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Association between organohalogenated pollutants in cord blood and thyroid function in newborns and mothers from Belgian population☆

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ABSTRACT

The last decades have seen the increasing prevalence of thyroid disorders. These augmentations could be the consequence of the increasing contamination of the environment by chemicals that may disrupt the thyroid function. Indeed, *in vitro* studies have shown that many chemicals contaminating our environment and highlighted in human serum, are able to interfere with the thyroid function. Given the crucial importance of thyroid hormones on neurodevelopment in fetus and newborns, the influence of these pollutants on newborn thyroid homeostasis is a major health concern. Unfortunately, the overall evidence for a deleterious influence of environmental pollutants on thyroid remains poorly studied. Therefore, we assessed the contamination by polychlorinated biphenyls (PCBs), organochlorine pesticides and perfluorinated compounds (PFC) in 221 cord blood samples collected in Belgium between 2013 and 2016. Our results showed that compared to previous studies performed on newborns recruited in Belgium during the two last decades, the present pollutant contamination is declining. Multivariate statistical analyses pointed out a decrease of thyroid stimulating hormone (TSH) level in male newborns with detectable level of 4,4′- dichlorodiphenyldichloroethylene (4,4′-DDE) in comparison with those with no detectable level ($p = 0.025$). We also highlighted a negative association between perfluorononanoic acid (PFNA) concentration and TSH in male newborns ($p = 0.018$). Logistic regression showed increased odds ratio for presentation of hypothyroid in mother for each one unit augmentation of log natural concentration of PFOA (OR = 2.30, [1.18–4.5]) and PFOS (OR = 2.03 [1.08–3.83]). Our findings showed that the residual contamination by PFCs and organochlorine pollutants in cord blood are correlated with thyroid hormone in the newborns and the risk of hypothyroid in mothers.

1. Introduction

Since decades, the volume of materials produced by chemical industry grows exponentially. A significant part of these chemicals reaches the environment and contaminates the living organisms. In parallel of this growing pollution, the incidence of several endocrine-related diseases is also increasing. Among them, thyroid disorders are no exception since the incidence of such diseases has been observed to increase while the mean age at presentation of Hashimoto's thyroiditis is declining (Barry et al., 2016; Benvenga et al., 2015; Leese et al., 2008). This interesting parallel have led many scientists to investigate the potential links between endocrine-related disorders and environmental pollution.

In laboratories, many studies demonstrated that several pollutants so called endocrine disruptors (ED) are able to interfere with the thyroid system and to alter the levels of thyroid hormones

Abbreviations: ED, endocrine disruptor; TH, thyroid hormone; T_4, thyroxine; T_3, triiodothyronine; PCB, polychlorinated biphenyl; TTR, transthyretin; TSH, thyroid stimulating hormone; HCB, hexachlorobenzene; DDT, dichlorodiphenyltrichloroethane; PFC, perfluorinated compound; PFOS, perfluorooctane sulfonate; BMI, body mass index; PFHxS, perfluorohexane sulfonate; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUdA, perfluoroundecanoic acid; PFHpA, perfluoroheptanoic acid; ESI, electronic negative ionization; RT, retention time; CV, cone voltage; CE, collision energy; β-HCH, β-hexachlorohexane; 4,4′-DDE, 4,4′-dichlorodiphenyldichloroethylene; DF, detection frequency.

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(THs) (Boas et al., 2012). Because of their structural resemblance to thyroxine (T_4) and triiodothyronine (T_3), interactions between polychlorinated biphenyls (PCBs) and the thyroid system have been investigated for many years: *in vitro* studies have shown that PCBs are able to bind to transthyretin (TTR), a protein responsible of THs transport in the blood (Chauhan et al., 2000; Marchesini et al., 2008). Fritsche et al. demonstrated that PCB 118 mimics the T_3 action and stimulates the neural differentiation via the TH pathway (Fritsche et al., 2005). In orally exposed rats, PCBs were observed to decrease T_4 but didn't induce any change in the thyroid stimulating hormone (TSH) level (Hallgren et al., 2001). Organochlorine pesticides were also examined concerning their potential thyroid-disrupting effects: studies led on laboratory animals have shown that hexachlorobenzene (HCB) would induce decrease of the circulating level of T_4 (Alvarez et al., 2005) while a reduction of levels of T_4, T_3 and TSH was observed after a chronic exposition to dichlorodiphenyltrichloroethane (DDT) (Liu et al., 2015). More recent pollutants such like perfluorinated compounds (PFCs) have also demonstrated their abilities to interfere with the thyroid system. For instance, Weiss et al. showed that, similarly to PCBs, PFCs are able to bind on TTR (Weiss et al., 2009). They also seemed to interfere with the TH metabolism since hepatic glucuronidation enzymes mRNA and deiodinases mRNA in the thyroid (two enzymes responsible of the metabolization of THs) were demonstrated to be up-regulated by a long term exposure to perfluorooctane sulfonate (PFOS) in rat (Yu et al., 2009). This alteration of the metabolism was accompanied by a reduction of the T_4 levels in the exposed animals (Yu et al., 2009).

