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Association between *in utero* perfluoroalkyl substance exposure and anti-Müllerian hormone levels in adolescent females in a British cohort

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Abstract

Evidence indicates that *in utero* environmental exposures could influence reproduction in female offspring. Perfluoroalkyl substances (PFAS) are synthetic, ubiquitous endocrine disrupting chemicals that can cross the placental barrier. Lower levels of anti-Müllerian hormone (AMH), a biomarker of ovarian reserve, are associated with reduced fertility. We investigated the association between *in utero* PFAS exposure and AMH levels in female adolescents using data from the Avon Longitudinal Study of Parents and Children, a British pregnancy cohort recruited between 1991 and 1992. Maternal serum samples were collected during pregnancy and analyzed for concentrations of commonly found PFAS—perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoic acid (PFNA). AMH levels were measured in serum of female offspring (mean age, 15.4 years) and log-transformed for analyses. We used a sample of 446 mother-daughter dyads for multivariable linear regression analyses, controlling for maternal age at delivery, pre-pregnancy body-mass index, and maternal education. Multiple imputation was utilized to impute missing values of AMH (61.2%) and covariates. Median PFAS concentrations (ng/mL) were as follows: PFOS 19.8 (IQR:15.1, 24.9), PFOA 3.7 (IQR: 2.8, 4.8), PFHxS 1.6 (IQR: 1.2, 2.2), PFNA 0.5 (IQR: 0.4, 0.7). The geometric mean AMH concentration was 3.9 ng/mL (95% CI: 3.8, 4.0). After controlling for confounders, mean differences in AMH per one ng/mL higher PFOA, PFOS, PFHxS, and PFNA were 3.6% (95% CI: −1.4%, 8.6%), 0.7% (95% CI: −0.2%, 1.5%), 0.9% (95% CI: −0.4%, 2.2%), and 12.0% (95% CI: −42.8%, 66.8%) respectively. These findings suggest there is no association between *in utero* PFAS exposure and AMH levels in female adolescents.

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Human subjects protection: Ethical approval for this study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committee. The U.S. Centers for Disease Control and Prevention (CDC) Institutional Review Board assessed and approved human subjects protection. Mothers provided informed consent at the time of enrollment.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Keywords

ALSPAC; perfluoroalkyl substances; anti-Müllerian hormone; ovarian reserve; endocrine disruptors

1. Introduction

Endocrine disrupting chemicals (EDCs), defined as chemicals that interfere with hormone action, may alter an individual's physiology at any time point, from fetal development into adulthood. [1, 2]. Researchers have conducted numerous studies on the impact of EDC exposure on human health outcomes including cardiovascular disease, obesity, female and male reproductive health, thyroid disruption, and neurodevelopmental and neuroendocrine effects [1].

A subset of EDCs known as perfluoroalkyl substances (PFAS) are synthetic, ubiquitous chemicals that were widely used in industrial and consumer products, as their high stabilities and low surface tensions make them ideal surfactants [3, 4]. Common consumer use of PFAS as surfactants include food packaging, non-stick coatings, and textile coatings [3]. PFAS accumulate in both the food chain and environment, which leads to potential human exposure through ingestion of contaminated food or drinking water [5]. The four most commonly detected PFAS are perflourooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), perfluorooctanoic acid (PFOA), and perfluorononanoic acid (PFNA) [6]. Although the main manufacturers phased out production of PFOS in 2002, PFAS exposure is an ongoing concern as PFAS have a half-life of up to 8.5 years in humans [3]. The United States National Health and Nutrition Examination Survey (NHANES) detected PFOS, PFOA, PFHxS, and PFNA in more than 95% of participants between 1999 and 2008 [6].

PFAS can cross the placental barrier into the fetal environment, which raises questions about the effect of prenatal PFAS exposure on the health of offspring [7–9]. Exposure to environmental toxins such as PFAS during fetal development could have long-term effects on the offspring [10, 11]. Previous work by Kristensen et al. suggests that *in utero* PFAS exposure could adversely affect reproduction in female offspring through changes in ovarian development and function [12].

Anti-Müllerian hormone (AMH), previously referred to as Müllerian Inhibiting Substance, is a member of the transforming growth factor-beta family, which helps regulate the process of ovarian follicle maturation [13]. AMH levels are strongly correlated with the number of primordial, or resting, ovarian follicles which form during fetal development and deplete over time [13, 14]. Women who experience a faster rate of depletion of the follicle pool are more likely to have a younger age at menopause [15]. Previous work found a strong correlation between serum levels of AMH and the number of ovarian primordial follicles, contributing to a body of research that suggests AMH is a biomarker of ovarian reserve in adult and adolescent females [16].

