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Maternal serum per- and polyfluoroalkyl substances during pregnancy and breastfeeding duration

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Background/objectives: Per- and polyfluoroalkyl substances (PFAS) are endocrine-disrupting chemicals that may affect breastfeeding duration. We examined associations between maternal PFAS concentrations during pregnancy and breastfeeding cessation. We investigated potential effect modification by parity status.

Methods: Among 555 women enrolled in the Healthy Start study (2009–2014), we quantified maternal serum concentrations of 5 PFAS during mid- to late-pregnancy (mean 27 weeks of gestation). Participants self-reported their breastfeeding practices through 18–24 months postnatally. Among all participants and stratified by parity, we estimated associations between maternal PFAS concentrations and breastfeeding discontinuation by 3 and 6 months, using Poisson regression, and breastfeeding duration, using Cox regression.

Results: Median PFAS concentrations were similar to those in the general US population. Associations between PFAS and breastfeeding duration differed by parity status. After adjusting for covariates, among primiparous women, associations between PFAS and breastfeeding cessation by 3 and 6 months were generally null, with some inverse associations. Among multiparous women, there were positive associations between perfluorohexane sulfonate, perfluorooctane sulfonate, perfluorooctanoate (PFOA), and perfluorononanoate and breastfeeding cessation by 3 and 6 months. For example, per ln-ng/mL increase in PFOA, the risk ratio for breastfeeding discontinuation by 6 months was 1.45 (95% confidence interval, 1.18, 1.78). Hazard ratios reflected similar patterns between PFAS and breastfeeding duration.

Conclusions: Among primiparous women, we did not find evidence for associations between PFAS concentrations and breastfeeding duration. In contrast, among multiparous women, PFAS serum concentrations were generally inversely associated with breastfeeding duration, though estimates may be biased due to confounding by unmeasured previous breastfeeding.

Keywords: Per- and polyfluoroalkyl substances; Pregnancy; Lactation; Breastfeeding

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Introduction

Breastfeeding confers several health benefits for both the mother and child, respectively.[1] For the mother, these include lower risk of postpartum blood loss, breast and ovarian cancer, and cardiovascular disease, and for the child, these include lower risk of allergic disease, obesity, and diabetes.[1] However, in 2015, the prevalence of adherence to the American Academy of Pediatrics and World Health Organization recommendation of exclusive breastfeeding for 6 months or more[2,3] was less than 25% in the United States.[4] Although there are many social, cultural, and psychological factors that may pose challenges to breastfeeding, there are also several biological factors, including inadequate milk supply, breast and nipple pain, and illness.[5,6] Exposure to environmental chemicals, particularly endocrine-disrupting chemicals, may be one potential explanation for physiological lactation problems.[7]

During pregnancy, the body undergoes intense anatomic and physiologic changes.[8] Accordingly, pregnancy is a distinct stage in the lifecourse for mammary gland morphogenesis.[9] Under the

What this study adds

Per- and polyfluoroalkyl substances (PFAS) may impact breastfeeding duration. Most existing studies were conducted in Scandinavian populations, and women in the only prior US study had higher concentrations of some PFAS relative to those of the general population. Therefore, we aimed to examine these associations in a Colorado-based cohort of women with PFAS concentrations representative of those in the general population. In contrast to other studies, among primiparas, we found null associations between maternal serum PFAS and breastfeeding duration. Among multiparas, we found inverse associations, though these estimates may be biased due to confounding by unmeasured previous breastfeeding.

control of tightly regulated endocrine signaling, the mammary ducts are highly proliferative in preparation for lactation.[9] Thus, pregnancy may be a window for mammary gland susceptibility to endocrine-disrupting environmental chemicals to adversely impact lactogenesis, and in turn breastfeeding duration.[7]

Per- and polyfluoroalkyl substances (PFAS) are a class of persistent environmental pollutants and known endocrine disruptors. PFAS are widely used in consumer and industrial products, and human non-occupational exposure occurs primarily through ingestion of contaminated food and water.[10] Some PFAS have half-lives of up to several years and are nearly universally detected in women of reproductive age in the United States.[11] PFAS can be detected in the placenta, fetal tissue, and human milk.[12–18] Evidence from animal and toxicological studies suggests PFAS may disrupt biological pathways involved in mammary gland development and lactation,[7,19–21] which could ultimately result in insufficient milk supply, which is a leading contributor to earlier-than-desired discontinuation of breastfeeding.[6,22]

Several studies have examined associations between pregnancy PFAS concentrations and breastfeeding duration.[7,23–29] In a recent systematic review of the six previous epidemiologic studies on this topic, five of the six found higher PFAS concentrations were associated with shorter breastfeeding duration.[29] Associations differed by specific PFAS but were most consistent for perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), and perfluorononanoic acid (PFNA).[29] All but one of the previous studies were conducted in Scandinavian countries. The sole US study was conducted in a population having higher serum PFOA concentrations relative to the general US population.[24] Therefore, our study aimed to investigate the relationship between PFAS serum concentrations during pregnancy and breastfeeding duration among women in a Colorado-based pregnancy cohort whose PFOA and other PFAS serum concentrations are similar to those of the general US population. We hypothesized that higher maternal serum concentrations of PFAS would be associated with shorter breastfeeding duration.

