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Longitudinal Changes in Maternal Serum Concentrations of Per- and Polyfluoroalkyl Substances from Pregnancy to Two Years Postpartum

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Supporting Information

The Supporting Information includes the data below.

Median and range of coefficients of variation for PFAS among the 25 blind duplicate samples analyzed for quality assurance (Table S1), geometric means (GMs) and 95% confidence intervals (CIs) of maternal serum concentration ratios of PFAS at each sample collection point compared to the 1st trimester of pregnancy (Table S2), Spearman correlation coefficients of maternal serum PFAS concentrations across the six collection time points (Table S3), univariate associations between maternal serum PFAS concentrations and potential determinants (Table S4), percent changes in geometric mean maternal serum PFAS concentrations over time after combining all three sub-periods (from the 1st trimester to 2 years postpartum) (Table S5), percent changes in maternal serum PFAS concentrations over time after additionally adjusting for maternal BMI at pre-pregnancy, maternal weight gain during pregnancy and child's birthweight in pregnancy and early postpartum models (Table S6), percent changes in geometric mean maternal serum PFAS concentrations over time after additionally adjusting for a binary exclusive breastfeeding duration (< 6, ≥ 6 months) in early postpartum models (Table S7), percent changes in maternal serum PFAS concentrations over time after adjusting for total breastfeeding duration, instead of exclusive breastfeeding duration, in late postpartum models (Table S8), percent changes in maternal serum PFAS concentrations over time stratified by exclusive breastfeeding duration, fitted using 3-, 6- and 24-months postpartum samples (Table S9), unadjusted annual percent changes in PFAS concentrations in 2009–2016 NHANES female population who were pregnant and/or breastfeeding at sample collection (n = 128) (Table S10), intraclass correlation coefficients (ICC) and 95% confidence intervals (CIs) of ln-transformed PFAS concentrations in maternal serum samples collected during the whole study period and three sub-periods (i.e., pregnancy, early postpartum, and late postpartum) (Figure S1), and sensitivity analysis - percent changes in maternal serum PFAS concentrations over time using ln-transformed concentration ratios of PFAS at each sample collection points to those at the 1st trimester of pregnancy as dependent variable (Figure S2).

Complete contact information is available at: https://XXX.

Conflict of interest

The authors declare that they have no actual or potential competing financial interest.

Ethics approval and consent to participate

The MARBLES study protocol and this study were approved by the institutional review boards for the State of California, the University of California-Davis (UC-Davis), and the University of Texas-Arlington (UT-Arlington). Participants provided written informed consent before collection of the data. The analysis of coded specimens at the Centers for Disease Control and Prevention (CDC) laboratory was determined by CDC not to constitute engagement in human subject research.

Credit authorship contribution statement

Jiwon Oh: Conceptualization, Methodology, Writing - original draft. **Deborah Bennett**: Writing - review & editing, Methodology, Funding acquisition. **Daniel J. Tancredi**: Methodology, Writing - review & editing. **Antonia M. Calafat**: Methodology, Writing - review & editing. **Rebecca J. Schmidt**: Funding acquisition, Writing - review & editing. **Irva Hertz-Picciotto**: Funding acquisition, Writing - review & editing, Methodology. **Hyeong-Moo Shin**: Conceptualization, Methodology, Funding acquisition, Writing - review & editing.

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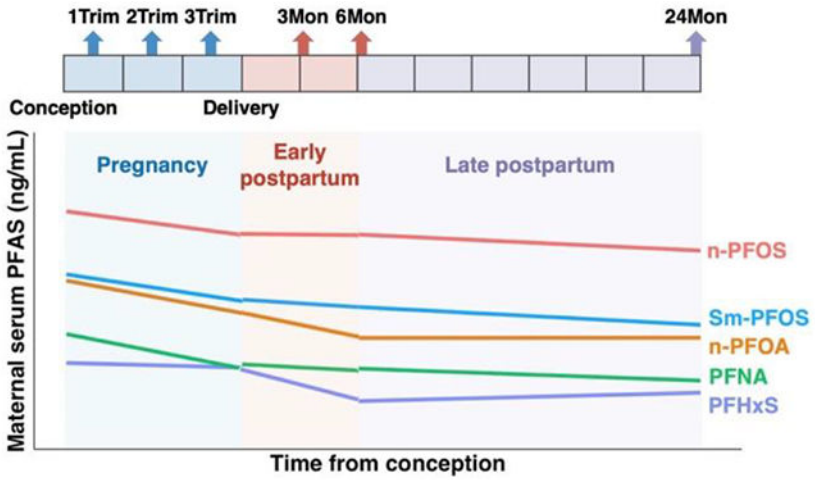
Abstract

Exposure to per- and polyfluoroalkyl substances (PFAS) during pregnancy and lactation is of increasing public health concern, but little is known about longitudinal changes in maternal PFAS concentrations from pregnancy to a few years postpartum. We quantified eleven PFAS in 251 serum samples prospectively collected from 42 Northern California mothers during the 1st, 2nd, and 3rd trimesters of pregnancy and at 3, 6, and 24 months after delivery over 2009–2017. We fit separate linear mixed models during pregnancy, early postpartum, and late postpartum to estimate percent changes of PFAS for each sub-period. Among five PFAS detected in more than 99% of samples, linear and branched perfluorooctane sulfonate (n- and Sm-PFOS), linear perfluorooctanoate (n-PFOA), and perfluorononanoate (PFNA) concentrations changed −4% to −3% per month during pregnancy. During early postpartum, perfluorohexane sulfonate (PFHxS) and n-PFOA concentrations changed −6% and −5%, respectively, per month, and Sm-PFOS and PFNA concentrations changed −1% per month. During late postpartum, n-PFOS, Sm-PFOS, and PFNA concentrations changed −1% per month. Breastfeeding duration was the primary determinant of n-PFOA and PFNA concentrations during late postpartum, showing negative associations. Our findings might be useful for reconstructing reliable prenatal or early-life PFAS exposures for offspring.

