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Relation between cadmium exposure and gestational diabetes mellitus

Yuling Xing[a], Wei Xia[a], Bin Zhang[b], Aifen Zhou[b], Zheng Huang[a], Hongling Zhang[c], Hongxiu Liu[a], Yangqian Jiang[a], Chen Hu[a], Xiaomei Chen[a], Shunqing Xu[a], Yuanyuan Li[a,*]

[a] Key Laboratory of Environment and Health (HUST), Ministry of Education & Ministry of Environmental Protection, State Key Laboratory of Environmental Health (Incubation), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China
[b] Wuhan Medical and Health Center for Women and Children, Wuhan, Hubei, People's Republic of China
[c] College of Health Sclence Nursing, School of Wuhan Polytechnic University, Wuhan, Hubei, People's Republic of China

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ABSTRACT

Background: Cadmium (Cd) has been associated with type 2 diabetes in general population. However, the role of Cd in the occurrence of Gestational diabetes mellitus (GDM) remains unclear.
Objectives: Our study was aimed at investigating whether Cd exposure during pregnancy was associated with increased risk of GDM.
Methods: Cd concentrations were measured in urine samples from 6837 pregnant women in Wuhan, China, from 2012 to 2014. A "modified Poisson" model with a robust error variance was used to examine the association of GDM with continuous natural logarithm (ln) transformed urinary Cd or quartiles of urinary Cd levels.
Results: For about 3-fold increase in Cd concentrations, there were 16% [relative risk (RR) =1.16; 95% confidence interval (CI): 1.03, 1.33] increase in risk of GDM. Compared with women in the lowest quartile of urinary Cd levels, women in the highest quartile had 1.30 higher risk of GDM [95% CI: 1.05, 1.61; p-trend < 0.05]. Further analyses indicated overweight/obese women with higher urinary Cd levels had significantly higher risk of GDM, compared with women in the reference category of lowest quartile of Cd and normal pre-pregnancy body mass index [RR =2.71; 95% CI: 1.81, 4.07].
Conclusions: Our study presented a significantly positive association between urinary Cd levels and risk of GDM, supporting the hypothesis that environmental exposure to Cd may contribute to the development of GDM.

1. Introduction

The prevalence of gestational diabetes mellitus (GDM), one of the most common pregnancy complications, has been greatly increasing over the past few decades in the world (American Diabetes, 2015; Meetoo et al., 2007; Yang et al., 2009). GDM is reported to have short-term and long-term negative effects on both mothers and infants, including high cesarean section rate, pre-eclampsia, and increased lifetime risks of type 2 diabetes and obesity, etc. (Hillier et al., 2007; Metzger et al., 2007; Seshiah et al., 2009; Xiang et al., 2010). In addition to the well-established risk factors such as age and high pre-pregnancy body mass index (pre-pregnancy BMI), recent studies have indicated that environmental risk factors may contribute to the increased prevalence of GDM (Aharoni et al., 1992; Ettinger et al., 2009; Peng et al., 2015; Shapiro et al., 2015; Woods et al., 2008).

Cadmium (Cd), a toxic heavy metal, is widely used in electroplating processes, batteries, alloys, dyes, plastics, etc. Environmental exposure to Cd can be through food, cigarette smoke, and pollutant air and water (Faroon et al., 2012; Peters et al., 2010). Cd has long been recognized as an occupational and environmental risk factor due to toxic effects on many organs (Akesson et al., 2005; McElroy et al., 2006a; Noonan et al., 2002; Satarug et al., 2011; Tellez-Plaza et al., 2013). The potential role of Cd in type 2 diabetes has been demonstrated in an increasing number of experimental and epidemiological studies. Both acute and sub-chronic exposures to Cd have been shown to induce diabetogenic effects in animal models (Edwards and Prozialeck, 2009; Han et al., 2003; Lei et al., 2007). A study using data from NHANES III suggested that urinary Cd levels were associated with both impaired fasting glucose and diabetes (Schwartz et al., 2003), which was confirmed by some following epidemiological studies in general population (Afridi et al., 2011; Afridi et al., 2008; Haswell-Elkins et al., 2008; Kolachi et al., 2011). However, at the present stage, evidence of relationship between Cd exposure and GDM remains limited. We are aware of only two studies addressed Cd-GDM relationship. A case–control study nested within a cohort of 1359 pregnant women in China presented a positive association between GDM and meconium Cd concentrations (Peng

* Corresponding author at: School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, People's Republic of China.
E-mail address: liyuanyuan@hust.edu.cn (Y. Li).

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et al., 2015), while a study from Canada did not find an association between GDM and blood Cd levels in early pregnancy (Shapiro et al., 2015). It is worth mentioning that urinary Cd concentration remains one of the best tools to assess long-term exposure to Cd in prospective and longitudinal studies (Vacchi-Suzzi et al., 2016). Till now, no prior published study has addressed the relation between Cd levels in urine and GDM.

In the present study, we aimed to evaluate whether the Cd exposure, which is reflected by urinary Cd concentrations, is associated with GDM. We also explored whether the Cd-GDM associations were modified by pre-pregnancy BMI, because pre-pregnancy BMI is reported to affect Cd body burden (Skalnaya et al., 2014; Tinkov et al., 2017) and be associated with GDM (Yang et al., 2009).

