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Determinants of Maternal and Fetal Exposure and Temporal Trends of Perfluorinated Compounds

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Abstract

In recent years, some perfluorinated compounds (PFCs) have been identified as potentially hazardous substances which are harmful to the environment and human health. According to limited data, PFC levels in humans could be influenced by several determinants. However, the findings are inconsistent.

In the present study, perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), and perfluorononanoic acid (PFNA) were measured in paired maternal and cord serum samples (N=237) collected between 1978 and 2001 in Southern Sweden to study the relationship between these and to investigate several potential determinants of maternal and fetal exposure to PFCs. Time trends of PFCs in Swedish women were also evaluated. The study is a part of the Fetal Environment and Neurodevelopment Disorders in Epidemiological Research project.

PFOS, PFOA, and PFNA levels (median) were higher in maternal serum (15, 2.1, and 0.24 ng/ml, respectively) than in cord serum (6.5, 1.7, and 0.20 ng/ml, respectively). PFC levels were among the highest in women originating from the Nordic countries and the lowest in women from the Middle East, North Africa, and sub-Saharan Africa. Multiparous women had lower serum PFOA levels (1.7ng/ml) than primiparous women (2.4ng/ml). Maternal age, body mass index, cotinine levels, gestational duration, and whether women carried male or female fetuses did not affect serum PFC concentrations. Umbilical cord serum PFC concentrations showed roughly similar patterns as the maternal except for the gestational age where PFC levels increased with advancing gestational age. PFOS levels increased during the study period in native Swedish women.

In summary, PFOS levels tend to increase while PFOA and PFNA levels were unchanged between 1978 and 2001 in our study population. Our results demonstrate that maternal country of origin, parity, and gestational duration might be associated with PFC exposure.

Keywords:

Perfluorinated compounds, Fetal exposure, Determinants, Country of origin, Parity, Gestational age, Time trends

Introduction

In recent years, some perfluorinated compounds (PFCs), mainly perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), have been identified as global pollutants with a wide dissemination in the environment, wildlife, and in humans throughout the world. The unique physical and chemical properties of PFCs make them widely used in industrial and consumer applications including polytetrafluoroethylene (e.g. Teflon) cookware, water and oil repellent surface coatings for textiles, carpets, paper, packaging, flooring, leather, and in firefighting foams (Kissa 2001; Schultz et al. 2003). PFCs have an exceptional stability which makes them persistent and resistant to degradation by strong acids and alkalis, oxidation and reduction, photolysis, and microbes (Kissa 2001; Schultz et al. 2003). Thus, PFCs have a potential to bioaccumulate and biomagnify in the environment (Giesy and Kannan 2001; Butt et al. 2010).

The human exposure routes to PFCs have been considered to be through consumption of contaminated water or food and through inhalation of contaminated air (Fromme et al. 2009). PFCs are distributed mainly to the liver and blood where they bind to serum proteins, mainly albumin (Han et al. 2003; Jones et al. 2003), and they are poorly eliminated in humans and have serum half-lives between 2 and 9 years (Lau et al. 2007; Olsen et al. 2007; Bartell et al. 2010; Brede et al. 2010; Seals et al. 2011).

PFCs have been shown to cross the placenta (Inoue et al. 2004; Liu et al. 2011; Gützkow et al. 2012) and thus have a potential to exert a direct influence on the developing fetus (Apelberg et al. 2007a; Fei et al. 2007). According to previous studies, the median PFC concentrations in cord blood ranged from 30 to 130% of the maternal concentrations (Liu et al., 2011, Kim et al. 2011a, Gützkow et al. 2012). PFCs have also been shown to be transmitted to the neonate through breast milk (Kärman et al. 2007; Sundström et al. 2011).

PFC levels in humans are affected by several determinants, including age, BMI, smoking, sex, race, and ethnicity. The potential determinants of maternal and fetal exposure to PFCs are poorly investigated and their potential to affect the concentrations of PFCs in pregnant women and fetuses is still unclear. Some studies have shown that PFOS levels are higher in black women than in white and Asian women (Apelberg et al. 2007b) and are also higher in nonsmokers than smokers (Fei et al. 2007; Washino et al. 2009). The PFOA levels decrease with increasing maternal age (Washino et al. 2009), BMI (Fei et al. 2007), and parity (Fei et

al. 2007; Apelberg et al. 2007b; Washino et al. 2009). The findings on the effect of infant sex (Inoue et al. 2004; Apelberg et al. 2007b) and gestational age (Apelberg et al. 2007a, b; Nolan et al. 2009) on the levels of PFCs are limited. Many of those studies on the determinants have contradicting results. Thus, more research on possible determinants is needed.

