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A Prospective Study of Pre-pregnancy Serum Concentrations of Perfluorochemicals and the Risk of Gestational Diabetes

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Abstract

OBJECTIVE—To examine preconception serum concentrations of perfluorooctanoic acid (PFOA) and six other PFCs in relation to gestational diabetes (GDM) risk.

DESIGN—Prospective cohort with longitudinal follow-up.

SETTING—16 counties in Michigan and Texas, 2005-2009.

PATIENT(S)—Among 501 women recruited upon discontinuing contraception for purposes of becoming pregnant, 258 (51%) became pregnant and were eligible for the study of which 28 (11%) women reported having physician-diagnosed GDM during followup.

INTERVENTION(S)—None.

MAIN OUTCOME MEASURE(S)—The odds ratios (ORs) and 95% confidence intervals (CIs) of GDM associated with each standard deviation (SD) increment of preconception serum PFOA concentrations (ng/mL, log-transformed) and six other PFCs were estimated using logistic

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

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Interpretation of data: All authors

regression after adjusting for age, pre-pregnancy body mass index, smoking, and parity conditional on gravidity.

RESULT(S)—Preconception geometric mean (95% CI) PFOA concentrations (in ng/ml) were higher for women with than without GDM (3.94 (3.15-4.93) vs. 3.07 (2.83-3.12), respectively). Each SD increment in PFOA was associated with a 1.87 fold increased GDM risk (adjusted OR (95% CI): 1.86 (1.14, 3.02)). A slightly increased risk associated with each SD increment for the six other PFCs was observed as well (all ORs >1.0; range 1.06-1.27), although the associations were not statistically significant.

CONCLUSIONS—Our findings suggested that higher environmentally relevant concentrations of PFOA were significantly associated with an increased GDM risk. If corroborated, these findings may be suggestive of a possible environmental etiology for GDM.

Keywords

perfluorochemicals (PFCs); perfluorooctanoic acid (PFOA); gestational diabetes; pregnancy

Introduction

Perfluorooctanoic acid (PFOA) and other perfluorochemicals (PFCs) have recently been associated with adverse health effects, including carcinogenicity (1; 2), hepatotoxicity (2; 3), and developmental and reproductive toxicity (2). An evolving body of experimental animal research suggests PFOA has ability to disrupt endocrine signaling and, subsequently, to mitigate metabolic and vascular functions (4; 5). PFCs repel grease/oil and are used to treat clothing and carpet to prevent staining, and in the manufacturing of certain food containers and wrappers. As such, humans are exposed to PFCs through various pathways such as through contaminated drinking water and food, inadvertent ingestion of indoor dust and, potentially, through inhalation (6). Of note, data from the National Health and Nutrition Examination Survey (NHANES) cross-sectional biomonitoring study indicated that >95% of participants had detectable serum concentrations for several PFCs (7) suggesting widespread human exposure.

Gestational diabetes (GDM), defined as glucose intolerance with onset or first recognition during pregnancy, is one of the most common pregnancy complications (8). GDM is a growing health concern and is related to short- and long-term adverse outcomes for both women and their offspring (8; 9). Affected women are at higher risk for type 2 diabetes following pregnancy. Offspring are more likely to be macrosomic at birth and to develop childhood obesity and glucose intolerance in adulthood (8). Furthermore, GDM incidence is escalating in parallel with increasing rates of overweight and obesity among women of reproductive age (10–12). Emerging epidemiologic data suggest that an association may exist between serum PFOA and serum lipids concentrations. In particular, a positive association has been reported between serum PFOA concentrations and serum cholesterol and triglycerides levels (13–17) and serum uric acid levels (18). All these traits have been implicated in the development of diabetes, including both type 2 diabetes and GDM. As yet, we are unaware of any past research focusing on PFOA and other PFCs and GDM which contrasts with an evolving body of evidence from cross-sectional studies of diabetes among

non-pregnant individuals (19–21). In the present study, we sought to prospectively evaluate preconception serum concentrations of PFOA and other PFCs, as measured in women upon discontinuing contraception for purposes of becoming pregnant in relation to the risk of GDM using data from the Longitudinal Investigation of Fertility and the Environment (LIFE) Study.