2. Methods

2.1. Study population

This was a retrospective cohort study conducted at the Wuhan Women and Children Medical Care Center, a major maternity hospital in Wuhan, China. Women who delivered a live singleton birth and provided urine samples before delivery were recruited. The study was approved by the ethics committees of Tongji Medical College, Huazhong University of Science and Technology, and the study hospital. Each participant signed an informed consent after the introduction of the study in details. From September 2012 to October 2014, 7302 women were enrolled. Women who had kidney disease (n = 4), missing information on education (n = 17), history of hypertension (n = 26) and diabetes (n = 3), Cd values suggestive of renal impairment [> 2 μg/g creatinine (n = 405)] (Hartwig et al., 2017; Nordberg et al., 2003), and women who smoked (n = 8) and drank during pregnancy (n = 2) were excluded. Finally, 6837 pregnant women were included in the present study.

2.2. Outcomes and covariates

The information on the diagnosis of GDM, which was made by obstetricians of the hospital, was derived from the medical records. After the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended the new set of diagnostic criteria for GDM (American Diabetes, 2011), an oral glucose tolerance test (OGTT) administrated between 24 and 28 gestational weeks, has become a part of routine prenatal care in the study hospital. Women were diagnosed with GDM by obstetricians based on the IADPSG's criteria (American Diabetes, 2011), that if any of the 75-g OGTT glucose levels met or exceeded the following criteria: fasting: 92 mg/dl (5.1 mmol/L), 1-h: 180 mg/dl (10.0 mmol.l), and 2-h: 153 mg/dl (8.5 mmol/L).

Face-to-face interviews, which were administered by specially trained research nurses, were conducted within 3 days before or after delivery in the hospital. Data on sociodemographic characteristics (age, education, household income, employment et al.) and lifestyle factors (such as smoking and drinking status during pregnancy) were collected. Self-reported pre-pregnancy body weight and height measured at the hospital, which were derived from records of the first prenatal visit, were used to calculate pre-pregnancy BMI. Gestational age (in days) was obtained based on the date of last menstrual period (LMP). Data on medical histories (delivery, reproductive history, pregnancy complications and disease) was obtained from medical records.

2.3. Cd exposure assessment

We assessed pregnant women's Cd exposures using urinary Cd concentrations. Urine samples were collected into polypropylene tubes within 3 days before delivery and were frozen at −20 °C until analysis. Urinary Cd levels were measured using inductively coupled plasma mass spectrometry (ICP-MS; Agilent 7700, Agilent Technologies, Waldbronn, Germany). We also measured the urinary concentrations of total arsenic (As) and chromium (Cr), as they were related to GDM in previous studies (Ettinger et al., 2009; Sundararaman et al., 2012). Briefly, urine samples were pre-thawed at room temperature and 1 mL of urine samples were nitrated with 4 mL of 3% HNO_3 overnight. After this, the resulting samples were digested by ultrasound at 40 °C for 1 h. The ICP-MS was operated in helium mode and ^{111}Cd were monitored. A blank control with 3% HNO_3 was set for each batch of samples to assess possible contamination. We used the standard Reference Material Human Urine (SRM2670a, National Institute of Standards and Technology, Gaithersburg, MD, USA) to assess the instrument stability in each batch. Field blank and procedure blank were also used for quality control, in which Cd was not detected. The limits of detection (LODs) for Cd, As, and Cr were 0.003, 0.003 and 0.005 respectively (μg/L), and there were no sample has concentration below the LODs. Urinary creatinine levels, which were measured using a creatinine kit (Mindray BS-200 CREA Kit, Shenzhen Mindray Bio-medical Electronics CO.,LTD, Shenzhen, China) were used to control for variations in urine dilution in spot urine specimens. The final concentration of urinary Cd was expressed as μg/g creatinine.

2.4. Statistical analysis

We first summarized baseline characteristics and Cd concentrations of the pregnant women overall and compared them according to GDM status. A “modified Poisson” model which uses sandwich error estimation to produce robust standard errors (Zou, 2004) was used to assess the adjusted relative risks (RRs) and the 95% confidence intervals (CIs), with exposure as a continuous variable [natural logarithm-transformed (ln-transformed)] or as a categorical variable (quartiles). The use of a robust error variance procedure is able to rectify the overestimated error for the estimated relative risk from traditional Poisson regression (Zou, 2004). Quartiles were defined based on the distribution of creatnine-corrected Cd levels. We conducted trend tests using the median value within each quartile of urinary Cd as the score variable. Variables were considered to be potential confounders based on biologic plausibility or statistical reason-altering parameter estimates of the main effect by over 10%. In the final models, age (years), pre-pregnancy BMI (kg/m^2), educational background (years), passive smoking during pregnancy (yes/no), and pregnancy-induced hypertension (yes/no) were included.

Given that pre-pregnancy BMI is known to be associated with the risk of GDM, we further evaluated potential effect modification by pre-pregnancy BMI. We evaluated the multiplicative effect modification using a interaction term between urinary Cd levels and pre-pregnancy BMI, and the additivity of effect by modeling the relative risk due to interaction (RERI) using the method of variance estimates recovery method (Zou, 2008). The group with the lowest quartile of Cd and normal pre-pregnancy BMI (18.5–23.9 kg/m^2) was defined as the reference category.

We did sensitivity analysis which excluded women who had urine albumin above 30 μg/mL, which was evidence of renal damage (Paschal et al., 2000). We also conducted exploratory analyses to assess whether adjustment for urinary total As and Cr levels, or iron and calcium intake during pregnancy affect Cd-GDM association. In addition, we conducted a stratified analysis by women's age to assessing the risk of GDM among women with different ages.

All statistical analyses used robust standard error estimates and the alpha level of 0.05 to define statistical significance, and were completed using SAS program (version 9.4; SAS Institute Inc., NC, USA).

3. Results

Table 1 shows the characteristics of the study population. Of all 6837 women, 656 (9.59%) women were diagnosed with GDM. Compared with non-GDM women, women who developed GDM were more