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Per- and polyfluoroalkyl substances (PFAS) and menstrual cycle characteristics in midlife women: The Study of Women's Health Across the Nation

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ABSTRACT

Objective: Evidence suggests exposure to endocrine-disrupting chemicals, including per- and polyfluoroalkyl substances (PFAS), may disrupt ovarian function and influence menstrual bleeding. PFAS have been associated with reproductive aging; however, longitudinal data on PFAS and menstrual cycle characteristics (cycle length, bleeding patterns) are limited.

Methods: We examined 952 women aged 45–55 years from the Study of Women's Health Across the Nation, with seven PFAS concentrations measured in serum collected in 1999–2000. Menstrual cycle data were collected prospectively using monthly calendars for two years following PFAS measurement. Menstrual cycle length (MCL) was evaluated using linear quantile mixed models at the 25th, 50th, 75th, and 90th percentiles. Bleed length and binary bleeding outcomes (long and heavy) were analyzed using linear and generalized linear mixed models. Models were adjusted for race/ethnicity, education, physical activity, menopause status, smoking status, body mass index, and baseline menstrual characteristics.

Results: Higher perfluorooctane sulfonic acid concentrations were associated with shorter short cycles (MCL at the 25th percentile) (-0.52 days; 95% CI, −1.09–0.05) and longer long cycles (MCL at the 90th percentile) (2.77 days; 95% CI, 1.96–3.58). Perfluorononanoic acid was associated with longer short cycles (0.56 days; 95% CI, 0.06–1.05). No PFAS was associated with median MCL. Most PFAS, except 2-(N-methyl-perfluorooctane sulfonamido) acetic acid and 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid, were associated with shorter menses and lower odds of long or heavy bleeding.

Conclusion: PFAS exposure may be associated with increased menstrual cycle variability and reduced bleeding. Further research in younger cohorts is needed.

1. Introduction

Alterations in menstrual characteristics can be an early warning sign of the impact of environmental exposures on ovarian and reproductive function [1–3]. Growing evidence suggests exposure to endocrine disrupting chemicals may alter menstrual bleeding as a result of effects on ovarian function [4,5], including the insecticide dichlorodiphenyltrichloroethane and its metabolite, dichlorodiphenyldichloroethylene [6–9], organophosphates [10], polychlorinated biphenyls [11,12], polybrominated diphenyl ethers [13], dioxin [14], di-2-ethylhexyl phthalate metabolites, and bisphenol A [15].

Given their widespread use, an emerging area of concern is the group of per- and polyfluoroalkyl substances (PFAS), often referred to as "forever chemicals." PFAS are persistent environmental chemicals present in industrial products, such as some fire-fighting foams, and in many consumer products, including non-stick cookware, food

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packaging, stain- and water-resistant coating for clothing, furniture, and carpets [16–18]. Long-chain legacy PFAS, such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), have been phased out of most consumer products in the United States and other regions since the early 2000s, resulting in marked declines in their concentrations in human blood [19,20]. These legacy PFAS may have been replaced by other PFAS in many applications [21]. PFAS have been associated with alterations in ovarian function and accelerated ovarian aging [22–25]. Recent findings from the Study of Women's Health Across the Nation (SWAN) Multi-Pollutant Study (MPS) have reported positive associations of PFOA and PFOS with follicle stimulating hormone (FSH) and inverse associations of PFOA and perfluorononanoic acid (PFNA) with estradiol (E2) in midlife women during the menopausal transition [26].

Studies on menstrual function are more limited. Most, but not all, studies have reported associations with irregular and longer menstrual cycles [27–31]. However, prior studies have been cross-sectional, relied on recalled information about women's past menstrual cycles, and lacked precision in measurement of menstrual characteristics. The present study takes advantage of two-years of menstrual calendars prospectively collected in SWAN and timed to the PFAS exposure assessment. We hypothesized that higher serum concentrations of PFAS would be associated with alterations in the distribution in menstrual cycle lengths and in the duration and amount of menstrual bleeding.

2. Materials and methods

2.1. Study population

The SWAN which began in 1996 is a multi-site, multi-race and -ethnic longitudinal study of the menopause transition. To be eligible at baseline, women had to be 42–52 years old, have an intact uterus, have at least one menstrual period in the previous three months, not be pregnant, and have no use of reproductive hormones in the previous three months. Initially, 3302 premenopausal women were enrolled at seven study sites, including White women at all sites, Black women at four sites (Boston, Pittsburgh, Southeast Michigan, and Chicago), Hispanic women at Newark, Chinese women in Oakland, CA, and Japanese women in Los Angeles. At baseline and subsequent approximately annual follow-up visits, women completed questionnaires about their menstrual, gynecological and medical history, including information on surgeries and exogenous hormone use, and were asked to complete a monthly menstrual calendar from enrollment until two years after their last menstrual period or for up to ten years. The study protocol was approved by institutional review boards, and all women gave written informed consent at all sites.