During pregnancy and early childhood, the THs play a critical role in the development of the fetus and the newborn, especially for the neurodevelopment (Evans et al., 1999; Howdeshell, 2002). Thereby, thyroid deficiency during this critical period may irreversibly impair the neurodevelopment in children. Therefore, the potential interferences of some pollutants on the thyroid system, especially during pregnancy and early childhood should be extensively investigated. Unfortunately, the current number of epidemiologic studies assessing the association between pollutant contamination and the thyroid system homeostasis in human fetus and newborns remains insufficient and the results of these studies are not consistent (El Majidi et al., 2014).

In Belgium, although declining due to their ban, the contamination of newborns by PCBs, organochlorine pesticides and PFCs remains significant (Schoeters et al., 2017) and the influence of these residual contaminations on the newborn thyroid homeostasis is an important concern. Thereby, the objectives of this study were to assess the exposure levels of some PCBs, some organochlorine pesticides and PFCs of Belgian newborns through their measurement in cord blood on one hand and on the other hand, to investigate potential link between the ED's contaminations and thyroid disorders in these newborns and their mothers.

2. Material and methods

2.1. Study participants

Between August 2013 and March 2016, women presenting for delivery at the obstetric service of the University Hospital of Liege (Belgium) were asked to participate to a study on neonatal asphyxia biomarkers as first intention and thyroid problems as second intention. A total of 281 participants gave written informed consent, and umbilical cord blood samples were collected, centrifugated and stored at −80 °C immediately after delivery. The present population (n = 214) was selected from this cohort. The exclusion criteria were: insufficient serum volume available (<0.5 mL), absence of TSH level record (measured during the neonatal screening performed 3 days after the birth), and congenital hypothyroidism diagnosed for the newborn (TSH >20 mUI/L).

The maternal information and newborn's characteristics were collected through the medical records and included newborn's weight, gestational age, age of the mother at delivery, parity, pre-pregnancy body mass index (BMI) of the mother, tobacco habits and hypothyroidism (according to levothyroxine treatment reported in the medical records during pregnancy). The demographic characteristics are gathered in Table 1.

2.2. Chemicals and reagents

PFOS, perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUdA) and perfluoroheptanoic acid (PFHpA) standards were purchased from Wellington Laboratories, Inc (Ontario, Canada). Labeled PFCs ($^{13}C_4$-PFOS, $^{13}C_4$-PFOA, ^{18}O-PFHxS, $^{13}C_5$-PFNA, $^{13}C_2$-PFDA, $^{13}C_2$-PFUdA and $^{13}C_4$-PFHpA) were used as internal standard and were also purchased from Wellington Laboratories. Oasis WAX SPE cartridges (3 cc, 60 mg, 30 μm) were purchased from Waters (Milford, MA, USA). Water (LC-MS grade), acetonitrile (LC-MS grade) and methanol (HPLC grade) were purchased from J. T. Baker (Deventer, The Netherlands). Formic acid (98–100%, analytical grade) ammoniac (25%, analytical grade) and acetate ammonium (analytical grade) were bought from Merck (Darmstadt, Germany). Fetal bovine serum was purchased from Sigma-Aldrich Co (S^t Louis, MO, USA).

2.3. Analyses

The serum specimens were analyzed for the determination of 7 PFCs: PFOS, PFOA, PFHxS, PFNA, PFDA, PFHpA and PFUdA. The analytical procedure used was based on the method previously described by Kärrman et al. (2007). Twenty microliters of an internal standard solution at 1 μg/mL and 2 mL of formic acid/water mixture (1:1) were added to 1 mL of serum sample, sonicated for 15 min and then centrifugated at 3000 rpm for 5 min. Then the sample was loaded on the Oasis WAX column previously washed and conditioned with 2 mL of methanol followed by 2 mL of water. The cartridge was then washed with 1 mL formic acid 2% in water followed by 1.5 mL of methanol. Finally, PFCs were eluted with 2 × 2 mL of ammonium hydroxide 2% in methanol. The sample was further evaporated until dryness under a gentle stream of nitrogen at 30 °C and residue was reconstituted in 80 μL of a mixture 2 mM ammonium acetate in acetonitrile/2 mM ammonium acetate in

Table 1
Demographic characteristics of the sample subjects.

	No	Mean	Range	SD	%
Pre-pregnancy body mass index		24,2	[16,4–48,9]	5,0	
Parity		0,9	[0,0–6,0]	1,1	
Primipare	98				46,0%
Multipare	115				54,0%
Age, years		29,2	[18,0–42,0]	4,9	
Gestational age, days		277	[242–293]	8	
Birth weight, g		3307	[2225–5015]	438	
Newborn gender					
Male	113				52,8%
Female	101				47,2%
Mother hypothyroid					
Yes	37				17,3%
No	177				82,7%
Smoking status					
Smoker	40				18,7%
Non-smoker	174				81,3%