Environmental Research 110 (2010) 773–777

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Prenatal exposure to PFOA and PFOS and risk of hospitalization for infectious diseases in early childhood

Chunyuan Fei [a,*], Joseph K. McLaughlin [b,c], Loren Lipworth [b,c], Jørn Olsen [a,d]

[a] Department of Epidemiology, University of California, Los Angeles, CA 90095-1772, USA
[b] International Epidemiology Institute, 1455 Research Boulevard, Rockville, MD 20850, USA
[c] Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center, Nashville, TN 37232, USA
[d] Institute of Public Health, University of Aarhus, Vennelyst Boulevard 6, DK 8000 Aarhus C, Denmark

ARTICLE INFO

Article history:
Received 11 February 2010
Received in revised form
16 July 2010
Accepted 9 August 2010
Available online 30 August 2010

Keywords:
Infectious disease
Child
Maternal blood
Perfluorooctanoate
Perfluorooctanesulfonate

ABSTRACT

Objectives: To examine whether prenatal exposure to perfluorooctanesulfonate (PFOS) or perfluorooctanoate (PFOA) is associated with the occurrence of hospitalization for infectious diseases during early childhood.
Methods: We randomly selected 1400 pregnant women and their offspring from the Danish National Birth Cohort (1996–2002) and measured PFOS and PFOA levels in maternal blood during early pregnancy. Hospitalizations for infection of the offspring were identified by the linkage to the National Hospital Discharge Register through 2008.
Results: Hospitalizations due to infections were not associated with prenatal exposure to PFOA and PFOS. On the contrary, the relative risks of hospitalizations ranged from 0.71 to 0.84 for the three higher quartiles of maternal PFOA levels compared with the lowest, but no dose-response pattern was found. No clear pattern was observed when results were stratified by child's age at infection, with the exception of an inverse association between maternal PFC levels and risk of hospitalization during the child's first year of life.
Conclusions: These findings suggest that prenatal exposure to PFOA or PFOS is not associated with increased risk of infectious diseases leading to hospitalization in early childhood.

1. Introduction

Infectious diseases are common and are leading causes of hospitalization and death in childhood, especially in developing countries (Elliott and Beeson, 2008; Yorita et al., 2008). Perinatal exposures to certain persistent organic pollutants, such as polycyclic aromatic hydrocarbons, polychlorinated biphenyls, and organochlorine compounds, may impair the immune system and could therefore increase the risk of infections (Hertz-Picciotto et al., 2005; Dallaire et al., 2006; Glynn et al., 2008).

The perfluorinated chemicals, perfluorooctanoic acid (PFOA) and perfluorooctane sulfate (PFOS), are persistent and bioaccumulative and are widespread in the environment and in humans(Lau et al., 2007). Several studies have suggested that both compounds are potentially immunotoxic in rodents (Yang et al., 2002, 2006; Dewitt et al., 2008, 2009; Keil et al., 2008; Lefebvre et al., 2008; Peden-Adams et al., 2007, 2008, 2009). Observed effects included altered inflammatory responses, production of cytokines and other proteins, reduced lymphoid organ weights, and altered antibody synthesis (DeWitt et al., 2009), some of which have been shown to occur at levels close to the upper range of concentrations reported in the general population (Peden-Adams et al., 2008). The C8 Health Project, which collected data from residents living in the vicinity of a PFOA plant, found that immunoglobulins (Ig) A and E and C reactive protein (CRP) levels decreased with increase in blood levels of PFOA(Fletcher et al., 2009). To our knowledge, no study has examined whether exposure to PFOA and PFOS at a time when the immune system is developing increases the risk of infectious diseases during early childhood. In this study we evaluated the association between maternal PFOS and PFOA levels during pregnancy and the incidence of infectious hospitalizations in their children, during up to 11 years of follow-up using data from the Danish National Birth Cohort (DNBC).