Materials and Methods

Study design, population, and data collection

The study population is composed of 272 women achieving pregnancy while participating in the LIFE Study and submitting pregnancy journal (22). Specifically, the cohort was recruited in 16 counties in Michigan and Texas, 2005-2009 upon discontinuing contraception for purposes of becoming pregnant and followed daily until an hCG positive pregnancy test and through the first eight weeks of pregnancy. Subsequently, women were followed monthly until delivery. By design, inclusion criteria were minimal: 1) females aged 18–40 years; 2) in a committed relationship; 3) menstrual cycle length between 21-42 days; 4) no injectable contraceptives within 12 months; 5) off contraception for < 2 months; 6) no physician diagnosed infertility; and 7) able to communicate in English or Spanish. Human subject approval was received from all collaborating institutions, and full consent was obtained from participants before any data collection.

Upon enrollment, women completed in-person interviews regarding their lifestyle and medical/reproductive history followed by standardized anthropometric assessments (22) that were performed by trained research assistants. Blood specimens were obtained by research nurses upon completion of the examination. Women were instructed in the completion of daily journals while trying for pregnancy (up to 12 months), and through the first 8 post-conception weeks gestation for women achieving pregnancy. Then, women completed monthly pregnancy journals that were designed to capture lifestyle during pregnancy and results from prenatal screening and testing. Specifically, women recorded the results of antenatal testing or any physician-diagnosed gravid along with other information from prenatal visits (i.e., ultrasonology findings and expected date of delivery). The ascertainment of GDM was based on self-report; women were queried from 9 weeks post-LMP gestation to record a physician-diagnosis of GDM. Full human subject research approval was obtained from all collaborating institutions, and all participants gave informed consent before participation. As universal screening of gestational diabetes is recommended starting at 24 weeks of gestation (8), the final analytical population of the study includes 258 women who had a pregnancy at least lasting 24 weeks of gestation.

Measurement of serum PFCs

Established operating protocols utilizing isotope dilution high performance liquid-chromatography-tandem mass spectrometry were used for the quantification (ng/ml) of PFOA and six other PFCs: 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid (Et-PFOSA-AcOH), 2-(N-methyl-perfluorooctane sulfonamido) acetic acid (Me-PFOSA-AcOH), perfluorodecanoic acid (PFDeA), perfluorononanoic acid (PFNA), perfluorooctane sulfonamide (PFOSA), perfluorooctane sulfonic acid (PFOS) (23; 24). All analyses were

conducted by the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention. Ongoing quality assurance and control procedures included the analysis of calibration standards, blanks and quality control (QC) materials in each batch to ensure the accuracy and reliability of the data. The concentrations of the QCs were evaluated using standard statistical probability rules (25). We used machine observed concentrations without substituting concentrations below the limits of detection consistent with contemporary methods aimed at minimizing bias associated with such practices (26; 27).

Statistical analysis

In the descriptive phase of analysis, we assessed the distributions of all PFCs and relevant covariates and, subsequently, by GDM status. Geometric means (GMs) (95% confidence intervals (CIs)) were calculated for PFCs. Logistic regression was used to estimate both the unadjusted odds of GDM (odds ratio; OR) (95%CI) per standard deviation (SD) increment in PFC concentration, and the odds when adjusting for *a priori* defined potential confounders: age (years), body mass index (BMI, weight in kilograms/height in meters^2), and parity conditional on gravidity (never pregnant/ pregnant without live birth/ pregnant with previous birth). In addition, we assessed the associations by adjusting for race/ethnicity (White/non-White), and preconception smoking indicator (yes/no at the time of the study). We assessed the linear functional form for PFC concentrations in logistic models in multiple ways and found it to be a reasonable. PFC concentrations were log (x+1) transformed and rescaled by their standard deviations to aid in the interpretation of point and interval estimates. Thus, the findings denote the OR per one SD increase in PFC concentration. Separate models were run for each of the seven PFCs to fully explore any association with GDM, and without making an *a priori* decision as to which PFC to assess, given the absence of prior research on PFCs and GDM. All analyses were conducted using SAS software (version 9.3; SAS Institute Inc., Cary, NC).

