) are flame-retardant additives that are widely used in aerospace, transportation, interior decoration, and other personal-care products to ensure fire safety[1]. PBDEs have been used since the 1970 s, until their toxicological effects (neurological, reproductive, immune toxicity and endocrine disruption) were found in a great deal of animal and epidemiological studies[2]. In general, people are exposed to PBDEs through dietary intake

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and respiratory and dermal absorption, and biological monitoring is used to estimate the exposure levels of PBDEs in humans. At present, the samples analyzed mainly include blood (e.g., whole blood, serum, plasma, and umbilical cord blood), urine, breast milk, hair, and tissues (e.g., fat, placenta, and liver)[3-5]. Maternal serum is the most commonly used bio sample to detect PBDE exposure level during pregnancy because of its easy availability.

Fetal growth restriction (FGR) is defined as a developmental problem in which the growth rate of the fetus is lower than the expected growth potential of an infant due to placental compromise[6]. FGR is one of the prime reasons of perinatal–neonatal morbidity and mortality and one of the causes of long-term chronic diseases[7-8]. Previous PBDEs are detected in the umbilical cord blood and placental tissues, and the concentration of PBDEs in umbilical cord blood serum is closely related to the placental area, suggesting that PBDEs can pass through the placental barrier and further threaten fetal growth and development[9-11]. Nonetheless, no epidemiological evidence determines whether prenatal PBDE exposure can affect the FGR birth through disturbance of placental growth.

In this study, we hypothesized that prenatal PBDE exposure can affect placental growth and lead to the increased risk of FGR birth. Therefore, a nested case-control study was designed to investigate the effects of prenatal PBDE exposure on placental size and birth outcomes of newborns based on a birth cohort in Wenzhou, China.

METHODS

Study Population and Sample Collection

This research was a nested case-control study within the Wenzhou Birth Cohort, a prospective birth cohort study conducted at the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University in Wenzhou, China to investigate the associations of fetal growth and prenatal environmental endocrine disruptor exposure. Participants were enrolled in the cohort when they underwent prenatal examination at their second trimester. The exclusion criteria were pregnant women with pregnancy complications, including hypothyroidism and gestational diabetes mellitus, that have significant effects on fetal weight, who actively smoked or drank alcohol, and had delivered twins and malformed fetus. FGR was defined as the newborn infant with birth weight below the 10^{th} percentile for the same gestational age. The healthy newborns were included as controls while matching with the FGR cases for infant sex and maternal age. FGR cases and controls were matched at 1:1 ratio. During the study period, we selected 101 FGR cases and matched 101 controls from 1,750 participants in Wenzhou Birth Cohort study. All participants signed written informed consent documents approved by the institutional review committee before participating in the study. The basic information of maternal-newborn pairs, such as maternal age, education level, monthly income, and pregnancy complications, was collected through questionnaires. Newborn birth weight, birth length, gestational age, sex, and delivery mode were obtained from hospital records. Quetelet index was calculated by the formula: birth weight/birth length × 1,000.

Maternal serum samples were collected at 34 weeks of gestation by medical staff, coded, frozen, and kept at −80 °C until chemical analysis. The placenta parameters were measured by medical staff immediately after childbirth. Placental surface area (cm^2) was calculated using the formula: length × breadth × $\pi/4$[12].

PBDE Measurement in Maternal Serum

A total of 19 common brominated diphenyle ether (BDE) congeners (BDE-17, -28, -33, -47, -49, -66, -99, -100, -138, -153, -154, -183, -190, -196, -203, -206, -207, -208, and -209) were determined by gas chromatography coupled to mass spectrometry. The methods for extraction and instrumental analysis of PBDEs from blood specimen were described in our previous studies[11]. The limits of detection (LOD) of individual BDE congener were 0.10 ng/mL for lower-brominate BDE congeners and 0.25 ng/mL for higher-brominate BDE congeners. The concentrations of PBDEs were lipid weight adjusted (ng/g lipid weight). For concentrations below the LOD, we imputed a value equal to the LOD divided by the square root of two for data analysis[13].

Statistical Analyses

Normally distributed continuous variables were expressed as mean ± standard deviation. For demographic characteristic, we used the Student's *t* test to identify statistically significant differences in continuous variables and the χ^2 test to identify differences in categorical variables. Mann–Whitney

U test was used to assess the concentrations of BDE congeners between FGR cases and healthy controls in maternal serum samples.

