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Menstrual cycle characteristics as determinants of plasma concentrations of perfluoroalkyl substances (PFASs) in the Norwegian Mother and Child Cohort (MoBa study)

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ABSTRACT

Introduction: Perfluoroalkyl substances (PFASs) are fluorinated organic compounds that have been used in a variety of industrial and consumer applications. Menstruation is implicated as a possible route of elimination for PFASs in women. The overall purpose of this study was to examine menstrual cycle characteristics as determinants of plasma PFAS concentrations in women.

Methods: Our study sample consisted of 1977 pregnant women from the Norwegian Mother and Child Cohort (MoBa) study. The women were asked about menstrual cycle regularity in the year before the pregnancy and typical menstrual cycle length as well as other demographic and reproductive characteristics in a questionnaire completed during the pregnancy. Blood samples were collected around 17–18 weeks gestation and PFAS concentrations were measured in plasma. We examined the association between menstrual cycle characteristics and seven PFASs (perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS), and perfluorooctane sulfonate (PFOS)) using multiple linear regression, adjusted for age, pre-pregnancy body mass index, smoking, education, income, parity, oral contraceptive use, inter-pregnancy interval, and breast-feeding duration.

Results: Irregular cycles were not associated with PFAS concentrations. Overall, we found no evidence of associations between menstrual cycle length and PFAS concentrations. In subgroup analyses we found some evidence, among parous women, of decreased PFHpS and PFOS with short menstrual cycles; we also found, among recent OC users (in the 12 months before the questionnaire) increased PFNA and PFUnDA with long cycle length. Limitations of our study include misclassification of menstrual cycle characteristics, small sample sizes in the sub-group analyses, and a lack of information on duration and volume of menses.

Conclusions: In the entire study sample, we found little evidence of menstrual cycle characteristics as determinants of PFAS concentrations. However, we observed some associations between cycle length and PFAS concentrations with some select PFAS compounds in subgroup analyses.

1. Introduction

Perfluoroalkyl substances (PFASs) are a class of human-made fluorinated organic compounds. PFASs have particular utility as surfactants and repellants. Potential commercial uses for these compounds include protective coatings for food packaging, paints, lubricants, stain repellants, nonstick cookware, and foams for firefighting. Production of long chain PFASs have been phased out in some western countries (Buck et al., 2011). However, long chain PFASs are persistent in the environment and bioaccumulate through the food chain (Lindstrom

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et al., 2011). Evidence suggests that the primary route of exposure in non-occupationally exposed populations is through food sources (Fromme et al., 2009; Haug et al., 2011; Lindstrom et al., 2011). PFASs have been detected in human blood, breast milk, and cord blood. Olsen et al. (2007) reported relatively long geometric mean half-lives for three common PFASs, perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), and perfluorohexane sulfonate (PFHxS), of 4.8, 3.5, and 7.3 years, respectively, in a group of retired workers who had been occupationally exposed to PFASs. Another study using a general population sample living near a previously contaminated drinking water source found a geometric median half life of 2.3 years (Bartell et al., 2010). Most recently, Li et al. (2018) estimated a geometric mean half-life of 3.4 years for PFOS, 2.7 years for PFOA, and 5.3 years for PFHxS using data from another general population sample with prior exposure via contaminated groundwater.

Lower concentrations of PFOS and PFOA are found in women compared with men (Calafat et al., 2007; Fromme et al., 2007; Kato et al., 2011; Midasch et al., 2006). Along with pregnancy and breastfeeding, menstruation has been implicated as a potential elimination route that may explain a portion of the sex difference (Harada et al., 2005; Wong et al., 2014). From a biological standpoint, PFASs are found at the highest levels in body compartments with high concentrations of proteins, such as the blood and liver (reviewed in Conder et al., 2008). Most of the PFASs in plasma are bound to albumin (Han et al., 2003; Jones et al., 2003) and menstrual fluid contains high levels of albumin (Cederholm-Williams et al., 1984). Further evidence implicating menstrual cycles as a potential elimination route for PFASs are epidemiologic studies finding higher concentrations of PFASs in postmenopausal women compared with women who are still menstruating (Knox et al., 2011; Taylor et al., 2014), and lower concentrations in premenopausal women with menorrhagia (Zhou, 2017). Pharmacokinetic modeling supports a role for menstrual cycles in affecting PFAS concentrations (Ruark et al., 2017; Wong et al., 2014).

There is considerable variability in menstrual cycles both within and between women. The International Federation of Gynecology and Obstetrics (FIGO) proposed guidelines for “normal” menstrual cycles, including cycle length between 24 and 38 days, duration of menses of 4.5–8 days, and menstrual flow within a cycle of 5–80 mL (Fraser et al., 2011, 2007). This group also suggested that irregular menstrual cycles be defined as a variation of 20 days or more in single menstrual cycles over the course of a year.