The SWAN Multi-Pollutant Study (MPS) was initiated to assess exposure to multiple environmental pollutants and to examine their associations with reproductive aging using repository serum and urine samples from the third SWAN follow-up (MPS baseline, 1999–2000) for environmental exposure assessment (n = 2694). Women from Chicago (n = 368) and Newark (n = 278) did not collect urine specimens and thus were not eligible for SWAN-MPS. A total of 648 women with insufficient serum or urine samples were excluded, providing a sample at the MPS baseline of 1400 eligible women from four race and ethnic groups (White, Black, Chinese, and Japanese).

Of the women in the MPS, 1384 completed at least one menstrual calendar. We excluded 157 women who were postmenopausal (natural or surgical) by the second SWAN follow-up (1998–1999). In these analyses, we included menstrual cycles that occurred in the two-year window, from one year before to one year after the MPS measure. Women were required to have completed at least three consecutive monthly calendars while not on hormone therapy (HT) within this two-year window, resulting in a sample of 952 women with eligible menstrual calendar data. One woman was excluded for missing typical flow length at baseline, resulting in a final analytical sample of 951 for models relating to bleed length. An additional four women were missing baseline education level, and 17 women were missing cycle length at baseline, resulting in an analytical sample of 931 for the final adjusted models of cycle length. Additional menstrual cycles were excluded from analyses if they occurred during HT use, HT-washout periods, pregnancy, or if there were gaps in menstrual calendar records, yielding a total of 16,929 cycles in longitudinal analyses of bleed length and 16,606 cycles for cycle length.

2.2. Cycle length and bleed length

On the monthly menstrual calendar, women noted each day they experienced any spotting or bleeding and the amount of bleeding, categorized as spotting, bleeding or very heavy bleeding (needing to change sanitary product every 1–2 h for more than four hours during the day). On the last day of the month, women answered questions about their HT use, gynecological procedures that could affect bleeding, cigarette use, and physical exercise. For months with missing HT information, menstrual cycles were coded as untreated if a woman never reported HT use in the study, if the menstrual cycle occurred before the first report of HT use, or if the menstrual cycle occurred in a year where no HT use was reported in the monthly calendars or annual interview. We calculated each woman's sequence of menstrual cycle lengths and bleed lengths during the two-year window. Menstrual cycle length (MCL) was calculated using World Health Organization bleeding definitions [32] adapted by the ReSTAGE Collaboration for application to perimenopausal women [33]. A menstrual cycle consists of a bleeding episode and a subsequent bleed-free interval of at least three days. We also created two categorical bleeding variables. A long bleeding episode was defined as a bleed length greater than eight days, and a heavy bleeding episode was defined as a three or more days of heavy bleeding [34,35].

2.3. PFAS exposure assessment

Concentrations of PFAS in serum collected in 1999–2000 were measured at the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC). The CDC laboratory's involvement did not constitute engagement in human-subjects research. Online solid phase extraction-high performance liquid chromatography-isotope dilution-tandem mass spectrometry was used to quantify 11 PFAS, including linear PFOA (n-PFOA), sum of branched PFOA isomers (Sb-PFOA), PFNA, perfluorodecanoic acid (PFDA), perfluoroundecanic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorohexane sulfonic acid (PFHxS), linear PFOS (n-PFOS), sum of perfluoromethylheptane sulfonate isomers (Sm-PFOS), and two PFOS precursors [36], namely 2-(N-methyl-perfluorooctane sulfonamido) acetic acid (MeFOSAA) and 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid (EtFOSAA) [37]. Total PFOS (hereafter, PFOS) was computed as the sum of n-PFOS and Sm-PFOS. The limit of detection (LOD) for all analytes was 0.1 ng/mL. Sb-PFOA, PFDA, PFUnDA, and PFDoDA had low detection frequencies (<50%) and were excluded from this analysis. Detection frequencies of included PFAS were > 97%. For these PFAS, concentrations below the LOD were substituted with LOD/$\sqrt{2}$. Comprehensive QA/QC procedures were conducted. The coefficient of variation of low- and high-concentration quality controls ranged from 5.9% to 12.1%, depending on the analyte.

