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Gestational diabetes and offspring birth size at elevated environmental pollutant exposures

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is associated with increased availability of glucose and macronutrients in fetal circulation and macrosomia. Therefore, the role of GDM in the association between metabolism-disrupting chemicals and birth size deserves attention.

Objective: We examined whether GDM may mediate or modify the associations between maternal environmental pollutant exposures and offspring birth size measures.

Methods: We analyzed 604 Faroese pregnant women and their offsprings born in 1997–2000. Maternal pregnancy serum concentrations of organochlorine compounds (OCs: polychlorinated biphenyl (PCB) congeners and dichlorodiphenyldichloroethylene (DDE)), and five perfluoroalkyl substances (PFASs), and hair and cord blood mercury concentrations were measured. We used regression (single-pollutants) and structural equation models (SEMs) (multiple-pollutant analyses using latent constructs of OCs, PFASs and mercury) to estimate the associations with GDM and birth size measures, accounting for mediation and/or effect modification by GDM.

Results: Serum-DDE and hair-mercury concentrations were associated with GDM (adjusted OR per concentration doubling: 1.29; 95% CI: 0.94, 1.77 for DDE, and 0.79; 95% CI: 0.62, 0.99 for mercury), but in multiple pollutant-adjusted SEMs only a positive association between OC exposure and GDM remained significant (change in GDM odds per OC doubling: 0.45; 95% CI: 0.05, 0.86). PCB and overall OC exposure were positively associated with head circumference (SEM; mean change per OC doubling: 0.13 cm; 95% CI, 0.01. 0.25). Overall PFAS exposure was inversely associated with birth weight (SEM; mean change per PFAS doubling: − 169 g; 95% CI: − 359, 21), and for many single-PFASs we found a pattern of inverse associations with birth weight and head circumference in boys, and positive or null associations in girls. None of the environmental pollutants was associated with offspring length. GDM neither modified nor mediated the associations with birth size measures.

Conclusions: We found associations with GDM and offspring birth size to be specific to the environmental pollutant or pollutant group. Associations with birth size measures appear to be independent of GDM occurrence.

1. Introduction

The prevalence of gestational diabetes mellitus (GDM) is on the rise, currently affecting between 3% and 25% of pregnancies, depending on the population and the clinical criteria used for diagnosis (Zhu and Zhang, 2016). GDM is associated with a higher risk of fetal macrosomia (i.e. increased fetal growth and body fat deposition) (Kc et al., 2015) as well as, with higher risks of metabolic abnormalities in later life in the mothers and also their offsprings (Bellamy et al., 2009: Ehrlich et al., 2013; Zhu and Zhang, 2016). The etiology of GDM is multifactorial, and modifiable risk factors likely include exposures to environmental pollutants that can act as endocrine and metabolism disruptors in

Abbreviations: BMI, body mass index; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltricloroethane; GAM, generalized additive models; GDM, gestational diabetes mellitus; LOD, limit of detection; OCs, organochlorine compounds; PCBs, polychlorinated biphenyl; PFASs, perfluoroalkyl substances; PFDA, perfluorodecanoic acid; PFNA, perfluorononanoic acid; PFHxS, perfluorohexane sulfonic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; POPs, persistent organic pollutants; SEMs, structural equation models

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promoting weight gain and insulin resistance (Janesick and Blumberg, 2016; Lee et al., 2014; Magliano et al., 2014; Taylor et al., 2013). Exposures to persistent organic pollutants (POPs), such as organochlorine compounds (OCs) and perfluoroalkyl substances (PFASs), and exposures to metals, such as mercury, have been associated with increased risk for type 2 diabetes (reviewed in Lee et al., 2014; Kuo et al., 2013; Magliano et al., 2014; Taylor et al., 2013). However, only a few previous studies, with inconclusive findings, have specifically focused on risk of GDM (Jaacks et al., 2016; Peng et al., 2015; Shapiro et al., 2015 and Shapiro et al., 2016; Smarr et al., 2016; Vafeiadi et al., 2016; Zhang et al., 2015).

Exposure to POPs and metals may also interfere with intrauterine growth and adversely affect birth size (Casas et al., 2015; Govarts et al., 2012; Vrijheid et al., 2016; Bach et al., 2015; Murcia et al., 2016). Because the exposure passes from the mother to the fetus through the placenta (Kim et al., 2014; Manzano-Salgado et al., 2015; Needham et al., 2011), early life health outcomes may be affected through the direct action and toxicity of the pollutants to the placenta and fetal tissues, or they may be indirectly affected through alterations in hormone balance and tissue functions of the mother. However, whether potentially diabetogenic effects of environmental pollutants in the mother may mediate health outcomes seen in the offspring has not been previously examined.

We evaluated the associations of maternal exposures to several pollutants (OCs, PFASs and mercury) in regard to GDM occurrence and offspring birth size measures in a Faroese birth cohort, where a wide range of exposures occur through the consumption of fish and seafood (Weihe et al., 1996 and Weihe et al., 2008). Given the suspected association of environmental pollutant exposures with GDM occurrence, and the causal role of maternal hyperglycemia in regard to fetal metabolic programming and macrosomia (Kahraman et al., 2014; Kc et al., 2015), we hypothesized that the occurrence of GDM may mediate the associations of diabetogenic environmental pollutants with birth size measures. An alternate and plausible hypothesis is that the increased availability of glucose and other macronutrients in fetal circulation through the placenta in GDM cases (Araujo et al., 2015) may change the metabolic responses of the fetus to intrauterine chemical exposures (Goran et al., 2013; La Merrill et al., 2014; Valvi et al., 2012). Thus, we have also tested GDM status as a potential modifier of the association between environmental pollutant exposures and birth size measures.