To our knowledge, four previous studies examined the association between PFAS concentrations and menstrual cycle characteristics (Fei et al., 2009; Lum et al., 2017; Lyngso et al., 2014; Zhou et al., 2017). Fei et al. (2009) found that women in the upper three quartiles of PFOS or PFOA exposure during pregnancy were more likely to report irregular periods before the pregnancy. Lyngso et al. (2014) linked higher pregnancy serum concentrations of PFOA to longer menstrual cycles ($\geq$ 32 days) prior to the pregnancy. However, Lum et al. (2017) found that higher PFOA concentrations in women trying to get pregnant were associated with a decrease in cycle length. Finally, Zhou et al. (2017) reported associations between higher levels of four PFASs (PFOA, PFNA, PFHxS, and PFOS) in women trying to conceive and both self-reported irregular cycles and menstrual cycles of greater than 35 days. Lyngso et al. (2014), Lum et al. (2017), and Zhou et al. (2017) hypothesized that PFASs may potentially impact reproductive health and conceptualized menstrual cycles as a marker of reproductive capacity. However, given the evidence discussed above, it is also possible that menstrual cycle characteristics may influence excretion of PFASs and therefore body burden.

The main goal of this study was to assess the role of menstrual cycle characteristics as potential determinants of PFAS concentrations. We specifically focused on two self-reported metrics of menstrual cycle characteristics: cycle regularity (i.e. regular in terms of frequency) and cycle length. We hypothesized that longer reported cycle length or irregularity may be associated with higher PFAS concentrations, for two reasons. First, we assumed that longer or irregular cycles would mean less menstrual fluid loss overall, and second, these metrics were associated with higher PFAS concentrations in two of the previous studies.

2. Materials and methods

2.1. Study sample and data collection

The study sample included a subgroup of women from the Norwegian Mother and Child Cohort (MoBa), a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (Magnus et al., 2016). Pregnant women were enrolled from throughout Norway between 1999 through 2008 by a mail invitation for the MoBa study prior to routine ultrasound examinations at around the 17th week of pregnancy. About 41% of the women agreed to participate. Nilsen et al. (2009) reported that the MoBa study sample had relatively fewer women who were younger, single, higher parity, or with a previous stillbirth in comparison to the general Norwegian population. Despite these differences, Nilsen et al. (2009) did not find evidence of selection bias in exposure-outcome associations comparing estimates from the sample and the general population. The women completed a first questionnaire around the time of study enrollment that ascertained menstrual cycle characteristics, contraceptive use, medical conditions, previous pregnancies, health-behavior habits, and socioeconomic status. A blood sample was obtained from the pregnant women at the time of study enrollment (Paltiel et al., 2014). The MoBa study also linked participants to information in the Medical Birth Registry of Norway (MBRN). The present analysis was based on data version 9 of the quality-assured data files released for research in 2015.

This analysis included participants from two earlier substudies in MoBa (Starling et al., 2014; Whitworth et al., 2012) (Appendix Figure 1). The first study (Study A) was designed to examine the association between PFAS concentrations and subfecundity (Whitworth et al., 2012). Eligible women for Study A enrolled in 2003–2004, supplied a blood sample at study enrollment, and delivered a live-born child. The second study (Study B) assessed the relation between PFAS concentrations and validated preeclampsia (Starling et al., 2014). Study B subjects were selected among nulliparous women with singleton pregnancies who enrolled in MoBa in 2003–2007. Additional eligibility criteria for Study B included the presence of a plasma sample from mid-pregnancy and no prior history of chronic hypertension. The present study includes 949 women eligible for Study A (400 cases and 549 randomly selected participants) and 1045 women eligible for Study B (496 cases and 549 randomly selected participants). Some women were in both studies, so the combined sample included 1977 unique subjects. We excluded 41 women missing information on cycle irregularity from the irregular cycle analysis. For the cycle length analysis, we excluded 97 women missing information on cycle length.

2.2. Outcomes: PFAS measurements

As noted above, maternal blood samples were collected around the time of study enrollment (17–18 weeks gestation). The samples were shipped overnight from collection site to Oslo, Norway at room temperature. In Oslo, plasma samples were stored at − 80 °C (Ronningen et al., 2006). Plasma concentrations of PFASs were determined using high-performance liquid chromatography/tandem mass spectrometry at the Norwegian Institute of Public Health. The procedure is described in greater detail elsewhere (Haug et al., 2009). We limited our analyses to the seven PFASs where more than 50% of the samples were above the limit of quantification (LOQ): PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), PFHxS, perfluoroheptane sulfonate (PFHpS), and PFOS. The LOQ for the seven included PFASs was 0.05 ng/mL. For Study B, 25 QA/QC samples from a single pool were run in batches with study specimens (Starling et al., 2014); the coefficient of variation for each of the seven

Table 1
Participant characteristics by menstrual cycle regularity and length among women in the MoBa cohort (n = 1977, years 2003–2007).