2.4. Covariates

Self-reported race/ethnicity (White, Black, Chinese, Japanese) and level of education (high school or less vs. some college or more) were assessed at SWAN baseline (1996–1997). Other covariates, including menopause status, smoking status (current versus former or never), body

mass index (BMI), and fibroids, were assessed at SWAN Visit 2 (1998–1999), the visit closest to the beginning of the two-year window of cycles included in these analyses. Physical activity was assessed at SWAN baseline and at Visit 3 (1999–2000). We chose to use the Visit 3 data, as it may better reflect physical activity levels during the follow-up period. If a covariate was missing at Visit 2, we used the measure at Visit 3 or the closest prior visit. Physical activity was based on a modified Kaiser Physical Activity Survey [38], adapted from the Baecke physical activity questionnaire [39], and ranged in total score from 3 to 15. BMI was calculated as measured weight in kilograms divided by measured height in meters squared; we categorized BMI as normal weight or underweight (<25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2). Menopause status was classified as pre-menopausal (menses in last 3 months and no change in predictability), early peri-menopausal (menses in the last 3 months but decreased predictability), late peri-menopausal (menses within the last year but not within the last 3 months), or unknown (due to either HT use or missing Visit 2). Menstrual characteristics at SWAN baseline were considered potential confounders, as menstrual bleeding is an important route of PFAS excretion in women [40–42]. At SWAN baseline, participants self-reported their cycle length (<26 days, 26–32 days, 33–35 days, <35 days, too variable to say) and typical menstrual flow length (1–2 days, 3–7 days, >7 days) during the past year.

2.5. Statistical analysis

We calculated means and SDs for continuous variables and frequencies for categorical variables. Due to the right-skewed distribution of the PFAS concentrations, we calculated medians and IQRs for all PFAS. We examined whether PFAS influenced the distribution of MCL, as disruptions to menstrual cyclicity often influence the probability of having both long and short cycles without necessarily altering the median cycle length. Thus, we ran linear quantile mixed models (LQMMs) to examine the associations between PFAS and MCL at the 25th, 50th, 75th, and 90th percentiles. To examine the effects of PFAS on bleeding, we used linear mixed models (LMMs) for bleed length (continuous) and generalized linear mixed models (GLMMs) with a logit link function for binary variables of long bleeding and heavy bleeding. Bleed lengths greater than or equal to 40 days were excluded from the LMMs of bleed length due to being extreme outliers ($n = 5$). Because of the right-skewed distribution of bleed length, we used robust, empirical standard error estimates in the LMMs.

Models included the two-year window of cycles, beginning with cycles that finished within one year prior to the PFAS measurement at Visit 3 and ending with those that began within one year after Visit 3. All models included a random intercept for each woman, an unstructured covariance, and were adjusted for race/ethnicity, BMI, and menopause status. Models of MCL were additionally adjusted for physical activity, education, and cycle length at SWAN baseline, while bleeding models were additionally adjusted for smoking status and typical menstrual flow duration at SWAN baseline. Covariate selection was based on *a priori* knowledge and significant associations in bivariate models. Menopause status was dichotomized (late peri vs. pre-menopausal/early peri/unknown due to HT) for models of cycle length but not bleed length due to the differential effect of being early peri versus pre-menopausal on bleed length but not cycle length. Each outcome was regressed on each PFAS separately. PFAS concentrations were log base-2 transformed in all models to capture log-linear dose-response relationships and to allow for interpretations per doubling in PFAS concentration.

We conducted several sensitivity analyses. First, for MCL and bleeding models, we additionally adjusted for the other menstrual characteristics at SWAN baseline (i.e., typical menstrual flow duration for MCL models and cycle length for bleeding models). Second, for bleeding models, we also evaluated the impact of further adjustment for fibroids and prior oral contraceptive use. Third, because menstrual characteristics vary by menopausal status, we performed stratified analyses to evaluate associations separately in pre- and early perimenopausal women. Women in late perimenopause and those with unknown menopausal status due to HT use were excluded from these analyses because of small numbers in these groups.

All analyses were run in SAS 9.4 (SAS Institute, Inc., Cary, North Carolina) except for the LQMMs, which were run in RStudio using the package lqmm (1.5.5) [43,44].