Methods

Study sample

This analysis included a subset of participants from the Healthy Start study, which is an ongoing longitudinal cohort study. From 2009 to 2014, pregnant women were recruited from the University of Colorado Obstetrics clinics. Women were eligible if they were >16 years of age, had no prior stillbirths, were expecting a singleton birth, and did not have a history of chronic disease (diabetes, cancer, asthma treated with steroids, or medication-dependent psychiatric illness). A total of 1410 pregnant participants enrolled in the Healthy Start study, of those 11 withdrew from the study before delivery, and 17 experienced fetal demise. Of the remaining 1382 participants, 652 were selected for quantification of PFAS in maternal serum during pregnancy. These 652 participants were selected based on availability of maternal serum and cord blood in a previous separately funded ancillary study.[30] We excluded 59 participants who did not intend to breastfeed, did not initiate breastfeeding, or were missing data on intention to breastfeed in the next 3 months, 30 who did not have any breastfeeding data available, and 8 pregnancies to women already included for a previous pregnancy in the study. After exclusions, there were 555 participants eligible for inclusion in this analysis (Supplemental Figure 1; http://links.lww.com/EE/A227). Study participants provided written informed consent. The Colorado Multiple Institutional Review Board approved all study protocols.

Quantification of PFAS in serum

Fasting maternal blood samples were collected during pregnancy [mean 27.3 weeks gestation, standard deviation (SD), 2.4 weeks]. Serum was separated and stored at −80 °C and shipped overnight on dry ice to the Division of Laboratory Sciences at the Centers for Disease Control and Prevention (CDC) for quantification. The analysis of de-identified specimens at the CDC laboratory was determined not to constitute human subjects research. Using the method previously published by Kato and colleagues,[31] we quantified 11 PFAS, including perfluorooctane sulfonamide, 2-(*N*-ethyl-perfluorooctane sulfonamido) acetate, 2-(*N*-methyl-perfluorooctane sulfonamido) acetate, perfluorohexane sulfonate (PFHxS), n-perfluorooctane sulfonate (n-PFOS), sum of perfluoromethylheptane sulfonate isomers (Sm-PFOS), sum of perfluorodimethylhexane sulfonate isomers (Sm2-PFOS), linear perfluorooctanoate (n-PFOA), sum of branched isomers of PFOA (Sb-PFOA), perfluorononanoate (PFNA), and perfluorodecanoate (PFDA). Analytic standards and quality control measures were performed for each batch. For PFOS and PFOA, concentrations were calculated as the sum of their respective linear and branched isomers. Serum PFAS levels were available to participants upon request. The limit of detection (LOD) for all PFAS was 0.1 ng/ml. For this analysis, we included only PFAS detectable in >90% of participants, which included PFHxS, PFOS, PFOA, PFNA, and PFDA. Concentrations below the LOD were replaced with LOD/2.

Outcome assessment

Women enrolled in the Healthy Start study self-reported infant feeding practices at an in-person visit following delivery and at two phone interviews that occurred during infancy, at approximately 4–6 and 18–24 months. At delivery, mothers reported the type of milk they intended to feed their baby. At the postnatal interviews, participants reported the age at breastfeeding discontinuation, and if formula was used, the age at introduction of formula. Based on responses during these follow-up interviews, we calculated the breastfeeding duration in months. Details are described in Supplemental Figure 2; http://links.lww.com/EE/A227. For comparability to other studies,[23,24,26,27] we investigated two dichotomous outcomes, discontinuation of any breastfeeding by 3 and 6 months after birth. We also investigated a continuous outcome, time to discontinuation of any breastfeeding.

Other variables

At enrollment, participants self-reported their age, race/ethnicity, marital status, employment status, educational attainment, and parity status (number of previous live births). Pre-pregnancy weight was obtained from the medical record, and height was measured at study enrollment. Maternal pre-pregnancy body mass index (BMI) was calculated using the following formula: pre-pregnancy weight (kg)/height^2 (m)^2. Gestational age at mid-pregnancy blood draw was recorded at the study visit.

Statistical analysis

We assessed pairwise Spearman correlations between the PFAS. We examined the distributions of the maternal characteristics and PFAS serum concentrations among all participants and stratified by parity status (classified as any versus no previous live births). PFAS concentrations were natural log-transformed to reduce the influence of outliers. We also calculated tertiles of PFAS concentrations for the full sample, with the exception of PFDA, which we dichotomized at the median because of limited variability in concentrations.