Limited evidence from studies assessing the relationship between PFAS exposure and reproductive outcomes, such as age of menarche and fertility, suggests prenatal exposures

may influence factors related to daughters' AMH levels later in life. The findings regarding the relationship between prenatal PFAS exposure and age at menarche are inconsistent. In the Avon Longitudinal Study of Parents and Children (ALSPAC), an analysis of 218 female adolescents with early menarche and 230 without early menarche found no association between prenatal PFAS exposure and early onset age at menarche among offspring [17]. Other researchers found no association between prenatal PFOS exposure and age of menarche, but their findings did suggest increased *in utero* PFOA exposure was associated with a 5.3 months later age of menarche compared to a low PFOA reference group in a sample of 377 women in a Danish national birth cohort [12]. Elucidating determinants of delayed menarche is clinically relevant as previous research suggests late menarche is associated with lower mineral bone density, shorter stature, negative physiological outcomes, and cardiovascular disease in adulthood [18–21]. The research exploring PFAS exposure with fertility and fecundity is also inconclusive and does not focus on prenatal PFAS exposure.[22]

A Danish national birth cohort found no associations between prenatal PFOS or PFOA exposure and concentrations of reproductive hormones, including AMH, in female offspring approximately 20 years old [12]. To our knowledge, no study has evaluated the association between prenatal PFAS exposure and AMH levels in adolescent females, which is an important age group as AMH levels deplete over time. The aim of this study was to examine the association of prenatal PFAS concentrations of PFOA, PFOS, PFxHS, and PFNA with AMH levels in female adolescent ALSPAC participants aged 14–16 years.

2. Methods

2.1 Study Population

ALSPAC is an ongoing longitudinal birth cohort, initially established to determine how genetic and environmental characteristics impact health and development in both parents and children. Pregnant women with expected delivery dates between April 1st 1991 and December 31st 1992 were recruited in three health districts in the former county of Avon, Great Britain [23]. A series of questionnaires and clinical assessments were administered to mothers during pregnancy and continue to be administered to children enrolled in ALSPAC to collect health and demographic information. Detailed ALSPAC study design and recruitment methods have been previously outlined elsewhere [23, 24]. The present study used data from 448 mother-daughter dyads identified for a nested case-control study exploring the associations between EDCs and adolescent development [25]. In the ancillary study, case-control status was determined by age at menarche. Cases were girls with early menarche, defined as menarche before 11.5 years, and controls were girls who attained menarche at or after 11.5 years of age. We constructed stratum-weighted linear regression models to account for the sampling selection probabilities where the weight for cases was 1 and the weight for controls was 15.1[25].

Ethical approval for this study was obtained from the ALSPAC Law and Ethics Committee, the Local Research Ethics Committee, and the Centers for Disease Control and Prevention (CDC) Institutional Review Board. All participants in the study provided written informed consent and parents provided written informed consent for their child. The study website

contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

2.2 Anti-Müllerian Hormone Assessment

AMH levels were measured from blood samples taken during a clinical assessment. Participants attending the morning 14–16 year clinic were asked to fast overnight and participants attending the clinic after lunch were asked to fast for a minimum of 6 hours. Blood samples were immediately spun and serum frozen at −80°C. As previously described, AMH was assayed on serum using the commercial AMH Generation II ELISA kit (Beckman Coulter UK Ltd, High Wycombe, United Kingdom) [26]. Both the inter- and intra-assay coefficients of variation were less than 5%. AMH values in this study are reported in ng/mL. Data on AMH levels during the 14–16 year clinic were collected on 3,741 daughters.

2.3 Perflouroalkyl Substances

PFOS, PFOA, PFHxS, and PFNA concentrations were measured in 448 stored maternal, gestational serum samples collected (median 15 weeks; interquartile range 10–28 weeks gestation) between 1991 and 1992. PFAS analyses were conducted at the National Center for Environmental Health of the Centers for Disease Control and Prevention (CDC) using a modification of a previously described analytical method [27]. The PFOS limit of detection was 0.2 ng/mL and the limit of detection for all other PFAS of interest was 0.1 ng/mL. No PFAS values were below the limit of detection.

2.4 Potential Confounders

Potential confounders in the relationship between prenatal PFAS exposure and AMH levels in female offspring were determined *a priori* based on biological plausibility and findings from the literature. The following variables were evaluated as potential confounders: pre-pregnancy body mass index (BMI; kg/m^2), maternal education (categorized as less than ordinary level (O-level), O-level, or greater than O-level), prenatal smoking (any vs. no current smoking during last two months of pregnancy), maternal age at delivery (years) [12, 17, [28].