3. Results

At the time of PFAS exposure assessment, women ranged in age from 45 to 55 years with a mean age of 49 years (Table 1). In the analytical sample, 50.3% of the women were White with other half of the sample including Black (18.0%), Chinese (14.4%), and Japanese women (17.4%). Most women had some college or greater education, were normal weight or underweight, were not current smokers, and did not have fibroids. At the beginning of the analytical window, most women were early peri-menopausal (72.0%), with 22.1% being pre-menopausal and 3.9% being late peri-menopausal; a small portion had unknown status due to HT use or a missed visit (2.0%). Across the 2-year window, individual cycle lengths showed considerable variation (Table 1). The median individual 25th percentile cycle length was 25 days (IQR: 23–27), whereas the 90th percentile was 41 days (IQR: 31–71). The medians (IQRs) of individual bleed length at 25th and 90th percentiles were 5 [4–6] days and 7 [6–9] days, respectively. During the 2-year window, 49.2% and 27.8% of women experienced at least one cycle with a long bleeding episode (>8 days) and heavy bleeding episode (≥ 3 days of heavy bleeding), respectively.

The median PFAS concentration was 4.0 ng/mL for n-PFOA; 0.6 ng/mL for PFNA; 1.4 ng/mL for PFHxS; 16.8 ng/mL for n-PFOS; 7.0 for Sm-PFOS, 23.9 ng/mL for PFOS; 1.4 ng/mL for MeFOSAA; and 1.2 ng/mL for EtFOSAA (Table 2).

No PFAS was associated with median MCL (50th percentile) (Table 3). Shorter MCLs at the 25th percentile were associated with doubling of PFOS (-0.52 days; 95% CI, −1.09–0.05); in contrast, PFNA was associated with longer MCLs at the 25th percentile (0.56 days; 95% CI, 0.06–1.05). All PFOS were associated with a longer MCL at the 90th percentiles (1.73 days (95% CI, 0.57–2.90) for n-PFOS; 1.54 days (95% CI, 0.05–3.03) for Sm-PFOS; and 2.77 days (95% CI, 1.96–3.58) for PFOS). The serum concentrations of all other PFAS were not associated with differences in MCL at the 25th, 75th, or 90th percentiles. Additional adjustment for typical flow length at baseline did not alter the results (Table S1).

In adjusted analyses, no significant associations were found with either MeFOSAA or EtFOSAA and any of the bleeding outcomes. Bleed length was inversely associated with a doubling of all other PFAS concentrations except MeFOSAA and EtFOSAA: n-PFOA (-0.29 days; 95% CI, −0.43 to −0.14), PFNA (-0.21 days; 95% CI, −0.34 to −0.09), PFHxS (-0.28 days; 95% CI, −0.37 to −0.18), n-PFOS (-0.28 days; 95% CI, −0.42 to −0.15), Sm-PFOS (-0.20 days; 95% CI, −0.32 to −0.09), and PFOS (-0.29 days; 95% CI, −0.42 to −0.16) (Table 4). Similarly, lower odds of long bleeds were associated with a doubling of all PFAS concentrations except MeFOSAA and EtFOSAA: n-PFOA (OR: 0.75; 95% CI: 0.62–0.89), PFNA (OR: 0.75; 95% CI: 0.63–0.88), PFHxS (OR: 0.72; 95% CI: 0.63–0.82), n-PFOS (OR: 0.68; 95% CI: 0.57–0.82), Sm-PFOS (OR: 0.79; 95% CI: 0.68–0.92), and PFOS (OR: 0.69; 95% CI: 0.57–0.82). Lower odds of heavy bleeding were also associated with a doubling of all PFAS concentrations except MeFOSAA and EtFOSAA: n-PFOA (OR: 0.64; 95% CI: 0.47–0.88), PFNA (OR: 0.64; 95% CI: 0.48–0.85), PFHxS (OR: 0.61; 95% CI: 0.48–0.78), n-PFOS (OR: 0.60; 95% CI: 0.44–0.81), Sm-PFOS (OR: 0.65; 95% CI: 0.50–0.85), and PFOS (OR: 0.58; 95% CI: 0.43–0.79). These associations remain essentially unchanged with further adjustment for baseline cycle length (Table S2), fibroids (Table S3), and oral contraceptive use (Table S4).

In sensitivity analyses stratified by menopausal status, the results were largely consistent between pre- and early perimenopausal women,

Table 1
Characteristics of study sample in the Study of Women's Health Across the Nation (N = 951).