Graphical Abstract



Keywords

PFAS; concentration changes; pregnancy; early postpartum; late postpartum; determinants; breastfeeding

I. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a class of synthetic chemicals that exhibit both hydrophilic and hydrophobic properties and thus are widely used in various industrial and consumer applications, such as fire-fighting foams and coatings of cookware, textiles, carpet, and food contact materials.[1] Humans are exposed to certain PFAS primarily via ingestion of contaminated food and water as well as non-dietary dust ingestion.[2–4] Since the early 2000s, serum concentrations of the two most studied PFAS, perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), have consistently decreased in the United States (U.S.), following regulatory and voluntary phase-out, while those of other long-alkyl chain PFAS showed less consistent trends, in some cases increasing, decreasing, or having mixed results.[5–8] However, widespread detection of common long-alkyl chain PFAS in environmental media, including food, drinking water, soil, and house dust, suggests continued exposure of the general population to these compounds.[3, 4, 9–12]

Prenatal and early-life exposure to PFAS is of particular concern due to PFAS's potential adverse effects on child's health. In laboratory animals, PFAS are shown to have liver toxicity, metabolic toxicity, reproductive and developmental toxicity, neurotoxicity, and immunotoxicity.[13, 14] Epidemiologic studies reported that prenatal or lactational exposure to PFAS was associated with reduced fetal or infant growth,[15–17] immune dysfunction,[18] neurodevelopmental disorders,[19–22] and thyroid disruption.[23, 24] PFAS have been commonly detected in blood of pregnant women,[25–34] the placenta,[35, 36] cord blood,[23, 37–39] and breast milk.[40–42] Moderate to high correlations of PFAS concentrations in maternal serum with those in paired cord serum and breast milk demonstrated that PFAS are transported from mother to child through the placenta during pregnancy and through breast milk during lactation.[23, 27, 37–39, 43–46]

Changes in maternal PFAS concentrations may differ not only between pregnancy and postnatal periods but also among individual PFAS. Several studies quantified PFAS in serial blood samples collected from the same women during pregnancy or early postpartum period.[16, 25, 34, 47] In these studies, maternal concentrations of several long-alkyl chain PFAS, including PFOA, PFOS, and perfluorononanoate (PFNA), decreased at different rates during pregnancy. Only one of the studies further collected postnatal samples and observed significant declines in mean PFOA concentrations and nonsignificant declines in mean PFOS concentrations between 3 weeks and 3 months postpartum, while mean PFNA concentrations did not change.[25] However, little is known about changes in maternal PFAS concentrations from early pregnancy to the postnatal period, especially during late postpartum when mothers are expected to cease exclusive breastfeeding.[48] As placental and lactational transfers of PFAS occur during pregnancy and breastfeeding, respectively, and the transfer efficiencies of PFAS are different across the compounds,[42, 49, 50] maternal PFAS concentrations are expected to change with different rates during pregnancy, early postpartum, and late postpartum periods.

In the present study, we quantified eleven PFAS in 251 blood serum samples prospectively collected from 42 mothers during the 1st, 2nd, and 3rd trimesters of pregnancy and 3, 6, and 24 months after delivery. Then, we separately examined changes in maternal serum PFAS concentrations and their potential determinants for three sub-periods: (1) during pregnancy (from 1st to 3rd trimesters), (2) early postpartum (from delivery to 6 months postpartum) and (3) late postpartum (from 6 to 24 months postpartum). We also investigated the influence of breastfeeding on maternal serum PFAS concentrations during the postnatal period. We anticipate that improved understanding of PFAS changes during pre- and postnatal periods from the current study will help future studies reconstruct PFAS exposure for pregnant women and their offspring.

2. Methods

2.1. Study population

This current study includes participants drawn from the MARBLES (***M***arkers of ***A***utism ***R***isk in ***B***abies – ***L***earning ***E***arly ***S***igns) study. Launched in 2006, MARBLES is an ongoing prospective birth cohort study that enrolls pregnant women who previously had a child who developed autism spectrum disorder (ASD).[51] The MARBLES families are primarily recruited from those who receive state-funded services for ASD in Northern California. Mothers are eligible if they have a child or other first degree relative with ASD, are pregnant and 18 years old or older, speak, read and understand English, and live within 2.5 hours of the Davis/Sacramento region at the time of enrollment. Details of study design, study population, eligibility criteria, and data collection are available elsewhere.[51] Any information or biological specimens were collected after completing informed consent. This study was approved by the institutional review boards for the State of California and the University of California Davis (UC Davis). The analysis of coded samples at the Centers for Disease Control and Prevention (CDC) laboratory did not constitute engagement in human subjects' research.

The MARBLES study started collecting serum in 2009, thus we included 42 mothers who prospectively provided six blood samples (during the 1st, 2nd, and 3rd trimesters of pregnancy and at 3, 6, and 24 months after delivery) since 2009 and conceived their baby by 2014. One of the 42 mothers did not provide the 1st trimester sample but was included in this study, thus a total of 251 maternal blood samples were used for statistical analyses.

2.2. Serum sample collection and PFAS quantification

Maternal blood was collected at home visits conducted during pregnancy and the first year after delivery and at visits to UC Davis Medical Investigations of Neurodevelopmental Disorders (MIND) Institute at two years postpartum.[51] After collection, whole blood was centrifuged to separate serum, stored at −80 °C and shipped to the CDC for PFAS quantification.

PFAS in maternal serum were quantified using online solid-phase extraction coupled to reversed-phase high-performance liquid chromatography-isotope dilution tandem mass spectrometry, as described elsewhere.[52] Eleven PFAS quantified include linear PFOA isomer (n-PFOA), branched PFOA isomers (Sb-PFOA), linear PFOS isomer (n-PFOS), branched PFOS isomers (Sm-PFOS), perfluorohexane sulfonate (PFHxS), PFNA, perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnDA), perfluorododecanoate (PFDoDA), 2-(N-methyl-perfluorooctane sulfonamido) acetate (MeFOSAA), and 2-(N-ethyl-perfluorooctane sulfonamido) acetate (EtFOSAA). The limit of detection (LOD), defined as 3 times the standard deviation as the concentration approaches zero, for all PFAS was 0.1 ng/mL; PFAS concentrations below the LOD were replaced with a value of the LOD divided by the square root of two.[53] Blank samples and low- and high-concentration quality control (QC) samples were analyzed with the study samples, following the approach used for the analysis of thousands of National Health and Nutrition Examination Survey (NHANES) samples.[54] The coefficient of variation of low- and high- QC materials ranged from 6% to 12%, depending on the analyte. We also included 25 blind duplicate samples that were analyzed along with study samples for quality assurance, and their median coefficient of variation ranged from 0% to 11% depending on the PFAS (Table S1).

