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Perfluoroalkyl substances and thyroid hormones in cord blood☆

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ABSTRACT

Background: Perfluoroalkyl substances (PFASs) are pollutants that tend to accumulate in the environment and organisms. The animal and human studies to date have focused on thyroid function, but the results are inconsistent.
Methods: A sample of 118 mother-infant pairs was obtained from the Taiwan Birth Panel Study (TBPS). Cord blood PFASs levels were evaluated using the Waters ACQUITY UPLC system coupled with a Waters Quattro Premier XE triple quadrupole mass spectrometer, and cord blood thyroid hormones were assessed using a Roche Analytics E170 modular analyser (Roche Diagnostics, Mannheim, Germany). PFASs concentrations were analysed in the final models to examine the associations between cord blood PFASs levels and thyroid hormone concentrations.
Results: The cord blood perfluorooctane sulfonate (PFOS) concentration was negatively associated with the cord blood thyroxine (T4) concentration [per ln unit: adjusted β (95% confidence interval, CI) = −0.458(−0.916, −0.001)]. Moreover, the level of cord blood thyroid stimulating hormone (TSH) was positively associated with the cord blood PFOS concentration [per ln unit: adjusted β (95% confidence interval, CI) = 0.346(0.101, 0.592)]. The sex stratified effects of PFOS on T4 were suggestive of differential effects in high-exposure groups compared with low-exposure group in boys.
Conclusions: We found that cord blood thyroid hormone levels are affected by PFASs, with a negative association between T4 and PFOS and a positive association between TSH and PFOS. The causal associations of thyroid hormones and PFASs require further exploration.

1. Introduction

Perfluoroalkyl substances (PFASs), compounds that are used for commercial and industrial purposes, were introduced in 1950 (Lau et al., 2007). PFASs tend to bio-accumulate and have long half-lives (Austin et al., 2003). Although attempts have been made to eliminate, or reduce, PFASs from the environment (US EPA, 2012), these compounds are still detected in surface water and soil as well as in animals and humans (Lau et al., 2007). One source of PFASs exposure in humans is migration from food packaging and cookware and drinking water (Haug et al., 2011). As perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) can be detected in umbilical cord blood and breast milk (Apelberg et al., 2007; Fromme et al., 2010; Inoue et al., 2004; SK Kim et al., 2011), the health effects of PFASs are of heightened concern, particularly for neonatal health outcomes. Furthermore, because the fetus obtains nutrition from the mother during pregnancy, neonates may have PFASs exposure, which may interfere with the balance of certain molecules, such as hormones. PFASs have been proposed to act as endocrine disruptors (Lau, 2012), and some studies to date have focused on the effects of PFASs on neonates, particularly on neonatal thyroid function. Thyroid functions are important for a child's brain development, and they also play a pivotal role in neurodevelopment during childhood (Bernal, 2005; de Escobar

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et al., 2004). An epidemiology study in a Dutch cohort revealed that cord plasma levels of PFOA and PFOS are associated with thyroxine (T4) and sex differentiation (de Cock et al., 2014). In addition, studies performed by Kim et al. in Korea (S Kim et al., 2011) and Wang et al. in Taiwan (Wang et al., 2014) found that maternal PFASs concentrations were associated with cord blood thyroid hormones. Most animal studies investigating associations between maternal PFASs exposure and thyroid hormones in neonates found T4 reduction to be associated with PFOS exposure and which were solid (Lau et al., 2003; Luebker et al., 2005; Yu et al., 2009).

Although studies have assessed associations between PFASs exposure and thyroid hormones in neonates, the results are inconsistent. Regardless, it is well known that PFASs exposure may be transferred to infants (Fei et al., 2008; Lau et al., 2003; Luebker et al., 2005), and cord blood measurement may reflect the stable exposure status during the entire pregnancy (Boas et al., 2012). Therefore, the aim of this study was to examine the associations between in utero PFASs exposure and cord blood thyroid hormone levels.

2. Materials and methods

2.1. Subjects and data collection

The Taiwan Birth Panel Study (TBPS), from April 2004 to January 2005, included one medical centre in Taipei City and one local hospital and two clinics in New Taipei City. Trained interviewers used a structured prenatal questionnaire to interview postpartum mothers. Cord blood at birth was stored at −80 °C for laboratory analysis. Initially, 439 mother-infant pairs were enrolled; however, no PFASs or thyroid hormone measurements were obtained for 321 of these subjects. Thus, 118 subjects with data were included in the present study. All participants and parents (for child participants) signed informed consent forms upon enrolment. The Ethics Committee of the National Taiwan University Hospital (Research Ethics Committee, NTUH) approved this study.