At follow-up visit 2 (1998–1999)	
	Mean (SD)
Age, years	48.0 (2.4)
Physical activity score (possible range 3–15)	7.8 (1.7)
	N (%)
Race/ethnicity	
Black	171 (18.0)
Chinese	137 (14.4)
Japanese	165 (17.4)
White	478 (50.3)
Education	
High school or less	162 (17.1)
Some college or more	785 (82.9)
Body mass index	
< 25 kg/m^2	448 (47.1)
25–29.9 kg/m^2	244 (25.7)
≥ 30 kg/m^2	259 (27.2)
Current smoker	
No	863 (90.7)
Yes	88 (9.3)
Menopause status	
Pre-menopause	210 (22.1)
Early peri-menopause	685 (72.0)
Late peri-menopause	37 (3.9)
Unknown due to HT use	19 (2.0)
Fibroids	
No	872 (91.7)
Yes	79 (8.3)
Oral contraceptive use ever	
No	244 (25.7)
Yes	707 (74.3)
Site	
Southeast Michigan	148 (15.6)
Boston, Massachusetts	145 (15.2)
Oakland, California	221 (23.2)
Los Angeles, California	284 (29.9)
Pittsburgh, Pennsylvania	153 (16.1)
At baseline (1996–1997)	
	N (%)
Length of typical menstrual flow during the last year	
1–2 days	14 (1.5)
3–7 days	900 (94.6)
More than 7 days	37 (3.9)
Average cycle length during typical menstrual cycle during the last year	
Less than 26 days	219 (23.4)
26–32 days	660 (70.6)
33–35 days	17 (1.8)
More than 35 days	18 (1.9)
Too variable to say	21 (2.3)
Longitudinal measures during 2-year window	
	Median (IQR)
Individual 25th percentile cycle length, days	25 (23–27)
Individual 50th percentile cycle length, days	28 (26–31)
Individual 75th percentile cycle length, days	31 (28–45)
Individual 90th percentile cycle length, days	41 (31–71)
Individual 25th percentile bleed length, days	5 (4–6)
Individual 50th percentile bleed length, days	6 (5–7)
Individual 75th percentile bleed length, days	7 (5–8)
Individual 90th percentile bleed length, days	7 (6–9)
	N (%)
At least 1 cycle with bleed length > 8 days	468 (49.2)
At least 1 cycle with heavy bleeding on 3 or more days	264 (27.8)

although some variation was observed in effects by different PFAS and in statistical significance, likely due to smaller sample sizes in each group (Tables S5 and S6).

4. Discussion

This is among the first longitudinal studies to examine the effect of PFAS on MCL and menstrual bleeding using prospectively collected monthly menstrual calendar data from midlife women undergoing the menopause transition. Several PFAS were associated with the distribution of MCL, with higher PFOS associated with shorter short cycles and longer long cycles, while PFNA was associated with longer short cycles. Higher concentrations of all PFAS except MeFOSAA and EtFOSAA were associated with a shorter duration of menses and lower odds of having a prolonged menses > 8 days or episodes of menses with 3 or more days of very heavy menstrual bleeding. These findings remained robust after

Table 2
Medians and interquartile ranges (IQRs) of PFAS concentrations (ng/mL) in serum collected in 1999–2000 for the Study of Women's Health Across the Nation (N = 951).

PFAS	Median (IQR)
n-PFOA	4.0 (2.7–5.7)
PFNA	0.6 (0.4–0.8)
PFHxS	1.4 (0.9–2.2)
n-PFOS	16.8 (12.0–23.8)
Sm-PFOS	7.0 (4.5–10.4)
PFOS	23.9 (17.1–34.7)
MeFOSAA	1.4 (0.9–2.3)
EtFOSAA	1.2 (0.7–2.2)

n-PFOA (linear perfluorooctanoic acid), PFNA (perfluorononanoic acid), PFHxS (perfluorohexane sulfonic acid), n-PFOS (linear perfluorooctane sulfonic acid), Sm-PFOS (branched perfluorooctane sulfonic acid isomers), MeFOSAA (2-(N-methyl-perfluorooctane sulfonamido) acetic acid), and EtFOSAA (2-(N-ethyl-perfluorooctane sulfonamido) acetic acid).
PFOS is the sum of n-PFOS and Sm-PFOS.

additional adjustment for baseline menstrual characteristics and were consistent between premenopausal and early perimenopausal women.