2.3. Potential determinants

Based on the literature review, we considered various maternal prenatal, perinatal, and demographic factors that were prospectively collected during our study period as potential determinants of maternal serum PFAS concentrations. Prenatal and perinatal factors included parity, maternal body mass index (BMI) at pre-pregnancy (kg/m^2), maternal weight gain during pregnancy (kg), birthweight (kg), total breastfeeding duration (month; until when a mother completely stopped breastfeeding), and exclusive breastfeeding duration (month; until when formula, solids, or liquids was introduced). Demographic factors included child's birth year (year), maternal age at delivery (year), maternal birthplace (U.S., non-U.S.), maternal race/ethnicity (non-Hispanic white, Hispanic/Asian/multiracial), maternal education (no bachelor's degree, bachelor's degree or higher), and homeownership (owner, non-owner).

2.4. Statistical analysis

All statistical analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). For eight PFAS detected in greater than 50% of all samples, we computed pairwise Spearman correlation coefficients among the six time points. We computed intraclass correlation coefficients (ICCs) and 95% confidence intervals (CIs) using ICCest() function in R to assess within-subject variability of ln-transformed PFAS concentrations.[55] An ICC is a ratio of between-subject variance to the sum of between- and within-subject variance, and a higher ICC indicates smaller within-subject variability.[56] We calculated maternal serum concentration ratios by dividing the PFAS concentrations at each point (i.e., 2nd and 3rd trimesters of pregnancy, 3, 6, and 24 months postpartum) by the 1st trimester concentration. For one mother who did not provide the 1st trimester sample, the concentrations at each point were divided by the 2nd trimester concentration. In order to account for right-skewed distributions, PFAS concentrations and concentration ratios were natural log (ln)-transformed in subsequent regression analyses.

To examine changes in maternal PFAS serum concentrations from pregnancy to two years postpartum, we used only five PFAS detected in more than 99% of the whole study samples (i.e., n-PFOS, Sm-PFOS, PFHxS, n-PFOA, and PFNA). We grouped our study samples into three sub-periods: (1) pregnancy included samples from the 1st, 2nd, and 3rd trimesters of pregnancy, (2) early postpartum included samples from 3rd trimester and 3 and 6 months postpartum, and (3) late postpartum included samples from 6 and 24 months postpartum. For each sub-period, we investigated univariate associations between average concentrations of each compound and *a priori* selected potential determinants by performing the Spearman correlation test for continuous variables and the Wilcoxon rank-sum test for binary variables.

Based on the univariate analyses, we included covariates that were associated with PFAS concentrations in all sub-periods ($p < 0.05$). Accordingly, child's birth year (centered to 2012), maternal age at delivery, parity, and maternal birthplace were adjusted in all models, and exclusive breastfeeding duration was additionally included in the late postpartum models. Prenatal maternal weight gain, which may represent early postnatal weight loss, was inversely associated with n-PFOS during early postpartum, but not during pregnancy, thus it was not included in the models. Then, we fitted the covariate-adjusted linear mixed models with random intercepts for maternal-child dyads to estimate changes in ln-transformed maternal serum PFAS concentrations for each sub-period. Given our small sample size, we performed parametric bootstrapping with 1000 replications and computed 95% bias corrected and accelerated confidence intervals (Cis) using bootMer() function in R.[57] We calculated percent changes in geometric mean maternal serum PFAS concentrations per one-unit increase in time as well as each covariate using the following equation $[(e^{\beta} - 1) \times 100$, where β is a regression coefficient for time and each covariate]. As a sensitivity analysis, we used ln-transformed concentration ratios of PFAS at each sample collection point to those at the 1st trimester of pregnancy as a dependent variable (instead of ln-transformed PFAS concentrations) in the linear mixed models to account for different initial concentrations. We also combined all three sub-periods (i.e., from the 1st trimester to 2 years postpartum) to estimate the monthly percent changes of PFAS for the whole period.

Maternal plasma volume increases approximately 45% throughout the pregnancy and returns to pre-pregnancy levels within 6 weeks postpartum.[58, 59] To account for the dilution effect in pregnancy and early postpartum models, we additionally adjusted for maternal BMI at pre-pregnancy, maternal weight gain during pregnancy, and child's birthweight, which are potential predictors for plasma volume expansion.[60, 61] To assess the effect of exclusive breastfeeding duration in the early postpartum models, we additionally adjusted for a binary exclusive breastfeeding duration variable (< 6, ≥ 6 months).We also investigated the effect of total breastfeeding duration in the late postpartum models by alternatively adjusting for total breastfeeding duration, instead of exclusive breastfeeding duration. To evaluate whether changes in ln-transformed maternal serum PFAS concentration differ by exclusive breastfeeding duration, we divided the mothers into two groups: women who exclusively breastfed their child longer or shorter than 4 months. For each group, we fitted a postpartum model to the PFAS concentrations at 3-, 6-, and 24-months postpartum without adjusting for exclusive breastfeeding duration and compared the monthly percent changes of PFAS. We also tested the postpartum model for an interaction term between time from conception (to the child's age at sample collection) and a binary exclusive breastfeeding duration variable (< 4, ≥ 4 months).

