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Association of serum levels of perfluoroalkyl substances with gestational diabetes mellitus and postpartum blood glucose

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ABSTRACT

This study was conducted to examine the association of perfluoroalkyl substance (PFAS) exposure with gestational diabetes mellitus (GDM) risk and postpartum fasting blood glucose. We used a 1:2 matched case–control study with 84 GDM subjects and 168 healthy pregnant women from Beijing, China. The maternal blood was collected at 1–2 days before delivery, and eight linear isomers and fourteen branched isomers were determined in maternal serum. Logistic regression analyses were performed to evaluate the associations after adjusting for potential confounders. The median of the sum of levels of total PFASs was 4.24 ng/mL with a interquartile range (IQR) of 2.82–6.54 ng/mL. Although maternal PFAS exposure was not associated with risk of GDM, significant positive associations were observed between evaluated exposure to specific PFAS congeners and increasing blood glucose. The odds ratio (ORs) of the highest category of postpartum fasting blood glucose for perfluoro-1-metylheptylsulfonat (1m-PFOS), perfluoro-3/4-metylheptylsulfonat (3m+4m-PFOS), perfluoro-5-metylheptylsulfonat (5m-PFOS), and perfluorohexane sulfonate (PFHxS) were 2.03 (95% CI: 1.09–3.77), 1.93 (95% CI: 1.04–3.58), 2.48 (95% CI: 1.33–4.65), and 2.26 (95% CI: 1.21–4.21), respectively, suggesting negative effects of maternal exposure to specific PFAS compounds on glucose metabolism.

Introduction

Perfluoroalkyl substances (PFASs) are high-volume synthetic chemicals that have been extensively used as surfactants, repellents, paper and textile coatings, non-stick frying pan coatings and food packaging, resulting in ubiquitous contamination and human exposure worldwide (Lau et al., 2007; Lindstrom et al., 2011; Shi et al., 2010; Wang et al., 2017; Zhao et al., 2014). Potential routs of human exposure include ingestion of diet, water, and indoor dust as well as inhalation, although the exposure pathways remain unclear (Lau et al., 2007). Detectable PFAS compounds in biological matrix from non-occupational populations in various countries/regions have been heavily reported (Choi et al., 2017). Due to their persistence, the elimination in human body is very slow, and the estimated half-life is 3–5 years for some well-known PFAS

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compounds, like perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) (Olsen et al., 2007).

PFAS compounds are structurally homologous with fatty acids and plausibly have endocrine-disrupting properties, and these chemicals may be involved in the development of energy metabolism dysfunction (Audouze et al., 2013; Lau et al., 2007; Lv et al., 2013; White et al., 2011). Exposure to PFASs could up-regulate the fatty acid oxidation pathways and increase oxidative stress that were associated with diabetes (Guruge et al., 2006; Hu et al., 2005; Karpe et al., 2011). However, on the other hand, PFASs have also shown the ability to bind peroxisome proliferator-activate receptors (PPARs) as agonist that are critical to improve insulin resistance (Staels and Fruchart, 2005; Vanden Heuvel et al., 2006). Thus, the potential mechanisms underlying disrupted glucose and lipid metabolism by PFAS exposure remain unclear and controversial. And some studies have statistically linked specific PFAS congeners exposure with insulin resistance (Fleisch et al., 2017; Lin et al., 2009; Lind et al., 2014; Timmermann et al., 2014), β-cell function (Conway et al., 2016), impaired glucose homeostasis and risk of type 2 diabetes (T2D) (Lind et al., 2014; Su et al., 2016).