Consistent with most but not all studies, we found that PFAS exposure was associated with increased variance in MCL. The Longitudinal Investigation of Fertility and the Environment (LIFE) Study followed women attempting pregnancy for 12 months [29]. They reported an association between serum PFDA concentrations and 3% longer MCL and between PFOA concentrations and 2% shorter MCL, while PFOS was not associated with MCL. Other previous studies of the association between PFAS and MCL have been cross-sectional, but report associations with menstrual irregularity and long menstrual cycles. In the Inuit-endocrine (INUENDO) three-country cohort, the highest tertile of serum PFOA concentration was associated with a 80% higher odds of having a MCL $\geq$ 32 days compared to the lowest tertile, while PFOS concentrations were not associated with MCL [28]. In a Chinese study, plasma concentrations of PFOA, PFOS, PFNA and PFHxS were associated with a 30%-80% higher odds of reporting irregular cycles, defined as variation in MCL of $>$ 7 days in the past year, and a 30%-70% higher odds of having MCL $>$ 35 days while no associations were found with perfluorobutane sulfonic acid, perfluoroheptanoic acid, PFDA, PFUnA, PFDoDA or perfluorooctane sulfonamide [30]. In the Danish National Birth Cohort women with higher plasma concentrations of PFOA and PFOS were more likely to report having irregular periods [27]. In a United Kingdom study of women undergoing fertility treatment, higher serum PFOS concentrations were observed among women with irregular versus regular menstrual cycles [45]. A study from the Veneto region in Italy, one of the areas worldwide that is heavily polluted with some PFAS, reported that the frequency of irregular menstrual cycles was significantly higher among highly exposed girls compared to other girls (29.5% versus 21.5%) [46]. In contrast to our findings, a Norwegian study that asked pregnant women to recall characteristics of their menstrual cycles in the year prior to pregnancy reported no association between plasma PFAS concentrations and menstrual regularity or MCL [47]. However, among recent oral contraceptive users, women with long cycles had higher concentrations of PFNA and PFUnDA compared to those with normal length cycles. As oral contraceptives are known to regulate menstrual cycles and reduce menstrual flow, this association may be due to reduced menstruation from recent oral contraceptive use resulting in higher plasma PFAS concentrations [47]. Additionally, a Danish birth cohort study that recruited pregnant women in 1988–1989 and followed their female offspring in 2008–2009 found no associations between prenatal maternal serum concentrations of PFOA and PFOS and MCL of female offspring [48]. The long-term effects of prenatal PFAS exposure on menstrual cycle characteristics, however, remain unclear and warrant further investigation.

Consistent with the fact that menstruation is an important route of elimination for PFAS [40–42], this longitudinal study found that higher serum concentrations of all PFAS–except MeFOSAA and EtFOSAA, which are PFOS precursors with relatively shorter half-lives [36]) and were not associated with any menstrual parameters–were associated with shorter duration of menses and lower odds of having prolonged or heavy bleeding. Notably, these associations were observed even after adjustment for baseline menstrual history that could influence blood PFAS concentrations as well as subsequent menstrual cycles during follow-up. These findings extend results from a prior cross-sectional analysis in the SWAN-MPS that reported higher serum PFAS concentrations in women who had not menstruated in the past three months compared to women who had menstruated [49]. Additionally, in a subset of the SWAN-MPS examining longitudinal trends in serum PFAS concentrations, women menstruating consistently showed lower concentrations of serum n-PFOA, PFNA and Sm-PFOS than women who had not experienced menstrual bleeding since the last visit [50]. The aforementioned Chinese study also found that high plasma concentrations of PFOA, PFOS, PFNA and PFHxS were associated with a 15–60% lower odds of reporting heavy or very heavy menses [30]. The Study of Environment, Lifestyle, and Fibroids also found strong inverse associations between PFHxS (-18.8%), PFOS (-16.4%), PFNA (-10.5%), and PFOA (-10.0%) and intensity of menstrual bleeding when comparing heavy versus light bleeding [51]. Importantly, the present study addresses concerns about reverse causation inherent in cross-sectional studies and supports a link between PFAS exposure and menstrual cycle variability and reduced bleeding, although residual confounding

Table 3
Differences in cycle length per doubling of PFAS serum concentrations at the 25th, 50th, 75th, and 90th percentiles of cycle length in the Study of Women's Health Across the Nation (N = 931).

