A prospective study of prepregnancy serum concentrations of perfluorochemicals and the risk of gestational diabetes

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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: Not applicable.
Patient(s): Among 501 women recruited upon discontinuing contraception for the purpose of becoming pregnant, 258 (51%) became pregnant and were eligible for the study, of which 28 (11%) reported having physician-diagnosed GDM during follow-up.
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 concentration (ng/mL, log-transformed) and six other PFCs were estimated with the use of logistic regression after adjusting for age, prepregnancy 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 1.86 [95% CI 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.
Conclusion(s): Our findings suggested that higher environmentally relevant concentrations of PFOA were significantly associated with an increased risk of GDM. If corroborated, these findings may be suggestive of a possible environmental etiology for GDM. (Fertil Steril® 2015;103:184–9. ©2015 by American Society for Reproductive Medicine.)
Key Words: Perfluorochemicals (PFCs), perfluorooctanoic acid (PFOA), gestational diabetes, pregnancy

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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 nonhuman animal research suggests that PFOA has the ability to disrupt endocrine signaling and, subsequently, to mitigate metabolic and vascular functions (4, 5). PFCs repel grease and 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

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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 after 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 lipid concentrations. In particular, a positive association has been reported between serum PFOA concentrations and serum cholesterol and triglyceride levels (13–17) as well as serum uric acid levels (18). All of these traits have been implicated in the development of diabetes, including both type 2 diabetes and GDM. As yet, we are unaware of any published research focusing on PFOA and other PFCs and GDM, which contrasts with an evolving body of evidence from cross-sectional studies of diabetes among nonpregnant individuals (19–21). In the present study, we sought to prospectively evaluate preconception serum concentrations of PFOA and other PFCs, as measured in women discontinuing contraception for the purpose of becoming pregnant in relation to the risk of GDM, with the use of data from the Longitudinal Investigation of Fertility and the Environment (LIFE) study.

MATERIALS AND METHODS

Study Design, Population, and Data Collection

The study population was composed of 272 women achieving pregnancy while participating in the LIFE study and submitting a pregnancy journal (22). Specifically, the cohort was recruited in 16 counties in Michigan and Texas during the years 2005–2009 upon discontinuing contraception for the purpose of becoming pregnant and were followed daily until an hCG-positive pregnancy test and then through the first 8 weeks of pregnancy. Subsequently, women were followed monthly until delivery. By design, inclusion criteria were minimal: 1) women aged 18–40 years; 2) in a committed relationship; 3) menstrual cycle length of 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 after completion of the examination. Women were instructed in the completion of daily journals while trying for pregnancy (for up to 12 months), and through the first 8 post-conception weeks of gestation for women achieving pregnancy. Then the women completed monthly pregnancy journals that were designed to capture lifestyle during pregnancy and results from prenatal screening and testing. Specifically, they recorded the results of antenatal testing or any physician-diagnosed gravidity along with other information from prenatal visits (i.e., ultrasonographic findings and expected date of delivery). The ascertainment of GDM was based on self-report; women were queried from 9 weeks after the last menstrual period to record a physician diagnosis of GDM. Full human subject research approval was obtained from all collaborating institutions, and every participant gave informed consent before participation. Because universal screening for GDM is recommended to start at 24 weeks of gestation (8), the final analytic population of the study included 258 women who had a pregnancy lasting ≥24 weeks of gestation.

Measurement of Serum PFCs

Established operating protocols using 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), and 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 QC samples were evaluated with the use of standard statistical probability rules (25). We used machine-observed concentrations without substituting concentrations below the limits of detection, which is 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 ratio (OR [95% CI]) of GDM per standard deviation (SD) increment in PFC concentration, and the OR 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