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Reliability of perfluoroalkyl substances in plasma of 100 women in two consecutive pregnancies

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ABSTRACT

The potential toxicity of background exposure to perfluoroalkyl substances (PFASs) is currently under active investigation. Such investigations typically rely on a single measure of PFAS concentration, yet the longer-term reliability of a single measure has not been well characterized, especially among reproductive-aged women. Our aim was to investigate the association between PFAS plasma concentrations of 100 women in two consecutive pregnancies and explore changes in plasma concentration related to reproductive factors. The women in our study were enrolled in the Norwegian Mother and Child Cohort Study (MoBa) from 2003 to 2009. About half of them breastfed exclusively for 6 months and the rest of the participants did not breastfeed between the two consecutive pregnancies (median time between pregnancies: 18 months). Maternal blood was collected at mid-pregnancy and plasma was analyzed for 10 PFASs. Statistical analyses were restricted to 6 PFASs that were quantifiable in more than 80% of the samples. We estimated the correlation between repeated PFAS measurements, the percentage change between pregnancies and the effect of several reproductive factors in multivariate linear regression models of PFAS concentrations in the second pregnancy. The Pearson correlation coefficient between repeated PFAS measurements was, for perfluorooctane sulfonate (PFOS), 0.80; perfluorooctanoate (PFOA), 0.50; perfluorohexane sulfonate (PFHxS), 0.74; perfluorononanoate (PFNA), 0.39; perfluoroundecanoate (PFUnDA), 0.71; and perfluorodecanoate (PFDA), 0.60. Adjustment for maternal age, delivery year, and time and breastfeeding between pregnancies did not substantially affect the observed correlations. We found 44–47% median reductions in the concentrations of PFOS, PFOA and PFHxS between pregnancies, while the change in concentrations between pregnancies was smaller and more variable for PFNA, PFUnDA and PFDA. The variation in plasma concentrations in the second pregnancy was mainly accounted for by the concentration in the first pregnancy; for PFOS, PFOA, and PFNA, breastfeeding also accounted for a substantial proportion. In conclusion, we found the reliability of PFAS measurements in maternal plasma to be moderate to high, and in these data, several factors, especially breastfeeding, were related to plasma concentrations.

1. Introduction

Perfluoroalkyl substances (PFASs) are synthetic fluorinated organic compounds used in industrial and consumer products over the last 50 years due to their chemical and thermal stability and water and oil repellency (Buck et al., 2011). Human exposure can occur via ambient indoor air, house dust and drinking water, though the main route is through food (Fromme et al., 2009; Haug et al., 2011; Vestergren and Cousins, 2009). Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are usually the most prevalent PFASs in human blood in background-exposed populations, are highly persistent, and have half-lives (geometric means) estimated to be from 3.5 (PFOA) to 4.8 (PFOS) years (Olsen et al., 2007). For PFOS and PFOA, after the 2000s, human exposure declined, as a result of national and international regulations and voluntary actions to phase-out or reduce production of these compounds. Meanwhile, increasing trends have been observed for some other PFASs (Glynn et al., 2012; Haug et al., 2009b; Kato et al., 2011).

In addition to exposure, elimination from the human body is another important determinant of PFAS concentration in plasma or

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serum. Women have lower plasma levels of PFOS and PFOA than men and shorter elimination half-lives due to loss through menstruation (Calafat et al., 2007; Wong et al., 2014). By comparing maternal blood, cord blood, and breast milk samples studies have shown that PFASs can cross the placenta and partition into milk; hence pregnancy and breastfeeding are additional elimination pathways for women (Fromme et al., 2010; Glynn et al., 2012; Gutzkow et al., 2012). PFOS and PFOA levels are lower in pregnant women than non-pregnant women and the levels decrease across trimesters, suggesting that trans-placental transfer starts from early gestation; other physiological changes during pregnancy also contribute to this trend (Jain, 2013; Javins et al., 2013; Morken et al., 2014).

In addition to the temporal trends in exposure to PFASs, parity and breastfeeding, other maternal characteristics have been found to be related to maternal PFAS levels, such as income, education, residence, ethnicity, body mass index, smoking status and diet (Brantsaeter et al., 2013; Halldorsson et al., 2008). A better understanding of how various factors, especially reproductive events, affect plasma concentration of PFAS may help improve epidemiologic study design and interpretation (Whitworth et al., 2012).

The potential for health effects from exposure to PFAS is under active investigation in various settings including occupational exposure, communities with above-average exposure, and background-exposed populations (Barry et al., 2013; Geiger et al., 2014; Raleigh et al.,2014; Steenland et al., 2013; Uhl et al., 2013; Winquist and Steenland, 2014). Many of the epidemiological findings on PFAS exposure and disease are affected by the long-term reliability of a single measurement of plasma or serum PFASs concentration. The reliability of a single measure of PFASs and the factors affecting it can be important for planning studies and interpretation. The correlations between repeated measurements of PFASs at different times in pregnancy have been reported (Fei et al., 2007; Glynn et al., 2012), but the correlations between repeated measurements of PFASs over a longer period have been examined in only one study, and all the subjects were male (Nost et al., 2014).