The manufacturing of PFCs began in the late 1940s (Schultz et al. 2003) and was mainly located to USA, Japan, and Europe (Kärman et al. 2006). The 3M Company was the major manufacturer of PFCs with the highest production between 1970 and 2002. When the 3M Company phased out its production of some of the PFCs in 2002, other companies start manufacturing these compounds to meet the market demand for them (Lindstrom et al. 2011). Several studies have assessed time trends of human serum PFC levels and found increasing levels of PFOS and PFOA from the early 1970s through the late 1990s, followed by leveling out and a decreasing trend right after the phaseout of the production (Olsen et al. 2005, 2011; Harada et al. 2007; Calafat et al. 2007; Haug et al. 2009). The same trends have been observed in the human breast milk (Kärman et al. 2007; Sundström et al. 2011). On the other hand, PFOA and PFOS have been substituted by other PFCs which have increased in humans during the last decade (Calafat et al. 2007; Haug et al. 2009; Glynn et al 2012, Olsen 2011).

In the present study, serum concentrations for several PFCs were analyzed in paired maternal and umbilical cord samples. The aim of the study was to investigate the correlation between PFCs in maternal and umbilical cord serum samples and to evaluate maternal age, parity, BMI, smoking, and maternal country of origin as potential determinants of maternal exposure and gestational age and sex of newborns as potential determinants of fetal exposure to PFCs. Another aim was to investigate temporal trends of PFC body burdens in Swedish women.

Materials and methods

Study population

Nearly all deliveries in Malmö, a city with around 300,000 inhabitants situated in Southern Sweden, take place at the Malmö University Hospital maternity unit. Since 1969, venous blood samples from mothers and umbilical cord blood samples from the newborns have routinely been collected at delivery and stored in the Malmö Maternity Unit Serum Biobank (MMUSB). There are samples from approximately 70,000 deliveries stored in the MMUSB.

Maternal blood has been collected during early labor by venous puncture in vacutainer tubes, and the cord blood has been decanted into sterile sample tubes immediately after birth. The sample tubes were stored overnight in a refrigerator at +8 °C for sedimentation. The next morning, the sera were collected and frozen in polypropylene plastic test tubes at -20 °C until analysis.

In the present study, maternal and corresponding cord serum samples (N=263) from year 1978 to 2001 were collected from the MMUSB. These samples represent controls for an upcoming case-control study on the possible association between PFCs and neurodevelopment disorders. Since it is more common for males to have a diagnosis as compared to females, the material has a skewed distribution with 75% male and 25% female fetuses.

From the Swedish Medical Birth Register, which contains medical information on nearly all (98–99%) deliveries in Sweden, we obtained data on the newborns' characteristics such as birth weight, gestational age, and the sex of the child, as well as maternal characteristics like mothers' age, parity, BMI, smoking habits during pregnancy, and country of origin.

At the booking visit in the Maternal Health Care System, the women were informed that the samples collected could be used for research purposes in the future and those who accepted gave their verbal informed consent. . The study protocol followed the requirements of the Declaration of Helsinki and was approved by the Research Ethics Committee at Lund University, Sweden.

Analysis of PFCs and cotinine

The analyses of perfluorohexane sulfonate (PFHxS), PFOS, PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), and cotinine were performed by a hybrid triple quadrupole linear ion-trap mass spectrometer (LC/MS/MS; UFLC^{XR}, Shimadzu Corporation, Kyoto, Japan; QTRAP 5500; Sciex, Framingham, MA, USA). The samples were analyzed according to the method of Lindh et al. (2012). Aliquots of 60 µl serum were added with internal standards for all evaluated compounds, and proteins were precipitated with 120 µl acetonitrile. An aliquot of 150 µl of sample was transferred to 96-well plates and further

diluted with 150 µl water. The PFCs were analyzed using two C₁₈ columns (4 µm, 2.1 mm i.d. × 20 mm; Genesis; Grace Vydac, Hesperia, CA, USA) connected in a 2D system. The mobile phase was 0.08% ammonia (NH₃) in water (A) and 0.08% NH₃ in acetonitrile (B). The results reported is the average of two measurements from the same sample worked up and analyzed on different days. In all sample batches, the quality of the measurements was controlled by analyzing chemical blanks and in-house quality control (QC) samples. The reproducibility, determined as the relative standard deviation, between measured duplicate samples was 11% for PFOS, 12% for PFOA, and 12% for PFNA. The reproducibility in QC samples was 8% for PFOS, 11% for PFOA, and 8% for PFNA. PFHxS, PFDA, PFUnDA, and PFDoDA could not be detected in the samples due to matrix effects. The analyses of PFOS and PFOA are part of the round robin intercomparison program (Professor Dr. med. Hans Drexler, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University of Erlangen-Nuremberg, Germany) with results within the tolerance limits. Among the 263 paired maternal and cord serum samples, PFCs could only be assessed in 237 pairs. The reason for this was that there was not enough amount of serum to perform the analyses.

Statistical analyses

Spearman's rank correlation coefficient with $p < 0.05$ defined as statistically significant was used to explore the correlations between the different PFCs in maternal samples, and for each PFC between maternal and cord serum samples. The transfer efficiencies of PFCs through placenta were calculated as well. The Wilcoxon signed-rank test was used to compare the levels between maternal and cord serum samples.

