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Prenatal exposure to perfluorinated compounds affects thyroid hormone levels in newborn girls

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ABSTRACT

Perfluorinated compounds (PFCs) are ubiquitous in the environment and have been detected in humans and wildlife. Exposure to PFCs has decreased in the United States recently, while exposure to PFCs continues in Asian countries, which represents a public health concern. Various mechanisms by which PFCs affect fetal growth have been proposed, such as activation of peroxisome proliferators, disruption of thyroid hormones and changes in lipid metabolism. However, the overall evidence for an association with thyroid hormones is not strong. Therefore, we examined the effect of various prenatal PFCs on cord blood thyroid hormones: triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH) levels, and explored the endocrine disrupting effect of these PFCs on thyroid hormone levels in children according to gender. Two hundred and seventy-nine study participants were selected from among the enrolled participants in the Ewha Birth & Growth Retrospective Cohort, a retrospective birth cohort study conducted at Ewha Womans University Hospital, Seoul, Korea between 2006 and 2010. A generalized linear model was constructed to explore the association of PFCs and thyroid hormones. Further, an analysis stratified by gender was conducted. Our study shows that cord blood perfluoro n-pentanoic acid (PFPeA) was positively associated with cord blood T4 ($p = 0.01$) level. Gender-specific analysis showed that prenatal PFCs: PFPeA and Perfluorohexane sulfonic acid (PFHxS) exposure significantly increased T4 ($p < 0.01$) and T3 ($p = 0.03$), respectively, while perfluorononanoic acid (PFNA) decreased TSH ($p = 0.04$) concentration in newborn girls. Thus, prenatal PFC exposure may disrupt thyroid hormone homeostasis. Thyroid hormones play a crucial role in fetal development and may have gender specific action. Hence, these results are of utmost importance in high-risk groups, such as pregnant women and children.

1. Introduction

Perfluorinated compounds (PFCs) are synthetic compounds produced for several decades during industrial and commercial manufacturing of non-stick cookware, waxes, carpets, foodstuff packaging, cosmetics and water-oil repellents (Kissa, 2001). The molecular structure of PFCs is responsible for their lipophilic and hydrophilic properties. Humans are exposed to PFCs through food, water, packaged food, indoor dust and outdoor air (Fromme et al., 2009). PFCs degrade slowly in the environment, and have entered the food chain. They exist widely and are ubiquitous in nature. The half-lives of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are 3.8 and 5.4 years, respectively (Olsen et al., 2007). Some PFCs are considered to be persistent organic pollutants and PFOS has been added to Annex B of the Stockholm Convention. The 3M (St. Paul, Minnesota) and other companies announced a voluntary phase-out of these compounds in the year 2000 in the United States. Exposure to PFCs has reduced in the United States, but it continues in Asian countries (So et al., 2004; Ji et al., 2012). The regional differences in PFC levels could be due to the environmental sources and exposures such as

Abbreviations: PFCs, perfluorinated compounds; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFDoDA, perfluorododecanoic acid; PFTrDA, perfluorotridecanoic acid; PFTeDA, perfluoro tetradecanoic acid; PFPeA, perfluoro-n-pentanoic acid; PFUnDA, perfluoroundecanoic acid; PFHxS, Perfluorohexane sulfonic acid; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; LOD, limit of detection; BMI, body mass index; TBG, thyroxine-binding globulin; LOQ, limit of quantification.

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diet and water in the yellow sea eco-region of China and Korea (Naile et al., 2010; Ji et al., 2012; Lee et al., 2013).

Animal studies have shown that PFCs can cause developmental toxicity (Luebker et al., 2005; Wolf et al., 2007). PFCs easily cross the placental barrier (Kim et al., 2011) and affect the developing fetus. Human studies have reported an inverse association of birth weight with PFOS (Apelberg et al., 2007; Washino et al., 2009; Maisonet et al., 2012), and some researchers found that prenatal exposure to PFOA reduced birth weight (Washino et al., 2009; Maisonet et al., 2012, Fei et al., 2007). Fecundity and thyroid function may be affected by PFCs (Fei et al., 2009).