	Regularity[a]			Cycle Length[b]			
	Regular N (%)	Irregular N (%)	p-value	Short (17–24 days) N (%)	Normal (25–31 days) N (%)	Long (32 + days) N (%)	p-value
Total	1541	395		126	1533	221	
Age at delivery (yrs)			0.0007				0.02
< 25	161 (10.4)	58 (14.7)		16 (12.7)	178 (11.6)	16 (7.2)	
25–29	541 (35.1)	150 (38.0)		38 (30.2)	533 (34.8)	101 (45.7)	
30–34	585 (38.0)	151 (38.2)		54 (42.9)	584 (38.1)	79 (35.7)	
≥ 35	254 (16.5)	36 (9.1)		18 (14.3)	238 (15.5)	25 (11.3)	
BMI pre-pregnancy (kg/m^2)			0.001				0.44
Missing	30	5		3	28	4	
Underweight (< 18.5)	35 (2.3)	10 (2.6)		2 (1.6)	33 (2.2)	6 (2.8)	
Normal (18.5– < 25)	929 (61.5)	212 (54.4)		82 (66.7)	908 (60.3)	126 (58.1)	
Overweight (25– < 30)	383 (25.3)	97 (24.9)		29 (23.6)	384 (25.5)	51 (23.5)	
Obese (≥ 30)	164 (10.9)	71 (18.2)		10 (8.1)	180 (12.0)	34 (15.7)	
Smoking at 17 weeks GA			0.19				0.02
Missing	16	0		2	14	0	
Never	746 (48.9)	197 (49.9)		49 (39.5)	754 (49.6)	113 (51.1)	
Former	673 (44.1)	161 (40.8)		65 (52.4)	645 (42.5)	101 (45.7)	
Current	106 (7.0)	37 (9.4)		10 (8.1)	120 (7.9)	7 (3.2)	
Education			0.07				0.02
Missing	4	2		0	5	0	
< High School	98 (6.4)	40 (10.2)		13 (10.3)	106 (6.9)	12 (5.4)	
High School + Other	470 (30.6)	113 (28.8)		48 (38.1)	460 (30.1)	51 (23.1)	
Some college	636 (41.4)	154 (39.2)		42 (33.3)	631 (41.3)	100 (45.2)	
4 + years of college	333 (21.7)	86 (21.9)		23 (18.3)	331 (21.7)	58 (26.2)	
Maternal Income (NOK/year)			0.06				0.56
Missing	45	17		2	50	7	
< 150,000	201 (13.4)	62 (16.4)		23 (18.5)	204 (13.8)	29 (13.6)	
150,000–299,999	684 (45.7)	185 (48.9)		54 (43.5)	682 (46.0)	105 (49.1)	
> 300,000	611 (40.8)	131 (34.7)		47 (37.9)	597 (40.3)	80 (37.4)	
Parity			0.31				0.13
0	1158 (75.1)	290 (73.4)		89 (70.6)	1147 (74.8)	175 (79.2)	
1	270 (17.5)	81 (20.5)		30 (23.8)	271 (17.7)	37 (16.7)	
2 +	113 (7.3)	24 (6.1)		7 (5.6)	115 (7.5)	9 (4.1)	
Use of OCs in past 12 months[c]			< 0.0001				< 0.0001
Missing	139	62		13	148	29	
No	788 (56.2)	232 (69.7)		59 (52.2)	786 (56.8)	147 (76.6)	
Yes	614 (43.8)	101 (30.3)		54 (47.8)	599 (43.2)	45 (23.4)	
Use of OCs			0.29				0.26
Missing	26	7		2	23	6	
Never	135 (8.9)	28 (7.2)		6 (4.8)	133 (8.8)	21 (9.8)	
Ever	1380 (91.1)	360 (92.8)		118 (95.2)	1377 (91.2)	194 (90.2)	

BMI, body mass index; GA, gestational age; NOK, Norwegian kroner; OC, oral contraceptive.
[a] Missing cycle regularity: N = 41.
[b] Missing cycle length: N = 97.
[c] Before inclusion in the study at 17–18 weeks gestation.

PFASs above ranged from 8.6 to 29.8, the median was 14.6.

2.3. Exposures: menstrual cycle characteristics

In the baseline questionnaire, women were asked: "Were your periods regular the year before you became pregnant?" We used the response to this question (yes or no) to classify women by whether or not they self-reported irregular periods. The baseline questionnaire also asked women to report: "How many days are there usually between the first day in your menstrual period and the first day in your next menstrual period?" We classified women into three categories of cycle length based on their responses: short cycles (17–24 days), normal cycles (25–31 days), and long cycles (32 + days) based on categories used by Lyngso and colleagues (Lyngso et al., 2014).

2.4. Statistical analysis

We examined the distribution of participant characteristics by irregular menstrual cycles and by categories of menstrual cycle length. We also evaluated the medians and interquartile ranges (IQRs: 25th percentile, 75th percentile) for the seven PFASs examined in our analysis. We examined the distribution of PFAS levels two ways: (1) restricted to PFAS values above the LOQ and (2) including PFAS values above the LOQ and measured values below the LOQ.