Results

Among the 272 women achieving pregnancy and submitting pregnancy journal, 258 (95%) had a pregnancy lasting >24 weeks gestation of which 28 women reported having been diagnosed with GDM (11%). GDM women were more likely to be smokers, parous and obese before the index pregnancy than unaffected women (Table 1), although the differences did not reach significance.

In general, women who reported having GDM had higher preconception geometric mean concentrations of PFCs in comparison to women without GDM, although the difference did not reach statistical significance (Table 2). The median serum concentration of PFOA in this population of women (3.3 ng/ml), similar to that reported in the NHANES' biomonitoring report for the U.S. population during a similar time period (median 3.5 ng/ml: year 2005-2006; median 3.7 ng/ml: year 2007-2008) (7; 23).

Table 3 presents the logistic regression results for PFOA and the other PFCs and odds of a GDM diagnosis. Serum PFOA concentrations were significantly and positively associated with GDM risk, reflecting more than 1.8 fold increased odds per increasing SD even after

the adjustment for age, parity, BMI, race/ethnicity, and smoking (OR 1.87; 95% CI 1.16, 3.63). For all the other PFCs, there was suggestive evidence of a slightly increased risk associated with each SD increment in the PFCs concentrations with all ORs >1.0, ranging from 1.06-1.27. However, all CIs were inclusive of one.

Discussion

In this prospective cohort study of women who were longitudinally followed from pre-conception through delivery, we found a significant and positive association between serum PFOA concentrations and GDM risk. Specifically, a one SD increase in log transformed serum PFOA concentrations was associated with more than a 1.8 fold increase in risk of GDM. This association remained significant after the adjustment for conventional risk factors for GDM, such as age, BMI, smoking, and parity. Of particular note, we observed the significant association at environmentally relevant concentrations, which were similar to those for the general U.S. population during a comparable time period (7; 23).

The notable strength of the present study is the prospective design that establishes a temporal relationship between PFC concentrations and the development of diabetes in pregnancy, and use of a standardized anthropometric assessment for determining BMI. Several potential limitations of the study merit discussion. First, identification of GDM was based upon self-reported physician diagnosis of high blood sugar in pregnancy. It is plausible that some women who had high blood sugar did not fully meet the diagnostic criteria for GDM. The incidence of GDM in this population is greater than that reported for pregnant U.S. women (i.e., 4-7%) (8), but 47% of the cohort was overweight or obese and may at least partly account for the higher incidence. Nonetheless, misclassification of non-GDM cases as GDM cases is likely to attenuate the association, therefore, cannot explain the positive PFOA-GDM association observed in the present study. In addition, because none of the women knew their PFC concentrations during the course of study, misclassification of GDM relative to exposure is unlikely. Universal prenatal glucose screening and testing for GDM have been recommended by both American Diabetes Association (8) and American College of Obstetricians and Gynecologists (28) with adaptation throughout U.S. clinics. Participating women prospectively recorded gravid diseases arising during the course of pregnancy allowing for the longitudinal capture of GDM. Given that women had been highly compliant with reporting in daily journals while pregnant and with monthly pregnancy journals (86% and 80% completion, respectively), we assume good capture of GDM. Although we adjusted for major risk factors of GDM including BMI in our analyses, residual confounding from other unmeasured risk factors may be plausible. However, our observation that the PFCs_GDM associations didn't change materially after the adjustment of the other available major risk factors alleviates our concern. Also, we had sufficient statistical power albeit our limited number for detecting a significant association between PFOA serum concentrations and GDM, as the empirical findings reflect. The consistent pattern of elevated ORs for the remaining other six PFCs is also worthy of note. The lack of significance for some PFCs may reflect unique structural properties or biologic activities of the various compounds in this chemical class, or their prevalence in populations. Consistent with our exploratory approach in the absence of previous findings on PFCs and GDM, we

report findings for all PFCs measured irrespective of their prevalence of exposure (i.e., frequency of detection).