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first recognition during pregnancy, is a growing health concern and related to the increased risk of T2D and cardiovascular diseases for both mother and offspring as well as other adverse outcomes like preeclampsia and fetal macrosomia (Metzger et al., 2007). The GDM incidence is escalating in parallel with dramatically increasing rates of T2D as well as obesity worldwide. Some risk factors for GDM, including maternal characteristics as well as lifestyle, and dietary habits, have been well documented and emerging data indicate a possible environmental etiology for GDM (Smarr et al., 2016; Vafeiadi et al., 2017; Zhang et al., 2016). So far, there is very scarce literature on investigating the correlation between PFASs exposure and the risk of GDM as well as maternal glucose metabolism (Zhang et al., 2015). In the present study, we conducted a 1:2 matched case–control study with a study population including 84 GDM subjects and 168 healthy pregnant women that were age-matched, and various PFASs were measured in maternal serum to evaluate the association of PFAS exposure with GDM and postpartum fasting blood glucose levels.

1. Methods

1.1. Study population

This study was designed as a 1:2 pair-matching case–control study. 84 GDM subjects were recruited from pregnant women diagnosed as GDM from January to March, 2013 at Haidian Maternal & Child Health Hospital in Beijing, China. The diagnoses of GDM follow the Diagnostic Criteria for Gestational Diabetes Mellitus (WS311-2011) released by Ministry of Health of China. Briefly, 75 g oral glucose test (OGTT) is applied, and GDM was diagnosed if one or more cut-off values were equal or exceed, which coincided with the recommendation from the International Association of Diabetes and Pregnancy Study Groups (IADPSG). The non-GDM controls were randomly selected from healthy pregnant women without family history of diabetes at the same hospital during the same study period. By the pair-matched design, each GDM case and control set had comparable age (difference between birthdays within 2 years). All subjects came back to the hospital for the six-week postpartum checkup and the levels of fasting blood glucose were measured and recorded.

The study was approved by the Ethics Committee of China National Center for Food Safety Risk Assessment. All pregnant women were told the purpose of the study and signed informed consent.

1.2. Blood sampling and analysis

Maternal vein blood samples were collected at 1–2 days before the delivery, and after centrifugation, serum samples were immediately frozen and stored at −80°C. The analysis of PFASs in serum samples were conducted using the similar method in our previous study (Wang et al., 2017) with silight modification. Briefly, after spiking with isotopic internal standards, 200 μL of 4% (V/V) phosphoric was added into 200 μL serum samples. The mixture was homogenized and subsequently cleaned using a WAX cartridge. 3 mL 9% ammonium hydroxide in methanol was applied to elute the analytes. The eluent was concentrated to near dryness and reconstituted by 200 μL of water/methanol mixture (1:1, V/V). PFASs were measured by an ultra-performance liquid chromatography (UPLC) system coupled to a triple quadrupole MS system (ACQUITY UPLC-Xevo TQ-S, Waters, USA) equipped with a HSS PFP column (2.1 mm × 150 mm × 1.8 μm). Eight kinds of linear PFASs and fourteen branched PFASs were measured in the present study, which listed in Appendix A **Table S1**.

Each batch for measurement includes two procedural blank and 20 serum samples as well as two QC samples. Procedural blank samples were analyzed to examine the potential contamination in our laboratory. Linear PFASs and branched isomers were quantified by their six-point standard calibrations (0.5–10 ng/mL), which were injected before each batch analysis and showed the strong linearity ($r^2 > 0.99$). The limit of detection of various PFASs was in the range of 0.003–0.1 ng/mL and the recovery ranged from 76.7% to 115.6% that were listed in details in Appendix A **Table S1**. Standard reference materials (SRMs), Organic contaminants in non-fortified human serum (SRM1957) and Organic contaminants in fortified human serum (SRM1958) purchased from National Institute of Standards and Technology (NIST) were employed to assess the accuracy of our measurements. The laboratory performance was validated by successfully participating in the Global Interlaboratory Assessment on Persistent Organic Pollutants in Human plasma organized by United Nations Environment Programme (UNEP) in 2016 and Z-scores for n-PFOA, PFNA, PFDA, PFUnDA, PFHxS, n-PFOS and branched PFOS isomers were in the range of −0.41–1.09.

1.3. Covariates

Previous epidemiologic studies have shown that age, family history of diabetes, and previous GDM or diabetes are associated with a raised prevalence of GDM. To address these important

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