We conducted multiple linear regression analyses to examine the association between each menstrual cycle characteristic and PFAS concentrations. We fit separate regression models for each PFAS. We natural log-transformed the PFAS concentrations because the distributions were skewed with a long tail to the right. We selected covariates that might be associated with menstrual cycle characteristics and may influence PFAS concentrations. Adjusted models included the following covariates: participant's age at child's birth (continuous), pre-pregnancy body mass index (BMI, kg/m^2) (underweight, normal, overweight, obese), smoking at ~17 weeks of pregnancy (never, former, current), educational level (< high school, high school or other, some college, 4 + years of college), and gross income (< 150,000 NOK, 150,000–299,999 NOK, 300,000 + NOK), parity (0 previous births, 1 previous births, 2 + previous births), use of oral contraceptives in the past 12 months, months between previous pregnancy and current pregnancy (tertile 1: < 28 months, tertile 2:28 - < 50 months, tertile 3: 50 + months), and months of breastfeeding following most recent live-birth (continuous). Because the study sample included

subfecundity cases and preeclampsia cases as well as two randomly selected samples, we adjusted analyses for the sampling group status (Richardson et al., 2007). We conducted sensitivity analyses where we restricted the analysis to the non-cases (i.e. we excluded subfertility and preeclampsia cases).

Since we were concerned that other factors, such as breastfeeding, blood loss during delivery or the postpartum period, and time since most recent pregnancy, might affect PFAS levels among parous women, we conducted analyses stratified by parity. Because oral contraceptive use masks underlying physiological differences in menstrual cycles, we also conducted analyses stratified by recency of use of oral contraceptives. Women were categorized as never using OCs, using OCs recently (in the year prior to the questionnaire) or using OCs in the past (more than a year prior to the questionnaire). We formally tested for effect modification by running regression models that included a product term between either previous birth or recency of oral contraceptive use and each exposure (i.e., cycle irregularity or cycle length).

All statistical analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC). We multiply imputed 10 datasets using PROC MI in SAS 9.4 (SAS Institute Inc., Cary, NC) to address missing unmeasured PFAS values below the LOQ (Lubin et al., 2004) and missing confounder information. Multiple linear regression models were run using PROC GENMOD and results across imputations were combined using PROC MIANALYZE. For ease of interpretation, we present our results as the percent change in PFAS concentration comparing one category of exposure to another category, calculated by $(\exp(\beta)-1)*100$.

3. Results

Women reporting irregular periods were more likely to be younger, obese, or have lower gross income than women reporting regular periods (Table 1). Additionally, among women reporting irregular periods, oral contractive use in the past 12 months was less frequent compared with women who had regular cycles. Women reporting long cycles were more likely to be in 25–29 year old age group and less likely to have used oral contraceptives in the past 12 months compared to women reporting short or normal cycle lengths. Women reporting shorter cycles had a greater likelihood of being former smokers or having lower educational ascertainment.

All PFOA and PFOS samples had concentrations above the limit of quantification (LOQ) (Table 2). The percent of women with concentrations above the LOQ was, for PFNA, 99.8; PFHxS, 99.6; PFUnDA, 89.3; PFHpS, 85.9; and PFDA, 72.0. The median (IQR: 25th, 75th percentiles) including all measured values above and below the LOQ was 12.87 (9.94, 16.62) for PFOS; 2.54 (1.87, 3.30) for PFOA; 0.65 (0.47, 0.91) for PFHxS; 0.45 (0.33, 0.63) for PFNA; 0.20 (0.11, 0.30) for PFUnDA; 0.15 (0.10, 0.21) for PFHpS; 0.11 (0.06, 0.17) for PFDA (Table 2).

Table 2
Distribution of perfluoroalkyl substance concentrations in plasma (ng/mL) collected from pregnant women at 17–18 weeks gestation in the MoBa study (n = 1977, years 2003–2007).

	Values ≥ LOQ			All measured values[a]		
	N (%)	Median	IQR	N	Median	IQR
PFOA	1977 (100.0)	2.54	1.87, 3.30	1977 (100.0)	2.54	1.87, 3.30
PFNA	1973 (99.8)	0.45	0.33, 0.63	1975 (99.9)	0.45	0.33, 0.63
PFDA	1424 (72.0)	0.13	0.09, 0.19	1798 (90.9)	0.11	0.06, 0.17
PFUnDA	1766 (89.3)	0.21	0.13, 0.32	1922 (97.2)	0.20	0.11, 0.30
PFHxS	1970 (99.6)	0.65	0.47, 0.92	1973 (99.8)	0.65	0.47, 0.91
PFHpS	1699 (85.9)	0.16	0.11, 0.22	1799 (91.0)	0.15	0.10, 0.21
PFOS	1977 (100.0)	12.87	9.94, 16.62	1977 (100.0)	12.87	9.94, 16.62

LOQ, limit of quantification; IQR, interquartile range; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUnDA, perfluoroundecanoic acid; PFHxS, perfluorohexane sulfonate; PFHpS, perfluoroheptane sulfonate; PFOS, perfluorooctane sulfonate.

[a] Includes values ≥ LOQ and measured values below LOQ.

