Environment International 114 (2018) 12–20

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Perfluoroalkyl substances, glucose homeostasis, and gestational diabetes mellitus in Chinese pregnant women: A repeat measurement-based prospective study

Hexing Wang[a], Jiaqi Yang[a], Hongyi Du[b], Linji Xu[c], Shuping Liu[c], Jianping Yi[c], Xu Qian[b], Yue Chen[d], Qingwu Jiang[e], Gengsheng He[a,*]

[a] *Department of Nutrition and Food Hygiene, School of Public Health, Key Laboratory of Public Health Safety, Ministry of Education, Fudan University, Shanghai 200032, China*
[b] *Department of Maternal, Child and Adolescent Health, School of Public Health, Key Laboratory of Public Health Safety, Ministry of Education, Fudan University, Shanghai 200032, China*
[c] *Maternal and Child Health Care Hospital, Tangshan Municipality, Tangshan 063000, Hebei province, China*
[d] *School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Ontario K1G5Z3, Canada*
[e] *Department of Epidemiology, School of Public Health, Key Laboratory of Public Health Safety, Ministry of Education, Fudan University, Shanghai 200032, China*

ARTICLE INFO

Handling Editor: Lesa Aylward

Keywords:
Perfluoroalkyl substances
Glucose homeostasis
Gestational diabetes mellitus
Repeat measurement
Prospective study
Chinese pregnant women

ABSTRACT

Background: Exposure to perfluoroalkyl substances (PFASs) can affect glucose homeostasis and has been suggested as a potential risk of diabetes mellitus, but data are limited for pregnant women.
Objectives: We aimed to explore the associations of exposure to PFASs with glucose homeostasis and gestational diabetes mellitus (GDM) in Chinese pregnant women.
Methods: The current study was conducted in Hebei Province of Northern China between 2013 and 2014 and 560 pregnant women were recruited in their early term of pregnancy and two representative serum PFASs, perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS), were measured. In 385 pregnant women who completed oral glucose tolerance test (OGTT), the associations of serum PFOA and PFOS concentrations with fasting blood glucose (FBG), fasting insulin (FIns), and homeostasis model assessment of insulin resistance (HOMA-IR) in the early, middle, and late terms of pregnancy and occurrence of GDM were examined using linear and Cox proportional hazard regression models. The reproducibility of serum PFASs during pregnancy was assessed in 230 pregnant women.
Results: The intraclass correlation coefficients of serum PFASs, covariates, and outcomes based on averaged repeat measurement (0.35–0.96) were higher than those based on single measurement (0.16–0.92). Serum PFOA was positively associated with averaged FIns and HOMA-IR in the early, middle, and late terms of pregnancy and averaged blood glucose level at 1 h and 2 h of OGTT, but serum PFOS tended to be negatively associated with averaged FBG and OGTT blood glucose. The adjusted hazard ratios of GDM associated with serum PFOA and PFOS were 1.98 (95% confidence interval: 0.70–5.57; p-value: 0.197) and 0.71 (0.29–1.75; 0.453), respectively.
Conclusions: Our data raised a possibility that exposure to PFASs might have different influences on glucose homeostasis and GDM in Chinese pregnant women. More lab and human studies are needed to further test the hypothesis and investigate potential mechanisms.

1. Introduction

Persistent organic pollutants (POPs) are a diverse group of ubiquitous environmental contaminants with properties of slow degradation, lipid solubility, and bio-magnification in the food chain (Lau et al., 2007) and primarily consisting of organochlorines, brominated compounds, and perfluorinated compounds (Taylor et al., 2013). Perfluoroalkyl substances (PFASs) are a family of perfluorinated compounds consisting of a carbon backbone (C4-C18) and a charged functional moiety (e.g. carboxylate, sulfonate, or phosphonate) (Giesy and Kannan, 2002). PFASs have been used as surfactants and surface protectors in numerous industrial and commercial applications for more than half a century (Manzano-Salgado et al., 2017). Consequently, aquatic environment and food are contaminated by PFASs (Eriksson

* Corresponding author at: No. 130 Dongan Road, Shanghai 200032, China.
E-mail address: gshe@shmu.edu.cn (G. He).

https://doi.org/10.1016/j.envint.2018.01.027
Received 4 November 2017; Received in revised form 7 January 2018; Accepted 26 January 2018
Available online 20 February 2018
0160-4120/

et al., 2013). The biological monitoring, especially in blood, has demonstrated that humans are extensively exposed to PFASs and the representative species are two C8-backbone derivatives, perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) (Kato et al., 2014; Kishi et al., 2015; Yang et al., 2016). PFASs have different chemical structures and applications and may have different metabolisms, action mechanisms, and adverse health effects compared with other groups of POPs (Conder et al., 2008; Lau et al., 2007).

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first recognition in pregnancy, has become a growing health concern (Feig et al., 2014; Zhang et al., 2016). GDM can pose adverse effects on both mothers and their children and its pathogenesis is different from type I or II diabetes mellitus (Lee et al., 2007). Mothers with GDM have an increased risk for type 2 diabetes mellitus after pregnancy and their children are more likely to become macrosomic, and to have childhood obesity and adulthood glucose intolerance (Zhang et al., 2016). Lab studies have suggested that PFASs could disturb glucose homeostasis by multiple mechanisms, such as sex or thyroid hormone endocrine (Lee and Choi, 2017; Sonthithai et al., 2016), supply of oxygen to islet cell (Conway et al., 2016), peroxisome proliferator-activated receptor alpha (PPARα) (Vanden et al., 2006), and oxidative stress derived from fatty acid oxidation (Guruge et al., 2006). Epidemiological studies have shown significant associations of exposure to PFASs with types I and II diabetes mellitus and other indices related to glucose homeostasis in both children and adults (Conway et al., 2016; Fleisch et al., 2017; Halldorsson et al., 2012; Karnes et al., 2014; Lin et al., 2009; MacNeil et al., 2009), but only three human studies examined the association of exposure to PFASs with glucose homeostasis and GDM in pregnant women and did not account for important covariates related to diet and physical activity (Shapiro et al., 2016; Valvi et al., 2017; Zhang et al., 2015) and one study ascertained GDM based on self-reporting (Zhang et al., 2015).