Multiple linear regression models were used to analyze the correlation of PBDE levels in maternal serum with placental growth indicator (length, breadth, and surface area) and birth outcomes (birth weight, birth length, gestational age, and Quetelet index). We used multivariate logistic regression to evaluate the correlation between the probability of FGR birth and the levels of PBDEs in maternal serum. Newborn's sex, gestational age, maternal age, maternal education level, family annual income, and pregnancy syndrome were considered as potential confounders and adjusted in logistic regression models. SPSS 24.0 was used to perform statistical analyzes, and $P < 0.05$ was considered significant.

RESULTS

Population Characteristics

Overall, 202 maternal-infant pairs (101 FGR cases and 101 controls) were enrolled in the present study. The population characteristics of FGR cases and healthy newborns were listed and compared (Table 1). The average birth weight and gestational age of FGR cases were (2.29 ± 0.43) kg and (36.4 ± 4.0) weeks, respectively, which were significantly lower than those of the controls (3.31 ± 0.34) kg and (39.1 ± 1.1) weeks, respectively, $P < 0.001$). The Quetelet index of FGR cases was significantly lower than that of controls [(48.31 ±

Table 1. Demographic characteristic of maternal-newborn pairs

Demographic characteristic	Total (*n* = 202)	FGR (*n* = 101)	Control (*n* = 101)	*P*-value
Gestational age (weeks)	37.8 ± 3.2	36.4 ± 4.0	39.1 ± 1.1	< 0.001*
Newborn's birth weight (kg)	2.81 ± 0.64	2.29 ± 0.43	3.31 ± 0.34	< 0.001*
Newborn's birth length (cm)	48.83 ± 3.79	47.47 ± 5.09	50.09 ± 0.69	< 0.001*
Quetelet index	57.49 ± 11.29	48.31 ± 7.56	66.03 ± 6.41	< 0.001*
Maternal age (years)	27.8 ± 4.3	27.1 ± 4.9	28.3 ± 3.7	0.097
Placental indicator				
Length (cm)	17.85 ± 2.26	17.03 ± 1.97	18.37 ± 2.29	< 0.001*
Breadth (cm)	17.82 ± 2.25	16.68 ± 2.15	18.54 ± 2.00	< 0.001*
Surface area (cm^2)	252.39 ± 59.54	224.21 ± 47.32	270.38 ± 59.77	< 0.001*
Neonate's sex				0.778
Male	96	49	47	
Female	106	52	54	
Delivery mode				0.198
Vaginal delivery	93	71	22	
Cesarean delivery	109	79	30	
Maternal education level				0.011*
Below high school	48	27	21	
High school	88	51	37	
College and above	66	23	43	
Monthly income (Yuan)				0.665
< 5,000	79	38	41	
> 5,000	123	63	60	
Pregnancy syndrome				0.150
No	149	70	79	
Yes	53	31	22	

Note. **P*-value < 0.05 is statistically significant.

7.56) *vs.* (66.03 ± 6.41), $P < 0.001$]. In terms of maternal feature, no significant difference was observed in the maternal age, delivery mode, monthly income, and pregnancy syndrome between the FGR cases and healthy controls. Regarding placental growth indicators, differences were detected in the placental length (17.03 *vs.* 18.37, $P < 0.001$), breadth (16.68 *vs.* 18.54, $P < 0.001$), and surface area (224.21 *vs.* 270.38, $P < 0.001$) between the FGR cases and controls.

Maternal Serum PBDE Levels

Table 2 shows the median (interquartile range) concentrations of PBDE congeners in maternal serum between the FGR and control groups. The detection rate of seven PBDE homologues were more than 50% (BDE-17, -47, -66, -153, -207, -208, and -209). The concentration of BDE-209 was the highest in the maternal serum of FGR cases and controls. The maternal serum PBDE concentrations of FGR group, especially BDE-207, -208, -209, and $\sum_{19}$PBDEs, were significantly higher than those of healthy controls.

Relationship between Maternal Serum PBDE Levels and Placental Size

Table 3 shows the associations between maternal serum PBDE levels and placental size. A unit increase in BDE-17, -153, -207, -209, and $\sum_{19}$PBDE concentrations in maternal serum was related to a decrease of 0.19–0.23 cm in placental length. Every unit increase in BDE-17, -153, -207, -208, -209, and $\sum_{19}$PBDE concentrations was associated with 0.18–0.31 cm decrease in placental breadth. Similarly, concentrations of BDE-17, -153, -207, -208, -209, and $\sum_{19}$PBDEs were significantly negatively correlated with the placental surface.