Spearman's rank correlation was used to test the correlation between the different PFCs and the investigated determinants. The Mann-Whitney *U* test and Kruskal–Wallis test were performed to determine if significant differences in the PFC levels exist between groups (e.g., maternal age, parity, BMI, smoking habits based on measured cotinine levels, country of origin, gestational duration, and newborns' sex). Maternal age was divided into three groups: <25, 25–35, and >35 years. BMI was classified according to the following standard values of the World Health Organization: underweight <18.5 kg/m², normal weight 18.5–24.9 kg/m², overweight 25–29.9 kg/m², and obese ≥30 kg/m². Underweight (N=3) and normal weight women (N=53) were merged together in one group due to the small number of samples for the

underweight women. For the same reason, obese ($N=6$) and overweight women ($N=24$) were merged together in one group. Women whose cotinine levels were below the limit of detection (0.2ng/ml) were defined as nonsmokers and those having a level higher than 15ng/ml were defined as active smokers (George et al. 2006). Women with cotinine levels between 0.2 and 15ng/ml were considered to be second-hand smokers. Infants born before 37 weeks of gestation were defined as preterm and those born at or after that week were considered term births. Countries of origin were merged together into the following groups based on shared geographical regions or cultural similarities: Sweden ($N = 164$), Finland ($N = 2$), Denmark ($N = 5$), Norway ($N = 1$), Western Europe and United States ($N = 2$), previous Eastern Europe ($N = 21$), sub-Saharan Africa ($N = 6$), Middle East and North Africa ($N = 22$), East Asia ($N = 5$), South America ($N = 5$), and unknown ($N = 4$). Country groups with less than five women were excluded from the analyses regarding the differences in PFC concentrations between different countries. PFC concentrations below the limit of detection (0.20ng/ml) in individual samples were replaced with the value 0.20ng/ml .

The association between the year of sampling and the measured PFC levels was tested for significance using linear regression. Data analyses were carried out in IBM SPSS Statistics version 20 (IBM Corporation 1989, 2011).

Results

PFOS, PFOA, and PFNA were the only detectable PFCs in the samples. PFOS concentrations were above the limit of detection (LOD) in 100% of maternal serum samples and in 99.6% of cord serum samples. Maternal PFOA serum concentrations were all above the LOD, but in cord serum, PFOA was below the LOD in 1.3% of the samples. For PFNA, 38% of the maternal PFNA samples and 66% of the cord PFNA samples were under LOD. In both maternal and cord sera, PFOS was found to be the most abundant PFC (Table 1). PFC levels were higher in maternal serum than in cord serum. The strongest correlation between maternal and cord serum PFC levels was found for PFOS, followed by PFOA and PFNA. The correlations between the different PFCs in maternal serum were significant ($r = 0.72$ for PFOS and PFOA, $r = 0.35$ for PFOS and PFNA, and $r = 0.37$ for PFOA and PFNA), with p values <0.01 .

Median cord PFOS, PFOA, and PFNA serum concentrations were 43, 80, and 99%, respectively, of the maternal concentrations (Table 1).

Maternal PFC levels between 1978 and 2001 are illustrated in Fig. 1. Linear regression analyses revealed a significant increase in maternal PFOS levels during the study period ($\beta = 0.40$, $p = 0.020$). For PFOA and PFNA, no obvious time trends were observed ($\beta = 0.02$, $p = 0.40$ and $\beta = -0.003$, $p = 0.64$, respectively). Since the number of samples was the highest between 1985 and 1996, we even performed the analyses for that period. The findings were the same for PFOA and PFNA. For PFOS, the results were no longer significant ($p = 0.071$) but the slope was roughly the same ($\beta = 0.42$).

No significant associations between maternal PFC levels and maternal age, BMI, cotinine levels, or gestational duration were found (Table 2). Multiparous women had lower PFOA concentrations than primiparous women, and women carrying male fetuses had higher levels of PFOA as compared to women with female fetuses (Table 2). Maternal PFC serum concentrations were strongly associated with the country of origin. PFC levels were among the highest in women and newborns originating from the two investigated Nordic countries and the lowest in women from the Middle East, North Africa, and sub-Saharan Africa (Table 2).

Umbilical cord serum PFC concentrations showed distributions similar to the distributions in maternal serum, with one exception. Cord PFNA levels were not associated with maternal country of birth ($p = 0.59$).

Gestational age at birth was positively correlated ($p < 0.05$) with cord PFOS, PFOA, and PFNA levels ($r = 0.20$, $r = 0.17$, and $r = 0.14$, respectively). No significant difference in cord serum PFC levels between preterm and term infants was found. When the analysis was restricted to Swedish women, preterm newborns ($N = 7$) had lower cord serum PFOS levels than term newborns ($N = 157$) ($p = 0.008$).

In order to avoid confounding by parity, analysis was carried out to investigate the effect of maternal age on PFC levels among primiparous women. No significant correlation was seen between maternal age and PFC levels in primiparous women. Among the multiparous women, 25% were born outside Western Europe. An analysis was carried out to investigate the effect

of parity on PFC levels among the native Swedish women. Multiparous women still had lower PFOA concentrations than primiparous women ($p < 0.001$).

