Plasma Concentrations of Perfluorooctane Sulfonamide and Time-to-pregnancy Among Primiparous Women

Kristina W. Whitworth,[a,b] *Line S. Haug,*[c] *Azemira Sabaredzovic,*[c] *Merete Eggesbo,*[c] *and Matthew P. Longnecker*[d]

Background: A previous study reported a negative association between perfluorooctane sulfonamide (PFOSA) concentrations and fecundability.

Methods: We examined this association among women enrolled in the Norwegian Mother and Child Cohort Study (MoBa), in 2003–2004. This analysis was restricted to 451 primiparous women to avoid bias due to previous pregnancy. Self-reported time-to-pregnancy (TTP) and plasma were obtained around 18 weeks of gestation. Approximately half of the women had measurable PFOSA levels; missing values were multiply imputed. We used the logistic analogue of discrete-time survival analysis to examine the adjusted association between PFOSA, other perfluoroalkyl substances, and TTP.

Results: The median-measured PFOSA concentration was 0.03 ng/ml (interquartile range = 0.02, 0.07). The age and body mass index-adjusted association between an interquartile distance increase in PFOSA and TTP was 0.91 (95% confidence interval = 0.71, 1.17). Imputation of missing PFOSA resulted in similar estimates. No association was observed with other perfluoroalkyl substances.

Conclusion: Based on a weakly decreased fecundability odds ratio, we found only limited support for an association between plasma PFOSA concentrations and TTP among primiparous women. See Video Abstract at http://links.lww.com/EDE/B79.

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Perfluoroalkyl substances (PFAS) are persistent synthetic compounds used in industry and consumer products.[1] Perfluorooctane sulfonamide (PFOSA) is a breakdown product of higher molecular weight PFAS that are manufactured; PFOSA can also be synthesized directly and has been used in various products.[2] A previous investigation of time trends of PFAS in Norway found the highest concentrations of PFOSA in the 1980s and 1990s and reported no correlation between serum concentrations of PFOSA with the more commonly studied PFAS: perfluorooctanoic acid and perfluoroctane sulfonic acid.[3] Although the use of some PFAS has been phased out in many countries, exposure is ongoing and potential risks, including decreased fecundability, continue to be assessed. In a recent prospective study (n = 501), serum concentration of PFOSA, but not other PFAS, was associated with decreased fecundability.[4] In that study,[4] the authors employed an exposome approach to examine 63 maternal chemical exposures in relation to time-to-pregnancy (TTP), and PFOSA was one of five that showed an association with TTP, suggesting that additional focus on this compound was warranted. However, in a second prospective study (n = 129), no association between PFOSA concentrations and fecundability was present.[5] Other studies of PFAS and fecundability have not evaluated PFOSA.[6–8]

We conducted a retrospective study of PFAS and fecundability with primary focus on the PFOSA–fecundability association.

METHODS

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective pregnancy cohort study conducted by the Norwegian institute of Public Health.[9,10] Participants were recruited from Norway from 1999 to 2008; 40.6% of invited women participated. MoBa was approved by the Regional Committee for Medical Research Ethics and the Norwegian

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From the [a]Department of Epidemiology, Human Genetics and Environmental Sciences, The University of Texas School of Public Health at Houston, San Antonio Regional Campus, San Antonio, TX; [b]Southwest Center for Occupational and Environmental Health, The University of Texas School of Public Health at Houston, Houston, TX; [c]Norwegian Institute of Public Health, Oslo, Norway; [d]Department of Health and Human Services, National Institute for Environmental Health Sciences, National Institutes of Health, Durham NC.

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Correspondence: Kristina Walker Whitworth, The University of Texas School of Public Health, San Antonio Regional Campus, 7411 John Smith Drive, Suite 1100, San Antonio, TX 78216. E-mail: Kristina.w.whitworth@uth.tmc.edu.

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Data Inspectorate and informed consent was obtained from each participant. The present study was based on MoBa data file v4.301.