3. Results

3.1. Population characteristics

Approximately half of the mothers gave birth in the later study period (2014–2015), and overall, their average age at delivery was 34.9 years (range: 22.4 to 42.8) (Table 1). On average, their pre-pregnancy BMI was 25.1 kg/m^2 (range: 18.9 to 39.9) and they gained 14.4 kg of weight during pregnancy (range: 1.4 to 26.1). More than half of the mothers were non-Hispanic white (57%), born in the U.S. (67%), had a bachelor's degree or higher (67%) or owned a home (67%). After delivery, all mothers breastfed their child, and the average duration was 14.2 months (range: 2.8 to 36.7). Their exclusive breastfeeding duration ending with introduction of formula, solids, or liquids was an average of 3.8 months (range: 0.0 to 9.6).

3.2. Maternal serum PFAS concentrations

During the whole study period, n-PFOS, Sm-PFOS, n-PFOA, and PFNA were detected in all study samples, and PFHxS, PFDA, PFUnDA, and MeFOSAA were detected in 99%, 81%, 57%, and 52% of the samples, respectively (Table 2). Sb-PFOA, PFDoDA, and EtFOSAA were detected in less than 50% of the study samples. The medians of n-PFOS, Sm-PFOS, n-PFOA, PFHxS, and PFNA were 2.0, 0.7, 0.3, 0.7, and 0.4 ng/mL, respectively, while those of PFDA, PFUnDA, and MeFOSAA were similar to the LOD (i.e., 0.1 ng/mL). Compared to the 1st trimester of pregnancy, the GMs of concentration ratios for PFAS detected in greater than 50% of the samples ranged from 0.79 to 1.01 during pregnancy and from 0.57 to 0.92 during a postnatal period (Table S2).

Concentrations of the eight PFAS detected in more than 50% of the samples showed moderate to high positive pairwise correlations across the six sample collection time points (r_{sp} [Spearman's correlation coefficient] = 0.56 to 0.97) (Table S3). PFAS concentrations

during the 1st, 2nd, and 3rd trimesters of pregnancy were more strongly correlated with each other (r_{sp} = 0.62 to 0.97) as well as with those at 3 and 6 months postpartum (r_{sp} = 0.57 to 0.96) than with those at 24 months postpartum (r_{sp} = 0.58 to 0.85). The ICCs of eight ln-transformed PFAS ranged from 0.63 to 0.92 for the whole study period, 0.67 to 0.94 for pregnancy, 0.65 to 0.97 for early postpartum, and 0.60 to 0.88 for late postpartum, indicating relatively small within-subject variability of maternal PFAS serum concentrations (Figure S1). Among three sub-periods, the smallest ICCs were observed during the late postpartum period.

3.3. Univariate associations of maternal serum PFAS concentrations with potential determinants

Among the five PFAS detected in more than 99% of the whole study samples, child's birth year was negatively correlated with maternal serum n-PFOS, Sm-PFOS, n-PFOA, PFHxS, and PFNA concentrations during all sub-periods (r_{sp} = −0.73 to −0.35), except for PFNA during pregnancy (Table S4). Mother's age at delivery was positively correlated with n-PFOS and PFHxS during pregnancy (r_{sp} = 0.31), n-PFOA during early postpartum (r_{sp} = 0.37), and n-PFOS, Sm-PFOS, PFHxS, n-PFOA and PFNA during late postpartum (r_{sp} = 0.32 to 0.53). Parity was negatively correlated with n-PFOA during pregnancy and early postpartum (r_{sp} = −0.39 and −0.33, respectively) and PFHxS during early postpartum and late postpartum (r_{sp} = −0.36 and −0.50, respectively). During late postpartum, total breastfeeding duration was negatively correlated with n-PFOA (r_{sp} = −0.59) and PFNA (r_{sp} = −0.36), and exclusive breastfeeding duration was negatively correlated with n-PFOA only (r_{sp} = −0.32). During all three sub-periods, mothers who were born in the U.S. had lower PFNA concentrations than those who were not.

3.4. Monthly percent changes in maternal PFAS serum concentrations over time and by potential determinants

Maternal serum concentrations of n-PFOS showed the fastest decreasing rate during pregnancy (percent change per month: −3.0%), while they rarely changed during early postpartum and relatively slowly decreased during late postpartum (−1.0%) (Figure 1). Sm-PFOS concentrations decreased with similar rates during pregnancy (−3.3%) and late postpartum (−1.2% per month), but further decreased during early postpartum (−1.4%). PFHxS concentrations decreased most rapidly during early postpartum (−5.6%), whereas they rarely changed during pregnancy and late postpartum. N-PFOA concentrations decreased rapidly during pregnancy (−4.0%) and early postpartum (−4.5%), while they did not change during late postpartum. PFNA showed the fastest decreasing rate during pregnancy (−4.3%), compared to early postpartum (−1.2%) and late postpartum (−0.8%).

During all three sub-periods, Sm-PFOS and PFHxS showed the fastest decline rates per child's birth year (−17.8% and −13.8% per year, respectively), and n-PFOS, n-PFOA, and PFNA concentrations decreased relatively slowly (−11.3%, −8.9, and −6.4% per year, respectively) (Table 3). Throughout the whole period, mothers who were born outside the U.S. had 50.3% to 52.9% higher PFNA than the U.S.-born mothers. With increasing parity, n-PFOA concentrations during pregnancy changed −11.4%, and PFHxS concentrations during early and late postpartum changed −14.5% and −16.8%, respectively.

During late postpartum, n-PFOA concentrations changed 5.3% per year with increasing maternal age at delivery. With increasing exclusive breastfeeding duration, n-PFOA and PFNA concentrations changed −5.1% and −4.1% per month, respectively, with borderline significance.

When using ln-transformed concentration ratios of PFAS at each time point to those at the 1st trimester of pregnancy as a sensitivity analysis, most monthly percent changes remained similar (Figure S2). When combining all sub-periods, the decreasing rates of five PFAS from the 1st trimester to 2 years postpartum were similar (−1.7% to −1.2% per month) (Table S5). When additionally adjusting for maternal BMI at pre-pregnancy, maternal weight gain during pregnancy and child's birthweight in pregnancy and early postpartum models to account for maternal plasma volume expansion, monthly percent changes did not change (Table S6). When additionally adjusting for a binary exclusive breastfeeding duration variable (< 6, ≥ 6 months) in early postpartum models, monthly percent changes did not change (Table S7). When adjusting for total breastfeeding duration, instead of exclusive breastfeeding duration, in late postpartum models, monthly percent changes were similar, and n-PFOA and PFNA concentrations significantly decreased with increasing total breastfeeding duration (Table S8).