There were many PFNA samples with values below the LOD. In order to be certain that the substitution of those values with LOD did not introduce a bias, all the analyses were even performed on matched maternal and cord serum samples with values over the LOD before substitution with LOD (N=71). The results were roughly the same as for the matched 237 maternal and cord PFNA serum samples (data not shown).

Discussion

The present study is one of the largest studies that focused on the potential determinants of maternal and fetal exposure to PFCs. Our results showed that parity, maternal country of origin, and gestational duration were the potential determinants of maternal and fetal exposure to PFCs.

In the present study, we have applied a precise and accurate method that uses only 0.1 ml serum and are therefore suitable to for analyzing samples stored in serum biobanks. The coefficient of variation of duplicate samples worked up and analyzed on different samples was generally below 10% for duplicate analysis of the same sample, analyzed in different sample batches on different days. Furthermore, a high accuracy of the method, at least for PFOS and PFOA, was proven by participation in an interlaboratory control program. The use of QCs and chemical blanks prevents drift and contamination during the analysis. However, we found both linear and branched PFOS but the branched PFOS was almost exclusively found in the cord blood. We see no reason why branched PFOS should be found in the blood of the fetus and not in the mother, and thus, we think that the cord blood has been contaminated during sampling. Therefore, we report only results for linear PFOS.

PFCs cross the placenta, but umbilical cord concentrations have in most studies been lower than those observed in maternal serum or plasma (Inoue et al. 2004; Fromme et al 2010; Jensen et al. 2012; Gützkow et al. 2012). In the present study, we found higher levels of PFCs in maternal serum than in cord serum, which is consistent with previous studies (Monroy et al. 2008; Hanssen et al. 2010; Beesoon et al. 2011). Maternal and cord PFOS and PFOA concentrations were among the highest in Europe (Midasch et al. 2007; Fei et al. 2007;

Needham et al. 2011) and even among the highest in the world (Liu et al. 2011; Kim et al. 2011a, b; Beesoon et al. 2011). Maternal and cord PFNA levels were lower than those measured in other countries (Monroy et al. 2008; Needham et al. 2011; Kim et al. 2011a; Beesoon et al. 2011).

The transfer efficiency (TE) of PFCs might be influenced by plasma volume expansion in pregnancy. The elimination rate of PFCs is extremely slow, and therefore, that would probably not affect the TE. Furthermore, our calculated transfer efficiencies mirror the literature to date.

We examined the temporal trends of PFCs in native Swedish women and found that the serum PFC levels were roughly unchanged between 1978 and 2001 except for PFOS which increased with time. Our samples were collected during the steady-state high-production period of PFCs, which probably explains the unchanged time trends for PFOA and PFNA. Use of PFOS in consumer and commercial products may be increased slightly in the country during the study period which might explain the increased trend for PFOS.

Consistent with previous studies (Fei et al. 2007; Apelberg et al. 2007b; Washino et al. 2009), our data confirm that increased parity is associated with lower levels of PFOA in both mother and fetus. The body burden of PFCs in multiparous women may decrease through transmission to the fetus during pregnancy and to the newborn through breastfeeding.

There was a strong heterogeneity between different countries for the investigated PFCs. Swedish and Danish women had higher levels of PFCs as compared to women originating from other countries but living in Sweden. One reason for the discrepancy might be that the women with non-Swedish origin come from countries with different background PFC exposure and have been living in Sweden for a short time. Unfortunately, we lack data on how long they have been living in Sweden. Another explanation for the discrepancy might be differences in sources, distribution, exposure routes, diets, and lifestyles between women with Swedish and non-Swedish origin. One might speculate that there is an interaction between genetic susceptibility and exposure to PFCs for women originating from different countries.

Studies on adult men (Eriksen et al. 2011) and pregnant women (Fei et al. 2007; Washino et al. 2009) have shown that nonsmokers have higher PFOS and PFOA levels than active smokers. The present study showed no such associations.

PFOS and PFOA levels were roughly the same across the maternal age groups, which is in accordance with the previous studies by Inoue et al. (2004) and Apelberg et al. (2007a). On the other hand, Washino et al. (2009) reported decreased maternal PFOS concentrations with increasing age, whereas Zhang et al. (2011) found a positive association between cord PFOS concentrations and mother's age.

In two previous studies, no associations between maternal BMI and maternal or cord serum PFC levels were found which are consistent with our results (Inoue et al. 2004; Rylander et al. 2009). Three other studies showed inverse associations between PFOS and PFOA levels and BMI in women or men (Fei et al. 2007; Eriksen et al. 2011; Lindh et al. 2012).

Pregnant women carrying male fetuses had higher PFOA levels compared to women with female fetuses. Consequently, higher levels of PFOA were measured in cord blood from male fetuses. Previous research on sex effect on PFC exposure is contradicting and has no reasonable explanation (Inoue et al. 2004; Apelberg et al. 2007a; Zhang et al. 2011). We believe that our finding is a chance finding and could be due to multiple testing.

