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Pregnancy urinary phthalate metabolite concentrations and gestational diabetes risk factors

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ABSTRACT

Background: Epidemiologic studies suggest phthalate metabolite concentrations are associated with type 2 diabetes. GDM is a strong risk factor for type 2 diabetes. Little is known about phthalates and GDM risk factors (i.e. 1st trimester body mass index (BMI), gestational weight gain (GWG), and 2nd trimester glucose levels).
Methods: A total of 350 women participating in Lifecodes pregnancy cohort (Boston, MA), delivered at term and had pregnancy urinary phthalate metabolite concentrations. Nine specific gravity-adjusted urinary phthalate metabolites were evaluated. General linear regression was used to assess associations between quartiles of phthalate metabolites and continuous 1st trimester BMI and late 2nd trimester blood glucose. Linear mixed models were used for total GWG. Multivariable logistic regression was used for phthalate concentrations and categorized GWG and impaired glucose tolerance defined as glucose≥140 mg/dL based on a 50-gram glucose load test. Models were adjusted for potential confounders.
Results: There were no associations between 1st trimester urinary phthalate metabolite concentrations and 1st trimester BMI. Mono-ethyl phthalate concentrations averaged across pregnancy were associated with a 2.17 increased odds of excessive GWG (95% CI: 0.98, 4.79). Second trimester mono-ethyl phthalate was associated with increased odds of impaired glucose tolerance (adj. OR: 7.18; 95% CI: 1.97, 26.15). A summary measure of di-2-ethylhexyl phthalate metabolite concentrations were inversely associated with impaired glucose tolerance (adj. OR: 0.25; adj. 95% CI: 0.08, 0.85).
Conclusions: Higher exposure to mono-ethyl phthalate, a metabolite of the parent compound of di-ethyl phthalate, may be associated with excessive GWG and impaired glucose tolerance; higher di-2-ethylhexyl phthalate was associated with reduced odds of impaired glucose tolerance.

1. Introduction

The incidence of gestational diabetes mellitus (GDM), traditionally defined as any type of glucose intolerance that first appears in pregnancy, has tripled in the last 20 years (Diabetes Care, 2013; Dabelea et al., 2005; Thorpe et al., 2005). In fact, GDM now occurs in 7% of all pregnancies worldwide, with an incidence of up to 14% in some populations. As such, GDM is one of the most common complications of pregnancy (Diabetes Care, 2013). Risk factors of GDM include pre-pregnancy obesity (Chu et al., 2007; Torloni et al., 2009) and high gestational weight gain (GWG) in early pregnancy (Morisset et al., 2010, 2011). Elevated glucose levels in pregnancy are a hallmark of GDM, which is attributed to insufficient insulin production and glucose intolerance that results in hyperglycemia in pregnancy (Diabetes Care, 2013; Kjos and Buchanan, 1999). Even among women without overt GDM, elevated glucose levels in pregnancy have been linked to adverse pregnancy outcomes (Group et al., 2008; Huang et al., 2015). While lifestyle factors are involved with many GDM risk factors (i.e. pre-pregnancy obesity, GWG, and elevated glucose levels during pregnancy), a growing body of evidence suggests that environmental chemicals may also be involved in obesity, weight gain, and elevated glucose levels in non-pregnant populations (Alonso-Magdalena et al., 2011; Casals-Casas and Desvergne,

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2011; Polyzos et al., 2012; Thayer et al., 2012). Yet, few studies have evaluated the question of whether environmental chemical exposures during pregnancy could impact these factors.

Phthalates are one class of chemicals with evidence suggesting associations with obesity, weight gain, and elevated glucose levels in non-pregnant populations (Huang et al., 2014; James-Todd et al., 2012; Lind et al., 2012; Svensson et al., 2011). This class of environmental chemicals is ubiquitous and found in a variety of consumer products, including cosmetics and other personal care products (Crinnion, 2010; Hauser and Calafat, 2005). These chemicals are thought to increase the risk of obesity and alter glucose levels through their ability to bind to human proliferator activated receptors (PPAR) alpha and gamma (Desvergne et al., 2009). By binding to PPAR alpha and gamma, phthalates may modulate target genes leading to alterations in hormones associated with adipogenesis and glucose metabolism (Desvergne et al., 2009). While studies are still somewhat inconclusive on the associations for phthalates with obesity and diabetes (Goodman et al., 2014), some evidence suggest associations between higher BMI and elevated levels of mono-butyl phthalate (MBP) and mono(2-ethylhexyl) phthalate (MEHP), metabolites of di-butyl phthalate and di-2-ethylhexyl phthalate (DEHP), respectively (Yaghjyan et al., 2015). A prospective cohort study of non-pregnant women found an association between more rapid weight gain and higher levels of MBP and mono-benzyl phthalate (MBzP), the latter being a metabolite of di-benzyl phthalate (Song et al., 2014). Also, a study found an association between these same, and several other phthalate metabolites and elevated glucose and insulin levels in non-pregnant women without diabetes (Huang et al., 2014). Interestingly, one cross-sectional NHANES study found a 50%–100% increased odds of type 2 diabetes (T2DM) in non-pregnant women with higher concentrations of monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), mono-3(carboxypropyl) phthalate, and di-2-ethylhexyl phthalate, in a representative sample of the U.S. population (James-Todd et al., 2012). Given these findings in non-pregnant populations, evaluating whether these chemicals could impact body mass index, gestational weight gain, and glucose levels in pregnant populations has implications for future maternal and child health.