Because the outcome (discontinuation of any breastfeeding by 3 and 6 months) was not rare, we performed Poisson regression with robust standard errors to estimate associations between PFAS serum concentrations during pregnancy and the risk of discontinuation of any breastfeeding by 3 and 6 months.[32] We considered participants (n = 20) as missing discontinuation of

breastfeeding by 6 months, if participants were currently breastfeeding and the infant was younger than 6 months of age at their last completed in-person visit. However, these participants were included in the time-to-event analysis with appropriate censoring.

We used Cox proportional hazards models to estimate associations between PFAS serum concentrations during pregnancy and breastfeeding duration. We evaluated the proportional hazards assumption through visual inspection of Schoenfeld residuals plotted against log-transformed breastfeeding duration. The proportional hazards assumption was violated for some PFAS. After the first 2 months, hazards appeared proportional. Because hazards were proportional for the majority of the follow-up period, we present time-independent hazard ratios (HRs) in our primary analysis, which can be interpreted as the weighted average of the effect over the entire follow-up period.[33] However, in a sensitivity analysis, we used extended Cox models with PFAS-by-time interaction terms that allowed the HRs to vary over time. Based on observations of the survival curves, we chose to estimate the HRs at two specific timepoints, one in early and one in late infancy (2 and 8 months).

For all regression analyses, we tested for interaction between PFAS concentrations and parity (primiparous vs. multiparous) using a cross-product term. Because we detected statistically significant interaction between several PFAS and parity, we fit models on the full sample and separately for primiparous and multiparous women. We performed a sensitivity analysis in which breastfeeding discontinuation was regressed on tertiles of PFAS concentrations, to assess the potential for non-linearity of the association between PFAS and breastfeeding duration. A set of covariates for inclusion in all multivariable models was identified by a directed acyclic graph (Supplemental Figure 3; http://links.lww.com/EE/A227) and by testing bivariate associations between PFAS and breastfeeding discontinuation at either 3 or 6 months ($P < 0.20$). The following covariates were included in all adjusted models: maternal age at delivery (years), pre-pregnancy BMI (kg/m^2), race/ethnicity (non-Hispanic white vs. all other race/ethnicities combined), highest education level attained (high school degree or lower vs. all other educational levels combined), marital status (not married vs. married), employment status during pregnancy (not employed vs. employed), and gestational age at blood sample collection (days). Models that were not stratified by parity were additionally adjusted for parity.

We used quantile-based g-computation (Qgcomp) to evaluate the overall association between PFAS as a mixture and breastfeeding duration. Qgcomp is an approach for estimating a single joint effect for a mixture.[34] In this study, each of the 5 PFAS were transformed into integer scores based on tertiles and entered into a Cox proportional hazards model, along with the same covariates used in the single PFAS models, to calculate a summary HR that estimates the relative change in the hazard of breastfeeding discontinuation per tertile increase in all 5 PFAS. Next, weights were calculated from the regression coefficients for each individual quantized PFAS. The weights represent the proportion of positive or negative effect each individual PFAS contributes. As in the single PFAS models, we performed the mixtures analysis among all participants and stratified by parity. We conducted the Qgcomp analysis using the qgcomp package v2.10.1 in R.

We conducted all analyses in SAS (Version 9.4, The SAS Institute, Cary, NC) and R (Version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

In general, the characteristics of the participants in this study sample were similar to those of the entire Healthy Start study, though our sample included slightly higher proportions of participants who were married and had attained a higher level of education. Additionally, compared to the entire Healthy Start study, multiparous women in this study sample on average breastfed for a slightly shorter duration (Supplemental Table 1; http://links.lww.com/EE/A227). Among 555 eligible participants, 291 were primiparous women and 264 multiparous women. The average maternal age at delivery was 28.2 (SD, 6.1) years, and the average maternal BMI was 25.8 (SD, 6.6) kg/m^2. Compared with primiparous women, on average, multiparous women tended to be older (29.7 vs. 26.8 years), less likely to be married (29.9% vs. 39.9%), and more likely to be employed (46.6% vs. 25.1%). Among all participants, 19.6% and 40.9% reported not breastfeeding by 3 and 6 months, respectively. Average breastfeeding duration for all participants was 8.6 (SD, 6.3) months. Breastfeeding duration was similar across parity groups (Table 1).

Distributions of PFAS among eligible participants are shown in Table 2. PFAS concentrations were generally higher in primiparous versus multiparous women (Table 2). PFAS were moderately to highly correlated with each other (Supplemental Figure 4; http://links.lww.com/EE/A227).

