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Prenatal exposure to perfluoroalkyl substances and birth outcomes in a Spanish birth cohort

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ABSTRACT

Background: Prenatal perfluorooctanoate (PFOA) exposure has been associated with reduced birth weight but maternal glomerular filtration rate (GFR) may attenuate this association. Further, this association remains unclear for other perfluoroalkyl substances (PFAS), such as perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA). We estimated associations between prenatal PFAS exposure and birth outcomes, and the influence of GFR, in a Spanish birth cohort.

Methods: We measured PFHxS, PFOS, PFOA, and PFNA in 1st-trimester maternal plasma (years: 2003–2008) in 1202 mother-child pairs. Continuous birth outcomes included standardized weight, length, head circumference, and gestational age. Binary outcomes included low birth weight (LBW), small-for-gestational-age, and preterm birth. We calculated maternal GFR from plasma-creatinine measurements in the 1st-trimester of pregnancy (n = 765) using the Cockcroft-Gault formula. We used mixed-effects linear and logistic models with region of residence as random effect and adjustment for maternal age, parity, pre-pregnancy BMI, and fish intake during pregnancy.

Results: Newborns in this study weighted on average 3263 g and had a median gestational age of 39.8 weeks. The most abundant PFAS were PFOS and PFOA (median: 6.05 and 2.35 ng/mL, respectively). Overall, PFAS concentrations were not significantly associated to birth outcomes. PFOA, PFHxS, and PFNA showed weak, non-statistically significant associations with reduced birth weights ranging from 8.6 g to 10.3 g per doubling of exposure. Higher PFOS exposure was associated with an OR of 1.90 (95% CI: 0.98, 3.68) for LBW (similar in births-at-term) in boys. Maternal GFR did not confound the associations.

Conclusions: In this study, PFAS showed little association with birth outcomes. Higher PFHxS, PFOA, and PFNA concentrations were non-significantly associated with reduced birth weight. The association between PFOS and LBW seemed to be sex-specific. Finally, maternal GFR measured early during pregnancy had little influence on the estimated associations.

Abbreviations: BMI, Body mass index; CI, Confidence interval; CRL, Crown-rump-length; GAM, Generalized additive model; GFR, Glomerular filtration rate; GM, Geometric mean; HPLC-MS/MS, High performance liquid chromatography–tandem mass spectrometry; INMA, Environment and Childhood Project (*INfancia y Medio Ambiente*); LBW, Low birth weight; LOQ, Limit of quantification; OR, Odds ratio; PBPK, Physiologically-based pharmacokinetic; PFAS, Perfluoroalkyl substances; PFHxS, Perfluorohexane sulfonate; PFOS, Perfluorooctane sulfonate; PFOA, Perfluorooctanoate; PFNA, Perfluorononanoate; SD, Standard deviation; SGA, Small-for-gestational-age

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1. Introduction

Birth outcomes are commonly used as indicators of fetal growth during pregnancy. Throughout pregnancy there is a constant interplay between the internal and the external maternal environment leading to better or worse health status of the offspring. This interplay can be influenced by many factors including exposure to environmental chemical pollutants such as perfluoroalkyl substances (PFAS). PFAS are synthetic chemicals that have been industrially and commercially used since the 1950's (Casals-Casas and Desvergne, 2011; Prevedouros et al., 2006). A number of PFAS - including perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorooctanoic acid PFOA, and perfluorononanoate (PFNA) - have been detected in maternal serum and cord blood samples suggesting that PFAS can cross the placental barrier exposing the fetus to PFAS (Fei et al., 2007; Inoue et al., 2004; Manzano-Salgado et al., 2015).

PFOA is one of the most abundant and studied PFAS (as reviewed by Vrijheid et al., 2016). Prenatal PFOA exposure has been associated with reduced birth weight in animal and human studies, whereas for PFOS the evidence is less consistent (reviewed by Bach et al., 2015a; Johnson et al., 2014; Lam et al., 2014). Large prospective studies assessing other PFAS, besides PFOA and PFOS, are scarce (Rappazzo et al., 2017). One of the most comprehensive study to date with > 1500 mother-child pairs and an assessment of 11 different PFAS - including PFOS and PFOA - only observed a small association between PFNA and reduced birth weight in girls but not in boys (Bach et al., 2015b). However, this and previous studies have not consider maternal glomerular filtration rate (GFR) during pregnancy, which may influence the association between PFAS and fetal growth (Verner et al., 2015). Maternal GFR indicates the speed at which the mother can clear chemicals from her body, and increases during the first half of pregnancy and then declines during the second half (Gibson, 1973; Verner et al., 2015). Lower GFR has been associated with higher PFAS blood levels (Verner et al., 2015; Watkins et al., 2013) and smaller babies (Gibson, 1973; Verner et al., 2015). Indeed, a recent study found that a large proportion of the association between PFOS and PFOA and LBW, if there is any, may be attributable to confounding by maternal GFR (Verner et al., 2015); this study used a physiologically-based pharmacokinetic (PBPK) model to generate pairs of predictions for PFAS level and birth weight. Only one epidemiological study has considered the role of GFR on the association between PFOA and birth weight in a sub-analysis in a Norwegian birth cohort concluding that maternal GFR attenuated by 66% the association between PFOA and birth weight (Morken et al., 2014).