In the current prospective study of 560 pregnant women conducted in Hebei Province of China, we examined the associations of exposure to two representative PFASs, PFOA and PFOS, with fasting blood glucose (FBG), fasting insulin (FIns), homeostasis model assessment of insulin resistance (HOMA-IR), and GDM incidence. Our study had repeat measurements of serum PFOA and PFOS and measured key covariates related to diet and physical activity.

2. Material and methods

2.1. Study population

A cohort study of pregnant women was conducted in the Maternal and Child Health Care Hospital of Tangshan City of Hebei Province between September 2013 and December 2014. Eligible subjects were healthy pregnant women aged 20–40 years in the early term of pregnancy (5–15 gestational weeks). Pregnant women were excluded if they had serious metabolic or immune diseases, such as pre-pregnant diabetes mellitus, chronic hypertension, systemic lupus erythematosus, hypothyroidism, and among others. A total of 924 pregnant women in their early term of pregnancy were recruited initially after they signed a written consent form. Among them, 86 were excluded due to multiple pregnancies, miscarriage, pregnancy termination, stillbirth, or communicable diseases. One hundred and forty-seven pregnant women were refused to be revisited during the follow-up and 691 were followed up to the date of delivery. The selection of pregnant women and their participation along pregnancy were detailed in Fig. 1.

Of 771 pregnant women who completed the questionnaire survey and provided blood specimens in the early term of pregnancy, 560 were randomly selected and measured for serum PFASs (Fig. 1). Among the 560 pregnant women, 385 aged 19–38 years (median: 27 years) were tested for oral glucose tolerance test (OGTT) in the middle term of pregnancy to determine if they had GDM and selected to explore the association of serum PFASs with glucose homeostasis and GDM. To assess the within-person variation, 230 out of 560 women had a repeat measurement of PFASs in the middle term of pregnancy. This study was reviewed and approved by the Institutional Review Board of Fudan University.

2.2. Analysis of PFASs

The concentrations of PFOA and PFOS in serum were determined using an isotope-dilution method based on ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry (UPLC-Q/TOF MS) following the method established in our lab. Briefly, after an aliquote (300 μL) of serum was spiked with 20 μL of isotope-labeled internal standard (PFOA-$^{13}C_8$) at a concentration of 2 μg/mL, the mixture was hydrolyzed by β-glucuronidase. The hydrolyzed mixture was purified by solid phase extraction and then PFASs were determined by UPLC-Q/TOF MS. The limit of quantification, defined as a signal-to-noise ratio of 10, was 0.04 ng/mL for PFOA and 0.05 ng/mL for PFOS. Their recoveries in spiked serum samples ranged from 81.5% to 105.8% with the relative standard deviations varying between 6.2% and 10.3%. The detailed information of analytical method was provided in Supplemental Material.

2.3. Outcomes

Study outcomes included FBG, FIns, HOMA-IR, and GDM. HOMA-IR was calculated from FBG × FIns/22.5 (Chen et al., 2017). GDM was determined in the middle term of pregnancy based on FBG and blood glucose levels at 1 h and 2 h of 75 g OGTT following the diagnostic criteria proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in 2010: FBG ≥ 5.1 mmol/L, blood glucose level at 1 h of OGTT ≥ 10.0 mmol/L, or blood glucose level at 2 h of OGTT ≥ 8.5 mmol/L (Metzger et al., 2010). OGTT was measured at the gestation week ranging from 21 to 26 with a mean (median) of 26.8 (26) and a standard deviation of 2.2. Obstetric nurses collected specimens of peripheral venous blood in their early, middle and late terms of pregnancy and FBG and FIns were determined in each term of pregnancy. Blood glucose and blood insulin were measured by using Beckman coulter AU5821 biochemical analyzer and Beckman coulter DXI800 chemiluminiscence analyzer following the standard protocols provided by the manufacturers.

2.4. Covariates

Fourteen potential covariates were selected empirically or based on literature (Table 2) (Radesky et al., 2008; Zhang et al., 2016). All covariates were obtained from structured questionnaires administrated by trained interviewers in their early, middle and late terms of pregnancy. There were four career types: white-collar job (clerk, technician, and administrator), blue-collar job (worker and peasant-worker), other category (commercial service people, self-employed people, private entrepreneur, and other), and unemployment or underemployment. Food frequency questionnaire (FFQ), part of the structured questionnaire, was slightly modified from the 2010 China National Nutrition and Health Survey questionnaire in the bases of local dietary preference and consisted of 100 food items of 11 food categories, including cereal, beans, vegetables, mushrooms and alga, fruits, dairy, meat, aquatic products, eggs, snacks, and drinks and spices. Aquatic products included 12 items of five categories (freshwater fish, marine fish, shrimp, crab, and mollusk). Daily intakes of meat, vegetable, aquatic products, and energy were calculated based on FFQ. Daily physical activity was measured using a modified Danish physical activity scale, which has been validated among urban pregnant women in eastern China (Jiang et al., 2015). Pre-pregnant body weight and height of women were self-reported and body mass index (BMI) was calculated from dividing body weight (kg) by body height square (m^2). Using the BMI-based cutoff values for Chinese adults proposed by the Working