Among all participants, after adjusting for covariates, there were null associations between the five examined PFAS and breastfeeding discontinuation by 3 months. We detected statistically significant interaction between several PFAS and parity. Among primiparous women, adjusted associations between PFAS and breastfeeding discontinuation by 3 months were generally null, with some inverse associations with PFOS, PFOA, and PFDA. For example, per ln-ng/ml increase in PFOA, the risk ratio (RR) for breastfeeding discontinuation by 3 months was 0.63 (95% CI, 0.48, 0.83). Among multiparous women, associations were generally null with some positive associations, although 95% CIs included the null (Table 3). In the sensitivity analysis, in which PFAS were modeled as tertiles, results were generally similar. Multiparous women in the highest tertiles of PFHxS and PFOA had greater risk of breastfeeding discontinuation by 3 months, compared with those in the lower tertiles, and the 95% CIs for these estimates did not include the null (Supplemental Table 2; http://links.lww.com/EE/A227).

Table 1.

Characteristics of eligible Healthy Start study participants, overall and stratified by parity status.

	All participants (n = 555)	Primiparous (n = 291)	Multiparous (n = 264)
Maternal age at delivery (years)	28.2 ± 6.1	26.8 ± 6.1	29.7 ± 5.7
Pre-pregnancy body mass index (kg/m^2)	25.8 ± 6.6	24.8 ± 6.1	26.9 ± 7.1
Race/ethnicity			
Non-Hispanic White	321 (57.8)	171 (58.8)	150 (56.8)
All other race/ethnicities combined [a]	234 (42.2)	120 (41.2)	114 (43.2)
Highest education level completed			
Higher than a high school degree	403 (72.6)	205 (70.5)	198 (75.0)
High school degree or lower	152 (27.4)	86 (29.6)	66 (25.0)
Marital status			
Married	360 (64.9)	175 (60.1)	185 (70.1)
Not married	195 (35.1)	116 (39.9)	79 (29.9)
Employment status during pregnancy			
Employed	359 (64.7)	218 (74.9)	141 (53.4)
Not employed	196 (35.3)	73 (25.1)	123 (46.6)
Gestational age at sample collection (weeks)	27.3 ± 2.4	27.3 ± 2.4	27.3 ± 2.5
Not breastfeeding (any) by 3 months	109 (19.6)	56 (19.2)	53 (20.1)
Not breastfeeding (any) by 6 months[b]	219 (40.9)	111 (39.6)	108 (42.4)
Any breastfeeding duration (months)	8.6 ± 6.3	8.5 ± 6.1	8.8 ± 6.5

Data are shown as Mean ± SD or n (%).

[a]Participants who identified their race/ethnicity as: Hispanic, non-Hispanic Black, or non-Hispanic other race/ethnicity.

[b]Missing data for not breastfeeding (any) by 6 months: all participants, n = 20, primiparous, n = 11; multiparous, n = 9.

Table 2.

Distributions of serum perfluoroalkyl substances (ng/ml) among eligible participants in the Healthy Start study (2009–2014), overall and stratified by parity status.

	All participants (n = 555)						Primiparous (n = 291)						Multiparous (n = 264)					
	Min.	Q1	Med.	Q3	Max.	Geometric mean (SE)	Min.	Q1	Med.	Q3	Max.	Geometric mean (SE)	Min.	Q1	Med.	Q3	Max.	Geometric mean (SE)
PFHxS	<LOD	0.50	0.80	1.30	10.90	0.77 (0.03)	<LOD	0.60	0.90	1.50	10.90	0.91 (0.04)	<LOD	0.40	0.60	1.00	5.50	0.63 (0.03)
PFOS	<LOD	1.50	2.40	3.70	15.60	2.32 (0.07)	<LOD	1.90	3.00	4.20	14.70	2.74 (0.11)	<LOD	1.30	1.90	2.95	15.60	1.92 (0.08)
PFOA	0.1	0.70	1.10	1.60	17.00	1.07 (0.03)	0.1	1.00	1.40	1.90	17.00	1.40 (0.05)	0.1	0.50	0.80	1.20	15.40	0.80 (0.03)
PFNA	<LOD	0.30	0.40	0.60	6.00	0.41 (0.01)	<LOD	0.30	0.50	0.70	4.30	0.48 (0.02)	<LOD	0.20	0.30	0.50	6.00	0.34 (0.01)
PFDA	<LOD	0.10	0.10	0.20	3.50	0.14 (0.00)	<LOD	0.10	0.10	0.20	2.20	0.15 (0.01)	<LOD	0.10	0.10	0.20	3.50	0.12 (0.00)

LOD was 0.1 ng/ml for all PFAS.

Table 3.

Adjusted risk ratios of maternal serum perfluoroalkyl substances and not breastfeeding by 3 months, overall and stratified by parity status, among women who initiated breastfeeding in the Healthy Start study.

