Environmental Research 166 (2018) 78–85

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

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

Alison B. Singer[a,*], Kristina W. Whitworth[b,c], Line S. Haug[d], Azemira Sabaredzovic[d], Antti Impinen[e], Eleni Papadopoulou[d], Matthew P. Longnecker[f]

[a] The Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA
[b] Department of Epidemiology, Human Genetics and Environmental Sciences, The University of Texas Health Science Center at Houston, School of Public Health in San Antonio, San Antonio, TX, USA
[c] Southwest Center for Occupational and Environmental Health, The University of Texas Health Science Center at Houston, School of Public Health, Houston, TX, USA
[d] Department of Environmental Exposures and Epidemiology, Norwegian Institute of Public Health, Oslo, Norway
[e] Department of Toxicology and Risk Assessment, Norwegian Institute of Public Health, Oslo, Norway
[f] National Institute for Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Durham, NC, USA

ARTICLE INFO

Keywords:
Perfluoroalkyl substances
Menstrual
Irregularity
Cycle length
MoBa

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

* Correspondence to: Department of Epidemiology, CB #7435, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.
E-mail address: alison_singer@unc.edu (A.B. Singer).

https://doi.org/10.1016/j.envres.2018.05.019
Received 12 December 2017; Received in revised form 20 April 2018; Accepted 16 May 2018

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