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Perfluoroalkyl acid levels in first-time mothers in relation to offspring weight gain and growth

Irina Gyllenhammar[a,*], Barbro Diderholm[b], Jan Gustafsson[b], Urs Berger[c,d], Peter Ridefelt[e], Jonathan P. Benskin[c], Sanna Lignell[a], Erik Lampa[f], Anders Glynn[a]

[a] National Food Agency, P.O. Box 622, 751 26 Uppsala, Sweden
[b] Department of Women's and Children's Health, Uppsala University, 751 85 Uppsala, Sweden
[c] Department of Environmental Science and Analytical Chemistry (ACES), Stockholm University, 106 91 Stockholm, Sweden
[d] Department Analytical Chemistry, Helmholtz Centre for Environmental Research – UFZ, 04318 Leipzig, Germany
[e] Department of Medical Sciences, Clinical Chemistry, Uppsala University, 751 85 Uppsala, Sweden
[f] UCR Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden

ABSTRACT

We investigated if maternal body burdens of perfluoroalkyl acids (PFAAs) at the time of delivery are associated with birth outcome and if early life exposure (in utero/nursing) is associated with early childhood growth and weight gain. Maternal PFAA body burdens were estimated by analysis of serum samples from mothers living in Uppsala County, Sweden (POPUP), sampled three weeks after delivery between 1996 and 2011. Data on child length and weight were collected from medical records and converted into standard deviation scores (SDS). Multiple linear regression models with appropriate covariates were used to analyze associations between maternal PFAA levels and birth outcomes (n = 381). After birth Generalized Least Squares models were used to analyze associations between maternal PFAA and child growth (n = 200). Inverse associations were found between maternal levels of perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA), and birth weight SDS with a change of − 0.10 to − 0.18 weight SDS for an inter-quartile range (IQR) increase in ng/g PFAA. After birth, weight and length SDS were not significantly associated with maternal PFAA. However, BMI SDS was significantly associated with PFOA, PFNA, and PFHxS at 3 and 4 years of age, and with PFOS at 4 and 5 years of age. If causal, these associations suggest that PFAA affects fetal and childhood body development in different directions.

1. Introduction

Owing to their stability and combined water and oil repelling properties, perfluoroalkyl moieties have been incorporated into numerous commercial products for over 50 years. Over 3000 per- and polyfluoroalkyl substances (PFASs) are known to exist on the global market. Among these, the perfluoroalkyl acids (PFAAs) have garnered considerable international attention due to their environmental persistence and global occurrence in humans and wildlife. Pathways of human exposure are numerous and include food, drinking water, dust and air. In addition to direct exposure to PFAAs via any one of the aforementioned routes, exposure can also occur via precursors which may transform to PFAAs following exposure (D'Hollander et al., 2010; Vestergren et al., 2012; Gebbink et al., 2015; Gyllenhammar et al., 2015).

Studies investigating associations between maternal PFAA concentrations in serum/plasma and birth weight in humans have reported conflicting results (Johnson et al., 2014; Bach et al., 2015). Most studies have focused on perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) although humans are exposed to numerous other PFASs, only a fraction of which are known.

Studies of associations between maternal PFAA levels and childhood weight gain are scarce. Previous work has pointed out negative associations between prenatal PFOA and PFOS exposure and child weight at 5 and 12 months of age (Andersen et al., 2010) and positive associations between maternal PFOS levels and weight at 20 months (Maisonet et al., 2012), and PFOA and risk of overweight at 20 years of age (Halldorsson et al., 2012). Increased prenatal PFAA exposure has also been associated with increased adiposity in 3–20-year-olds (Halldorsson et al., 2012; Braun et al., 2016; Mora et al., 2017). However, results from studies of prenatal PFAA exposure and childhood weight gain and adiposity are not consistent as some of them show no significant associations (Andersen et al., 2013; Barry et al., 2014).

* Corresponding author.
E-mail address: Irina.gyllenhammar@slv.se (I. Gyllenhammar).

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Intra uterine growth restriction (IUGR) and/or being born small for gestational age (SGA) have been related to increased risk of impaired glucose tolerance, increased adiposity, and increased blood pressure later in life, especially among individuals with an early and rapid catch-up in weight after birth (Ibanez et al., 2006; Kerkhof et al., 2012; Gishti et al., 2014). Therefore, it is of interest to investigate fetal/neonatal PFAA exposure in relation to fetal, infant and child weight development and growth.

The aim of the present study was to investigate if maternal body burdens of PFAA at delivery are associated with birth outcomes and offspring weight gain and growth. Based on the present knowledge, we hypothesize that fetal PFAA exposure could lead to a decreased birth weight and thereby possibly also influence offspring weight development.

2. Materials and methods

2.1. Participants

Serum samples were collected 1996–2011 from first-time mothers from Uppsala County, Sweden, within the POPUP study (Persistent Organic Pollutants in Uppsala Primiparas). The study was restricted to singleton births with no birth defects. All women were Swedish born and almost all women had a full-term pregnancy (37–42 weeks), except in a few cases with the shortest gestational length being 35 weeks and the longest 43 weeks. The women in the POPUP cohort are homogenous regarding ethnic background, as indicated by the fact that only about 4% of the Swedish population had one or two foreign-born parents in 2006 (Socialstyrelsen, 2009). Samples were taken three weeks after delivery and thereafter biobanked at the Swedish National Food Agency. For details about recruitment, blood sampling, and collection of personal characteristics data see Glynn et al. (2007) and Lignell et al. (2009). In total 381 mothers who delivered their first child were analyzed for PFAAs (Table 1). During the first years of the study (1996–1999) women were also sampled in the 3rd trimester of pregnancy. The study was approved by the local ethics committee in Uppsala, Sweden, and the participating women gave informed consent for themselves and for their children.