In regressions only adjusting for study group, we found a suggestion of decreased plasma PFAS concentrations among women reporting irregular periods for PFOA, PFNA, PFDA, and PFUnDA (Table 3). For example, report of irregular menstrual cycles was associated with a 7% decrease in PFOA concentration (95% confidence interval (CI): − 11%, − 2%) compared with women who reported regular cycles. These results were attenuated following adjustment for maternal age, pre-pregnancy BMI, smoking at 17 weeks of pregnancy, highest level of education, maternal income, parity, use of oral contraceptives in the past 12 months, interval between pregnancy, and months of breastfeeding (Table 3). The results of adjusted analyses restricted to non-cases from the two earlier MoBa studies were similar to the main results (Appendix Table 1). In the entire study sample, we saw no evidence of an association between cycle length and PFAS levels (Table 3). Adjusted results were similar in analyses restricted to non-cases (Appendix Table 1).

We observed evidence of interactions between cycle length and previous birth for PFNA, PFHpS and PFOS. Among nulliparous women, we found no link between menstrual cycle characteristics and PFAS concentrations (Table 4). However, among parous women, short cycles were associated with decreased concentrations of PFHpS (−34%, 95% CI: −49%, −14%) and PFOS (−13%, 95% CI: −23%, −2%) (Table 4). There were suggestive, albeit non-statistically significant, associations between shorter cycles and lower PFNA and PFUnDA, and between longer cycles and lower PFOS. In models including product terms to formally access for effect modification, we observed interactions between cycle length and PFNA (F-test p-value .06), PFHpS (F-test p-value .01) and PFOS (F-test p-value .09) (Appendix Table 2). In analyses restricted to non-cases, among parous women, we found suggestions of associations between shorter cycles and decreased PFNA, PFUnDA, PFHpS, and PFOS, although the association was only significant for PFNA and PFHpS (Appendix Table 3).

Among women never using oral contraceptives, we found no associations between menstrual cycle characteristics and PFAS concentrations (Table 5). However, among women reporting recent use of OCs (in the 12 months prior to questionnaire administration), long cycles were associated with a 17% increase in PFNA concentration (95% CI: 2%, 34%) and a 38% increase in PFUnDa concentration (95% CI: 6%, 79%) compared to women with normal length cycles (Table 5). When we formally tested for effect modification, we observed an interaction between cycle length and recency of oral contraceptive use for PFNA (F-test p-value .01) (Appendix Table 4). Results were generally similar in analyses restricted to non-cases, though the association between long cycle length and higher PFUnDA among women recently using OCs was no longer statistically significant (Appendix Table 5).

4. Discussion

In our study, self-reported irregular menstrual cycles were generally not associated with PFAS concentrations after adjustment for confounders. We found no evidence for cycle length as a predictor of plasma PFAS levels overall. Our results were generally similar when we restricted to non-cases from the subfecundity and preeclampsia studies. However, among parous women short cycles were associated with statistically significant decreased concentrations of PFHpS and PFOS, with borderline associations with decreased PFNA and PFUnDa. Among women using oral contraceptives less than 12 months before the questionnaire, we observed associations between longer cycles and increased concentrations of PFNA and PFUnDA.

We recently reported on the association between OCs and PFAS levels using data from the controls groups from our same study sample (Rush et al., 2017). OC use in the 12 months prior to the administration

Table 3
Crude and adjusted estimates of the percent change (%) and 95% confidence intervals in plasma PFAS concentrations in relation to prior menstrual cycle characteristics in pregnant women in the MoBa study [a].

	PFOA % change (95% CI)	PFNA % change (95% CI)	PFDA % change (95% CI)	PFUnDa % change (95% CI)	PFHxS % change (95% CI)	PFHpS % change (95% CI)	PFOS % change (95% CI)
Cycle Irregularity (N = 1936)							
Adjusted 1[b]							
Regular	REF	REF	REF	REF	REF	REF	REF
Irregular	−7 (−11, −2)	−9 (−14, −4)	−17 (−27, −6)	−14 (−22, −5)	−1 (−7, 6)	−5 (−12, 4)	−3 (−7, 2)
Adjusted 2[c]							
Regular	REF	REF	REF	REF	REF	REF	REF
Irregular	− 3 (−7, 1)	− 3 (−9, 2)	− 5 (−16, 8)	− 3 (−12, 6)	4 (−3, 11)	− 1 (−9, 8)	0 (−4, 5)
Cycle Length (N = 1880)							
Adjusted 1[b]							
Normal	REF	REF	REF	REF	REF	REF	REF
Short	−3 (−10, 5)	−5 (−13, 5)	−3 (−21, 19)	−7 (−21, 9)	−3 (−13, 9)	−10 (−22, 3)	−8 (−14, 0)
Long	0 (−6, 7)	1 (−6, 8)	2 (−13, 19)	−4 (−15, 9)	4 (−4, 14)	0 (−10, 11)	−2 (−7, 4)
Adjusted 2[c]							
Normal	REF	REF	REF	REF	REF	REF	REF
Short	−1 (−8, 6)	−3 (−11, 6)	0 (−18, 22)	−6 (−19, 10)	−2 (−12, 9)	−10 (−21, 3)	−6 (−13, 1)
Long	0 (−5, 6)	2 (−5, 9)	4 (−11, 21)	0 (−11, 13)	5 (−4, 14)	0 (−10, 12)	−1 (−7, 5)

PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUnDA, perfluoroundecanoic acid; PFHxS, perfluorohexane sulfonate; PFHpS, perfluoroheptane sulfonate; PFOS, perfluorooctane sulfonate; LOQ, limit of quantification.