2. Methods

2.1. Study population and data collection

We used information from 604 of the mother-child pairs recruited at 34 weeks of gestation at the National Hospital in Torshavn in the Faroe Islands between 1997 and 2000 (92% of the 656 mother-child pairs initially enrolled with complete data on key covariates). The ethical review committee of the Faroe Islands and the institutional review board at the Harvard T.H. Chan School of Public Health approved the study protocol, and written informed consent was obtained from all pregnant women.

Only singleton births were included. Information about maternal age at delivery, gestational age and child sex was extracted from the obstetric and medical records. Additional information was collected through interviews with the mothers at 14 days postpartum and included maternal education, parity, pre-pregnancy body mass index (BMI, i.e. weight in kg/[height in m]^2), gestational weight gain, family history of diabetes and smoking during pregnancy. Offspring weight (nearest 0.1 kg) and head circumference (nearest 0.1 cm) were measured at birth, and length (nearest 0.5 cm) was measured at postpartum day 14 by the midwife.

GDM diagnosis was extracted from the medical records. Following standard clinical guidelines (Berger et al., 2003) women with elevated fasting blood glucose concentrations and/or those considered at elevated risk for GDM based on their age, pre-pregnancy BMI, family history of diabetes, GDM in previous pregnancy, previous stillbirth, macrosomia in previous delivery and polyhydramnios were identified at 24–28 weeks of gestation and given a 2 h-oral glucose tolerance test (OGTT) (13% of the analysis population) to establish a possible GDM diagnosis (Berger et al., 2003; Dalgard et al., 2016). The reference group (GDM-free category) consisted of women at low risk who did not undergo an OGTT, and women non-diagnosed for GDM based on the OGTT results. Information from medical records was extracted also in regard to related pregnancy comorbidities including preeclampsia, which was not frequent in this cohort (prevalence equal to 1.5%).

2.2. Assessment of environmental pollutant exposures

Maternal serum was obtained at gestational week 34. Cord blood and maternal hair were collected at parturition, and transition milk 4–5 days later. All blood and milk samples were stored at − 80 °C until chemical analyses were performed at the University of Southern Denmark, as previously detailed (Grandjean et al., 2012; Heilmann et al., 2010).

OC concentrations in maternal serum were measured using gas chromatography with electron capture detection as the standard at the time. The OCs quantified included the major PCB congeners 138, 153 and 180, *p,p′*-dichlorodiphenyldichloroethylene (DDE) and *p,p′*-dichlorodiphenyltricloroethane (DDT). OC concentrations measured in breast milk were used to estimate serum concentrations for 20% of the mothers who did not have measured OC concentrations in serum (Pearson r between milk and serum concentrations ≥ 0.87 depending on OC) (Needham et al., 2011; Tang-Peronard et al., 2014). We substituted serum concentrations below the limit of detection (LOD) of 0.03 ng/mL by a value equal to half of the LOD. We calculated the sum of PCB congeners in maternal serum (ΣPCB) as the sum of PCB congeners 138, 153 and 180 multiplied by 2, because these were the most commonly detected congeners representing close to 50% of the total serum PCB concentrations (Grandjean et al., 1995). Because OCs are highly lipophilic concentrations were divided by the serum lipid concentrations and are expressed in μg/g lipid. The serum lipid content was calculated from cholesterol and triglyceride concentrations (Phillips et al., 1989) as determined by a kit-based analysis on a Konelab 20 Clinical Chemistry Analyzer (Thermo Fischer Scientific, Waltham, MA, US). In complimentary sensitivity analyses associations of OC concentrations uncorrected for lipids (in ng/mL) were adjusted by including the lipid content as a separate covariate in the models.

Maternal serum PFAS concentrations were measured using high-pressure liquid chromatography with tandem mass spectrometry. The quantified substances were: perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), perfluorodecanoic acid (PFDA) and perfluorononanoic acid (PFNA). Concentrations in all samples were above the LOD (> 0.03 ng/mL) and are expressed in ng/mL.

Hair and cord-blood mercury analyses have been described previously (Grandjean and Budtz-Jorgensen, 2007; Kim et al., 2014). Total mercury concentrations were measured in the proximal 1-cm hair segment (expressed in μg/g hair) that mainly reflects methylmercury exposure in particular during the second and third trimesters (Grandjean et al., 1999). Mercury in umbilical cord blood (expressed in μg/L) is almost entirely found in its methylated form, which can pass the placental barrier, and it is considered a better proxy of recent fetal exposure as compared to hair mercury (Grandjean et al., 1999). All measured concentrations in hair and cord blood were above the LODs.

2.3. Statistical analysis

A total of 604 mother-child pairs had complete information about maternal serum PFAS concentrations and the study outcomes, and fewer mother-child pairs had information about OC concentrations