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Prenatal exposure to persistent organic pollutants and methylation of LINE-1 and imprinted genes in placenta: A CHECK cohort study

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ABSTRACT

Prenatal exposure to persistent organic pollutants (POPs) has been linked to numerous adverse birth outcomes among newborn infants in many epidemiological studies. Although epigenetic modifications have been suggested as possible explanations for those associations, studies have rarely reported a relationship between POP exposure during pregnancy and DNA methylation in the placenta.

In the present study, we investigated the association between prenatal exposure to several POPs, including organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), and polychlorinated biphenyls (PCBs), and methylation levels of long interspersed element 1 (LINE-1), as well as imprinted genes in placental DNAs among Korean mother-child pairs (N = 109). We assessed the association of DNA methylation not only with each target POP (single-POP models) but also with multiple POPs applying principal component analysis (multiple-POP models). Potential associations between placental DNA methylation and birth outcomes of newborn infants were also estimated.

In single-POP models, significant associations were detected between OCP measurements and placental DNA methylation. Elevated concentrations of β-hexachlorhexane (β-HCH) in maternal serum collected during delivery were significantly associated with a decrease in methylation of LINE-1 in the placenta. Higher levels of *p,p′*-dichlorodiphenyltrichloroethane (*p,p′*-DDT) in maternal serum were associated with hypermethylation of *insulin-like growth factor 2* (*IGF2*). In multiple-POP models, a significant and positive association between DDTs and *IGF2* methylation was also observed. Placental LINE-1 methylation was inversely associated with birth length. Our observations indicate that prenatal exposure to several POPs including DDTs is associated with the changes in methylation of genes, including major imprinted genes in the placenta. The consequences of these epigenetic alterations in placenta during development deserve further investigation.

1. Introduction

The production and use of many persistent organic pollutants (POPs) have been restricted for several decades. However, many POPs, including organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs) are still detected in the environment worldwide, attributable to their persistence. POPs in water, soils, sediments, and air (Fu et al., 2003; Hale et al., 2003) can lead to their accumulation in biota such as birds and aquatic organisms, and eventually be transferred up to humans through the food web

Abbreviations: BMI, body mass index; CI, confidence interval; HCH, hexachlorocyclohexane; IGF2, insulin-like growth factor 2; IQR, interquartile range; LINE-1, long interspersed element-1; LOQ, limit of quantification; OCPs, organochlorine pesticides; OxyCHD, oxy-chlordane; PBDEs, polybrominated diphenyl ethers; PCA, principal component analysis; PCBs, polychlorinated biphenyls; POPs, persistent organic pollutants; *p,p′*-DDE, *p,p′*-dichlorodiphenyldichloroethylene; *p,p′*-DDT, *p,p′*-dichlorodiphenyltrichloroethane; SD, standard deviation; tNonaCHD, trans-nonachlordane

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(Norstrom, 2002). Therefore, these compounds have been frequently reported in breast milk, adipose tissue, serum, and cord serum of humans (Antignac et al., 2009; Becker et al., 2002; Kalantzi et al., 2004).

Because POPs can cross the placenta during pregnancy (Porpora et al., 2013; Vizcaino et al., 2014), in utero exposure to POPs may lead to adverse health outcomes in developing fetuses and newborns. Exposure to chlordanes and PCBs among mothers was associated with reduced birth weights, length, and head circumference in the newborns (Tan et al., 2009). Maternal exposure to dichlorodiphenyldichloroethylene (DDE) was also associated with lower infant birth weights (Wolff et al., 2007).

Although the underlying mechanisms are largely unknown, epigenetic alterations have been suggested as one possible explanation for the associations between POP exposure and adverse birth outcomes. DNA methylation, one of the most studied mechanisms for epigenetic regulation, refers to the addition of methyl groups to the 5-carbon position of cytosine, which can change gene expression heritably without changes in DNA sequence (Wolffe and Matzke, 1999). POP exposure has been associated with global methylation changes among healthy adult humans (Itoh et al., 2014; Kim et al., 2010; Lee et al., 2017; Lind et al., 2013; Rusiecki et al., 2008). However, studies examining epigenetic changes following prenatal exposure to POPs have rarely been carried out (Huen et al., 2014; Kobayashi et al., 2017; Zhao et al., 2016b).