[a] Multiple imputation was used to address unmeasured values below the LOQ and missing confounder information.

[b] Adjusted for sampling group status.

[c] The full multiple regression models adjusted for age at child's birth, pre-pregnancy BMI, smoking at ~17 weeks of pregnancy, highest level of education, gross income, parity, use of oral contraceptives in the past 12 months, months between previous pregnancy and current pregnancy, months of breastfeeding following most recent live-birth, and sampling group status.

of the questionnaire was associated with statistically significant higher levels of PFOA, PFNA, and PFOS (Rush et al., 2017). Women reporting recent OC use (in the 12 months prior to questionnaire completion) and past OC use had higher levels of plasma PFOA, PFHpS, and PFOS compared to those never using OCs, though the association were stronger for women recently using OCs (Rush et al., 2017). Women with a lifetime OC use of 10 or more years had higher concentrations of PFOA, PFNA, PFHxS, PFHpS, and PFOS than women never using OCs (Rush et al., 2017). Oral contraceptive use will regulate cycles and reduce menstrual flow, masking the natural menstrual cycle characteristics of the woman. Given the long half-lives of PFASs, long term use of oral contraceptives resulting in greater regularity over many years may be a stronger predictor of PFAS concentrations than recent cycle irregularity or recent differences in cycle length.

The reason for the associations between some PFAS compounds and cycle length in subgroup analyses is not clear. Recently discontinuing birth control has been linked to longer menstrual cycles (Gnoth et al., 2002; Nassaralla et al., 2011) and decreased menstrual fluid loss (Nassaralla et al., 2011). In our study sample, we found that women with recent OC use were less likely to have reported longer cycles than

Table 4
Adjusted estimates of the percent change and 95% confidence intervals in plasma PFAS concentrations in relation to prior menstrual cycle characteristics in pregnant women in the MoBa study **stratified by parity** [a].

	N	PFOA % change (95% CI)	PFNA % change (95% CI)	PFDA % change (95% CI)	PFUnDa % change (95% CI)	PFHxS % change (95% CI)	PFHpS % change (95% CI)	PFOS % change (95% CI)
NULLIPAROUS[b]								
Cycle Irregularity	1448							
Regular	1158	REF	REF	REF	REF	REF	REF	REF
Irregular	290	−3 (−8, 2)	−3 (−9, 3)	−7 (−20, 8)	−3 (−13, 9)	2 (−6, 10)	1 (−9, 11)	1 (−5, 7)
Cycle Length	1411							
Normal	1147	REF	REF	REF	REF	REF	REF	REF
Short	89	−1 (−9, 7)	3 (−7, 13)	2 (−19, 29)	−1 (−18, 19)	1 (−12, 15)	4 (−12, 21)	−3 (−12, 6)
Long	175	0 (−6, 7)	4 (−4, 12)	8 (−9, 28)	4 (−9, 20)	6 (−4, 17)	3 (−9, 16)	1 (−6, 8)
PAROUS[c]								
Cycle Irregularity	488							
Regular	383	REF	REF	REF	REF	REF	REF	REF
Irregular	105	−2 (−9, 6)	−3 (−13, 9)	6 (−17, 36)	0 (−16, 18)	9 (−4, 23)	−4 (−19, 15)	−1 (−9, 7)
Cycle Length	469							
Normal	386	REF	REF	REF	REF	REF	REF	REF
Short	37	1 (−11, 14)	−14 (−28, 3)	−8 (−37, 34)	−20 (−38, 3)	−8 (−24, 12)	−34 (−49, −14)	−13 (−23, −2)
Long	46	2 (−9, 14)	−3 (−18, 14)	−4 (−32, 36)	−10 (−29, 13)	4 (−13, 24)	−7 (−27, 19)	−8 (−18, 2)

PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUnDA, perfluoroundecanoic acid; PFHxS, perfluorohexane sulfonate; PFHpS, perfluoroheptane sulfonate; PFOS, perfluorooctane sulfonate; LOQ, limit of quantification.

[a] Multiple imputation was used to address unmeasured values below the LOQ and missing confounder information.

[b] Among nulliparous women, the multiple regression models adjusted for age at child's birth, pre-pregnancy BMI, smoking at ~17 weeks of pregnancy, highest level of education, gross income, use of oral contraceptives in the past 12 months, and sampling group status.

