



Review article

Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: A systematic review of epidemiologic studies



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ABSTRACT

Introduction: Thyroid hormones (THs) are especially important for brain maturation and development during the fetal period and childhood. Several epidemiological studies have assessed the possible association between exposure to perfluoroalkyl substances (PFAS) and thyroid outcomes during the early stages of life. We aimed to review this evidence.

Methods: We conducted a systematic review in compliance with the PRISMA Statement (search conducted in PubMed and Embase, as well as in the citations of the selected articles). We chose studies if they dealt with thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxin (T4), or thyroid dysfunctions, and perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS) or perfluorononanoic acid (PFNA) measured in the blood of pregnant women and/or children up to 19 years old.

Results: We included in this review three cross-sectional, one case-control, and six cohort studies (publication: 2011–2015), focusing on prenatal life ($n = 7$), childhood ($n = 2$) or both periods ($n = 1$). We observed a high degree of heterogeneity across studies in terms of sampling time (different gestational weeks, at birth, or childhood), outcomes, adjustment for potential confounders, and statistical approach. We found some evidence of a positive association between PFHxS and PFOS exposure and TSH levels measured in maternal blood, and PFNA and TSH levels measured in the blood of boys aged ≥ 11 years.

Conclusion: Although there is a small number of studies with comparable data, we found some consistency of a positive association between maternal or teenage male exposure to some PFAS and TSH levels based on the current literature. However, further studies are required to confirm these possible relationships.

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1. Introduction

Perfluoroalkyl substances (PFAS) are synthetic chemicals with unique properties, such as insolubility in both organic solvents and water, and the ability to repel oils and water. They have been manufactured for industrial applications since the 1940s, and they are found and used in many common industrial and consumer products such as fire-fighting foams, alkaline cleaners, floor polishes, photographic films, shampoos, ant insecticides, soil- and stain-resistant coatings for fabrics, carpets and leather, as well as in grease- and oil-resistant coatings for paper products, among others (OCDE, 2005; Renner, 2001; WHO, 2013). In the general population, the main routes of exposure to these substances are *via* food, food packaging and drinking water (Domingo et al., 2012; Vestergren et al., 2008). Nearly all individuals, including pregnant women and children, in the many populations studied worldwide (Fromme et al., 2009; Kato et al., 2011; Manzano-Salgado et al., 2016; Mondal et al., 2012; Mørck et al., 2015; Zhao et al., 2012), showed measurable blood concentrations of four PFAS (perfluorohexane sulfonate [PFHxS], perfluorooctanoic [PFOA], perfluorooctane sulfonate [PFOS], and perfluorononanoic acid [PFNA]). Although there have been phase-out agreements regarding the production of certain PFAS by the industry in U.S. and Europe (WHO, 2013), due to their ubiquitous presence, long half-life in humans (Bartell et al., 2010; Olsen et al., 2007), and a tendency for bioaccumulation and biomagnification (WHO, 2013), exposure to this class of compounds will persist for many years, thereby making them a potential threat to humans.

Concern about exposure to PFAS has increased after the publication of recent studies showing that these chemicals have endocrine-disrupting properties and, among their possible health effects, PFAS may have the ability to impair thyroid function (Jensen and Leffers, 2008). Our review focuses on PFAS and thyroid disruption during the prenatal and childhood periods because thyroid hormones (THs) are especially important during brain maturation and the development of the fetus and children (Dussault and Ruel, 1987). THs are involved in the processes of dendritic and axonal growth, synaptogenesis, neurogenesis, and myelination during intrauterine life (Bernal, 2007). After birth, they are still essential, since some of

these neurodevelopmental processes, such as myelination, are not completed until adolescence (Rice and Barone, 2000; Schug et al., 2015) and they also play a role in the behavior and cognitive functions of the young and adolescent brain (Anderson, 2001). In fact, disorders involving TH availability, even subclinical maternal hypothyroidism (Haddow et al., 1999) or subtle changes in TH homeostasis during the first years of life (Freire et al., 2010; Julvez et al., 2013) may lead to delays in child neuropsychological development. Additionally, TH deficiency during infancy, childhood and puberty causes growth delay and precocious puberty in both sexes, and hirsutism in females (Papi et al., 2007). Finally, postnatal alterations of TH levels are also correlated with a variety of adverse effects in the pulmonary (Krude et al., 2002; Mendelson and Boggaram, 1991) and cardiovascular (Asvold et al., 2007; Biondi et al., 2005; Osman et al., 2002) systems. Therefore, the possible effects of PFAS on thyroid function during fetal and child life is a matter of public concern.

Prompted by the worldwide exposure to four PFAS (PFHxS, PFOA, PFOS, and PFNA) and the essential role of the thyroid system in the development and normal functioning of the body, we aimed to assess the evidence of associations between exposure to PFAS and thyroid function in pregnant women and children up to 19 years old.

2. Methods

We developed a protocol and performed a systematic review in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2010).

2.1. Eligibility criteria and search strategy

Studies selected for the review were those carried out in populations of pregnant women or children up to 19 years old, written in English or Spanish, and published before the end of December 2015. In this first selection of articles, we did not impose any restrictions on outcomes if at least one of the four chemicals (PFHxS, PFOA, PFOS, PFNA) or the generic PFC, PFAA, and PFAS were included (more details about search syntax can be found in Supplementary data). We did not include other PFAS

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