	All participants (n = 555)		Primiparous (n = 291)	Multiparous (n=264)
	RR (95% CI)[b] (not breastfeeding by 3 months)	*P* value for PFAS* parity interaction[c]	RR (95% CI)[d] (not breastfeeding by 3 months)	RR (95% CI)[d] (not breastfeeding by 3 months)
PFHxS (ng/ml)[a]	0.99 (0.81, 1.22)	0.01	0.79 (0.61, 1.01)	1.35 (0.98, 1.86)
PFOS (ng/ml)[a]	0.90 (0.72, 1.13)	<0.01	0.65 (0.54, 0.79)	1.43 (0.94, 2.19)
PFOA (ng/ml)[a]	0.99 (0.75, 1.31)	<0.01	0.63 (0.48, 0.83)	1.44 (0.95, 2.18)
PFNA (ng/ml)[a]	1.05 (0.81, 1.36)	0.14	0.83 (0.54, 1.28)	1.23 (0.85, 1.77)
PFDA (ng/ml)[a]	0.73 (0.53, 1.01)	0.17	0.52 (0.33, 0.83)	0.88 (0.55, 1.39)

LOD was 0.1 ng/ml for all PFAS.

[a]Natural log-transformed, risk ratios are per natural log unit increase in each perfluoroalkyl substance.

[b]Adjusted for maternal education, marital status, parity, race/ethnicity, employment status during pregnancy, maternal age at delivery, pre-pregnancy BMI, and gestational age at blood draw.

[c]*P* value for the interaction term in models additionally including a PFAS-by-parity interaction.

[d]Adjusted for maternal education, marital status, race/ethnicity, employment status during pregnancy, maternal age, pre-pregnancy BMI, and gestational age at blood draw.

Among all participants, adjusted associations between PFAS and breastfeeding discontinuation by 6 months were generally null, with the exception of PFOA (RR, 1.18 per ln-ng/ml increase; 95% CI, 1.01, 1.37). There was a statistically significant interaction between concentrations of several PFAS and parity. Among primiparous women, adjusted RRs of the association between PFAS and breastfeeding discontinuation by 6 months were null, with some evidence of a slightly protective effect, although 95% CIs included the null. In contrast, among multiparous women, there were positive associations between PFHxS, PFOS, PFOA, and PFNA and risk of discontinuation by 6 months. For example, per ln-ng/ml increase in PFOA, the RR for breastfeeding discontinuation by 6 months was 1.45 (95% CI, 1.18, 1.78) (Table 4). Results were similar from the sensitivity analysis in which PFAS were modeled as tertiles (Supplemental Table 3; http://links.lww.com/EE/A227).

HRs from adjusted Cox proportional hazards models confirmed that associations between PFAS and breastfeeding duration differed by parity status. Among all participants, associations between PFAS and time to breastfeeding discontinuation were generally null, with positive associations with PFOA and PFNA. Among primiparous women, HRs between PFAS and time to breastfeeding discontinuation were generally null, with some evidence of a protective effect, although 95% CIs included the null. In contrast, among multiparous women, higher PFHxS, PFOS, PFOA, and PFNA concentrations were associated with higher hazard of breastfeeding discontinuation. For example, per ln-ng/ml increase in PFNA, the HR for breastfeeding discontinuation was 1.38 (95% CI, 1.13, 1.70) (Table 5). Results were similar when PFAS were modeled as tertiles (Supplemental Table 4; http://links.lww.com/EE/A227).

In extended Cox regression models that allowed time-dependent associations, when PFAS were categorized into tertiles, there were generally stronger positive associations between PFAS and hazard of breastfeeding discontinuation at 8 versus 2 months, among all participants and in the stratum of multiparous women. Among primiparous women, there were inverse associations at 2 months that generally were not present at 8 months (Supplemental Table 5; http://links.lww.com/EE/A227).

The weights used in the quantile g-computation are displayed in Supplemental Figure 5; http://links.lww.com/EE/A227. The overall patterns we observed in the single-PFAS models were reflected in the overall effect estimates for the mixture. The HR of breastfeeding discontinuation for a tertile increase in all PFAS was 1.22 (95% CI 1.01, 1.48) among all participants, 0.88 (95% CI 0.68, 1.14) among primiparous women, and 1.61 (95% CI 1.21, 2.14) among multiparous women (Table 6).

Table 4.

Adjusted risk ratios of maternal serum perfluoroalkyl substances and not breastfeeding by 6 months, overall and stratified by parity status, among women who initiated breastfeeding in the Healthy Start study.

	All participants (n = 535)[b]		Primiparous (n = 280)	Multiparous (n = 255)
	RR (95% CI)[c] (not breastfeeding by 6 months)	*P* value for PFAS*parity interaction[d]	RR (95% CI)[e] (not breastfeeding by 6 months)	RR (95% CI)[e] (not breastfeeding by 6 months)
PFHxS (ng/ml)[a]	1.02 (0.91, 1.15)	0.04	0.88 (0.75, 1.04)	1.22 (1.03, 1.44)
PFOS (ng/ml)[a]	1.08 (0.94, 1.23)	<0.01	0.84 (0.72, 0.99)	1.39 (1.14, 1.69)
PFOA (ng/ml)[a]	1.18 (1.01, 1.37)	0.01	0.88 (0.71, 1.10)	1.45 (1.18, 1.78)
PFNA (ng/ml)[a]	1.11 (0.97, 1.27)	0.06	0.94 (0.76, 1.15)	1.28 (1.06, 1.54)
PFDA (ng/ml)[a]	0.94 (0.80, 1.11)	0.67	0.86 (0.66, 1.12)	0.98 (0.80, 1.20)

LOD was 0.1 ng/ml for all PFAS.