This analysis is based on a previous case-base study of PFAS and subfecundity among MoBa women with a live birth, enrolled in 2003–2004 (refer to eTable 1; http://links.lww.com/EDE/B69).[11] The base group of the previous study consisted of a random sample of women, regardless of TTP, and the case group was a random sample of subfecund (TTP > 12 months) women. Following the drop in women's PFAS concentrations during pregnancy and lactation, levels begin to return to baseline; thus, the time it takes for women's next pregnancy to occur is positively related to PFAS in the absence of a causal relation.[11–16] Because including parous women may result in biased estimates (refer to the directed acyclic graph in eFigure 1; http://links.lww.com/EDE/B69), the present analyses are restricted to primiparous women. Because some investigators support including parous women in the analysis, we have provided the results for all women in the supplementary material (eTable 2; http://links.lww.com/EDE/B69). Four women missing prepregnancy body mass index (BMI) were excluded, leaving 451 women, of which 204 (45.2%) were originally in the base sample and 247 (54.8%) were originally in the case sample. All women in the analysis had planned pregnancies.

Women completed a questionnaire at enrollment, providing demographic information and reproductive history, including number of months of regular intercourse without contraception before becoming pregnant, from which TTP was derived. Women additionally provided plasma samples at enrollment.[17] Among the women included in the present analysis, the median gestational age at the time of the blood draw was 18 weeks (interquartile range [IQR] = 17, 20). As described elsewhere, 13 PFAS compounds were measured in plasma using high-performance liquid chromatography/tandem mass spectrometry.[18] As previously mentioned, the focus of the present analysis is on PFOSA. Although 66 women (15%) had PFOSA concentrations above the limit of quantitation (LOQ; 0.05 ng/ml), an additional 160 (36%) had measured PFOSA concentrations <LOQ, resulting in 226 (50%) women with a nonmissing PFOSA value (Table). (In the previous report by Buck Louis et al.,[4] 10% of the sample had nonmissing PFOSA

TABLE. Crude and Adjusted Fecundability OR[a] for the Association Between Perfluoroalkyl Substances (ng/ml) and Time-to-pregnancy Among 451 Primiparous Women from a Case-base Study Among the MoBa Study, 2003–2004

					Crude	Adjusted[f]
	n (%) >LOQ[b]	n[c]	Median A (IQR)[d]	Median B (IQR)[e]	Fecundability OR (95% Confidence Interval)	Fecundability OR (95% Confidence Interval)
Perfluorinated sulfonamide						
PFOSA	66 (15)	226	0.04 (0.03, 0.04)	0.03 (0.02, 0.07)	0.95 (0.75, 1.2)	0.91 (0.71, 1.2)
Perfluorinated carboxylates						
PFBA	0 (0)	-	-	-	-	-
PFHpA	63 (14)	-	-	-	-	-
PFOA	451 (100)	451	2.8 (2.2, 3.5)	2.8 (2.2, 3.5)	1.1 (0.92, 1.2)	1.0 (0.90, 1.2)
PFNA	451 (100)	451	0.43 (0.32, 0.57)	0.43 (0.32, 0.57)	1.1 (0.96, 1.3)	1.1 (0.92, 1.3)
PFDA	336 (75)	429	0.11 (0.05, 0.16)	0.11 (0.06, 0.17)	1.0 (0.89, 1.2)	1.00 (0.85, 1.2)
PFUnDA	421 (93)	447	0.23 (0.14, 0.34)	0.23 (0.14, 0.34)	1.0 (0.85, 1.2)	0.93 (0.78, 1.1)
PFDoDA	114 (25)	410	0.04 (0.03, 0.05)	0.04 (0.02, 0.06)	0.96 (0.84, 1.1)	0.91 (0.77, 1.1)
PFTrDA	122 (27)	353	0.04 (0.03, 0.06)	0.04 (0.02, 0.07)	1.1 (0.89, 1.2)	1.00 (0.85, 1.2)
PFTeDA	4 (0.01)	-	-	-	-	-
Perfluorinated sulfonates						
PFHxS	450 (100)	451	0.70 (0.53, 1.1)	0.70 (0.53, 1.1)	0.98 (0.91, 1.1)	0.97 (0.90, 1.1)
PFHpS	412 (91)	446	0.15 (0.10, 0.22)	0.16 (0.10, 0.22)	1.0 (0.88, 1.2)	1.0 (0.87, 1.2)
PFOS	451 (100)	451	14.6 (11.7, 18.5)	14.6 (11.7, 18.5)	1.0 (0.89, 1.1)	1.00 (0.88, 1.1)

[a]Fecundability ORs represent the odds of conception in a given month per interquartile increase in perfluoroalkyl substance (ng/ml) concentration, based on the interquartile distance corresponding to median B.