Relationship between Maternal Serum PBDE Concentrations and Birth Outcomes

Table 4 shows the relationships between maternal serum PBDE levels and birth outcome indicators, including birth weight, birth length, gestational age, and Quetelet index. A unit increase in BDE-47, -66, -153, -207, -208, -209, and $\sum_{19}$PBDE concentrations was related to a decrease of 0.160.27 g

Table 2. PBDE level in maternal serum between FGR cases and controls (ng/g)

PBDE congener	Detection rate (%)	FGR	Control	*P*-value
		Median (P_{25}, P_{75})	Median (P_{25}, P_{75})	
BDE-17	64.4	0.644 (0.154, 1.594)	0.436 (0.090, 1.040)	0.140
BDE-28&33	40.0	0.175 (< LOD, 1.962)	0.313 (< LOD, 1.498)	0.934
BDE-47	56.9	0.524 (< LOD, 1.645)	0.455 (<LOD, 1.255)	0.279
BDE-49	26.7	< LOD (< LOD, 0.322)	< LOD (< LOD, 1.286)	0.022*
BDE-66	63.9	0.540 (0.158, 3.751)	0.526 (< LOD, 1.793)	0.160
BDE-99	24.8	< LOD (< LOD, 0.205)	< LOD (< LOD, 0.435)	0.929
BDE-100	29.2	< LOD (< LOD, 0.298)	< LOD (< LOD, 0.320)	0.812
BDE-138	39.1	< LOD (< LOD, 1.839)	0.221 (< LOD, 1.941)	0.371
BDE-153	65.3	2.531 (0.703, 5.348)	1.825 (0.412, 3.122)	0.059
BDE-154	31.2	< LOD (< LOD, 0.391)	< LOD (< LOD, 0.724)	0.856
BDE-183	6.9	< LOD (< LOD, < LOD)	< LOD (< LOD, < LOD)	0.040*
BDE-190	8.9	< LOD (< LOD, < LOD)	< LOD (< LOD, <LOD)	0.366
BDE-196	24.3	< LOD (< LOD, 0.704)	< LOD (< LOD, 0.862)	0.984
BDE-203	20.3	< LOD (< LOD, 0.439)	< LOD (< LOD, < LOD)	0.690
BDE-206	46.0	1.709 (< LOD, 9.007)	< LOD (< LOD, 3.379)	0.035*
BDE-207	52.0	2.598 (< LOD, 8.449)	0.698 (< LOD, 3.058)	0.002*
BDE-208	55.0	1.562 (0.298, 5.259)	1.041 (< LOD, 2.679)	0.012*
BDE-209	57.4	7.867 (< LOD, 46.264)	5.908 (< LOD, 18.732)	0.045*
$\sum_{19}$PBDEs	83.7	31.948 (14.119, 93.455)	22.630 (9.204, 43.939)	0.009*

Note. LOD: limit of detection. *P-value < 0.05 is statistically significant.

in birth weight. Every unit increase in BDE-207, -208, -209, and $\sum_{19}$PBDE concentrations were associated with 0.18, 0.21, 0.18, and 0.20 cm decreases in birth length, respectively. Meanwhile, gestational age significantly decreased with the increase in BDE-207, -208, -209, and $\sum_{19}$PBDEs. Likewise, concentrations of BDE-47, -66, -153, -207, -208, -209, and $\sum_{19}$PBDEs showed a significantly negative association with Quetelet index.

Association between PBDE Exposure and FGR Risk

The effect of each BDE congener on FGR birth was assessed after adjusting for potential confounders, including gestational age, education, monthly income, and pregnancy syndrome. As shown in Table 5, BDE-66 [odds ratio (*OR*) = 1.17; 95% confidence interval (*CI*): 1.04 to 1.32], BDE-153 (*OR* = 1.12; 95% *CI*: 1.01 to 1.23), BDE-207 (*OR* = 1.11; 95% *CI*: 1.04 to 1.19), BDE-208 (*OR* = 1.11; 95% *CI*: 1.03 to 1.20), BDE-209 (*OR* = 1.02; 95% *CI*: 1.01 to 1.03), and $\sum_{19}$PBDEs (*OR* = 1.11; 95% *CI*: 1.00 to 1.02) concentrations in maternal serum were significantly associated with the increased risk of FGR. After adjusting for confounders, the association of BDE-207 (*OR* = 1.10; 95% *CI*: 1.02 to 1.19) and $\sum_{19}$PBDE (*OR* = 1.01; 95% *CI*: 1.00 to 1.02) concentrations with FGR birth remained statistically significant.