	25th Percentile		50th Percentile		75th Percentile		90th Percentile	
PFAS	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**
n-PFOA	0.05 (-0.47, 0.58)	0.836	0.11 (-0.20, 0.42)	0.487	-0.05 (-0.83, 0.74)	0.905	0.53 (-1.33, 2.40)	0.568
PFNA	0.56 (0.06, 1.05)	0.028	0.10 (-0.32, 0.53)	0.632	-0.14 (-0.68, 0.40)	0.610	-0.01 (-1.45, 1.43)	0.992
PFHxS	-0.19 (-0.68, 0.31)	0.458	0.08 (-0.16, 0.31)	0.508	0.05 (-0.25, 0.35)	0.757	0.23 (-0.68, 1.14)	0.617
n-PFOS	-0.50 (-1.20, 0.20)	0.161	-0.28 (-0.86, 0.29)	0.325	0.65 (-0.21, 1.51)	0.136	1.73 (0.57, 2.90)	0.004
Sm-PFOS	-0.32 (-0.72, 0.08)	0.113	-0.03 (-0.31, 0.25)	0.834	0.38 (-0.25, 1.01)	0.232	1.54 (0.05, 3.03)	0.043
PFOS	-0.52 (-1.09, 0.05)	0.074	-0.31 (-0.85, 0.22)	0.247	0.85 (-0.11, 1.80)	0.083	2.77 (1.96, 3.58)	$<$ 0.001
MeFOSAA	0.35 (-0.18, 0.87)	0.189	-0.04 (-0.33, 0.24)	0.771	-0.21 (-0.56, 0.14)	0.234	-0.32 (-1.53, 0.88)	0.591
EtFOSAA	0.19 (-0.12, 0.49)	0.222	-0.12 (-0.33, 0.09)	0.261	-0.24 (-0.54, 0.06)	0.108	-0.20 (-1.05, 0.66)	0.649

β coefficients and 95% confidence intervals (CIs) were calculated using linear quantile mixed models (LQMMs). All models adjusted for race/ethnicity, menopause status, body mass index, physical activity, education, and baseline cycle length.
n-PFOA (linear perfluorooctanoic acid), PFNA (perfluorononanoic acid), PFHxS (perfluorohexane sulfonic acid), n-PFOS (linear perfluorooctane sulfonic acid), Sm-PFOS (branched perfluorooctane sulfonic acid isomers), MeFOSAA (2-(N-methyl-perfluorooctane sulfonamido) acetic acid), and EtFOSAA (2-(N-ethyl-perfluorooctane sulfonamido) acetic acid). PFOS is the sum of n-PFOS and Sm-PFOS.

Table 4
Differences in bleed length and odds of long or heavy bleeds per doubling of PFAS serum concentration in the Study of Women's Health Across the Nation (N = 951).

	Bleed Length		Long Bleed		Heavy Bleed	
PFAS	**β (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
n-PFOA	-0.29 (-0.43, −0.14)	< 0.001	0.75 (0.62, 0.89)	0.001	0.64 (0.47, 0.88)	0.006
PFNA	-0.21 (-0.34, −0.09)	0.001	0.75 (0.63, 0.88)	< 0.001	0.64 (0.48, 0.85)	0.002
PFHxS	-0.28 (-0.37, −0.18)	< 0.001	0.72 (0.63, 0.82)	< 0.001	0.61 (0.48, 0.78)	< 0.001
n-PFOS	-0.28 (-0.42, −0.15)	< 0.001	0.68 (0.57, 0.82)	< 0.001	0.60 (0.44, 0.81)	0.001
Sm-PFOS	-0.20 (-0.32, −0.09)	< 0.001	0.79 (0.68, 0.92)	0.002	0.65 (0.50, 0.85)	0.002
PFOS	-0.29 (-0.42, −0.16)	< 0.001	0.69 (0.57, 0.82)	< 0.001	0.58 (0.43, 0.79)	< 0.001
MeFOSAA	-0.02 (-0.13, 0.08)	0.659	0.97 (0.83, 1.12)	0.666	0.91 (0.70, 1.18)	0.480
EtFOSAA	0.00 (-0.08, 0.09)	0.975	0.97 (0.87, 1.09)	0.590	0.95 (0.78, 1.15)	0.590

β coefficients or odds ratios (ORs) along with 95% confidence intervals (CIs) were calculated using linear mixed models for continuous bleed length and generalized linear mixed models with a logit link function for binary long bleed and heavy bleed. All models adjusted for race/ethnicity, menopause status, body mass index, smoking status, and typical flow length at baseline.
n-PFOA (linear perfluorooctanoic acid), PFNA (perfluorononanoic acid), PFHxS (perfluorohexane sulfonic acid), n-PFOS (linear perfluorooctane sulfonic acid), Sm-PFOS (branched perfluorooctane sulfonic acid isomers), MeFOSAA (2-(N-methyl-perfluorooctane sulfonamido) acetic acid), and EtFOSAA (2-(N-ethyl-perfluorooctane sulfonamido) acetic acid). PFOS is the sum of n-PFOS and Sm-PFOS.

by unmeasured menstrual characteristics may remain.