[a]Natural log-transformed, risk ratios are per natural log unit increase in each perfluoroalkyl substance.

[b]Sample size for this analysis is 535 due to 20 participants being censored before 6 months.

[c]Adjusted for maternal education, marital status, parity, race/ethnicity, employment status during pregnancy, maternal age at delivery, pre-pregnancy BMI, and gestational age at blood draw.

[d]*P* value for the interaction term in models additionally including a PFAS-by-parity interaction.

[e]Adjusted for maternal education, marital status, race/ethnicity, employment status during pregnancy, maternal age at delivery, pre-pregnancy BMI, and gestational age at blood draw.

Table 5.

Adjusted HRs of maternal serum perfluoroalkyl substances and breastfeeding discontinuation, overall and stratified by parity status, among women who initiated breastfeeding in the Healthy Start study.

	All participants (n = 555)		Primiparous (n = 291)	Multiparous (n = 264)
	HR (95% CI)[b] (event = breastfeeding discontinuation)	*P* value for PFAS* parity interaction[c]	HR (95% CI)[d] (event = breastfeeding discontinuation)	HR (95% CI)[d] (event = breastfeeding discontinuation)
PFHxS (ng/ml)[a]	1.06 (0.93, 1.20)	0.10	0.93 (0.78, 1.12)	1.21 (1.01, 1.45)
PFOS (ng/ml)[a]	1.15 (0.99, 1.33)	<0.01	0.82 (0.66, 1.01)	1.47 (1.19, 1.81)
PFOA (ng/ml)[a]	1.30 (1.10, 1.54)	<0.01	0.86 (0.66, 1.12)	1.69 (1.34, 2.14)
PFNA (ng/ml)[a]	1.25 (1.07, 1.47)	0.07	0.97 (0.75, 1.27)	1.38 (1.13, 1.70)
PFDA (ng/ml)[a]	1.10 (0.93, 1.30)	0.50	0.97 (0.76, 1.23)	1.19 (0.93, 1.51)

LOD was 0.1 ng/ml for all PFAS.

[a]Natural log-transformed, HRs are per natural log unit increase in each perfluoroalkyl substance.

[b]Adjusted for maternal education, marital status, parity, race/ethnicity, employment status during pregnancy, maternal age at delivery, pre-pregnancy BMI, and gestational age at blood draw.

[c]*P* value for the interaction term in models additionally including a PFAS-by-parity interaction.

[d]Adjusted for maternal education, marital status, race/ethnicity, employment status during pregnancy, maternal age at delivery, pre-pregnancy BMI, and gestational age at blood draw.

Table 6.

Quantile g-computation HRs of the mixture of maternal serum perfluoroalkyl substances and breastfeeding discontinuation, overall and stratified by parity status, among women who initiated breastfeeding in the Healthy Start study.

	All participants (n = 555)	Primiparous (n = 291)	Multiparous (n = 264)
	HR (95% CI)[b] (event = breastfeeding discontinuation)	HR (95% CI)[c] (event = breastfeeding discontinuation)	HR (95% CI)[c] (event = breastfeeding discontinuation)
PFAS mixture[a]	1.22 (1.01, 1.48)	0.88 (0.68, 1.14)	1.61 (1.21, 2.14)

[a]PFAS mixture included: PFDA, PFHxS, PFNA, PFOA, and PFOS. LOD was 0.1 ng/ml for all PFAS. HRs can be interpreted as the HR for a tertile increase in all 5 PFAS in the mixture.

[b]Adjusted for maternal education, marital status, parity, race/ethnicity, employment status during pregnancy, maternal age at delivery, pre-pregnancy BMI, and gestational age at blood draw.

[c]Adjusted for maternal education, marital status, race/ethnicity, employment status during pregnancy, maternal age at delivery, pre-pregnancy BMI, and gestational age at blood draw.

Discussion

Among 555 women enrolled in a Colorado-based prospective birth cohort study, we found that associations between serum concentrations of PFAS during pregnancy and the risk of breastfeeding discontinuation differed by parity status. Among primiparous women, we generally found null or some inverse associations between PFAS and breastfeeding discontinuation risk, while among multiparous women, we generally found positive associations. In the mixtures analysis, the overall effect of the PFAS mixture in each parity group followed the same patterns observed in the single-PFAS analyses. Importantly, maternal serum PFAS concentrations in our study were generally similar to those of the US general population during this time period.[11]

In previous literature, the association between PFAS and pregnancy and birth outcomes in first-time mothers is generally considered to be less subject to confounding bias. This is because maternal PFAS concentrations are influenced by her previous pregnancy and breastfeeding history, likely due to transfer of PFAS during pregnancy, delivery, and breastfeeding.[12,35–38] Given that past breastfeeding predicts future breastfeeding,[39] bias could be produced if multiparous women who had previously breastfed had lower concentrations of PFAS and were also more likely to breastfeed for a longer duration for the current pregnancy. Because the Healthy Start study did not collect data about prior breastfeeding, the observed relationships in multiparous women may be due to residual confounding that biased the estimates away from the null.

