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Association of prenatal exposure to perfluoroalkyl substances with cord blood adipokines and birth size: The Hokkaido Study on environment and children's health

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ABSTRACT

Perfluoroalkyl substances (PFASs) are synthetic chemicals that persist in the environment and in humans. There is a possible association between prenatal PFASs exposure and both neonate adipokines and birth size, yet epidemiological studies are very limited. The objective of this study was to examine associations of prenatal exposure to PFASs with cord blood adipokines and birth size. We conducted birth cohort study, the Hokkaido Study. In this study, 168 mother-child pairs were included. Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in maternal blood were determined by liquid chromatography tandem mass spectrometry. Cord blood adiponectin and leptin levels were measured by ELISA and RIA, respectively. Birth weight and ponderal index (PI) were obtained from birth record. The median maternal PFOS and PFOA were 5.1 and 1.4 ng/mL, respectively. The median total adiponectin and leptin levels were 19.4 μg/mL and 6.2 ng/mL, respectively. Adjusted linear regression analyses found that PFOS level was positively associated with total adiponectin levels (β = 0.12, 95% CI:0.01, 0.22), contrary was negatively associated with PI (β = −2.25, 95% CI: −4.01, −0.50). PFOA level was negatively associated with birth weight (β = −197, 95% CI: −391, −3). Leptin levels were not associated with PFASs levels. PFOS and adiponectin levels showed marginal dose-response relationship and both PFOS and PFOA and birth size showed significant dose-response relationships. Results from this study suggested that prenatal PFASs exposure may alter cord blood adiponectin levels and may decrease birth size.

1. Introduction

Perfluoroalkyl substances (PFASs) are widely used in the industry including textile impregnation, furnishings, non-stick housewares, and food packaging (Lau et al., 2007) and found in the environment, animals, and humans. The main exposure pathway to PFASs in human occurs orally via intake of contaminated food and water. (Fromme et al., 2009). Even though the use of PFOS has been diminishing globally since they were included in Annex B of the Stockholm Convention on persistent organic pollutants in 2009 (UNEP, 2007), due to their bioaccumulation and presence in older products, PFOS and PFOA are still detectable in human and environmental samples (Olsen et al., 2012; Okada et al., 2013). Since PFASs can cross the placental barrier and can be transferred from mother to fetus (Inoue et al., 2004; Midasch et al., 2007), studies in prenatal exposure to PFASs and its adverse health effects on fetus are warranted.

Adiponectin and leptin are hormones produced by adipocyte and have been used as biomarkers of metabolic function. The known roles of these hormones are metabolic homeostasis and regulation (Farooqi and O'Rahilly, 2014; Fiaschi et al., 2014). Child adiponectin levels at birth and birth weight have been examined in the previous studies however, were inconsistent. Volberg et al. reported no relations (Volberg et al., 2013), while the others reported positive association between cord blood adiponectin levels with birth weight (Mantzoros et al., 2009) and the association between lower adiponectin and small for gestational age (SGA) and preterm birth (Palcevska-Kocevska et al., 2012; Yeung et al., 2015). A progressively significant negative association between adiponectin and BMI at 2, 5, and 9 years of age has been reported (Volberg et al., 2013). In adults, low adiponectin levels are the implication of obesity, metabolic syndrome and type 2 diabetes (DM2) (Mather and

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Goldberg, 2014). Studies have suggested that both too high and too low leptin in fetus result in non-optimal fetal growth phenotypes that subsequently increase long term obesity risk (Ornoy, 2011). High cord blood leptin levels have been known to positively associated with birth weight (Karakosta et al., 2011), while low cord blood leptin levels have been associated with SGA (Ren and Shen, 2010).

Importance of investigating adipokine levels at birth have been suggested from the studies that found cord blood leptin levels may modify child growth trajectory (Parker et al., 2011; Kaar et al., 2014; Karakosta et al., 2016). There have been reported that cord blood adiponectin levels were negatively correlated with body weight at one year, weight gain after one year and with BMI at one year (Mazaki-Tovi et al., 2011) and that cord serum adiponectin levels were significant predictors of BMI Z-score gain from birth to 3 years of age (Nakano et al., 2012). Thus alternation of cord blood adiponectin levels may cause adverse effects on early childhood growth.

Previous epidemiological studies including our group have found that reduction of birth weight in association with prenatal exposure to PFASs (Olsen et al., 2009; Washino et al., 2009; Verner et al., 2015). In addition to birth weight, our group has reported that prenatal exposure to PFASs could results in disrupting various hormones balance including reproductive, thyroid and steroid hormone of neonates. PFOS were inversely associated with testosterone/estradiol, progesterone (P4) and inhibin B among boys and with P4 and prolactin among girls (Itoh et al., 2016). PFOS, but not PFOA were inversely correlated with maternal TSH and positively associated with infant serum TSH (Kato et al., 2016). Similarly, PFOS, but not PFOA was negatively associated with glucocorticoids in cord blood (Goudarzi et al., 2017).