In our study, we found a positive correlation between cord PFCs and gestational age. As for PFOS, we also found in subgroup analyses comprising native Swedish women higher levels in term than in preterm newborns. This is not in accordance with other studies where no significant associations were found for gestational age (Apelberg et al. 2007a, b; Fei et al. 2007; Nolan et al. 2009). However, a new study by Chen et al. (2012) found an inverse association between PFOS levels and gestational age. PFC levels increase in fetuses as pregnancy progresses as a recent study by Jensen et al. (2012) showed that PFOS increased in amniotic fluid by gestational week. Advancing gestational duration might therefore result in decreased maternal body burden of PFCs.

In summary, maternal PFC concentrations were higher than umbilical cord PFC concentrations in our Swedish population who were from the southern parts of the country. PFOS levels tended to increase between 1978 and 2001, while PFOA and PFNA levels were unchanged during the same period. Women originating from Nordic countries had higher levels of PFCs than women from the rest of the world. To our best knowledge, this is the first study to report a positive association between PFCs and gestational age. Increasing cord PFCs and decreasing maternal PFOA concentrations with advancing gestational age and increased parity, respectively, suggest that pregnancy might serve as a body purifier for PFCs. Our

findings are of special interest when studying the impact of perinatal PFC exposure on postnatal health outcomes.