When stratifying postnatal samples (i.e., 3, 6, and 24 months) by median exclusive breastfeeding duration (> 4 months, ≤ 4 months), n-PFOA concentrations significantly decreased (−1.4% per month) among the mothers who exclusively breastfed longer than 4 months, while they did not decrease among the mothers who did not (Table S9). Concentrations of n-PFOS, Sm-PFOS, and PFNA changed −1.3%, −1.4%, and −1.4% per month among the mothers who exclusively breastfed longer than 4 months and −0.7%, −1.0%, and −0.4% per month among the mothers who exclusively breastfed shorter than 4 months, respectively. The decreasing rates of n-PFOA and PFNA were significantly greater among the mothers with exclusive breastfeeding duration longer than 4 months (*p*-value for interaction ≤ 0.01).

4. Discussion

In this study, we quantified eleven PFAS in prospectively collected maternal blood during the 1st, 2nd, and 3rd trimesters of pregnancy and at 3, 6, and 24 months after delivery and examined changes in PFAS concentrations for three sub-periods (i.e., pregnancy, early postpartum, and late postpartum). Maternal serum concentrations of n-PFOS, Sm-PFOS, n-PFOA, and PFNA decreased 3% to 4% per month during pregnancy, those of Sm-PFOS, PFHxS, n-PFOA, and PFNA declined 1% to 6% per month during early postpartum, and those of n-PFOS, Sm-PFOS, and PFNA declined 1% per month during late postpartum. We also explored prenatal, perinatal, and demographic factors affecting maternal serum PFAS concentrations. In all sub-periods, mothers who gave birth in a later study period had lower n-PFOS, Sm-PFOS, PFHxS, n-PFOA, and PFNA concentrations, and mothers who were born outside the U.S. had higher PFNA concentrations. During late postpartum, we identified that higher n-PFOA and PFNA concentrations were associated with shorter exclusive breastfeeding duration, which was confirmed by stratified analysis.

Decreases in our maternal serum PFAS concentrations from pregnancy to postnatal periods are consistent with those from other studies that repeatedly measured PFAS concentrations during pregnancy and/or early postpartum within the same women. Two previous studies collected three maternal blood samples during the 1st, 2nd, and 3rd trimesters of pregnancy and observed decreases in most of the PFAS concentrations, including PFOS, PFOA, PFNA, PFDA, PFUnDA, and PFDoDA, while PFHxS concentrations did not change, as in the current study.[16, 47] Kato et al. collected two maternal blood samples at 16 weeks of pregnancy and at delivery from 71 women.[34] They observed 25% to 43% decreases in GM serum concentrations of PFOS and PFOA (sum of linear and branched isomers), PFHxS, and PFNA between the two time points, and the unadjusted monthly percent changes during pregnancy (when assuming 6 months interval) were −7% for PFOS and PFOA, −4% for PFHxS, and −5% for PFNA, which showed faster decreasing rates than this study. We did not quantify PFAS in serum collected shortly after delivery, but the GM concentration ratios of Kato et al. (0.71 for PFOS, 0.79 for PFHxS, 0.70 for PFOA, and 0.77 for PFNA) were comparable to those between the 1st trimester of pregnancy and 3 months postpartum in our study (0.85 for n-PFOS, 0.79 for Sm-PFOS, 0.73 for PFHxS, 0.66 for n-PFOA, and 0.78 for PFNA) (Table S2). Glynn et al. serially collected maternal blood samples during the 1st and 3rd trimesters of pregnancy and at 3 weeks and 3 months after delivery from 19 women.[25] They observed 11% to 33% decreases in mean serum concentrations of PFOS (sum of linear and branched isomers), PFOA, and PFNA between the 1st and 3rd trimester of pregnancy, and the unadjusted monthly percent changes (when assuming 6 months interval) were −3% for PFOS, −2% for PFOA, and −6% for PFNA. Only maternal mean PFOA concentrations, but not PFOS and PFNA, further decreased between 3 weeks and 3 months postpartum.

Although we did not use direct evidence of placental transfer of PFAS such as concentrations in umbilical cord blood, placental transfer from mother to fetus may explain declines in maternal serum PFAS concentrations during pregnancy because PFAS concentrations in maternal serum have been shown to be moderately to highly correlated with those in cord blood[23, 27, 37–39, 43–46] and fetal tissues.[62] Specifically, Mamsen et al. observed that PFOS, PFOA, and PFNA in maternal serum were positively correlated with those in placenta, fetal liver, lung, heart, and adipose tissue, while they did not observe significant correlations for PFHxS, PFDA, and PFUnDA.[62] Previous studies also suggested that maternal blood volume expansion during pregnancy can also explain decreases in PFAS concentration[16, 25] because blood volume increases approximately 45% throughout the pregnancy.[58] However, we observed that changes in maternal serum PFAS concentrations during pregnancy remained similar after adjusting for potential predictors of maternal blood volume expansion (Table S6).