Animal studies have suggested that developmental exposure to PFOS may contribute to lipid metabolic disorder in adulthood in rats (Lv et al., 2013). There was only one study in human that found inverse association between PFOS exposure and polyunsaturated fatty acid levels in pregnant women (Kishi et al., 2015). Developmental exposure to lower levels of PFOA induced elevated serum leptin and overweight in mid-life in female mice through increasing of fatty acid metabolism by activation of proliferator-activated receptors (PPAR)-alpha (Hines et al., 2009). However, findings from animal data may not be applicable to humans. To our knowledge, there has been only a few prospective cohort studies that examined associations between early life exposure to PFASs and metabolic function such as adipokine levels (Halldorsson et al., 2012; Fleisch et al., 2016; Ashley-Martin et al., 2017). One study found no evidence of an adverse effect of PFASs exposure on metabolic function in mid-childhood (Fleisch et al., 2016) and contrary, the other study suggested that prenatal PFOA exposure significantly associated with leptin and adiponectin levels in female at age of 20 years (Halldorsson et al., 2012). These studies only investigated postnatal adipokine levels at childhood and early adulthood, but not examined adipokine levels at birth. The recent study in Canada (MIREC Study) is the only one to examine associations between maternal PFAS concentrations and birth weight and cord blood concentrations of leptin and adiponectin (Ashley-Martin et al., 2017), which found null associations.

The fetal time period is critical window of adipocyte development and thus, exposures to PFASs during fetal period may change postnatal growth trajectory and increase the risk of obesity and metabolic disorders later in life (Grün and Blumberg, 2009; Hatch et al., 2010). Though prenatal exposure to PFASs and birth outcomes such as birth size have been studied, adipokines at birth, the metabolic related biomarkers have not been well investigated and understood.

The objectives of this study was to examine the association between prenatal exposure to PFASs and neonatal adipokines including adiponectin and leptin levels in cord blood along with birth size.

2. Materials and methods

2.1. Study population and questionnaire

This prospective birth cohort study was based on the Sapporo Cohort, the Hokkaido Study on Environment and Children's Health (Kishi et al., 2011, 2013). The Sapporo Cohort is an ongoing cohort study that began in 2002. Briefly, pregnant women at 23–35 weeks of gestation were recruited between July 2002 and October 2005 from the Sapporo Toho Hospital in Hokkaido, Japan. 514 women agreed to participate in the cohort study. All participants were residents in Sapporo City or surrounding areas.

The participants completed the self-administered questionnaire including baseline information such as their dietary habits, exposure to chemical compounds in their daily life, smoking history, alcohol consumption, caffeine intake, family income, educational levels of themselves and partners. Maternal anthropometric measurement data and medical history were obtained from medical record and birth weight and length were collected from birth records. We used the following criteria to include the participants into the analyses; singleton baby born at term (37–42 weeks of gestation). Participants with no PFASs measurement (n = 22) or those with blood collected after delivery (n = 124) were excluded since PFOS and PFOA concentrations were significantly lower in post-delivery blood samples (Goudarzi et al., 2016; Itoh et al., 2016). Finally, 168 mother-child pairs who had both PFASs and adipokine measurements were included into the statistical analyses (Fig. 1). This study was conducted in accordance with the Declaration of Helsinki, and the protocol used in this study was

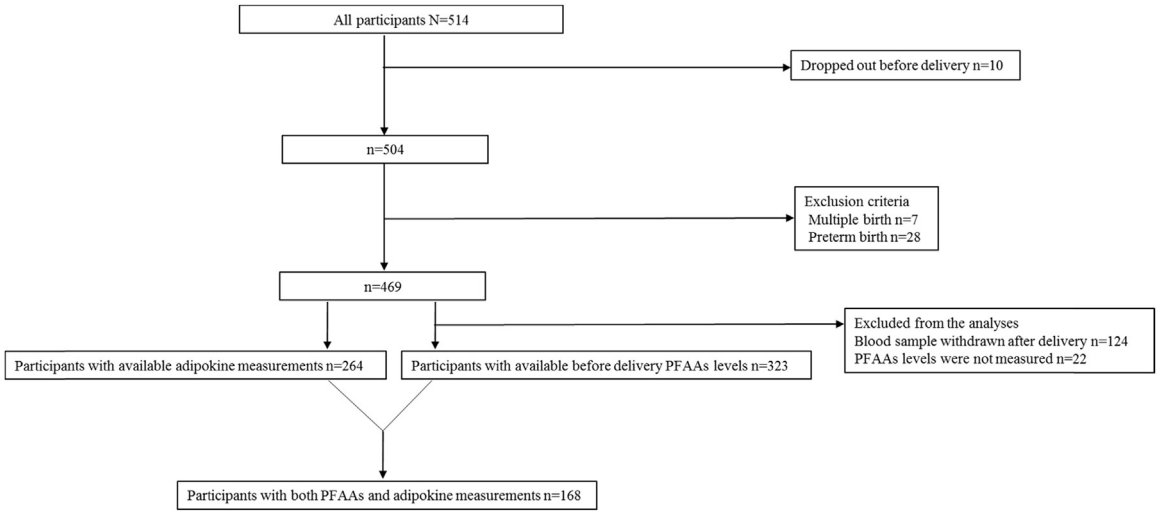

Fig. 1. Flowchart of participants' selection.