Only one study to our knowledge has evaluated phthalates and GDM and impaired glucose tolerance risk, finding that in ~2000 women there was little association when evaluating urinary phthalate metabolites in early first trimester and risk of GDM assessed between second and third trimesters (Shapiro et al., 2015). However, this study only assessed the exposure to phthalates, a non-persistent chemical, at one time-point. Also, they evaluated the association between urinary phthalate metabolites and overt GDM, without assessing risk factors related to GDM or actual glucose levels to determine whether these chemicals had an effect on GDM risk factors or elevated glucose levels in pregnancy (Shapiro et al., 2015). Evaluating the relationship of these risk factors with urinary phthalate metabolites is important, given that pre-pregnancy obesity confers a 2- to 3-fold increased risk of GDM, while excessive GWG in early pregnancy is associated with an ~70% increased risk of GDM (Hedderson et al., 2010; Solomon et al., 1997).

To this end, we evaluated the associations between urinary phthalate metabolites and risk factors associated with GDM. These associations were evaluated in a subset of a large multi-racial/ethnic U.S. pregnancy cohort. Specifically, we assessed first trimester urinary phthalate metabolites and first trimester BMI; average phthalate metabolite concentrations with period-specific and total GWG; and first and second trimester phthalate metabolite concentrations with later second trimester glucose levels.

2. Methods

2.1. Study population

Starting in 2006, the Lifecodes pregnancy cohort recruited pregnant women during the first trimester of pregnancy (at a median of 10 weeks gestation). (28) For inclusion into the cohort, all women had to plan to deliver at Brigham and Women's Hospital (Boston, MA), be <15 weeks gestation at entry into the cohort, and could not be pregnant with >3 fetuses. Lifecodes study participants provided blood and urline samples at 4 different study visits. Participants completed a questionnaire, which queried sociodemographic and lifestyle factors (McElrath et al., 2012).

A nested case-control study was started in 2011 based on women who delivered between 2006 and 2008. Specific details of the case-control study have been previously published. Our study population was comprised of the control population from the nested case-control study, specifically those women who delivered at term (>37 weeks gestation; $n = 350$ women) (Ferguson et al., 2014a). Term births were selected for this study, to be able to assess the full-course of pregnancy, particularly for GDM-related factors, such as GWG. All women provided informed consent. This study was approved by the Partners Human Subjects Committee at Brigham and Women's Hospital, and the University of Michigan's Health Sciences Institutional Review Board.

2.2. Urinary phthalate metabolites

Spot urine samples were collected at the time of clinic visit and stored at −20 °C at the following median gestation weeks: visit 1: 9.9 weeks gestation; visit 2: 17.9 weeks gestation; visit 3: 26.1 weeks gestation; and visit 4: 35.3 weeks gestation. Among the 350 women, most had available data at all 4 time points, with 99% of women having samples available at visit 1; 87% at visit 2; 86% at visit 3, and 90% at visit 4.

A total of nine commonly studied phthalate metabolites were measured, specifically, MBP (metabolite of dibutyl phthalate), mono-ethyl phthalate (MEP) (metabolite of diethyl phthalate), mono-isobutyl phthalate (MiBP) (metabolite of diisobutyl phthalate), MBzP (metabolite of benzyl butyl phthalate), mono-(3-carboxypropyl) phthalate (MCPP) (metabolite of di-n-octyl phthalate), MEHP, Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), and mono-2-ethyl-5-oxohexyl phthalate (MEOHP) (these latter 4 are metabolites of di-2-ethylhexyl phthalate). Due to the high degree of correlation between DEHP metabolites (Ferguson et al., 2014a), we used a summary measure of DEHP based on the sum of the molar concentrations of four DEHP metabolites (MEHHP, MECPP, MEOHP, and MEHP). All phthalate metabolites were analyzed by National Science Foundation International, Inc. (Ann Arbor, MI) using protocol from the Centers for Disease Control and Prevention described elsewhere (Ferguson et al., 2014a; CDC. (Centers for Disease Control and Prevention), 2005). Specifically, solid phase extraction and high performance liquid chromatography were used, along with tandem mass spectrometry (Ferguson et al., 2014a; CDC. (Centers for Disease Control and Prevention), 2005). The limits of detection were in the low ranges; however, when levels were below the limit of detection, we used the standard method of dividing the limit of detection by the square root of two to assign values (Hornung and Reed, 1990).

We used specific gravity to account for urine concentration. We used the formula: $P_c = P[(1.015 - 1) / SG - 1]$ to account for urine volume (Ferguson et al., 2014a, 2014b). For this, P_c is the SG-adjusted concentration, P is the measured urinary concentration, SG is the specific gravity for the individual sample and 1.015 is the median SG over all samples (Chu et al., 2007; Crinnion, 2010). We excluded urine samples with SG > 1.04, as these urines are outside of normal range of specific gravity ($n = 2$ women) (Boeniger et al., 1993). For these analyses of phthalate metabolites, we evaluated each phthalate metabolite, as well as the DEHP summary measure, in quartiles based on the study population's distribution. The lowest concentration (first quartile) was considered the referent category for all analyses. As an exploratory analysis, we assessed phthalate mixtures. First, we constructed a summary phthalate variable to evaluate those phthalates with anti-androgenic activity (i.e. molar sum of MBP, MBzP, MiBP, MEHHP, MECPP, MEOHP, and MEHP). Second, we constructed a summary phthalate variable to evaluate