Breastfeeding is a major PFAS excretion route for lactating mothers.[40, 63, 64] We observed that maternal serum concentrations of n-PFOS, PFHxS, n-PFOA, and PFNA decreased from the 3rd trimester to 6 months postpartum and that longer breastfeeding duration was negatively associated with n-PFOA and PFNA after 6 months postpartum. Moreover, the decreasing rates of postnatal n-PFOA and PFNA concentrations were greater among mothers who exclusively breastfed their child longer than 4 months, compared to those who did not. This finding suggests that breastfeeding may be an important exposure route for nursing infants and thus those who are longer breastfed may experience higher postnatal

exposure to PFOA and PFNA. In a study that quantified PFOA and PFOS in breast milk serially collected during one year of breastfeeding, PFOA showed −7.7% of monthly percent changes in breast milk, which was 2.5 times greater than PFOS (−3.1% per month), indicating its greater excretion rate through the breastfeeding.[40] Several mother-child studies observed higher concentration ratios of breast milk to maternal serum for PFOA and PFNA compared to PFOS and PFHxS.[38, 42] We also observed that Sm-PFOS, but not n-PFOS, decreased during early postpartum, and our differences in monthly percent changes between two PFOS isomers were greater during early postpartum compared to pregnancy and late postpartum. Although previous studies reported higher placental transfer efficiency of Sm-PFOS than n-PFOS due to the weaker protein binding affinity,[44, 45, 50] little is known about the differences in lactational transfer rates of PFOS isomers, thus further studies are needed to confirm our findings. This study did not quantify PFAS concentrations in breast milk and child serum during early postpartum, thus future studies may benefit by collecting PFAS measurement in breast milk to gain insight on lactational transfer of PFAS during early postpartum.

Unlike the other four PFAS, maternal PFHxS did not decrease significantly during pregnancy, although its coefficient was negative, consistent with other PFAS. In addition to the possibility of placental transfer and plasma volume expansion, these results can be partly explained by a longer half-life of PFHxS. The serum half-life of PFHxS ranged from 5.3 to 15.5 years and is longer than PFOA (2.3 to 3.8 years) and PFOS (3.4 to 5.4 years).[65–70] As indicated by the positive monthly percent change of PFHxS during late postpartum, the slower elimination of PFHxS, in conjunction with a continued exposure, might have obscured any decreases from the effects of placental transfer and plasma volume expansion. On the other hand, we observed that maternal PFHxS decreased with the highest percent change during early postpartum but was not associated with breastfeeding duration during late postpartum. As observed for PFOA, maternal serum concentrations of PFHxS appeared to stabilize after 6 months postpartum. Several previous studies reported that longer breastfeeding duration was associated with lower PFHxS in the serum of mothers of 2- to 5-year-old children[63, 71] or higher PFHxS in the serum of exclusively breastfed 2- to 4-month-old infants.[72] However, another study observed decreases in child's serum PFHxS concentrations during the first year of life, suggesting that early postnatal exposure to PFHxS may relate to sources other than breast milk.[64] As the evidence on the lactational transfer of PFHxS is still inconclusive, further studies are needed.

From pregnancy through two years postpartum, maternal serum PFAS concentrations were negatively associated with child's birth year, ranging from 6% to 18% decreases per year. Previous studies examined temporal trends of PFAS in the serum of pregnant women[28, 29, 33, 73] as well as mothers of 2 to 5 years old.[71] Because there were nationwide efforts to phase out PFOS, PFOA and related compounds in early 2000s, the studies dealing with trends after 2000 reported decreased serum PFAS concentrations over calendar years. Kim et al., who investigated similar periods (i.e., 2009–2017) in the same study region, reported similar annual percent changes for PFOS (−10.8%) and PFOA (−10.7%) and smaller annual percent change for PFHxS (−8.0%), compared to our study.[71] We also compared the annual percent changes in PFAS concentrations in this study with those in the 2009–2016 NHANES female population who were pregnant and/or breastfeeding at

the sample collection. Compared to our study, their unadjusted annual decreasing rates were comparable for PFOS (−13.8%) and PFOA (−10.2%), smaller for PFHxS (−0.5%), and greater for PFNA (−15.8%) (Table S10). Furthermore, we observed that mothers who were born outside the U.S. had approximately 50% higher PFNA concentrations than the U.S.-born mothers throughout the whole study period. Similarly, Park et al. observed lower PFNA concentrations in midlife women (45–56 years old) born in the U.S. than those who are not.[74] Other European studies also reported differences in PFAS concentrations of pregnant women according to country of birth.[27, 30, 75] This suggests that the countries of birth can affect a mother's diet and lifestyle, which can further result in different patterns of exposure to PFAS.[4, 76]

To our knowledge, this is the first study that examined changes in maternal serum PFAS concentrations from pregnancy to two years postpartum by using repeated serum samples within the same women and adjusting for relevant covariates for each sub-period. Despite the relatively small sample size, the longitudinal study design with six specimens per mother-child dyad enabled us to estimate decreasing rates of maternal PFAS concentrations during each sub-period with precision. Furthermore, according to the Third Unregulated Contaminant Monitoring Rule, the drinking water of the catchment areas of the MARBLES study was rarely contaminated by PFAS during 2013–2015 (https://www.waterboards.ca.gov/pfas/docs/3_pfas_in_california.pdf). Therefore, out study population may represent the PFAS levels in the U.S. general population. However, some limitations should be noted. First, the current study did not collect the maternal blood samples during a pre-pregnancy period and at delivery. Aversion to foods and morning sickness may affect dietary choices and intake and therefore, associated PFAS exposure between a pre-pregnancy period and pregnancy for some mothers. We used maternal serum PFAS concentrations at the 3rd trimester of pregnancy as surrogates of those at delivery, but there may be additional decreases in certain PFAS concentrations due to blood loss at delivery, which was not considered in this study.[77] Second, the mothers in this study population were recruited from those who received state-funded services for ASD and had longer breastfeeding duration compared to those in the NHANES.[48] As this study population may not be generalizable, our results should be interpreted with caution.

From this study, we observed decreases in serum concentrations of n-PFOS, Sm-PFOS, n-PFOA, and PFNA during pregnancy, Sm-PFOS, PFHxS, n-PFOA, and PFNA during early postpartum, and n-PFOS, Sm-PFOS, and PFNA during late postpartum. Throughout the whole study period, later child's birth year was associated with decreased concentrations of n-PFOS, Sm-PFOS, PFHxS, n-PFOA, and PFNA which appear to reflect regulations and manufacturing changes for these compounds. Longer breastfeeding duration was associated with decreased n-PFOA and PFNA concentrations during late postpartum. Maternal serum PFAS concentration changes from pregnancy to two years postpartum may improve understanding of pregnancy and lactational transfers. Furthermore, our findings might be useful for reconstructing reliable pregnancy or early-life PFAS exposure for case-control or cross-sectional epidemiologic studies with only postpartum PFAS serum concentrations.[78]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Synopsis:

This study showed that maternal body burdens of five individual PFAS decreased at different rates and patterns during pregnancy, early postpartum, and late postpartum periods.