The placenta is a master regulator of the intrauterine environment and plays an important role in fetal growth (Konkel, 2016). Owing to its importance in development and susceptibility to chemical exposure, the placenta is often recognized as a key tissue for understanding the developmental origins of health and diseases; therefore, epigenetic changes in the placenta in response to chemical exposures have received much attention (Konkel, 2016; Marsit, 2016). For example, placental epigenetic changes induced via bisphenol A or phthalate exposure have been extensively studied (LaRocca et al., 2014; LaRocca et al., 2016; Nahar et al., 2015; Zhao et al., 2016a; Zhao et al., 2015). However, few studies have examined associations of in utero exposures to POPs with epigenetic changes in the placenta (Kappil et al., 2016; Zhao et al., 2016b).

Therefore, this study was conducted to investigate the association between prenatal exposure to several POPs, including OCPs, PBDEs, and PCBs, and placental DNA methylation by utilizing resources from the Children's Health and Environmental Chemicals in Korea (CHECK) cohort. Because we assessed the association of multiple POPs, we used a multi-pollutant approach employed in a previous study with a similar design (Agay-Shay et al., 2015). A repetitive element, i.e., long interspersed element-1 (LINE-1), and two reciprocal imprinted genes, i.e., *insulin-like growth factor 2* (*IGF2*) and *H19*, were chosen to measure epigenetic changes. LINE-1 is one of the surrogate markers of global methylation (Yang et al., 2004). As its methylation could be related to genomic instability, it has been used as a biological indicator for some diseases (Kazazian and Goodier, 2002; Pogribny and Beland, 2009; Robertson, 2005). *IGF2* and *H19* play important roles in placental and fetal growth, and are controlled at differentially methylated regions (DMRs) by DNA methylation. The results of this study would provide better understanding of the possible mechanisms underlying adverse developmental outcomes associated with POP exposure.

2. Materials and methods

2.1. Study population and sample collection

Archived placenta samples collected from the CHECK cohort of Korea were used for the methylation analysis (Table 1). 148 healthy pregnant women were recruited in 2011 before full-term delivery from five university hospitals located in four Korean cities, including Seoul, Anyang, Ansan, and Jeju. A total of 109 placental samples were available. During delivery, maternal blood was collected using serum separation tubes on site and stored at −80 °C until analysis. Collection protocols for placenta followed the method of Adibi et al. (2009) with small modifications. Briefly, several parts of placental tissue adjacent to the cord insertion, measuring 1 cm wide and 1 cm deep, were collected to minimize contamination from maternal decidua and were stored at −25 °C until analysis. Among the women whose placenta tissues were collected, the levels of serum OCPs, PBDEs, and PCBs were available for 108, 107, and 109 mothers, respectively. A questionnaire regarding sociodemographic characteristics, diet, and lifestyle characteristics was administered. Birth outcomes including birth weight, birth length, and head circumference were also recorded. The Institutional Review Boards from the School of Public Health, Seoul National University, and all participating university hospitals approved the study. In addition, informed written consent was obtained from the participating women. All samples and data were processed in blinded fashion.

Table 1
Characteristics of the study population (N = 109).

	Value or N (%)	
Maternal characteristics		
Age (years)		
Mean ± SD	33.1 ± 3.7	
Range	25–41	
Smoke during pregnancy		
No	104	(95.4)
Yes	5	(4.6)
Drink during pregnancy		
No	68	(82.9)
Yes	14	(17.1)
Missing	27	
BMI before pregnancy (kg/m^2)		
Mean ± SD	22.0 ± 3.7	
Missing	28	
Mode of delivery		
Normal vaginal delivery	77	(70.6)
Caesarean section	32	(29.4)
Parity		
0	54	(49.5)
≥1	55	(50.5)
Gestational age at delivery (days)		
Mean ± SD	276 ± 8	
Range	261–293	
Infant characteristics		
Infant sex		
Female	54	(49.5)
Male	55	(50.5)
Birth weight (kg)		
Mean ± SD	3.29 ± 0.36	
Range	2.51–4.32	
Birth length (cm)		
Mean ± SD	50.0 ± 2.1	
Range	40–54	
Missing	1	
Head circumference (cm)		
Mean ± SD	34.1 ± 1.6	
Range	28–38	
Missing	9	
Ponderal index (g/cm^3)		
Mean ± SD	2.64 ± 0.44	
Range	1.91–4.69	
Missing	1	

2.2. Data collection

Levels of maternal serum POPs, including 19 OCPs, 19 PBDE congeners, and 19 PCB congeners, were obtained from the dataset and published elsewhere (Kim et al., 2013). Serum POPs were measured using a high-resolution gas chromatography interfaced with a high-resolution mass spectrometer (HRGC/HRMS; JMS 800D, JEOL, Tokyo, Japan). The detailed analytical conditions of the HRGC/HRMS have been described previously (Kim et al., 2013).