2.5 Analyses

All analyses were conducted using SAS 9.3 (Cary, NC). Two of the original 448 samples had missing information on at least one PFAS of interest and were not included in the sample. Descriptive analyses were conducted on the subset of 446 mother daughter dyads with complete exposure information for each PFAS. AMH levels were log-transformed for analyses due to a gross violation of normality in the distribution of the outcome. Pre-pregnancy BMI, maternal education, maternal age at delivery, and breastfed status were also assessed as potential effect modifiers. Crude estimates from linear regression models of PFAS exposure and AMH levels were compared to adjusted estimates for each potential confounder. Final parsimonious models using mother-daughter dyads with complete information on PFAS exposure and AMH levels (N=173) were achieved through

assessment of variables in a hierarchal manner. The final model was adjusted for maternal age at delivery, pre-pregnancy BMI, and maternal education.

Multiple imputation by fully conditional specification (FCS) was applied to a subset of mother-daughter dyads with missing data on covariates of interest and AMH [29]. The imputation model included all variables used for analyses. A total of 10 imputations were used to create the complete dataset of interest, providing a total study sample of 446 mother-daughter dyads with no missing data. Previously identified multiple linear regression models were applied to the imputed dataset to arrive at the final estimates for the crude and adjusted association between prenatal PFAS exposure and AMH levels in female offspring.

3. Results

Mothers in this study were predominantly white women with relatively high levels of education, the majority of whom did not smoke during pregnancy (Table 1). Among mothers in the study population, median PFAS concentrations (ng/mL) were: PFOS 19.8 (IQR: 15.1, 24.9), PFOA 3.7 (IQR: 2.8, 4.8), PFHxS 1.6 (IQR: 1.2, 2.2), PFNA 0.5 (IQR: 0.4, 0.7). Median PFOS concentrations were lower among mothers who reported any prenatal smoking compared to mothers who reported no prenatal smoking.

The geometric mean AMH concentration was 3.9 ng/mL (95% CI: 3.8, 4.0). The distribution of study population characteristics differed between the mother-daughter dyads with no missing data on AMH and the mother-daughter dyads with missing data on AMH (61.2%). Mothers of daughters with missing AMH were more likely to smoke at least one cigarette during pregnancy and never breastfeed during pregnancy compared to mothers of daughters without missing AMH (Table 2).

Model results of imputed analyses (N=446) were compared to the multivariable linear regression analyses for the complete-case analysis (Supplementary Table 1) with no missing AMH (N=173). Differences between the two results suggested the complete-case analysis was biased with respect to exclusion of missing data. Due to the discrepancy between the imputed analyses and complete-case analyses, results using the imputed model were reported (Table 3).

No significant associations were observed between maternal PFAS exposure and AMH levels in daughters. In the unadjusted models, mean differences in AMH per one ng/mL higher in PFOS, PFOA PFHxS, and PFNA were 0.7% (CI: −0.1%, 1.5%), 3.8% (CI: −1.4%, 9.0%), 1.0% (CI: −0.3%, 2.2%), and 13.3% (CI: −43.7%, 70.3%). The multivariable adjusted and unadjusted models were similar (Table 3). The results of the adjusted models indicate mean differences in AMH per one ng/mL higher PFOS, PFOA, PFHxS, and PFNA were 0.7% (CI: −0.2%, 1.5%), 3.6% (CI: −1.4%, 8.6%), 0.9% (CI: −0.4%, 2.2%), 12.0% (−42.8%, 66.8%). There was no evidence of effect modification by pre-pregnancy BMI, maternal education, maternal age at delivery, or breastfed status.

4. Discussion

In this study, we observed no associations between a range of prenatal PFAS exposures, including PFOS, PFOA, PFHxS, and PFNA, and AMH, a marker of ovarian reserve, in female offspring at 15 years of age. These findings are consistent with the only previous study, to our knowledge, that evaluated the association between maternal PFAS exposure and AMH levels in young adult females. The prior study used a Danish cohort (N=343 daughters) and found no associations between prenatal PFOS or PFOA exposure and concentrations of AMH in female offspring who were approximately 20 years old [12].

In a study of 540 young adults aged 12 to 30 years in Taiwan, Tsai et al. explored the association between serum PFAS concentrations and levels of reproductive hormones, but did not assess AMH [30]. Among female participants ages 12 to 17, researchers concluded that PFOA was associated with decreased sex hormone-binding globulin and perfluorodecanoic acid (PFUA) was associated with decreased follicle-stimulating hormone (FSH) in females [30]. The results of this study provide evidence to suggest prenatal PFAS exposure can be associated with reproductive hormone levels in female adolescents.