The aim of our study was to investigate the reliability of PFAS concentrations across pregnancies and determinants of change in PFAS concentrations between pregnancies.

2. Material and methods

2.1. Study population

Our study population included 100 women from the Norwegian Mother Child cohort study (MoBa) who were enrolled during two consecutive pregnancies. In brief, the MoBa study is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (Magnus et al., 2006; Ronningen et al., 2006). Pregnant women from all over Norway were recruited from 1999 to 2008 at 17–18 weeks of pregnancy. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. Data used in this study are based on version 4.301 of the quality-ensured data files, released for research in June 2010. The study was approved by The Regional Committee for Medical Research Ethics in South-Eastern Norway; 40.6% of invited women consented to participate.

Approximately 15,000 women were enrolled in MoBa for more than one pregnancy. From these, we selected women who had a mid-pregnancy plasma (weeks 17–18) specimen available for two consecutive pregnancies, whose first MoBa pregnancy was in 2003 or later, when blood was drawn into EDTA tubes, yielding plasma that was preferred for the laboratory assay (heparin was used before 2003). We further restricted the eligible women to those who had not moved in the past three years before the second pregnancy, so as to focus on those for whom exposure would have been more constant over time. This left 97 women who did not breastfeed between the two pregnancies and 4770 who breastfed exclusively for at least 6 months between the two pregnancies. In order to assure that the effect of breastfeeding would be well characterized, our study population was chosen so that about 50 women were selected at random from the 97 who did not breastfed, and about 50 were selected at random from the 4770 who breastfed exclusively for at least 6 months between the two pregnancies.

2.2. PFAS measurements in maternal Blood

Maternal non-fasting blood samples were collected in EDTA tubes at hospitals and maternity clinics at the time of study enrollment and shipped at ambient temperature to the MoBa biorepository in Oslo. Most samples were received and processed the day after collection (Ronningen et al., 2006). At the biorepository, plasma was separated, aliquoted, and stored at −80 °C. Changes in PFAS concentrations in transit are believed to be negligible, as PFASs are chemically stable (Fromel and Knepper, 2010), and a recent study showed no evidence of change over time in concentrations of four PFASs in serum maintained at room temperature for 10 days (Kato et al., 2013). Additionally, the ratio of PFAS concentrations in plasma to whole blood is consistently just above 2 (Ehresman et al., 2007; Hanssen et al., 2013), indicating that PFASs do not partition into blood cells or associate with their membranes. Thus, in non-hemolyzed specimens we have no reason to be concerned about shipping effects. The differences in PFASs concentrations between non-hemolyzed and hemolyzed samples ($n=22$), however, were further examined. Concentrations (in ng/mL) of ten PFASs were measured in maternal plasma by high-performance liquid chromatography/tandem mass spectrometry at the Norwegian Institute of Public Health. Details of the analytic process have been published previously (Haug et al., 2009a). The measured PFASs were perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS), perfluorooctane sulfonate (PFOS), perfluoroheptanoate (PFHpA), perfluorooctanoate (PFOA), perfluorononanoate (PFNA), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnDA), perfluorododecanoate (PFDoDA) and perfluorotridecanoate (PFTrDA). For quantification of PFOS, the total area of linear and branched isomers was integrated. Statistical analyses were limited to six PFASs (PFOS, PFOA, PFHxS, PFNA, PFUnDA, and PFDA) that were quantifiable in more than 80% of the samples. The limit of quantification (LOQ) was 0.05 ng/mL for all estimated PFASs. For values below the LOQ we used the measured concentrations when a signal was observed in the instrument during the analysis (Analytical Methods, 2001). Missing values were cases where no signal was observed and these values were replaced with LOQ/$\sqrt{2}$ (5 values for PFHxS, 8 for PFUnDA, and 25 for PFDA). A total of 25 quality assurance/quality control (QA/QC) plasma samples from a single pool were analyzed in batches alongside the specimens of our study participants. The laboratory technicians were blinded to their identity, and the QA/QC samples were indistinguishable from the plasma samples of the study participants. The inter-assay coefficient of variation was 11.4 for PFOS, 8.6 for PFOA, 14.6 for PFHxS, 13.3 for PFNA, 22.2 for PFUnDA, and 27.0 for PFDA (Starling et al., 2014a).

2.3. Maternal characteristics

Information on maternal and pregnancy related characteristics that have been identified as important determinants of PFAS concentrations in maternal plasma were collected (Brantsaeter