2.2. Exposure assessment

Cord blood plasma samples were analysed for PFOA, PFOS, perfluoroundecanoic acid (PFUnDA), and perfluorononanoic acid (PFNA) using a Waters AC QUITY UPLC system (Waters Corporation, Milford, MA) coupled with a Waters Quattro Premier XE triple quadrupole mass spectrometer. Details on the analytic method used to detect PFASs levels have been described previously (Lien et al., 2011). Briefly, 12 PFASs in cord blood were initially assessed; PFOA, PFOS, PFUnDA, and PFNA were above the 60% limit of quantitation (LOQ). The detection rates of PFOA, PFOS, PFNA, and PFUnDA were 82%, 100%, 68.5% and 85.5%, with LOQs of 1.58, 0.22, 0.84, and 3.1 ng/mL and with limit of detection (LODs) of 1.23,0.066, 0.67, and 2.4 ng/mL, respectively. When the concentration was below the level of quantification, we used a proxy value of half of the LOQ due to acceptable precision and accuracy. Investigators performing the laboratory analyses were blinded to the characteristics of the subjects.

2.3. Assessment of thyroid hormones

Concentrations of hormones including thyroxine (T4), triiodothyronine (T3), thyroid stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) were measured using an immunoluminometric assay with the Roche Analytics E170 modular analyser (Roche Diagnostics, Mannheim, Germany). The intra-assay coefficients of variation were all below 10%, and the inter-assay coefficients of variation were all below 15%.

2.4. Statistical analysis

Linear regression was performed to analyse associations between PFASs and thyroid hormones. Due to the right-skewed distribution for the PFASs, natural log-transformed PFASs values were used in the models. Moreover, we also divided the PFASs into four different categories. The detection rates of PFOS, PFOA, and PFUnDA were 100%, 82%, and 85.5%. The PFOS, PFOA, and PFUnDA were divided to <30, 30–59, 60–89, and ≥90th percentiles; PFNA were divided to <40, 40–59, 60–89, and ≥90^{th} due to 68.5% of detection rate. The lowest level was established as a reference for investigating the dose-response relationship.

Covariates included maternal age at delivery, newborn sex, maternal body mass index (BMI; kilograms per metre squared), maternal education (≤high school and >high school), primipara, birth weight, gestational age, maternal smoking during pregnancy, and delivery type (normal vaginal and cesarean section). However, a high correlation between birth weight and gestational age was observed, and only a small number of mothers smoked during pregnancy. Birth weight, primipara, and mothers smoked during pregnancy were no significant influences in the models. Thus, we considered maternal age at delivery, newborn sex, gestational age, maternal BMI, maternal education, and delivery type in our complete models.

For thyroid hormones, we examined the distribution of these hormones in the first step. However, as T3, FT3, and FT4 also showed a right-skewed distribution, their values were natural log-transformed; T4 and TSH were not. Each PFASs model was analysed independently. SAS (version 9.3; SAS Institute Inc., Cary, NC, USA) was used to perform all of the statistical analyses, and p-values <0.05 determined statistical significance.

3. Results

Table 1 shows the basic characteristics of the study population. The average maternal age was 32 years, and the percentage of those

Table 1
Basic characteristic of the sample subjects (n = 118).

Characteristics	Total
Mothers	
Age at delivery (years); mean (SD)	32.2 (3.7)
Body mass index (kg/m^2); mean (SD)	26.3 (3.1)
Primipara; %	48 (43.2)
Education ≤12 year; %	59 (50.0)
Smoking during pregnancy; %	6 (5.1)
Neonates	
Girl; %	54 (45.8)
Gestational age (weeks); mean (SD)	38.5 (1.8)
Birth weight (gm); mean (SD)	3159.1 (508.2)
Type of delivery	
Cesarean section; %	42 (35.6)
Normal spontaneous delivery; %	76 (64.4)
PFASs in cord blood (ng/mL)	mean (SD); detection rate
PFOA	3.14 (2.75); 82%
PFOS	7.24 (7.11); 100%
PFNA	7.55 (10.93); 68.5%
PFUnDA	15.94 (16.90); 85.5%
Thyroid hormone concentration	mean (SD); range
T3 (μg/dl)	0.03 (0.01); 4.97–13.2
T4 (μg/dl)	8.98 (1.66); 12.8–118.9
FT3 (pg/ml)	1.49 (0.42); 1.0–3.7
FT4 (ng/dl)	1.20 (0.21); 0.8–2.3
TSH (μIU/ml)	2.92 (1.91); 0.008–14.1

PFASs, perfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFNA, perfluorononanoic acid; PFUnDA, perfluoroundecanoic acid; T3,triiodothyronine; T4,thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.