While we did not control for race/ethnicity in this analysis due to the small number of non-white girls in the sample, previous work suggests AMH levels do not vary greatly by race/ethnicity [31]. Additionally, we did not control for prenatal smoking in the final analysis as it was not statistically determined to be a confounder. This is in line with an ALSPAC analysis among 1,144 mother daughter-dyads, which found no strong association between maternal smoking and AMH levels in daughters 15 years of age [32]. However, our results also indicated median PFOS concentrations among mothers differed by prenatal smoking status. This particular finding is consistent with previous PFAS research among 306 mother-daughter dyads in Japan, which found significant differences in maternal PFOS concentrations by smoking status during pregnancy.[33]

This analysis contributes to a growing body of literature examining the effects of environmental exposures, specifically PFAS, on human health. Previous research found no association between PFOA and PFOS and AMH levels in female offspring at 20 years old (n=344) [13]. This analysis assessed the effect of two additional PFAS, PFHxS and PFNA, with AMH levels in daughters at 15.5 years of age and utilized a larger sample size (n=446). These findings provide a valuable contribution because the lack of association between PFAS and AMH in a younger sample strongly supports the findings of the previous study and indicates that a relationship does not exist [12]. Researchers utilized a well-characterized dataset for all analyses and had access to a wide range of covariates.

Limitations of this study include the use of maternal gestational serum PFAS concentrations as a proxy for prenatal PFAS exposure among female offspring. However, this method of assessing prenatal PFAS exposure is commonly used in multiple studies as PFAS can cross the placental barrier [12]. Further, the small number of non-white girls in the sample prevented researchers from assessing race/ethnicity as a potential effect modifier in the relationship between PFAS and AMH. Additionally, a limitation of this study is the sizeable proportion of missing information on AMH levels in daughters. However, previous studies

suggest that multiple imputation using FCS can be less biased than a complete case-analysis in the presence of missing data[34].

4.1 Future Directions

Future studies could utilize a population that includes a greater percentage of non-white girls to assess the relationship between prenatal PFAS exposure and AMH levels in daughters. This type of population would allow for the assessment of race/ethnicity as a potential effect modifier. Additional analyses might evaluate this relationship at earlier time points in the daughter's life to establish whether potential effects may weaken or strengthen over time. Lastly, future studies could assess the underlying mechanism for the effect of PFAS on reproductive outcomes.

5. Conclusions

In summary, we examined the association between prenatal exposure to four commonly found PFAS and AMH levels in 15-year-old daughters in the ALSPAC cohort. Our results indicated there was no association between *in utero* PFAS exposure and AMH levels in female adolescents within this cohort.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Study population characteristics in a subset of the Avon Longitudinal Study for Parents and Children (N=446 mother-daughter dyads)

	Frequency[a] [n(%)]	PFOS (ng/mL) Median (IQR)	PFOA (ng/mL) Median (IQR)	PFHxS (ng/mL) Median (IQR)	PFNA (ng/mL) Median (IQR)
Overall	446	19.8 (15.1, 24.9)	3.7 (2.8, 4.8)	1.6 (1.2, 2.2)	0.5 (0.4, 0.7)
Maternal pre-pregnancy BMI [b]					
Underweight (<18.5)	18 (4.0)	16.9 (14.0, 22.6)	3.5 (2.8, 4.7)	1.5 (1.2, 2.3)	0.5 (0.3, 0.6)
Normal (18.5–24.9)	289 (64.8)	20.1 (15.1, 25.5)	3.8 (2.8, 4.8)	1.6 (1.2, 2.2)	0.5 (0.4, 0.7)
Overweight (25.0–29.9)	62 (13.9)	20.9 (17.5, 25.6)	3.7 (3.2, 4.9)	1.9 (1.5, 2.5)	0.6 (0.4, 0.7)
Obese (≥30.0)	31 (7.0)	19.2 (13.8, 23.4)	3.6 (2.7, 5.0)	1.4 (1.2, 2.3)	0.6 (0.3, 0.7)
Prenatal smoking					
Any	79 (17.7)	17.2 (13.4, 21.4)*	3.4 (2.9, 4.4)	1.7 (1.3, 2.4)	0.5 (0.3, 0.7)
None	346 (77.6)	20.6 (15.4, 25.6)*	3.8 (2.8, 4.9)	1.6 (1.2, 2.2)	0.6 (0.4, 0.7)
Maternal race					
White	422 (94.6)	19.9 (15.2, 25.3)	3.8 (2.9, 4.8)*	1.6 (1.2, 2.2)	0.5 (0.4, 0.7)
Non-white	7 (1.6)	14.6 (11.8, 19.2)	2.4 (2.0, 2.9)*	1.4 (1.0, 1.7)	0.5 (0.2, 0.7)
Maternal age at delivery [c]					
<25	92 (20.6)	18.5 (14.1, 23.1)	3.9 (3.0, 4.8)	1.6 (1.2, 2.1)	0.5 (0.4, 0.6)
25–29	164 (36.8)	20.7 (15.4, 25.4)	3.8 (3.0, 4.9)	1.6 (1.2, 2.1)	0.6 (0.4, 0.7)
>29	187 (41.9)	19.7 (15.1, 25.6)	3.6 (2.5, 4.6)	1.7 (1.2, 2.4)	0.5 (0.4, 0.7)
Maternal education [d]					
Less than O-level	89 (20.0)	18.2 (14.9, 23.3)	3.6 (2.8, 4.4)	1.6 (1.3, 2.2)	0.5 (0.4, 0.7)
O-level	140 (31.4)	19.6 (15.1, 26.0)	3.7 (2.9, 5.0)	1.6 (1.2, 2.3)	0.6 (0.4, 0.7)
Greater than O-level	198 (44.4)	20.4 (15.2, 25.3)	3.9 (2.8, 4.8)	1.7 (1.2, 2.2)	0.5 (0.4, 0.7)
Breastfed status					
Never	82 (18.4)	19.8 (15.3, 25.5)	4.1 (3.1, 5.1)	1.6 (1.3, 2.3)	0.5 (0.4, 0.7)
Ever	332 (74.4)	19.8 (15.0, 24.8)	3.7 (2.8, 4.8)	1.6 (1.2, 2.2)	0.5 (0.4, 0.7)