DISCUSSION

Proper placental development is a necessary condition for a successful pregnancy, whereas abnormal placentation contributes to the pathophysiology of adverse birth outcomes[14-15]. FGR is a heterogeneous condition whose manifestation is usually due to placental compromise[16]. In the current study, we measured PBDE congener levels in maternal serum samples collected from 202 mother-newborn pairs to assess the contribution of prenatal exposure to PBDEs on placental size and FGR birth.

Table 3. Correlation between PBDE concentrations and placental indicator

PBDE congener	Length		Breadth		Surface area	
	Beta	*P*-value	*Beta*	*P*-value	*Beta*	*P*-value
BDE-17	−0.234	0.004*	−0.184	0.024*	−0.224	0.006*
BDE-47	−0.122	0.135	−0.079	0.335	−0.107	0.191
BDE-66	−0.031	0.705	−0.069	0.397	−0.041	0.618
BDE-153	−0.233	0.004*	−0.314	< 0.001*	−0.283	< 0.001*
BDE-207	−0.190	0.019*	−0.211	0.009*	−0.204	0.012*
BDE-208	−0.104	0.201	−0.220	0.007*	−0.173	0.034*
BDE-209	−0.209	0.010*	−0.270	0.001*	−0.252	0.002*
$\sum_{19}$PBDEs	−0.228	0.005*	−0.296	< 0.001*	−0.274	0.001*

Note. * *P*-value < 0.05 is statistically significant.

Table 4. Correlation between PBDE concentrations and birth outcome indicator

PBDE congener	Birth weight		Birth length		Gestational age		Quetelet index	
	Beta	*P*-value	*Beta*	*P*-value	*Beta*	*P*-value	*Beta*	*P*-value
BDE-17	−0.127	0.099	−0.041	0.599	−0.054	0.483	−0.126	0.106
BDE-47	−0.162	0.036*	−0.058	0.461	−0.122	0.113	−0.173	0.026*
BDE-66	−0.228	0.003*	−0.102	0.189	−0.086	0.266	−0.228	0.003*
BDE-153	−0.183	0.017*	−0.139	0.075	−0.105	0.174	−0.180	0.020*
BDE-207	−0.268	< 0.001*	−0.184	0.018*	−0.198	0.010*	−0.242	0.002*
BDE-208	−0.253	0.001*	−0.213	0.006*	−0.280	< 0.001*	−0.204	0.008*
BDE-209	−0.255	0.001*	−0.176	0.023*	−0.247	0.001*	−0.258	0.001*
$\sum_{19}$PBDEs	−0.284	< 0.001*	−0.201	0.010*	−0.261	0.001*	−0.277	< 0.001*

Note. * *P*-value < 0.05 is statistically significant.

The PBDE levels detected in the serum of pregnant women in Wenzhou city were lower than those in Indianapolis, USA[17] but higher than those in Korea[18-19]. Regional differences occurred in the concentration and congener profiles of PBDEs *in vivo* because of the diverse populations and environmental backgrounds and the usage of PBDEs in different areas and laboratory methods in various studies. In general, a low BDE-209 level was suspected in human blood because it is notably less likely to bioaccumulate[20]. High levels would thus mirror an ongoing high exposure to BDE-209, and in occupationally exposed individuals, the BDE-209 serum levels can be considerably higher. For example, a median level of BDE-209 of 35 ng/g was observed in the serum of Swedish rubber production workers[21]. In our study, the serum level of BDE-209 was the highest among all the PBDE congeners studied, followed by BDE-207 and BDE-153, which is similar to the research by Darnerud et al.[22]. BDE-209 is the most dominant congener in human serum from Southeast China. This condition may be due to the production and unrestricted usage of Deca-BDE in China.

To our knowledge, PBDEs can cross the placenta, and maternal exposure may lead to fetal exposure during the period of gestation[23-24]. In this study, prenatal PBDE exposure may disturb placental growth as the result of reduced placental size, which is consistent with our previous finding[11]. Although the mechanism of improper placentation has not been fully elucidated, the role of impaired trophoblast invasion has been implicated in several studies[25-26]. Park et al.[26] showed that PBDEs increased the production of reactive oxygen species (ROS) to stimulate the response of prostaglandin, which might affect placental development because prostaglandins regulate the trophoblast functions necessary for placentation and pregnancy. Similarly, Manuguerra et al. observed that sub-lethal doses of PBDEs can increase the production of ROS over a long period time, altering the energetic metabolism, cell cycle, and antioxidant balance and determining possible adverse effects on cell multiplication balance[27].