Abbreviations: PFCs, perfluorinated chemicals; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfate; Ig, immunoglobulin; CRP, C reactive protein; DNBC, Danish National Birth Cohort; GPs, general practitioners; CATI, computer-assisted telephone interviews; LLOQ, the lower limit of quantitation; DNHR, the *Danish* National Hospital Register; ICD, International Classification of Diseases; AIC, Akaike Information Criterion; *BIC*, Bayesian *Information Criterion*; BMI, body mass index; SES, socio-occupational status; CIs, confidence intervals; IRR, incidence rate ratio

* Corresponding author.
E-mail address: cfei@ucla.edu (C. Fei).

0013-9351/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.envres.2010.08.004

2. Materials and methods

The present study population consists of 1400 mother–infant pairs randomly selected from the DNBC, which recruited pregnant women in Denmark from 1996 to 2002. Details on study design and recruitment procedures of the DNBC have been presented elsewhere (Olsen et al., 2001; Fei et al., 2007). Briefly, pregnant women were recruited through their general practitioners (GPs) at the first antenatal care visit (around weeks 6–12 of gestation). About 50% of all GPs in the country participated in the recruitment, and about 60% of invited women accepted the invitation. Women took part in four computer-assisted telephone interviews (CATI) at approximately 12 and 30 weeks of gestation and approximately 6 and 18 months after birth. They also provided two maternal blood samples, the first of which was taken during routine screening at the first antenatal care visit between gestational weeks 4 and 14 (median, 8 weeks) and was used for the present analyses. We selected 1400 women at random from 43,045 eligible women who provided the first maternal blood sample, gave birth to a single live born child without congenital malformation, and completed all four telephone interviews (Fei et al., 2007).

Plasma concentrations of PFOS and PFOA were measured blindly at the 3M Toxicology Laboratory (St. Paul, Minnesota) using high performance liquid chromatography–tandem mass spectrometry based on the methods described by Ehresman et al.(2007). All values were above the lower limit of quantitation (LLOQ: 1.0 ng/ml) except one PFOA value that was assigned a value of half the LLOQ. Twelve frozen whole blood samples were measured with regard to the plasma component, and these were multiplied by 2 to make them comparable to plasma measurements(Ehresman et al., 2007).

The outcome of interest was any hospitalization due to infections in early childhood. We linked the cohort to the *Danish* National Hospital Register (DNHR) by means of a unique civil registry number assigned to all Danish citizens at birth. If a child changed hospital department, a new record was added even though it was the same hospitalization. In order to avoid counting the same hospitalization more than once, we set a buffer zone of one week after the first hospital admission and then excluded all records for that child during the following week. The number of hospitalizations were counted for each child during the follow-up period, which began on the date of birth and ended on the date of death, emigration, or December 31, 2008, whichever occurred first. Hospitalizations with a discharge diagnosis of any selected infectious diseases were included in this analysis (Table 1), and the diagnoses were classified according to the International Classification of Diseases, Tenth Revision (ICD-10).

2.1. Statistical methods

Poisson regression was used to model the number of hospitalizations (SAS Genmod Procedure, Version 9.1), with child's age at the end of follow-up as an offset variable. We adjusted for overdispersion by introducing an option SCALE=DSCALE in the model statement. The negative binomial model and zero-inflated regression were also considered since our count data may exhibit overdispersion and excess zeroes. However, Poisson regression with adjustment for overdispersion *was chosen because this model* had the lowest Akaike Information Criterion (AIC) and Bayesian *Information Criterion (BIC).*

Table 1
ICD-10 codes for the selected infectious diseases included in the study.