*Denotes statistical significance at p<0.05 based on Kruskal-Wallis test

[a]Numbers may be inconsistent because of missing values

[b] Maternal pre-pregnancy BMI, measured in kg/m^2

[c] Maternal age at delivery, measured in years

[d] <O-level=none, Certificate of Secondary Education, and vocational education, which are equivalent to no diploma or a GED in the United States. O-levels (ordinary levels) are required and completed at the age of 16. >O-level=A-levels (advanced levels) completed at 18, which are optional, but required to get into university; and a university degree.

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Table 2:

Distribution of study population characteristics comparing individuals with missing AMH to individuals without missing AMH (N=446)

	No Missing AMH[b]	Missing AMH[b]
	Frequency [n(%)]	Frequency [n(%)]
Overall	173	273
Maternal pre-pregnancy BMI, kg/m^2		
Underweight (<18.5)	8 (4.6)	10 (3.7)
Normal (18.5–24.9)	113 (65.3)	176 (64.5)
Overweight (25.0–29.9)	26 (15.0)	36 (13.2)
Obese (≥30.0)	8 (4.6)	23 (8.4)
Prenatal smoking		
Any	21 (12.1)	58 (21.3)
None	146 (84.4)	200 (73.3)
Maternal age at delivery, years		
<25	23 (13.3)	69 (25.3)
25–29	65 (37.6)	99 (36.3)
>29	84 (48.6)	103 (37.7)
Maternal education [a]		
Less than O-level	26 (15.0)	63 (23.1)
O-level	50 (28.9)	90 (33.0)
Greater than O-level	92 (53.2)	106 (38.8)
Breastfed status		
Never	23 (13.3)	59 (21.6)
Ever	138 (79.8)	194 (71.1)

[a] <O-level=none, Certificate of Secondary Education, and vocational education, which are equivalent to no diploma or a GED in the United States. O-levels (ordinary levels) are required and completed at the age of 16. >O-level=A-levels (advanced levels) completed at 18, which are optional, but required to get into university; and a university degree.

[b] Numbers may be inconsistent because of missing values.

Table 3:

Crude and Adjusted[a] Models using Multiple Imputation (N=446)

	Model	Beta	95% CI
PFOS	Crude	0.0069	(−0.001, 0.015)
	Adjusted	0.0066	(−0.002, 0.015)
PFOA	Crude	0.0377	(−0.014, 0.090)
	Adjusted	0.0358	(−0.014, 0.086)
PFHxS	Crude	0.0095	(−0.003, 0.022)
	Adjusted	0.0090	(−0.004, 0.022)
PFNA	Crude	0.1333	(−0.437, 0.703)
	Adjusted	0.1200	(−0.428, 0.668)

[a] adjusted for maternal age at delivery (years), pre-pregnancy BMI (kg/m^2), and maternal education (< O-level, O-level, > O-level)