[c] Among parous women, the multiple regression models adjusted for age at child's birth, pre-pregnancy BMI, smoking at ~17 weeks of pregnancy, highest level of education, gross income, use of oral contraceptives in the past 12 months, months between previous pregnancy and current pregnancy, months of breastfeeding following most recent live-birth, and sampling group status.

Table 5
Adjusted estimates of the percent change and 95% confidence intervals in plasma PFAS concentrations in relation to prior menstrual cycle characteristics in pregnant women in the MoBa study, stratified by recency of oral contraceptive use.

	N	PFOA % change (95% CI)	PFNA % change (95% CI)	PFDA % change (95% CI)	PFUnDa % change (95% CI)	PFHxS % change (95% CI)	PFHpS % change (95% CI)	PFOS % change (95% CI)
Never Used OCs	163							
Regular	135	REF	REF	REF	REF	REF	REF	REF
Irregular	28	−12 (−28, 7)	−2 (−24, 27)	−22 (−52, 29)	−17 (−45, 24)	0 (−27, 37)	−14 (−42, 27)	−12 (−28, 9)
Recent OC Use	715							
Regular	614	REF	REF	REF	REF	REF	REF	REF
Irregular	101	0 (−8, 8)	−6 (−15, 4)	−9 (−28, 15)	−3 (−19, 17)	12 (−1, 26)	−3 (−16, 13)	−3 (−11, 6)
Past OC Use	857							
Regular	653	REF	REF	REF	REF	REF	REF	REF
Irregular	204	−6 (−11, 0)	−1 (−8, 7)	−2 (−18, 16)	−1 (−13, 14)	−7 (−15, 3)	0 (−11, 13)	2 (−4, 9)
Never Used OCs	160							
Normal	133	REF	REF	REF	REF	REF	REF	REF
Short	6	−15 (−42, 24)	−19 (−51, 32)	−40 (−76, 49)	−24 (−64, 60)	−38 (−66, 13)	−29 (−67, 51)	−16 (−43, 26)
Long	21	−10 (−28, 13)	−20 (−40, 7)	−20 (−53, 35)	−11 (−43, 38)	1 (−28, 44)	−13 (−44, 35)	−5 (−25, 21)
Recent OC Use	698							
Normal	599	REF	REF	REF	REF	REF	REF	REF
Short	54	3 (−7, 14)	4 (−9, 18)	8 (−20, 45)	−7 (−27, 19)	1 (−14, 19)	−11 (−27, 8)	−3 (−13, 8)
Long	45	6 (−5, 19)	17 (2, 34)	30 (−7, 80)	38 (6, 79)	12 (−6, 34)	7 (−13, 33)	3 (−9, 16)
Past OC Use	832							
Normal	653	REF	REF	REF	REF	REF	REF	REF
Short	53	−1 (−10, 10)	−5 (−17, 7)	−4 (−28, 30)	−5 (−25, 20)	6 (−11, 26)	−5 (−23, 17)	−8 (−17, 3)
Long	126	−2 (−9, 5)	2 (−7, 11)	−3 (−21, 19)	−7 (−21, 9)	2 (−10, 14)	−1 (−14, 14)	−4 (−11, 3)

[a] Multiple imputation was used to address unmeasured values below the LOQ and missing confounder information.
[b] The full multiple regression models adjusted for age at child's birth, pre-pregnancy BMI, smoking at ~17 weeks of pregnancy, highest level of education, gross income, parity, months between previous pregnancy and current pregnancy, months of breastfeeding following most recent live-birth, and sampling group status. PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUnDA, perfluoroundecanoic acid; PFHxS, perfluorohexane sulfonate; PFHpS, perfluoroheptane sulfonate; PFOS, perfluorooctane sulfonate; LOQ, limit of quantification.

women with past OC use (Table 5). However, women reporting recent OC use may have had lighter periods in the year before the pregnancy than women with past OC use, potentially explaining the association between long cycles and higher concentrations of two PFAS compounds. Unfortunately, our study did not capture any information of the usual duration and heaviness of menstrual fluid loss.

PFAS concentrations are on average lower in parous women compared to nulliparous women (Berg et al., 2014; Brantsaeter et al., 2013; Jusko et al., 2016; Kato et al., 2014; Lewin et al., 2017; Ode et al., 2013; Sagiv et al., 2015). Brantsaeter et al. (2013) suggest mechanisms for this elimination include placental transfer, aggregation in the placenta, higher glomerular filtration rate during the pregnancy, and breastfeeding. Other explanations for lower PFAS levels in parous women may include bleeding during delivery and the post-partum period. In multiparous women, lower PFAS concentrations are linked to longer duration of previous breastfeeding (Brantsaeter et al., 2013; Jusko et al., 2016; Kato et al., 2014; Lauritzen et al., 2016; Manzano-Salgado et al., 2016; Sagiv et al., 2015; Timmermann et al., 2017). It is possible that more frequent menses may be associated with a greater percent decrease in PFHpS concentration and PFOS concentration among parous women because their baseline levels of these compounds are lower than levels in nulliparous women.