Classification	ICD-10	Number of hospitalizations
Certain infectious and parasitic diseases	A00-B99	142
Inflammatory diseases of the central nervous system	G00-G09	4
Diseases of eye	H00, H10	9
Diseases of ear	H60, H65-66, H70, H72, H73	77
Diseases of the respiratory system	J00-J06, J10-J18, J20-J22, J30-32, J35-37, J40-J42, J85-J86	284
Appendicitis	K35-K37	10
Diseases of the skin and subcutaneous tissue	L00-L08	33
Diseases of the musculoskeletal system and connective tissue	M00-M03	5
Diseases of the genitourinary system	N10-N12, N30, N390	13
All		577

Covariates of interest were selected a priori based on a review of the literature and also based on the change-in-estimate principle(Maldonado and Greenland, 1993). The following factors were considered in the analyses: maternal age at delivery, parity, pre-pregnancy body mass index (BMI), smoking and alcohol consumption during pregnancy, maternal socio-occupational status (SES), birth season, birth year, house density, number of children in the household and age difference with the youngest sibling, gender of child, duration of breastfeeding, and gestational age at blood drawing. Data on breastfeeding practices were collected in the interviews at 6 and 18 months after birth and were categorized as never breastfeeding or breastfeeding <1 months, 1–2 months, 3–5 months, and ≥ 6 months. We defined maternal SES according to women's education and current job titles. Women with a higher education (4 years beyond secondary school education) or in management level jobs were classified as "high" social status; women with middle-range training and skilled workers were classified as "middle"; and unskilled workers or unemployed were classified as "low." Home density was defined as the total number of rooms divided by the total number of persons in the house. The birth seasons were spring (March–May), summer (June–August), autumn (September–November), and winter (December–February). We also considered child daycare attendance during the first 18 months after birth, maternal smoking after delivery, and smoking while child present (after birth), but the results did not change when these variables were introduced into the models and so they were excluded.

We further examined potential effect modification by child's gender, child's age at infection, and parity by including product terms with PFOA and PFOS levels in the models. The interaction terms were added in the multiple regression models and if interaction was indicated ($p<0.05$), we calculated stratum-specific rate ratios and 95% confidence intervals (CIs).

3. Results

Data on PFOA and PFOS concentrations in this study have been published elsewhere (Fei et al., 2007). The mean concentration was 5.6 ng/mL (range < LLOQ to 41.5) for PFOA and 35.3 ng/mL (range 6.4–106.7) for PFOS. Maternal PFOS and PFOA concentrations decreased with increase in parity, maternal age, and birth year. Higher concentrations of PFCs were observed in obese and overweight women. Concentrations of PFOS but not PFOA were higher in women who had higher socioeconomic status (SES).

Out of 1400 children, 363 (25.9%) were hospitalized at least once during the follow-up period due to infectious diseases. During 11,350 person-years of follow-up, the total number of hospitalizations was 577 (crude incidence rate 50.9 per 1000 person-years). At the end of follow-up, the average age of children was 8.2 years (range: 5.8–10.7). Risk of hospitalization for childhood infections was higher among boys, children with a smaller age difference to their youngest sibling, children of overweight or obese mothers, children of mothers who smoked during pregnancy, and children who were born in the autumn. Lower house density (more rooms per person) and breastfeeding more than 3 months were associated with lower incidence rates of hospitalization for infections (Table 2).

Children who were prenatally exposed to higher levels of PFOA had lower risks of hospitalization due to infections, but the incidence rate ratio (IRR) was statistically significant only for the second quartile of exposure [IRR=0.71, 95% confidence interval (CI) 0.53–0.94] compared with the first. No significant association was observed for PFOS (Table 3). After stratifying by child's age at infection, prenatal exposure to PFOA or PFOS was associated with a lower risk of hospitalization for infections during the first year of life but with no dose-response pattern. Beyond the first year, there was no apparent pattern of hospitalization risk according to either PFOA or PFOS exposure (Table 3).

In analyses stratified by child's gender, we observed among girls a slightly higher risk of hospitalization for infections associated with higher maternal PFOS or PFOA levels, with the IRRs ranging from 1.14 to 1.61 for PFOS and 1.20 to 1.74 for PFOA in the higher three quartiles compared with the lowest (Table 4). In contrast, the IRRs were all below 1.0 among boys whose mothers were exposed to higher levels of PFCs, compared to