Findings from six previous studies examining associations between PFAS and breastfeeding duration have taken various approaches to address this potential for confounding by breastfeeding history, and results have been inconsistent (Supplemental Table 6; http://links.lww.com/EE/A227). Among 1300 women in the Danish National Birth Cohort (1996–2002), Fei and colleagues reported positive associations between PFOA and PFOS and cessation of any breastfeeding by 3 and 6 months, only among multiparous women.[23] They did not have information on previous breastfeeding. Similarly, in our study, we found higher concentrations of PFOA and PFOS, as well as PFHxS and PFNA, were associated with shorter breastfeeding duration, only among multiparous women. In another study, among 1716 women in the Norwegian Mother and Child Cohort Study (MoBa), after adjusting for parity and previous breastfeeding duration, Rosen et al. found inverse associations between continuous PFNA, PFDA, and perfluoroundecanoate (PFUnDA) and risk of cessation of breastfeeding by 3 and 6 months and longer breastfeeding duration, and null results for other examined PFAS, including PFOA and PFOS.[27] These results agree with our findings in primiparous women, as we noted mostly null and some protective results, in which higher PFDA, PFOS, and PFOA were associated with lower risk of breastfeeding discontinuation by 3 months, and higher PFOS, PFOA, and PFNA were associated with lower risk of breastfeeding discontinuation by 6 months, and PFOA and PFNA were also associated with longer breastfeeding duration. Interestingly, when Rosen et al. analyzed multiple PFAS together, they found the direction of the effect for PFOS changed, and higher PFOS concentrations were associated with shorter breastfeeding duration. Their mixtures analysis also identified interaction effects between some PFAS.[27]

The other four previous studies on this topic identified inverse associations of PFAS with breastfeeding duration (Supplemental Table 6; http://links.lww.com/EE/A227).[24–26,28] Among 1092 women in Faroese birth cohorts, Timmermann et al. found higher serum concentrations of PFOS, PFOA, PFNA, and PFDA were associated with shorter duration of total breastfeeding, in both primiparous and multiparous women.[25] Results were similar in one study among 1300 women enrolled in the Odense Child cohort in Denmark.[28] In a study of 2,374 women exposed to PFAS-contaminated drinking water in Ronneby, Sweden, Nielsen et al. found evidence of associations between PFAS exposure and higher risk of cessation of exclusive breastfeeding by 3 months and cessation of any breastfeeding by 6 months, along with shorter duration, compared to women residing in a reference (lower-exposed) municipality, though only among primiparous women.[26] In the only existing US study, among 336 women enrolled in a prospective Ohio-based Health Outcomes and Measures of the Environment (HOME) study, Romano et al. found positive associations, adjusted for parity and previous breastfeeding history, between PFOA and PFOS and risk of cessation of breastfeeding by 3 and 6 months. In a sensitivity analysis in this study, results were comparable after stratification by parity. Furthermore, in another sensitivity analysis, the authors compared estimates from models that did and did not include a variable for prior breastfeeding and showed that adjustment for prior breastfeeding generally led to an attenuation of effect estimates, though positive statistically significant associations remained.[24]

There are several potential explanations for the discrepancies in results among studies. Notably, PFAS concentrations

in the Healthy Start study were generally lower than those in previous studies (Supplemental Table 6; http://links.lww.com/EE/A227). Concentrations of PFNA, PFDA, and PFHxS in the Healthy Start study were most comparable to those in the Odense Family cohort[28] and MoBa,[27] though concentrations of PFOS and PFOA in these studies were still somewhat higher than those in Healthy Start. Interestingly, only our study and the MoBa study found some inverse associations between some PFAS, including PFNA and PFDA, and longer breastfeeding duration.[27] In a sensitivity analysis, after stratification by parity, Rosen et al. showed these protective associations were only present in primiparous women, which agrees with our findings.