Thyroid hormones are important for proper growth and development of the fetus. Animal studies have found that serum concentrations of thyroxine (T4) and triiodothyronine (T3) are associated with PFOS (Chang et al., 2008; Luebker et al., 2005). Some studies have reported negative associations of prenatal exposure to PFCs with fetal T4 levels (Kim et al., 2011; Wang et al., 2014). A Canadian case-control study in pregnant women did not find an association of prenatal PFC exposure with thyroid disorders (Chan et al., 2011). The results of previous human studies on the effect of prenatal PFC exposure on thyroid hormones are inconsistent. Thyroid hormones are sensitive to environmental chemicals such as PFCs (de Cock et al., 2014). Prenatal exposure to thyroid hormone endocrine disruptors can affect birth weight, cause preterm births, and may affect the glucose and lipid metabolism (Molehin et al., 2016). PFCs are suspected endocrine-disrupting chemicals that affect thyroid hormone levels (de Cock et al., 2014). Thus, PFC exposure may have clinical implications by altering thyroid hormone homeostasis during the prenatal period.

Therefore, the aim of this study was to examine the effect of various cord blood PFCs on the cord blood thyroid hormones: T3, T4 and thyroid stimulating hormone (TSH), and to explore the endocrine disrupting effect of these PFCs on thyroid hormones in children according to gender.

2. Materials and methods

2.1. Study participants

Study participants were selected from the Ewha Birth & Growth Retrospective Cohort (EBGRC), a retrospective birth cohort study conducted at Ewha Woman's University Hospital, Seoul, Korea between 2006 and 2010. Details of the cohort study have been published previously (Kwon et al., 2016). Pregnant females receiving prenatal care at 24–28 weeks of gestation were included in the study. The study was approved by the ethics committee of the Institutional Review Board (IRB) of Ewha Woman's University Hospital, Seoul, Korea. A total of 301 pregnant women were enrolled from 2006 to 2010 in the EBGRC. All participants gave their written informed consent for enrollment in this study. Information on demographic data was collected by trained researchers through a structured questionnaire. Data on biochemistry was collected from cord blood samples. Of the 301 enrolled participants, 22 were excluded due to pregnancy complications (hypertension and diabetes) and missing information for gestational age and gender. The final number of eligible participants was 279.

2.2. Cord blood PFC analysis

Cord blood samples obtained from EBGRC were analyzed for PFOS, PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluorododecanoic acid (PFDoDA), perfluorotridecanoic acid (PFTrDA), perfluorotetradecanoic acid (PFTeDA), perfluoro-n-pentanoic acid (PFPeA), perfluoroundecanoic acid (PFUnDA) and perfluorohexane sulfonic acid (PFHxS) exposure. All the PFCs were linear molecules. Ten milliliters of blood were collected in EDTA tubes and stored at −70 °C until PFC exposure analysis. Briefly, 20 μL of labeled internal standards were spiked into 200 μL serum and 500 μL of 0.1% formic acid diluted in water. Solid phase extraction (SPE) was performed using oasis weak anion exchange cartridges (WAX; 1 cm^3, 30 mg; Waters, Milford, MA, USA). The resulting extract of PFCs was then eluted with 4 mL of 0.1% ammonium hydroxide in methanol, evaporated and reconstituted in 0.2 mL acetonitrile. Quality control samples and calibration standards were subjected to SPE using bovine serum samples previously spiked with standard mixture and internal standards (Kwon et al., 2016).