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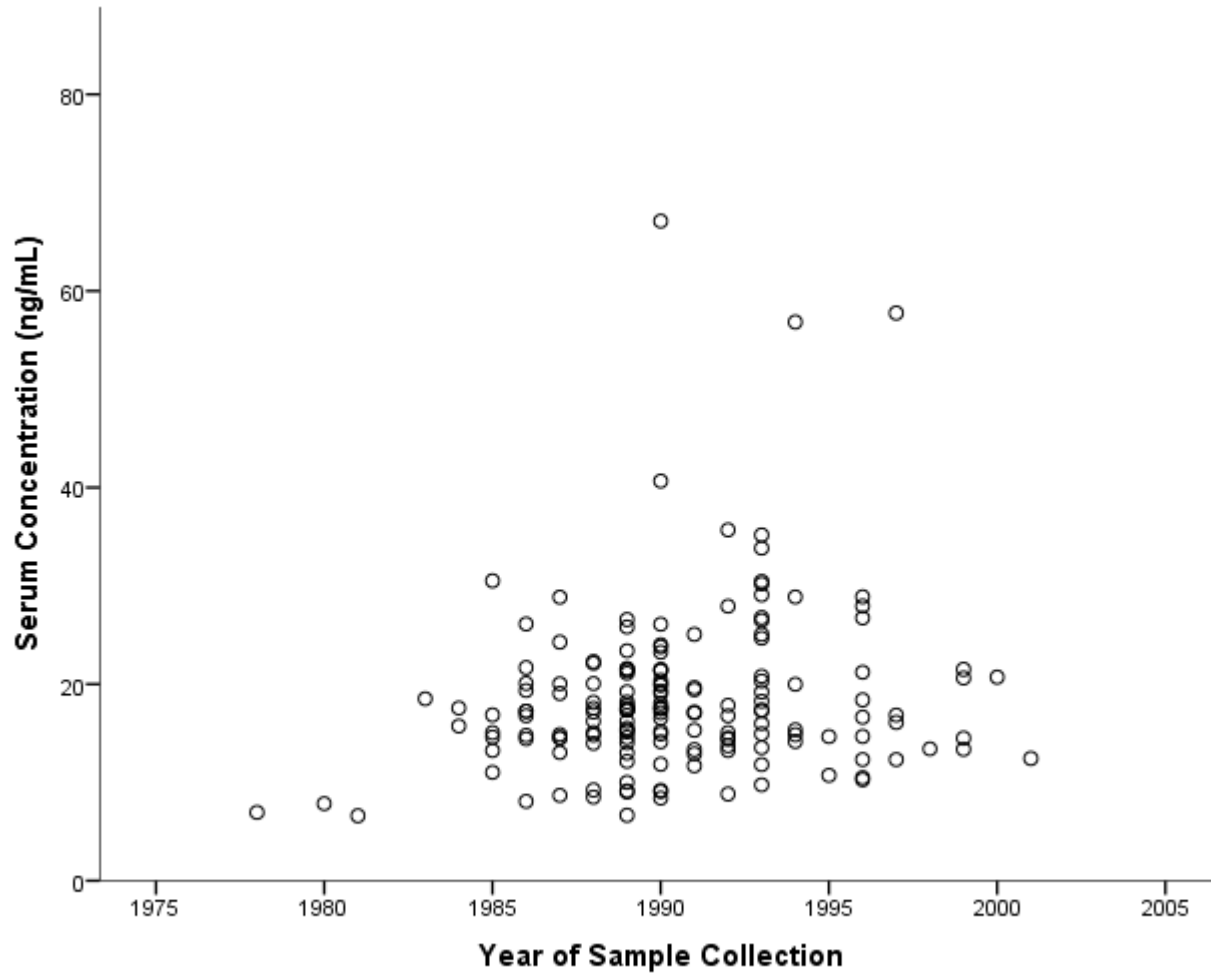
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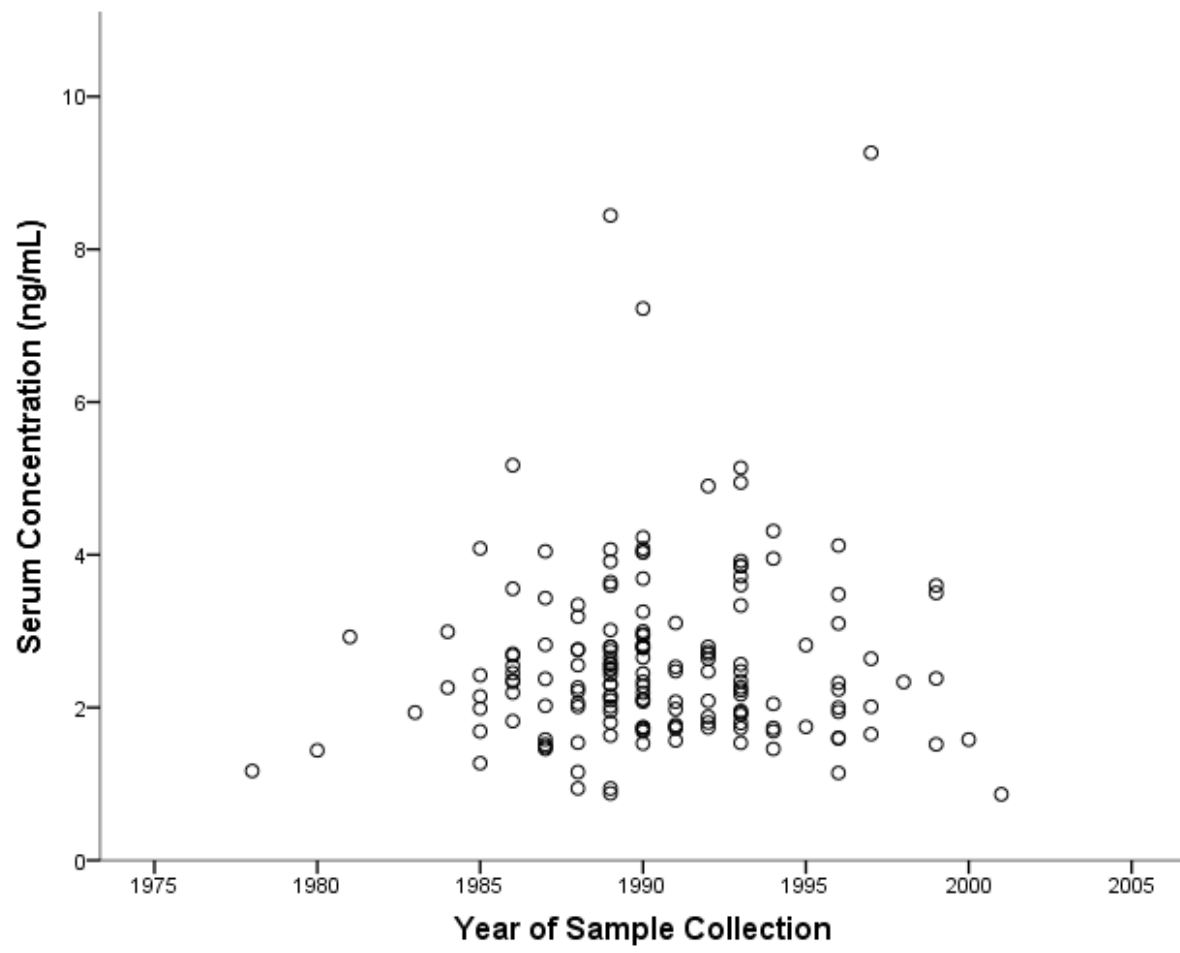
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A