2.2. Chemical analyses

Serum levels of 7 PFAAs, including perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS), were determined in mothers three weeks after delivery. In a subset of the participating women (n = 20), the aforementioned PFAAs were also analyzed in 3rd trimester serum in order to investigate correlations in levels between late pregnancy and 3 weeks after delivery. The analytical procedure has been described previously (Glynn, 2012; Vestergren et al., 2012). Briefly, serum was spiked with isotopically-labeled internal standards, extracted with acetonitrile, and then subjected to clean-up with graphitized carbon, prior to instrumental analysis by ultra performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). Method detection limits (MDLs) were defined based on the quantified background contamination signals. In the absence of procedural blank contamination, MDLs were defined as the lowest concentration in a serum sample giving a signal-to-noise ratio of 3. All batches included a procedural blank (water) and a control sample (replicate pooled human serum, n = 21). In addition, NIST SRM 1957 was analyzed to evaluate the accuracy of the method. CVs for control samples were typically between 15 and 22% with the exception of PFBS which showed higher variability, owing to concentrations closer to MDLs (Supplementary data, Table A1). Analysis of NIST reference material revealed that measured concentrations were consistent with reference values for all targets (Supplementary data, Table A2).

Table 1
Characteristic of the mothers and children participating in the study.

Characteristics	N	Mean (range)	%
Mothers			
Age (years)	381	29 (20–41)	
Pre-pregnancy BMI[a] (kg/m^2)	380	23 (16–40)	
Weight gain during pregnancy (%)[b]	379	22 (−4.1–54)	
Weight loss from delivery to sampling (%)[c]	343	14 (4.3–28)	
Fish consumption (g/day)	360	30 (0 − 220)	
Years of education	372		
≤ 4 years of high school	123		33
1–3 years of higher education	81		22
> 3 years of higher education	168		45
Smoking during pregnancy	380		
Smoker	44		12
Non-smoker	234		62
Former smoker	102		27
Children			
Boys	217		57
Girls	164		43
Gestational length (days)	381	280 (244–302)	
Birth weight (g)	381	3575 (2159–5420)	
Birth weight (SDS)	381	−0.15 (−3.1–3.1)	
Birth length (SDS)	381	−0.057 (−3.9–3.0)	
Head circumference	376	−0.37 (−3.6–3.3)	
SGA_W[d]	14		3.6
SGA_L[d]	21		5.5
GFR_{cc}[e] (mL/min/1.73 m^2)	305	103 (48–176)	
GFR_{creat}[f] (mL/min/1.73 m^2)	305	92 (60–166)	
Total breastfeeding (months)	192	6.5 (0– > 12)	
Breastfeeding at 3 months	184		96
Breastfeeding at 6 months	161		84

[a] Body mass index.
[b] Weight gain was calculated as weight of the mother just before delivery (W_d) compared to weight before pregnancy (W_{bp}): $[(W_d - W_{bp}) / W_{bp}] \times 100$.
[c] Weight of the mother just before delivery (W_d), weight of the mother at the time of blood sampling (W_s), and the birth weight of the child (W_b) were used to calculated this weight loss: $[(W_d - W_s - W_b) / W_d] \times 100$.
[d] Small for gestational age, weight or length < −2SDS.
[e] Estimated glomerular filtration rate, calculated using cystatin C-levels.
[f] Estimated glomerular filtration rate, calculated using creatinine-levels.

2.3. Infants/children

Weight, length and head circumference of the newborn infants (n = 381) were collected from the Swedish Medical Birth Register. During infancy and childhood, measurements of weight, length/height and head circumference at 3, 6, 12 and 18 months and 3, 4 and 5 years of age (n = 200) were collected from child health records in Uppsala County. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared at ages 3, 4, and 5 years. Standard deviation scores (SDS) were calculated from growth standards according to Karlberg et al. (2001), Wikland et al. (2002), and Niklasson and Albertsson-Wikland (2008).

2.4. Glomerular filtration rate (GFR)

In order to calculate estimated maternal GFR (eGFR), levels of creatinine and cystatin C were analyzed in serum samples from the mothers three weeks after delivery. In 20 women creatinine and cystatin C were also measured in late pregnancy, in order to investigate if the eGFR at this time point corresponded to that estimated after delivery.

Serum samples were analyzed on Abbott Architect ci8200 and ci16200 instruments (Abbott Park, IL, USA). Reagents (8L24-02) for the enzymatic IDMS-traceable creatinine method were from Abbott. Reagents for the immunoturbidimetric cystatin C method (Cystatin C reagent kit, no 1101) were from Gentian (Moss, Norway), and the recently described IFCC-certified international calibration procedure (Grubb et al., 2014) was used. The total analytical imprecision of