We also observed that the increased maternal serum PBDE concentration was related to the decrease in birth outcome indicators (birth weight, birth length, gestational age, and Quetelet index). The relationships among PBDE exposure, placenta size, and fetal growth support the assumption that the adverse effect of PBDE exposure on fetal growth may restrict placental growth. Zhao et al. discovered that prenatal PBDE exposure can adversely affect infant birth outcomes, especially birth weight[28]. Another research of Infancia y Medio Ambiente–Environment and Childhood Project in Spain also showed that PBDEs can impair fetal growth in late pregnancy and reduce birth size[29].

Our study showed that maternal PBDE exposure level in FGR cases was significantly higher than that in controls, and the placental growth of FGR cases fell behind healthy infants. To the best of our knowledge, the size of placenta is directly proportional to its function, resulting in a reduction in the area of nutrition exchange between the pregnant woman and fetus[7]. Thus, maternal PBDE exposure may affect the development of the placenta and lead to FGR birth. Furthermore, the results of multivariate logistic regression indicated

Table 5. Effects of PBDEs in maternal serum on FGR risk

PBDE congener	Unadjusted		Adjusted[a]	
	OR (95% *CI*)	*P*-value	*OR* (95% *CI*)	*P*-value
BDE-17	1.23 (0.92, 1.63)	0.157	1.21 (0.87, 1.67)	0.254
BDE-47	1.16 (0.99, 1.36)	0.058	1.13 (0.92, 1.38)	0.249
BDE-66	1.17 (1.04, 1.32)	0.010*	1.16 (0.98, 1.39)	0.087
BDE-153	1.12 (1.01, 1.23)	0.027*	1.12 (0.98, 1.27)	0.089
BDE-207	1.11 (1.04, 1.19)	0.001*	1.10 (1.02, 1.19)	0.016*
BDE-208	1.11 (1.03, 1.20)	0.006*	1.10 (0.98, 1.23)	0.125
BDE-209	1.02 (1.01, 1.03)	0.003*	1.01 (0.99, 1.03)	0.092
$\sum_{19}$PBDEs	1.01 (1.00, 1.02)	0.001*	1.01 (1.00, 1.02)	0.037*

Note. *P-value < 0.05 is statistically significant; [a]Adjusting for gestational age, education, income, and pregnancy syndrome.

that high concentrations of PBDEs in maternal serum were associated with the risk of FGR birth. Our study raises growing concerns about the effect of exposure to PBDEs during pregnancy on birth outcomes.

Changes in DNA methylation may play a critical key role in improper placenta development and therefore affect fetal growth. Placental DNA methylation is associated with intrauterine PBDE exposure[30]. A CHECK cohort study estimated the underlying relationship between DNA methylation in placental and neonatal outcomes. Their results showed that a unit percent increase in placental long interspersed element-1 methylation was correlated with a 0.19 cm decrease in birth length[31]. Thus, changes in DNA methylation in the placenta may be part of a potential biological pathway between PBDE exposure in the womb and FGR.

The strength of this study lies in the design of nested case-control to evaluate the PBDE exposure of FGR infants during the prenatal and neonatal periods. Our results provide evidence for the important role of placenta in mediating the effects of prenatal exposure to PBDEs on fetal growth. Nevertheless, we acknowledge several limitations of our study. The sample size was relatively small, and maternal serum during pregnancy was only tested once. Although maternal blood in the third trimester may better reflect PBDE exposure during pregnancy, the availability of maternal blood in the first, second, and third trimester can yield more accurate findings. Thus, larger prospective cohort studies are needed to validate the findings of our study. Moreover, we lack data on other environmental contaminants, such as organochlorine, heavy metal pesticides, and polychlorinated biphenyls, which also adversely affect placenta and fetal growth.

CONCLUSIONS

In this study, we found a negative association between PBDE levels in maternal serum and placental size and birth outcome. Our results suggest that prenatal PBDE exposure may be associated with elevated risk of the incidence of FGR birth.

AUTHOR CONTRIBUTIONS

CHEN Shang Qin, ZHANG Yun Hui, and YANG Qing designed this work. JIN Yu Ting, ZHAO Ying Ya, LI Jia Lin, and SONG Qi performed the experiments and analyzed the data. JIN Yu Ting and DENG Xiao Kai wrote the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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