The results in the three previous studies on PFAS as a determinant of menstrual cycle irregularity show a positive association (Fei et al., 2009; Lyngso et al., 2014; Zhou et al., 2017), whereas our results generally indicated a null association. Of the three previous studies, the results from the Shanghai Birth Cohort Study (Zhou et al., 2017) contrast most strongly with ours – their findings were adjusted for several potentially confounding factors and were statistically significant. The prevalence of use of oral contraceptives among women in the Shanghai study may be very low because oral contraceptive use is low in China (United Nations, 2015). In an ancillary analysis using the same subset of MoBa participants, we found that women reporting irregular menstrual cycles were less likely to report anemia ($p < 0.05$) (data not shown). This finding that women with irregular periods were less likely to report anemia compared to women with regular periods might explain why higher PFAS would be seen among women with irregular cycles in other studies. Interestingly, as noted above, in the Shanghai study menorrhagia was inversely related to serum PFAS concentrations, which is consistent with our hypothesis that menstrual excretion is an important determinant of serum PFAS concentrations.

The results in the previous three studies on PFASs and menstrual cycle length (Lum et al., 2017; Lyngso et al., 2014; Zhou et al., 2017) were not consistent, though the larger studies (Lyngso et al., 2014; Zhou et al., 2017) provide support for increased PFAS concentrations being associated with longer cycles. In our overall study sample, we found no association between cycle length and PFAS compounds. Though we did see some associations with cycle length among parous women and among women recently using OCs. Reasons for variation in results across studies include differences in the wording of questions about menstrual cycle characteristics, study design, culture, and prevalence of oral contraceptive use. Some of these previous studies collected samples and information on menstrual cycle characteristics from women trying to get pregnant (Lum et al., 2017; Zhou et al., 2017) whereas other studies, including our own, collected samples from pregnant women and asked about menstrual cycles prior to the pregnancy (Fei et al., 2009; Lyngso et al., 2014). Thus, our results are only generalizable to women capable of conceiving. Among women in Study A, those reporting longer time to pregnancy were more likely to report irregular periods. This suggests that there could be substantial differences in menstrual cycle characteristics comparing study samples of women capable of conceiving to those in the process of trying to conceive. Finally, concentrations varied substantially across the different studies. For example, the Zhou et al. (2017) study was conducted in China, where PFOA and PFOS is still produced, and the concentrations of plasma PFOA and PFNA were higher than in our study. In Fei et al. (2009) levels of PFOA and PFOS were also higher than concentrations measured in our study sample.

Misclassification is a concern in our study. During the pregnancy, the women retrospectively reported menstrual cycle characteristics in the year before the pregnancy. Women were asked to report exact number of days in a menstrual cycle. However, menstrual cycle lengths,

even among healthy women, can vary from cycle to cycle (Chiazze et al., 1968; Creinin et al., 2004), which may have been a barrier to accurate reporting of menstrual cycle lengths in our study. In fact, a number of studies described inconsistencies between retrospectively self-reported average menstrual cycle lengths and prospectively collected lengths from menstrual diaries (Creinin et al., 2004; Jukic et al., 2008; Small et al., 2007; Steiner et al., 2001). Furthermore, women may have different opinions about the definition of regular menstrual cycles and the questionnaire did not objectively clarify this definition, which may have resulted in some misclassification. We did not have information on duration of menses or volume of menstrual flow in our analyses. These might be more important menstrual predictors of PFAS concentrations than cycle length and irregularity. Since we examined multiple associations in this work, multiple testing is also a concern.

Pregnancy concentrations of PFASs may not be representative of PFAS concentrations prior to conception. However, PFAS concentrations have been found to be moderately to highly correlated comparing samples collected from the same women over two consecutive pregnancies (Papadopoulou et al., 2015), suggesting that PFAS measures may be reliable over a time frame of a few years. Finally, the MoBa blood samples were shipped overnight at room temperature and the stability of PFAS compounds in the samples is unclear. One study found that concentrations of PFHxS, PFOA, PFOS, and PFNA in thawed serum samples stayed stable even if left at room temperature for 10 days (Kato et al., 2013). Another study found differences in the concentrations of many PFASs when samples were immediately processed and frozen as plasma, compared to when samples were transported by mail at ambient temperature when the transportation occurred during the winter months (Bach et al., 2015).

5. Conclusions

We did not have information on other menstrual characteristics, such as duration of menses and volume of menstrual flow, which might be more critical predictors of PFAS concentrations. We also recognize that the collected menstrual cycle information may be prone to misclassification and that sample sizes in some of our sub-group analyses were small. However, in conclusion, we found that self-reported irregular menstrual cycles and length of menstrual cycles was not associated with PFAS concentrations in a large sample of women enrolled in the MoBa cohort.

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Ethical approvals

This study was approved by The Regional Committee for Medical Research Ethics in South-Eastern Norway and the IRB of the National Institute of Environmental Health Sciences, NIH. The Office of Human Research Ethics at the University of North Carolina at Chapel Hill determined that this secondary data analysis did not require IRB approval.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2018.05.019.

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