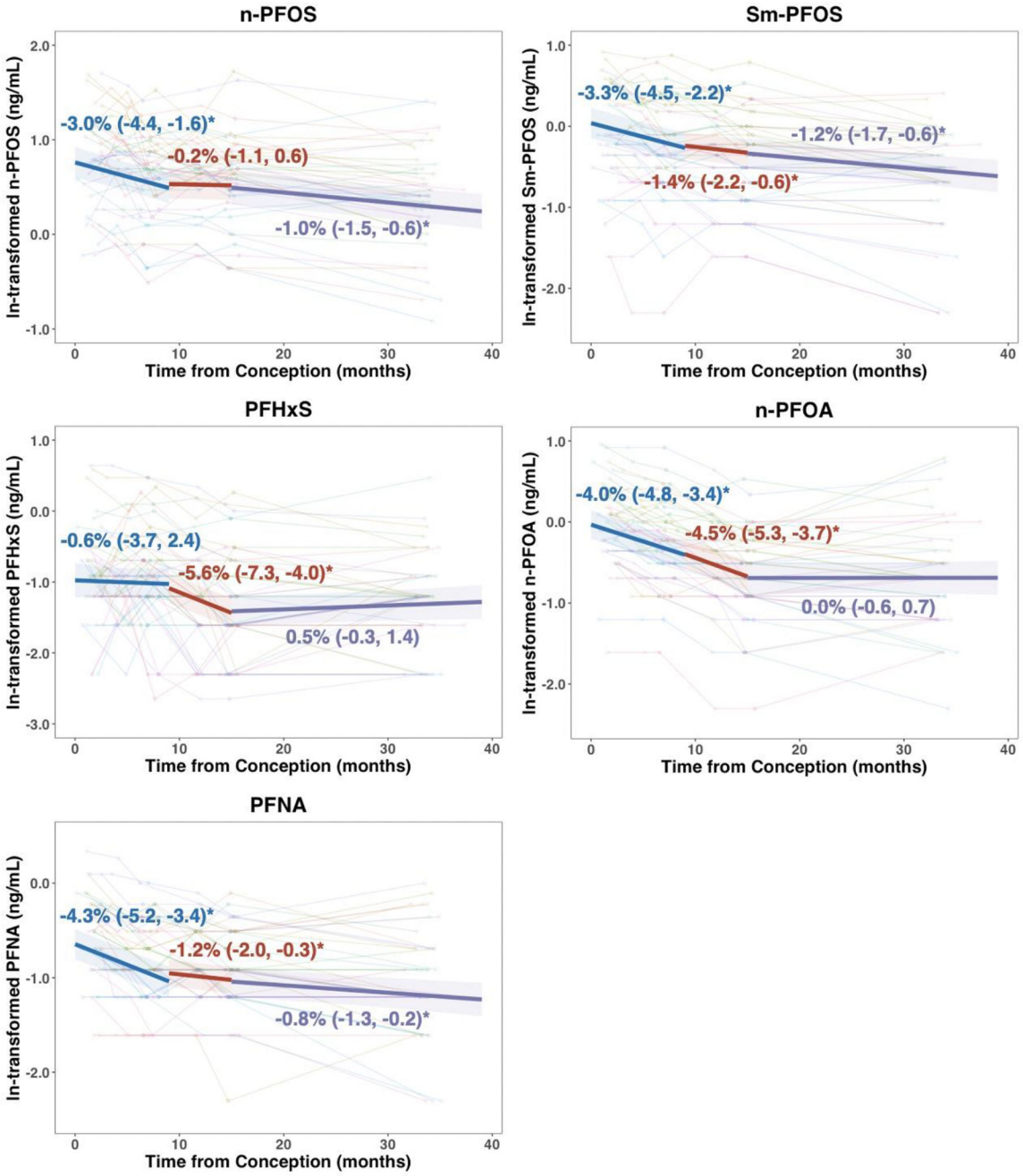

Figure 1.

Adjusted monthly percent changes and 95% Cis in maternal serum PFAS concentrations during pregnancy, early postpartum, and late postpartum. Thick lines in blue, red and purple represent adjusted mean concentrations during pregnancy, early postpartum (3rd trimester to 6 months postpartum), and late postpartum (6 to 24 months postpartum), respectively, and shaded areas represent corresponding 95% Cis. Thin lines and dots represent individual trajectory of PFAS concentrations. Asterisk represents significant changes in PFAS concentrations over time. All models were adjusted for child's birth

year, maternal age at delivery, parity, and maternal birthplace. Late postpartum models were additionally adjusted for exclusive breastfeeding duration.

Table 1.

Demographic and other characteristics of the study participants (n = 42).

Characteristics	*n*	%
Child's birth year		
2009	2	5%
2010	7	17%
2011	6	14%
2012	2	5%
2013	5	12%
2014	10	24%
2015	10	24%
Maternal race/ethnicity		
Non-Hispanic white	24	57%
Hispanic/Asian/multiracial[a]	18	43%
Maternal birthplace		
United States	28	67%
Non-United States	14	33%
Maternal education		
No bachelor's degree	14	33%
Bachelor's degree or higher	28	67%
Homeownership		
Non-owner	14	33%
Owner	28	67%
	Mean ± SD	**Range**
Maternal age at delivery (year)	34.9 ± 4.3	22.4 – 42.8
Maternal BMI at pre-pregnancy (kg/m^2)	25.1 ± 4.8	18.9 – 39.9
Maternal weight gain during pregnancy (kg)	14.4 ± 5.4	1.4 – 26.1
Birthweight (kg)	3.4 ± 0.5	1.6 – 4.3
Parity	2.1 ± 1.4	1 – 7
Total breastfeeding duration (month)	14.2 ± 8.3	2.8 – 36.7
Exclusive breastfeeding duration (month)	3.8 ± 2.7	0.0 – 9.6

[a]Hispanic (19%), Asian (21%) and multiracial (2%).