[b]The LOQ for PFBA was 0.1 ng/ml; the LOQ for all other compounds was 0.05 ng/ml.

[c]The number of observations included in the analysis (i.e., this is the number of women with perfluoroalkyl substance concentration >LOQ plus women with measured perfluoroalkyl substance concentration <LOQ). We did not analyze PFBA, PFHpA, or PFTeDA for lack of observations.

[d]Medians were calculated among all 451 women, assigning a value equal to the LOQ/sqrt(2) for nonmeasured perfluoroalkyl substance concentrations.

[e]Medians were calculated among women included in the analysis (i.e., women with perfluoroalkyl substance concentration >LOQ plus women with measured perfluoroalkyl substance concentration <LOQ).

[f]Adjusted for maternal age at conception and prepregnancy BMI.

PFBA, perfluorobutanoic acid; PFDA, perfluorodecanoic acid; PFDoDA, perfluordodecanoic acid; PFHpA, perfluoroheptanoic acid; PFHpS, perfluoroheptane sulfonate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA, perlurooctanoic acid; PFOS, perfluorooctane sulfonate; PFTeDA, perfluorotridecanoic acid; PFTrDA, perfluorotridecanoic acid; PFUNDA, perfluoroundecanoic acid.

values.) To calculate the median PFAS concentrations among all women, we assigned missing PFAS concentrations a value equal to the LOQ divided by the square root of two.

We used the logistic analogue of discrete-time survival analysis in SAS v9.4 (Cary, NC) to estimate fecundability odds ratios (fecundability ORs) and 95% confidence intervals (CIs) for the associations between plasma PFAS concentrations and TTP. PFAS concentrations were divided by the interquartile distance of the distribution of values among women with a nonmissing value. Therefore, the fecundability ORs represent the odds of conception in a given month per interquartile increase in PFAS concentration. To avoid medical intervention bias, TTP was censored at 13 months. Three women reported receiving infertility treatment for the index pregnancy at or before 12 months and were censored at TTP-1 month, such that they only contributed unsuccessful pregnancy attempts to analyses.

Maternal age at the pregnancy attempt (years) and prepregnancy BMI (kg/m^2) were included in the model a priori. A directed acyclic graph-informed approach was used to identify additional covariates (eFigure 1; http://links.lww.com/EDE/B69). We chose the following potential confounders based on previous knowledge of their association with plasma PFAS concentration and potential to influence fecundity: maternal education, maternal annual income, maternal prepregnancy smoking, maternal shellfish, lean fish, and oily fish consumption (g/day), menstrual cycle length, and frequency of intercourse during the month before pregnancy. The inclusion of any of these variables to age and BMI-adjusted models did not alter the effect estimates; the final models included only maternal age and BMI.

We implemented three multiple imputation models, assuming a missing-at-random pattern and using Markov Chain Monte Carlo methods to impute PFOSA values for 225 (50%) women missing this information. The three models differed according to predictors included in the model (eMaterial; http://links.lww.com/EDE/B69).

RESULTS

Women in this study were relatively young (76% < 30 years old), of normal weight (61% had BMI of 18.50–24.99), and well educated (64% had at least some college; eTable 3; http://links.lww.com/EDE/B69). The median PFOSA concentration among all 451 women was 0.04 (IQR = 0.03, 0.04) and median concentration among the 226 women for which we had a measured value was 0.03 ng/ml (IQR = 0.02, 0.07; Table).

Among the 226 primiparous women with measured plasma PFOSA concentrations, the adjusted association between PFOSA and TTP was 0.91 (95% CI = 0.71, 1.2; Table). Using imputed values of PFOSA concentrations resulted in similar estimates (Figure). We did not observe an association between any other PFAS and TTP among primiparous women (Table). The adjusted fecundability OR for the association between PFOSA and TTP among all women was 0.85 (95% CI = 0.83, 1.1, eTable 2; http://links.lww.com/EDE/B69).