A high-performance liquid chromatography (HPLC) series 1100 system (Agilent Technologies, Palo Alto, CA) using 2.0 × 150 mm, 3 m YMC C18 column (waters) was used for analysis of PFCs. The injection volume was 3 μL and the flow rate was 200 μL/min in gradient mode, with 70% of mobile phase A (5 mM ammonium acetate with 0.02% formic acid in water) and 30% B (methanol), to 100% of B within 10 min and it was maintained for 7 min. Identification and quantification of analytes were done by using an API 4000 triple quadrupole mass spectrometer (Applied Biosystems, Foster City, CA, USA), operated in the electrospray ionization (ESI) negative mode with multiple reaction monitoring (MRM). The ESI conditions for analyzing targeted PFCs were optimized to ion source voltage at −4.5 kV, ESI temperature of 400 °C, curtain gas at 15 psi, nebulizer gas GS1 at 40 psi, and GS2 at 60 psi, entrance potential of −10.0 V, and dwell time of 45 msec. The mass analyzer was operated in the MRM mode for PFHxS (m/z 399 → 80), PFOA (m/z 413 → 369), PFOS (m/z 499 → 80), PFNA (m/z 463 → 419), PFDA (m/z 513 → 469), PFUnDA (m/z 563 → 519), PFDoDA (m/z 613 → 569) and PFTrDA (m/z 663 → 619) (Kwon et al., 2016).

Table 1
General characteristics of study subjects (N = 279).

	N	%	T3 (ng/dl) Mean ± SD	T4 (μg/dl) Mean ± SD	TSH (mU/L) Mean ± SD
Mother's					
Age (yrs)					
<30	65	23	62.7 ± 18.3*	8.6 ± 1.7	11.5 ± 7.7
≥30	214	77	58.4 ± 9.9	8.5 ± 1.4	10.5 ± 7.4
Education					
<University	52	18	59.4 ± 10.3	8.4 ± 1.4	9.7 ± 7.2
≥University	227	82	59.4 ± 12.9	8.5 ± 1.5	11.0 ± 7.5
Monthly income (thousand KRW/month)					
≤3000	52	47	60.3 ± 10.0	8.1 ± 1.4	10.9 ± 7.7
>3000	58	53	61.2 ± 14.9	8.3 ± 1.3	11.1 ± 7.4
Pre-pregnancy BMI[a] (kg/m^2)					
<23	34	12	61.6 ± 17.2	9.0 ± 1.8	11.7 ± 9.2
≥23	245	88	59.1 ± 11.7	8.4 ± 1.4	10.6 ± 7.2
Alcohol history					
No	212	82	58.1 ± 11.6	8.6 ± 1.5	10.7 ± 7.4
Yes	46	18	64.7 ± 16.4	8.4 ± 1.2	11.6 ± 8.7
Children's					
Birth order					
0	147	53	60.4 ± 14.3	8.7 ± 1.5**	11.7 ± 8.1*
≥1	132	47	58.3 ± 10.0	8.3 ± 1.3	9.8 ± 6.5
Mode of delivery					
Normal	204	76	60.0 ± 13.1	8.7 ± 1.5*	11.9 ± 8.1*
C-section	67	24	57.4 ± 11.0	8.0 ± 1.3	7.2 ± 3.6
Gender					
Boy	132	47	59.0 ± 10.7	8.5 ± 1.4	10.6 ± 6.8
Girl	147	53	59.7 ± 13.9	8.6 ± 1.5	10.9 ± 8.0
Gestational age (wks)					
<37	6	2	59.3 ± 12.4	7.6 ± 1.7	11.1 ± 7.4
≥37	273	98	59.4 ± 15.6	8.5 ± 1.4	10.7 ± 7.4
Birth weight (g)					
<2500	4	1	58.9 ± 20.1	7.5 ± 1.1	9.0 ± 3.5
≥2500	275	99	59.4 ± 12.4	8.5 ± 1.5	10.8 ± 7.5

Numbers of subgroups varies slightly due to missing value for each variable.
T3 — triiodothyronine, T4 — thyroxine, TSH — thyroid stimulating hormone.
[a] BMI — body mass index.
* $p < 0.05$.
** $p < 0.10$.

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