There are other potential reasons for discordant results. In the Healthy Start study, PFAS concentrations were measured in maternal blood collected at a mean of 27.3 weeks (SD, 2.4 weeks), which is later in pregnancy compared to many,[23,24,27,28] but not all,[25,26] of the prior studies. As such, our study only investigated associations between maternal PFAS and breastfeeding at a single timepoint in mid-to-late pregnancy, and we were unable to examine the potential for trimester-specific associations. However, PFAS concentrations across pregnancy are highly correlated.[40] Furthermore, there are several physiological characteristics inherent to pregnancy that may affect maternal serum PFAS concentrations, including transplacental PFAS transfer and pregnancy-related changes to hemodynamics and renal function.[12,36,41–44]

It is possible that there is a true association between greater pregnancy PFAS concentrations and earlier breastfeeding cessation in multiparous women only. However, this seems unlikely because, compared to primiparous women, multiparous women had overall lower PFAS concentrations, likely related to previous transfer of PFAS during pregnancy, delivery, and potentially prior breastfeeding. We adjusted for previous pregnancies, but we did not have data on previous breastfeeding. As in our study, Fei et al. did not have information on prior breastfeeding, and similarly, they only observed a harmful effect of PFAS on breastfeeding duration among multiparous women.[23] However, in the Romano et al. study, certain PFAS were positively associated with the risk of breastfeeding cessation, even after adjustment for previous breastfeeding. Specifically, women in the highest quartile of PFOA concentrations had an RR of 1.93 (95% CI, 1.41, 2.64) for discontinuing breastfeeding before 6 months. However, this estimate was attenuated to an RR of 1.41 (95% CI, 1.03, 1.87), after adjustment for prior breastfeeding.[24] By contrast, after stratification by parity, Rosen et al. found the inverse associations observed in the full sample between PFNA, PFDA, and PFUnDA and breastfeeding cessation only remained in primiparous women, and effect estimates among multiparous women were in the opposite direction, though confidence intervals generally included the null.[27] In our study, compared to primiparous women, multiparous women had lower median serum concentrations of all five PFAS, suggesting the possibility for our estimates in multiparous women to be biased by residual confounding by unmeasured previous breastfeeding or another variable.

Findings from toxicologic studies support several potential mechanisms through which PFAS may disrupt breastfeeding.[7,19,20,45,46] Maternal PFAS concentrations during pregnancy may interfere with mammary gland development.[19] For example, mice exposed to PFOA during pregnancy showed delayed epithelial differentiation in the mammary gland, which resulted in later peak milk production, compared to unexposed mice.[19] PFOA has also been associated with inhibitory effects on prolactin-family hormones in the placenta[20] and maternal serum.[46] Prolactin is the primary lactation hormone and plays an integral role in lactation activation and maintenance, including mammary alveologenesis and signaling that leads to increased expression of milk secretion genes.[47,48] Although these results were not replicated in a recent human study.[28] Finally, PFAS are known to activate peroxisome proliferator-activated receptor-alpha (PPARα), a member of a transcription factor family with a major role in lipid metabolism.[49] However, PPARα is also involved in mammary development, and aberrant activation of PPARα leads to defects in mammary lobuloalveolar development during pregnancy.[21] Additional mechanistic studies in humans are necessary to better define the pathways through which PFAS may impact breastfeeding duration.

Our study has several strengths. We used data from a Colorado-based pregnancy cohort study. To our knowledge, there is only one other US study on this topic, and the PFOA concentrations in that population were higher than in the general US population at that time.[24] Therefore, our study addresses this question in a population with PFAS concentrations that are closer to those of the general US population during the same time period.[11] In addition to biological reasons for early breastfeeding cessation, there are several social, economic, cultural, and psychological factors at play. Therefore, it is important to establish this relationship in settings with different contextual factors that influence breastfeeding practices, which are likely to differ between the United States and Europe. Furthermore, the Healthy Start study has well-characterized data that captures maternal sociodemographic characteristics during pregnancy, which allowed us to adjust for several variables that may confound the relationship.

Our study also has several limitations. We did not have data describing whether participants in our study had previously breastfed, which may have led to residual confounding in estimates of PFAS and breastfeeding duration among multiparous women. We present stratified estimates by parity to examine the potential magnitude of this bias. Additionally, we did not have extensive information on reasons for breastfeeding cessation. Therefore, we cannot rule out residual confounding by additional unmeasured socioeconomic factors that may contribute to early breastfeeding cessation. PFAS concentrations were only quantified in sera collected during mid-to-late pregnancy, and therefore, we are unable to assess associations between PFAS in early or late pregnancy and breastfeeding duration. Finally, we were unable to examine whether PFAS affected breastfeeding initiation, because the large majority of women in the Healthy Start study who intended to breastfeed did initiate breastfeeding.

Conclusions

Among women in a Colorado-based cohort, we observed serum PFAS concentrations during pregnancy that were generally similar to those in the general US population. We found associations between maternal PFAS and the risk of early cessation of breastfeeding were modified by parity status. Specifically, we observed largely null associations in women with no previous pregnancies. In contrast, among multiparous women, we found that concentrations of PFAS were generally inversely associated with breastfeeding duration. Future studies must collect information on previous breastfeeding and reproductive history to fully interpret biomarkers of PFAS levels in women of reproductive age.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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