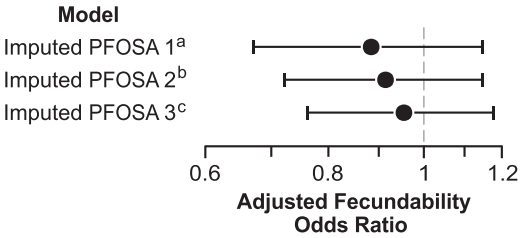

FIGURE. Maternal age and prepregnancy BMI-adjusted fecundability OR for the association between PFOSA (ng/ml) and time-to-pregnancy among primiparous women from the Norwegian Mother and Child Cohort Study, 2003–2004. Fecundability ORs represent the odds of conception in a given month per interquartile increase in PFOSA concentration. [a]Imputation model 1 included the following covariates as predictors of PFOSA concentrations: maternal age at conception, maternal prepregnancy BMI, maternal education, maternal annual income, maternal prepregnancy smoking, maternal consumption of shellfish, lean fish, and oily fish during pregnancy, menstrual cycle regularity, oral contraceptive use in the previous 12 months, and serum albumin concentration (g/dl). [b]Imputation model 2 included all of the model 1 covariates as well as concentrations of PFDA, PFDoDA, PFHpS, PFHxS, PFNA, PFOA, PFOS, PFTrDA, and PFUnDA. [c]Imputation model 3 included the model 1 variables plus PFNA concentrations, which had the strongest correlation with PFOSA concentrations (r = 0.27). PFDA indicates perfluorodecanoic acid; PFDoDA, perfluordodecanoic acid; PFHpS, perfluoroheptane sulfonate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA, perlurooctanoic acid; PFOS, perfluorooctane sulfonate; PFTrDA, perfluorotridecanoic acid; PFUnDA, perfluoroundecanoic acid.

DISCUSSION

Based on a weakly decreased fecundability OR, we found only limited support for an association between plasma PFOSA concentrations and TTP among primiparous women in MoBa. Although nearly half of the women had missing PFOSA measurements, we employed multiple imputation techniques to overcome this limitation. Few previous studies have examined the association between PFOSA and fecundity. In a recent report from a prospective cohort which recruited couples during 2005–2007, reduced fecundity was associated with a SD increase in the log-transformed serum concentration of PFOSA (fecundability OR = 0.8, 95% CI = 0.7, 0.9).[4] In that study, multiple imputation techniques were employed to impute missing values for 90% of women with missing PFOSA levels.[4] Results from a second prospective study[5] indicated no association between PFOSA (as a log-transformed and continuous variable) and TTP (fecundability OR = 1.0; 95% CI = 0.9, 1.2) and are consistent with the results from the present analysis. In both studies, the geometric mean or median PFOSA concentration was roughly 0.11 ng/ml.[4,5]

In the present study, women were recruited in 2003–2004; 15% of women had PFOSA levels >0.05 ng/ml. However, 36% of the women with values <LOQ had measured values which we utilized, imputing values for the remaining 50% of subjects. We explored three sets of variables to assess the robustness of the imputation model. PFAS concentrations measured in MoBa were lower than reported in either Vestergaard et al.[5] or Buck Louis et al.,[4] where collection of biologic specimens occurred in the first trimester. In the present study, blood draws occurred around week 18 when plasma volume expansion may have resulted in lower measured levels of PFAS.[19] The correlation among PFAS concentration across different points in pregnancy, however, has been shown to be relatively high, e.g., 0.87 for perfluoroctane sulfonic acid and 0.88 for perfluorooctanoic acid between measures in the first and second trimester, respectively.[20] The present analysis employed a retrospective assessment of TTP. Previous studies of the validity of retrospectively assessed TTP revealed individual inaccuracies in self-reported TTP, with less accurate recall for longer TTP,[21,22] although it has been noted that the overall distribution of retrospectively assessed TTP is valid.[23] Although women were unaware of their exposure, PFAS could vary according to factors related to better TTP recall, such as education. Adjustment for education did not affect the results and we believe that differential misclassification of TTP by exposure was unlikely. The exclusion of women who are sterile or who have pregnancy losses from the present analysis may have limited the generalizability of our results or resulted in bias. Due to the influence of parity, we restricted our analysis to primiparous women to avoid the potential for reverse causality between PFAS concentrations and TTP among parous women.[11–16] Due to the original selection of women for a case-base study of subfecundity, a large proportion (55%) of women in this analysis are subfecund. When analyses were restricted to women selected from the base sample, results were not meaningfully changed. Overall, our results do not support an association between plasma PFAS concentrations and decreased fecundity.

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