Table 2.

Distribution of PFAS concentrations in 251 serum samples collected from 42 mothers during the 1st, 2nd, and 3rd trimesters of pregnancy and 3, 6, and 24 months after delivery.

		Whole period			1Trim	2Trim	3Trim	3Mon	6Mon	24Mon
	DF[a]	Percentiles (ng/mL)								
		25th	50th	75th	50th	50th	50th	50th	50th	50th
n-PFOS	100	1.40	2.00	2.60	2.20	2.40	2.00	1.95	1.95	1.50
Sm-PFOS	100	0.50	0.70	1.10	0.90	0.85	0.70	0.75	0.70	0.60
PFOS[b]	100	1.95	2.80	3.60	3.20	3.20	2.70	2.85	2.75	2.35
PFHxS	99	0.20	0.30	0.50	0.40	0.40	0.40	0.30	0.20	0.30
n-PFOA	100	0.50	0.70	1.00	1.00	0.85	0.80	0.60	0.55	0.50
Sb-PFOA	0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
PFNA	100	0.30	0.40	0.60	0.60	0.50	0.40	0.40	0.40	0.30
PFDA	81	0.10	0.10	0.20	0.20	0.20	0.10	0.10	0.10	0.10
PFUnDA	57	<LOD	0.10	0.10	0.10	0.10	0.10	0.10	<LOD	0.10
PFDoDA	26	<LOD	<LOD	0.10	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
MeFOSAA	52	<LOD	0.10	0.10	0.10	0.10	<LOD	<LOD	0.10	<LOD
EtFOSAA	2	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

[a]Detection frequency. The limit of detection is 0.1 ng/mL for all PFAS.

[b]Sum of n-PFOS and Sm-PFOS.

Note: One of the 42 mothers did not provide the 1st trimester sample but was included in this study.

Table 3.

Adjusted percent difference (95% CI) in geometric mean maternal serum PFAS concentrations per one-unit increase of each potential determinants for each sub-period.

Potential determinants[a]	n-PFOS	Sm-PFOS	PFHxS	n-PFOA	PFNA
Pregnancy					
Child's birth year (year)	**−11.3 (−16.3, −5.9)**	**−17.8 (−23.4, −11.6)**	**−13.8 (−21.1, −6.5)**	**−8.9 (−14.9, −2.0)**	**−6.4 (−12.1, −0.6)**
Maternal age at delivery (year)	1.4 (−1.6, 4.4)	0.6 (−2.7, 4.5)	1.2 (−2.9, 5.4)	2.3 (−1.1, 5.5)	−1.0 (−4.0, 2.2)
Parity	1.7 (−7.4, 11.6)	−5.0 (−15.7, 6.2)	−5.9 (−17.5, 6.5)	**−11.4 (−20.8, −1.5)**	4.2 (−4.9, 15.2)
Maternal birthplace					
United States	Ref	Ref	Ref	Ref	Ref
Non-United States	31.4 (−0.9, 71.7)	−27.5 (−47.4, 3.0)	37.4 (−6.2, 100.8)	10.1 (−22.3, 54.1)	**51.2 (11.7, 100.8)**
Early postpartum					
Child's birth year (year)	**−9.7 (−15.1, −4.2)**	**−17.4 (−22.6, −11.7)**	**−17.1 (−24.3, −9.4)**	**−9.5 (−15.6, −2.7)**	**−8.2 (−13.2, −2.8)**
Maternal age at delivery (year)	1.2 (−1.8, 4.2)	1.1 (−2.1, 4.3)	1.2 (−2.6, 5.4)	3.0 (−0.4, 6.8)	−0.7 (−3.4, 2.1)
Parity	1.7 (−7.2, 11.4)	−4.8 (−14.5, 4.8)	**−14.5 (−24.6, −2.9)**	−9.2 (−18.9, 1.1)	4.7 (−4.7, 14.2)
Maternal birthplace					
United States	Ref	Ref	Ref	Ref	Ref
Non-United States	26.8 (−5.7, 69.0)	−23.1 (−44.5, 1.1)	29.7 (−12.1, 93.8)	8.6 (−22.1, 48.6)	**50.3 (15.0, 94.3)**
Late postpartum					
Child's birth year (year)	**−8.0 (−14.4, −1.4)**	**−15.5 (−21.5, −9.1)**	**−11.4 (−19.2, −2.5)**	**−8.3 (−15.1, −0.4)**	**−10.0 (−15.6, −3.6)**
Maternal age at delivery (year)	2.6 (−0.9, 6.1)	2.0 (−1.7, 5.9)	2.5 (−1.6, 7.0)	**5.3 (1.2, 9.3)**	0.6 (−2.5, 3.7)
Parity	4.5 (−5.8, 16.2)	−2.4 (−13.0, 8.2)	**-16.8 (−27.1, −5.1)**	−4.9 (−15.2, 6.4)	6.8 (−3.3, 18.4)
Exclusive breastfeeding duration (month)	−0.5 (−5.4, 4,7)	−0.4 (−5.4, 5.2)	−0.3 (−5.7, 5.7)	−5.1 (−10.4, 0.4)	−4.1 (−8.3, 0.4)
Maternal birthplace					
United States	Ref	Ref	Ref	Ref	Ref
Non-United States	32.7 (−4.3, 80.7)	−22.4 (−45.7, 8.0)	32.3 (−8.6, 93.0)	14.2 (−19.9, 60.4)	**52.9 (15.0, 102.6)**

[a]P-values were from linear mixed models with ln-transformed PFAS concentration as dependent variable and that mutually adjusted for time from conception and potential determinants for each sub-period, where the null hypothesis is the regression coefficients of each potential determinant equals to zero. Estimates with P-values less than 0.05 are highlighted in bold.