Without accounting for hormone use, the association between PFAS and menstrual cycle characteristics could be confounded [42]. To mitigate the influence of exogenous HT use, the present study excluded women who reported current use of HT as well as menstrual cycle data occurring during HT use or HT-washout periods.

The precise mechanisms by which PFAS affect the menstrual cycle length and regularity are not yet fully understood, but research suggests that PFAS may act as endocrine disruptors by interfering with ovarian folliculogenesis and steroidogenesis [2,24,42]. *In vitro* and *in vivo* studies have documented that PFAS exposure can adversely affect folliculogenesis and steroidogenesis, altering the timing and quality of follicle and oocyte development [2]. PFAS exposure has been linked to impaired proliferation and differentiation of granulosa and theca cells [52,53], both of which are essential for normal follicle development [1]. Specifically, PFAS may disrupt the uptake of cholesterol by theca cells and its conversion to androgens, leading to reduced estradiol production by granulosa cells with resultant decreased endometrial proliferation in the follicular phase of the cycle. Lower total volume of endometrium would manifest as shorter and/or lighter bleeding episodes. Potential molecular mechanisms underlying these effects include activation of peroxisome proliferator-activated receptors, disruption of intercellular communication between oocytes and granulosa cells, interference with thyroid hormone synthesis, and increased of oxidative stress [2].

This study had some limitations. First, at the start of the two-year assessed in this study, women were aged 43–56 years. Although we adjusted for menopausal stage, prior research indicates that PFAS exposures are associated with an earlier age at menopause [25]. Therefore, we cannot rule out the possibility that our findings may, at least in part, reflect menstrual cycle changes associated with loss of ovarian reserve and the transition to menopause, rather than direct effects of PFAS on MCL. It should be noted our findings remain consistent in stratified analyses between premenopausal and early perimenopausal women, suggesting that the impact of menstrual cycle changes among women approaching menopause is minimal. Prospective studies involving younger cohorts of women will provide critical data to confirm whether PFAS exposures directly affect MCL. Findings for each individual chemical require cautious interpretation, as multiple comparisons were not taken into account. Additionally, although we controlled for a range of potential confounding covariates, it is possible that residual or unmeasured confounding might have biased our effect estimates.

This study also had several strengths. Our prospective design with PFAS serum concentrations assessed at baseline and menstrual data measured longitudinally helps address concerns related to reverse causation. Menstrual data were collected prospectively on monthly menstrual calendars, with clear definitions provided for coding the amount of menstrual flow. Consequently, menstrual cycle measures in this study are not subject to recall bias, and thus assessment of MCL and duration of bleeding are likely to be more accurate. Furthermore, this large community-based study included multiple racial and ethnic groups, increasing the generalizability of our results.

In conclusion, this longitudinal study with prospectively recorded menstrual data found that multiple PFAS serum concentrations were associated with increased variance in MCL and reduced menstrual bleeding. These findings support evidence from previous studies that PFAS exposure may alter ovarian function and menstrual cyclicity. Alterations in MCL can serve as early markers of adverse impacts of environmental exposures, with potential implications for a range of reproductive outcomes including fertility and timing of menopause. It also provides confirmatory evidence that menstruation is an important route of PFAS elimination, suggesting the potential health benefits of normal menstrual function in reducing body burden of these persistent environmental contaminants.

CRediT authorship contribution statement

Sung Kyun Park: Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Ellen Gold:** Writing – review & editing, Methodology, Investigation. **Randolph John:** Writing – review & editing, Methodology, Investigation. **Antonia Calafat:** Writing – review & editing, Methodology, Investigation. **Rachael Brooks:** Writing – review & editing, Methodology, Investigation. **Michelle Hood:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Siobán Harlow:** Writing – original draft, Supervision, Investigation, Conceptualization.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC. Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the US Department of Health and Human Services.

Attestation statements

- Data regarding any of the subjects in the study has not been previously published unless specified.
- The appropriate checklist for this study design was followed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.reprotox.2026.109207.

Data Availability

SWAN provides access to public use datasets that include data from SWAN screening, the baseline visit and follow-up visits (https://agingresearchbiobank.nia.nih.gov/). To preserve participant confidentiality, some, but not all, of the data used for this manuscript are contained in the public use datasets. A link to the public use datasets is also located on the SWAN web site: http://www.swanstudy.org/swan-research/data-access/. Investigators who require assistance accessing the public use dataset may contact the SWAN Coordinating Center at the following email address: swanaccess@edc.pitt.edu.

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