To our knowledge, our findings are the first to assess PFCs and GDM and to report a significant association with PFOA. Our findings are consistent with previous findings suggesting a potential association between serum PFOA and type 2 diabetes mortality among women who were not pregnant and among occupationally exposed workers (19–21). For example, workers occupationally exposed to PFOA (20) had an approximately twofold increased risk in diabetes mortality compared with non-exposed workers (SMR = 1.97; 95% CI, 1.23–2.98). In an occupational study, a similar excess risk of diabetes mortality was observed among probable and definitively exposed workers in comparison to unexposed workers (RR = 3.7; 95% CI, 1.4–10.1) (21). Studies of PFOA and diabetes morbidity, however, are sparse and findings are controversial. In a cross-sectional study of diabetes prevalence in a community exposed to high levels of PFOA via contaminated drinking water, no significant association of serum PFOA with diabetes risk was observed (19). Paradoxically in this same study restricted to long-term residents, PFOA serum concentrations were even inversely associated with type 2 diabetes risk (19). The authors speculated that a positive association between diabetes and PFOA could have been obscured and reversed because of survival bias if diabetes cases with higher PFOA serum concentrations died earlier or were lost to follow-up due to other medical complications related to high exposure to PFOA. It should also be noted that all the published studies of diabetes morbidity thus far have utilized retrospective or cross-sectional data where PFOA concentrations were measured using blood samples collected after or at the same time of the diagnosis of diabetes, thereby, limit the ability to establish a temporal ordering during a relevant sensitive window such as pregnancy.

While the precise underlying molecular mechanisms have yet to be elucidated, emerging data supports a biologically plausible association between PFOA and GDM. For example, data from animal studies demonstrated that PFOA can activate the peroxisome proliferator-activated receptor-α (PPAR-α), a ligand-activated transcription factor that regulates gene expression, lipid modulation, glucose homeostasis, and inflammation. (29). In transiently transfected human fibroblast-like cell line COS-1, PFOA also induced PPAR-α in a concentration-dependent fashion (30). In epidemiological studies, PFOA exposure has been positively associated to serum cholesterol, triglycerides levels (13–17), and serum uric acid levels (18) in most though not all studies. More recently, PFOA was positively associated with levels of alanine transaminase (ALT), a marker for hepatocellular damage in both a population based study (31) and an occupational cohort (32). All these traits have been implicated in the development of glucose intolerance. Reported half-life of serum PFOA ranges from 2 to 8 years (33–35). In the present study, although PFOA was measured using serum samples collected before pregnancy, the observed PFOA-GDM association may also reflect the effect of PFOA during peri-conception and pregnancy period given the long half-life of PFOA.

Conclusion

In summary, our findings are the first known to us that suggest environmentally relevant concentrations of PFOA are significantly associated with a higher risk of GDM. Such findings await future corroboration. If corroborated, our findings in the context of mechanistic and animal research are suggestive of a possible environmental etiology for GDM.

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Table 1

Characteristics of women by gestational diabetes (GDM) status, LIFE Study, 2005–2009.

Characteristic*	ALL (N=258)	Non-GDM (N=230)	GDM (N=28)
Age (years)	29.7 (3.7)	29.6 (3.8)	30.2 (2.9)
Race, non-white (%)	16	15	17
Current smoker (%)	6.6	6.5	7.1
Pre-pregnancy BMI (kg/m^2)	26.2 (6.3)	26.1 (6.4)	27.0 (4.6)
BMI (kg/m^2) (%)			
<18.5	1.2	1.3	0.0
18.5–24.9	52.3	53.0	46.4
25.0–29.9	27.5	27.8	25.0
≥30.0	19.0	17.8	28.6
Parity (% nulliparous)	47.3	47.8	42.9
Not College graduate (%)	14.8	14.5	17.9
No health insurance (%)	2.7	2.6	3.6

* Data presented are mean (standard deviation) unless otherwise specified

BMI: body mass index

Table 2

Serum concentrations of PFCs (ng/ml) by gestational diabetes (GDM) status, LIFE Study, 2005–2009