B



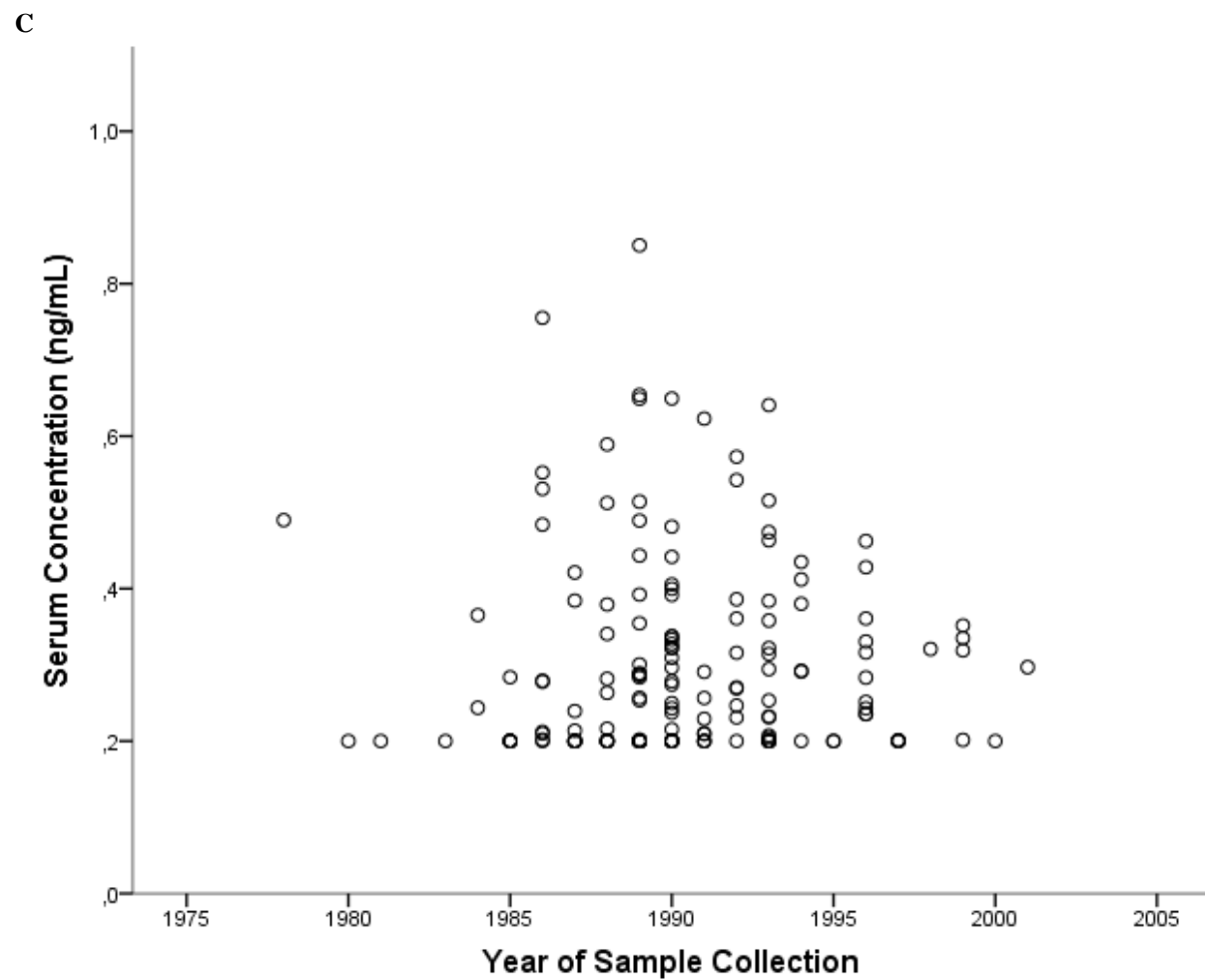


Fig. 1 Time trends of **a** perfluorooctane sulfonate, **b** perfluorooctanoic acid, and **c** perfluorononanoic acid in Swedish women ($N = 164$) between 1978 and 2001. The extreme value for PFNA (3.4 ng/ml) is not shown in the figure

Table 1

Mean (5% percentile, median, 95% percentile) concentrations of perfluorinated compounds (in nanogram per milliliter) in 237 matched maternal and umbilical cord serum samples from Southern Sweden

	Mean (5 % percentile, median, 95% percentile)			Correlation ^a	Difference between maternal and cord PFC levels (<i>p</i> value) ^b
	Maternal	Cord	Transfer efficiency (%)		
PFOS	17 (5.7, 15, 31)	7.4 (2.3, 6.5, 15)	45 (24, 43, 72)	0.76*	<0.001
PFOA	2.3 (0.61, 2.1, 4.6)	2.8 (0.39, 1.7, 6.0)	130 (45, 80, 160)	0.74*	<0.001
PFNA	0.31 (0.20, 0.24, 0.55)	0.26 (0.20, 0.20, 0.55)	93 (46, 99, 140)	0.51*	<0.001

PFOS perfluorooctane sulfonate, *PFOA* perfluorooctanoic acid, *PFNA* perfluorononanoic acid

*Correlations were significant at $p \leq 0.01$ level; A(correlations were significant at this level)

^a Spearman's Correlation Coefficient correlation coefficient between maternal and cord serum, Bserum

^b Comparison between maternal and cord serum by Wilcoxon signed-rank test

Table 2

Mean (5 % percentile, median, 95 % percentile) concentrations (in nanogram per milliliter) of perfluorinated compounds in maternal serum by maternal and fetal characteristics in 237 maternal samples from Southern Sweden