We evaluated the association between prenatal exposure to four different PFAS and birth outcomes including weight, length, head circumference, and gestational age in a Spanish birth cohort. We also assessed the influence of maternal GFR during pregnancy on the association between PFAS and birth outcomes.

2. Methods

2.1. Study population

In this study we used data from the INMA (Environment and Childhood - *INfancia y Medio Ambiente*) birth cohort. From 2003 to 2008, a total of 2150 pregnant women from the regions of Gipuzkoa, Sabadell, and Valencia were recruited during their 1st-trimester of pregnancy. The inclusion criteria were: being at least 16 years old, singleton pregnancy, no communication barrier, no reproductive assistance, and giving birth in the reference hospital (Guxens et al., 2012). We had 1242 mother-child pairs (58% from the full sample) with data on PFAS concentration and at least one birth outcome. From these, 40 mother-child pairs did not have complete information on the covariates of interest (i.e. 3.3% of the sample). For the purpose of this study, we only included the 1202 mother-child pairs with data on prenatal PFAS exposure and at least one birth outcome, and also complete data on the covariates of interest (Supplementary Material Fig. S1).

2.2. Birth outcomes

Birth weight (grams) was measured by trained midwives at delivery. Birth length (cm) and head circumference (cm) were measured within the first 12 h-of-life by a nurse when the newborn arrived at the hospital ward. Gestational age was calculated using the self-reported last menstrual period (LMP). An early crown-rump-length (CRL) was also available and was used to estimate gestational age when the LMP differed by ≥ 7 days from the ultrasound date (Westerway et al., 2000). Because gestational age has a large influence on weight, length, and head circumference at birth we standardized these outcomes to week 40 of gestation using the Box−Cox power exponential method (Rigby and Stasinopoulos, 2004). These outcomes were further adjusted by sex and region of residence (Casas et al., 2015; Estarlich et al., 2011). We defined small-for-gestational-age (SGA) if newborns weights were below 10th percentile for gestational age and sex according to national references (Carrascosa et al., 2004). We considered a birth preterm if delivery was before 37 weeks of gestation. Newborns with weights < 2500 g were defined as LBW. Newborns with LBW born greater than or equal to 37 weeks were defined as LBW-at-term.

2.3. PFAS determination

Maternal blood samples were collected during the first trimester of pregnancy [mean: 12.3 weeks; standard deviation (SD): 5.6 weeks]. Plasma was aliquoted in 1.5 mL cryotubes and stored at − 80 °C until their analysis at the Institute for Occupational Medicine, RWTH Aachen University (Aachen, Germany), as previously described (Manzano-Salgado et al., 2015). Briefly, plasma concentrations of PFHxS, PFOS, PFOA, and PFNA were determined by column-switching liquid chromatography (Agilent 1100 Series HPLC apparatus) coupled with tandem mass spectrometry (Sciex API 3000 LC/MS/MS system in ESI-negative mode) according to a modified protocol described by Kato et al. (2011). The limit of quantification (LOQ) was 0.20 ng/mL for PFHxS, PFOS, and PFOA and 0.10 ng/mL for PFNA (Manzano-Salgado et al., 2015). The between day imprecision ranged from 8.7% for PFHxS (0.7 ng/mL) to 11.1% for PFNA (0.7 ng/mL).

2.4. Maternal and newborn covariates

Maternal socio-demographic and dietary information was collected by questionnaires administered during the 1st and 3rd - trimesters of pregnancy. Data regarding the maternal health status during pregnancy and delivery (e.g. gestational weight gain, preeclampsia, and gestational diabetes) was collected from clinical records. Plasma creatinine levels in the 1st-trimester of pregnancy were determined using non-compensated kinetic alkaline picrate method (ABX-Pentra 400) in 800 pregnant women that had available blood in the same sample used to measure PFAS concentrations. The creatinine levels were used to calculate maternal GFR using the Cockcroft-Gault formula [GFR = (140-maternal age) × weight (kg) × 1.04/serum creatinine (μmol/L)]. For this study, we only analyzed GFR in mothers that had available PFAS, birth outcomes, and the other covariates (n = 765). In this same subsample of women, we determined serum albumin using Bromocresol green assay (ABX-Pentra 400). Mothers completed a 100-item food frequency questionnaire (FFQ) that was administered by trained interviewers and was used to assess the usual food and nutrient intake during the first trimester of pregnancy. The response to each food item was converted to an average daily intake for each participant. Consumption of a range of food groups was assessed: dairy products, meat, eggs, cereals, pasta, and fruit and vegetables, and fish intake. This FFQ was an adapted version of Willett's questionnaire (Willet et al.,