	Non-GDM (N=230)	GDM (N=28)	P-value
PFOA (perfluorooctanoic acid)			
% <LOD* (LOD=0.1)	0	4	
Geometric mean (95% CI)	3.07 (2.83–3.32)	3.94 (3.15–4.93)	0.98
Et-PFOSA-AcOH (2-(N-ethyl-perfluorooctane sulfonamido) acetic acid)‡			
%<LOD* (LOD=0.2)	95.	93	
Geometric mean (95% CI)	0.11 (0.10–0.12)‡	0.11 (0.09–0.14)‡	0.20
Me-PFOSA-AcOH (2-(N-methyl-perfluorooctane sulfonamido) acetic acid)			
%<LOD* (LOD=0.2)	26	21	
Geometric mean (95% CI)	0.29 (0.26–0.33)	0.30 (0.21–0.42)	0.95
PFDeA (perfluorodecanoic acid)			
%<LOD* (LOD=0.2)	9	4	
Geometric mean (95% CI)	0.40 (0.37–0.43)	0.41 (0.32–0.51)	0.52
PFNA (perfluorononanoic acid)			
%<LOD* (LOD=0.1)	2	0	
Geometric mean (95% CI)	1.20 (1.12–1.30)	1.23 (0.99–1.52)	0.33
PFOSA (perfluorooctane sulfonamide)‡			
%<LOD* (LOD=0.1)	88	89	
Geometric mean (95% CI)	0.11 (0.10–0.12)‡	0.13 (0.05–0.34)‡	0.88
PFOS (perfluorooctane sulfonic acid)			
%<LOD* (LOD=0.2)	0	0	
Geometric mean (95% CI)	12.04 (11.12–13.05)	13.10 (10.52–16.33)	0.10

*LOD: limit of detection (in ng/ml).

‡Most concentrations for this analyte are below the LOD.

Table 3

Association between serum concentrations of PFCs and risk for gestational diabetes (GDM), LIFE Study, 2005–2009.

	Unadjusted OR (95% CI)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)
PFOA (perfluorooctanoic acid)			
Per SD increment (0.43)	1.61 (1.05,2.49)	1.85 (1.15,2.98)	1.86 (1.14,3.02)
Et-PFOSA-AcOH (2-(N-ethyl-perfluorooctane sulfonamido) acetic acid)‡			
Per SD increment (0.05)	1.26 (0.89,1.79)	1.24 (0.87,1.79)	1.25 (0.87,1.80)
Me-PFOSA-AcOH (2-(N-methyl-perfluorooctane sulfonamido) acetic acid)			
Per SD increment (0.24)	1.06 (0.72,1.55)	1.06 (0.72,1.55)	1.05 (0.71,1.54)
PFDeA (perfluorodecanoic acid)			
Per SD increment (0.21)	1.07 (0.73,1.55)	1.07 (0.72,1.58)	1.04 (0.70,1.53)
PFNA (perfluorononanoic acid)			
Per SD increment (0.32)	1.08 (0.73,1.60)	1.09 (0.72,1.63)	1.06 (0.70,1.60)
PFOSA (perfluorooctane sulfonamide)‡‡			
Per SD increment (0.03)	1.08 (0.76,1.55)	1.08 (0.76,1.55)	1.07 (0.74,1.55)
PFOS (perfluorooctane sulfonic acid)			
Per SD increment (0.55)	1.15 (0.78,1.70)	1.16 (0.77,1.76)	1.13 (0.75,1.72)

OR1 adjusted for age (years), BMI (kg/m2), and parity conditional on gravidity (never pregnant/pregnant without live birth/ pregnant with previous birth)

OR2 Adjusted for age (years), BMI (kg/m2), parity conditional on gravidity (never pregnant/pregnant without live birth/ pregnant with previous birth), race/ethnicity (White/non-White) and smoking (yes/no)

‡95% concentrations for this analyte are below the LOD

‡‡89% concentrations for this analyte are below the LOD

SD values presented were log transformed of the original SD