Characteristics	N (%)	Mean (5% percentile, median, 95% percentile)			Differences among groups (<i>p</i> value) ^a			Pairwise differences between groups (<i>p</i> value) ^b		
		PFOS	PFOA	PFNA	PFOS	PFOA	PFNA	PFOS	PFOA	PFNA
Age at delivery (years)					0.37	0.81	0.44			
<25	59 (25)	15 (3.5, 15, 29)	2.2 (0.45, 2.2, 4.6)	0.28 (0.20, 0.22, 0.55)				0.26	0.83	0.18
25–35	154 (65)	18 (5.7, 16, 31)	2.4 (0.61, 2.1, 4.9)	0.32 (0.20, 0.25, 0.54)				Reference	Reference	Reference
>35	24 (10)	20 (7.8, 16, 57)	2.2 (0.43, 1.9, 4.1)	0.32 (0.20, 0.24, 0.65)				0.92	0.51	0.81
Parity										
Primiparous	115 (48)	18 (5.6, 17, 31)	2.7 (0.75, 2.4, 5.1)	0.32 (0.20, 0.25, 0.55)				Reference	Reference	Reference
Multiparous	122 (52)	17 (5.7, 15, 29)	2.0 (0.43, 1.7, 3.9)	0.29 (0.20, 0.23, 0.55)				0.023	<0.001	0.26
Body Mass Index^c										
Underweight and normal	56 (65)	19 (6.1, 16, 57)	2.4 (0.69, 1.9, 5.3)	0.29 (0.20, 0.25, 0.54)				Reference	Reference	Reference
Overweight and obese	30 (35)	19 (5.6, 14, 37)	2.4 (0.61, 1.6, 6.5)	0.26 (0.20, 0.21, 0.51)				0.23	0.19	0.22
Smoking status^d					0.56	0.44	0.22			
Nonsmoker	113 (48)	17 (5.6, 16, 34)	2.2 (0.43, 2.0, 4.9)	0.30 (0.20, 0.24, 0.54)				Reference	Reference	Reference
Second-hand smoker	62 (26)	17 (6.0, 15, 27)	2.5 (0.65, 2.1, 4.2)	0.36 (0.20, 0.26, 0.65)				0.41	0.54	0.87
Active smoker	62 (26)	17 (6.7, 16, 30)	2.3 (0.92, 2.2, 4.1)	0.28 (0.20, 0.21, 0.57)				0.75	0.20	0.13
Country of origin					<0.001	<0.001	0.020			
Sweden	164 (72)	19 (9.0, 17, 30)	2.6 (1.4, 2.3, 4.2)	0.32 (0.20, 0.26, 0.59)				Reference	Reference	Reference
Denmark	5 (2.2)	31 (13, 22, 68)	3.9 (1.4, 2.7, 7.5)	0.25 (0.20, 0.25, 0.29)				0.31	0.62	0.59
Previous Eastern Europe	21 (9.2)	20 (5.6, 14, 30)	2.3 (0.68, 1.5, 5.3)	0.28 (0.20, 0.24, 0.45)				0.029	<0.001	0.51
Sub-Saharan Africa	6 (2.6)	9.1 (7.2, 8.5, 12)	1.1 (0.36, 1.1, 1.9)	0.26 (0.20, 0.20, 0.52)				<0.001	<0.001	0.23
Middle East	22 (9.6)	9.9 (3.1, 6.3, 29)	0.72 (0.22, 0.65, 1.4)	0.25 (0.20, 0.20, 0.51)				<0.001	<0.001	0.003
East Asia	5 (2.2)	13 (6.9, 12, 24)	1.5 (0.61, 1.0, 2.7)	0.48 (0.22, 0.33, 1.05)				0.075	0.041	0.12
South America	5 (2.2)	14 (7.3, 12, 24)	1.9 (0.75, 0.97, 3.7)	0.24 (0.20, 0.20, 0.35)				0.13	0.22	0.23

Gestational age								
Preterm	11 (5.0)	17 (6.0, 15, 37)	2.5 (1.1, 1.7, 6.5)	0.26 (0.20, 0.20, 0.46)		0.90	0.72	0.30
Term	226 (95)	17 (5.7, 15, 30)	2.3 (0.61, 2.1, 4.3)	0.31 (0.20, 0.24, 0.55)		Reference	Reference	Reference
Sex of newborns								
Male	177 (75)	17 (6.0, 16, 30)	2.3 (0.65, 2.2, 4.3)	0.32 (0.20, 0.24, 0.59)		Reference	Reference	Reference
Female	60 (25)	19 (5.3, 14, 54)	2.2 (0.37, 1.7, 6.9)	0.28 (0.20, 0.24, 0.50)		0.11	0.014	0.67

PFOS perfluorooctane sulfonate, *PFOA* perfluorooctanoic acid, *PFNA* perfluorononanoic acid

^aDifferences between groups obtained from Kruskal-wallis test; BPair-wise Kruskal–Wallis test

^bPairwise difference to reference group obtained from Mann–Whitney U-test; CU test

^cInformations were available for 86 paired maternal and cord samples; Dsamples

^dResults are based on measured cotinine concentrations in maternal serum