International Journal of Hygiene and Environmental Health 218 (2015) 324–330

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

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

Urinary phthalate metabolite concentrations and blood glucose levels during pregnancy

Candace A. Robledo[a,*], Jennifer D. Peck[a], Julie Stoner[a], Antonia M. Calafat[b], Hélène Carabin[a], Linda Cowan[a,1], Jean R. Goodman[c]

[a] Department of Biostatistics & Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center, 801 NE 13th St., Room 309, Oklahoma City, OK 73104, USA
[b] Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC), 4770 Buford Hwy, Atlanta, GA 30341, USA
[c] Department of Obstetrics and Gynecology, Maternal–Fetal Medicine, Stritch School of Medicine, Loyola University Health System, 2160 South First Avenue, Building 103, Maywood, IL 60153, USA

ARTICLE INFO

Article history:
Received 29 October 2014
Received in revised form 16 January 2015
Accepted 23 January 2015

Chemical compounds studied in this article:
Mono-2-ethylhexyl phthalate (PubChem CID: 20393)
Mono-2-ethyl-5-hydroxyhexyl phthalate (PubChem CID: 53437104)
Mono-2-ethyl-5-oxohexyl phthalate (PubChem CID: 12080048)
Mono-2-ethyl-5-carboxypentyl phthalate (PubChem CID: 148386)
Monoethyl phthalate (PubChem CID: 75318)
Mono-n-butyl phthalate (PubChem CID: 8575)
Mono-iso-butyl phthalate (PubChem CID: 92272)
Monobenzyl phthalate (PubChem CID: 31736)
Mono-3-carboxypropyl phthalate (PubChem CID: 53435015)

Keywords:
Phthalate
Pregnancy
Blood glucose

ABSTRACT

Purpose: To examine associations between phthalate metabolite urinary concentrations during early pregnancy and blood glucose levels obtained at the time of screening for gestational diabetes mellitus (GDM).
Methods: Upon initiation of prenatal care, women with a mean gestational age of 12.8 weeks were recruited for a study of environmental chemical exposures ($n = 110$) and provided a spot urinary specimen. Blood glucose concentrations (mg/dl) were obtained from the electronic medical record for those patients who did not experience a pregnancy loss and did not transfer care to another facility prior to glucose screening ($n = 72$). Urinary concentrations of nine phthalate metabolites and creatinine were measured at the US Centers for Disease Control and Prevention. Associations between tertiles of phthalate metabolites concentrations and blood glucose levels were estimated using linear regression.
Results: Compared to pregnant women in the lowest concentration tertile, women with the highest urinary concentrations (≥3rd tertile) of mono-iso-butyl phthalate (tertile: ≥15.3 μg/l, $\beta = -18.3$, 95% CI: −35.4, −1.2) and monobenzyl phthalate (tertile: ≥30.3 μg/l, $\beta = -17.3$, 95% CI: −34.1, −0.4) had lower blood glucose levels at the time of GDM screening after adjustment for urinary creatinine and demographic covariates.
Conclusion: Because maternal glucose levels increase during pregnancy to provide adequate nutrition for fetal growth and development, these findings may have implications for fetal health. However, given the limitations of our study, findings should be interpreted cautiously.

Abbreviations: BzBP, benzylbutyl phthalate; DEHP, di-2-ethylhexyl phthalate; DBP, dibutyl phthalates; DOP, di-n-octyl phthalate; GDM, gestational diabetes mellitus; MBzP, monobenzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MECPP, mono-2-ethyl-5-carboxypentyl phthalate; MEHP, mono-2-ethylhexyl phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MEOHP, mono-2-ethyl-5-oxohexyl phthalate; MiBP, mono-iso-butyl phthalate; MEP, monoethyl phthalate; MnBP, mono-n-butyl phthalate; NHANES, National Health and Nutrition Examination Survey.

* Corresponding author at: 3500 Camp Bowie Blvd, Fort Worth, TX 76107, USA. Tel.: +1 817 735 2619; fax: +1 817 735 2783.
E-mail addresses: candace.robledo@unthsc.edu (C.A. Robledo), jennifer-peck@ouhsc.edu (J.D. Peck), julie-stoner@ouhsc.edu (J. Stoner), acalafat@cdc.gov (A.M. Calafat), helene-carabin@ouhsc.edu (H. Carabin), linda-cowan@ouhsc.edu (L. Cowan), jrgoodman@lumc.edu (J.R. Goodman).
[1] Deceased, December 31, 2013.

http://dx.doi.org/10.1016/j.ijheh.2015.01.005
1438-4639/

Introduction

Widespread exposure to endocrine disrupting chemicals such as phthalates has led to growing concerns about potential associations with adverse health effects. Phthalates, the diesters of 1,2-benzenedicarboxylic acid, are a group of synthetic chemicals that are ubiquitous in the environment because of their wide array of industrial applications (Graham, 1973). Phthalates impart plastics with flexibility and are found in many products such as cosmetics, automotive plastics and personal-care products. Phthalates may also be found in food packaging materials. High molecular weight (HMW) phthalates (≥250 Da), such as di(2-ethylhexyl) phthalate (DEHP) are primarily used in the manufacture of flexible vinyl and can be found in flooring, medical devices and consumer products. Low molecular weight (LMW) phthalates (<250 Da) comprise metabolites of diethyl phthalate and dibutyl phthalates (DBP). These phthalates are commonly found in personal care products and are used in the making of lacquers, varnishes and in the coatings of medications (Graham, 1973). Dietary intake of contaminated food, dermal contact and inhalation are potential pathways of exposure to phthalates in the general population (Hauser and Calafat, 2005; Schettler, 2006). Upon exposure, phthalates undergo phase I and phase II transformations into their biologically active monoester metabolites which are excreted in urine and can be measured to estimate phthalate exposure in human populations (Frederiksen et al., 2007; Wittassek and Angerer, 2008).

Certain phthalates have anti-androgenic properties and can activate peroxisome proliferator activated receptors (PPAR), properties that have led researchers to suspect that phthalate exposure can impact energy balance and metabolism (Desvergne et al., 2009; Grun and Bloomberg, 2009). Experimental studies in rats have shown that diets supplemented with DEHP can induce glucose intolerance (Martinelli et al., 2006; Mushtaq et al., 1980), decrease blood insulin and increase blood glucose levels (Gayathri et al., 2004). Although limited in number, several cross-sectional studies that include adult men (Stahlhut et al., 2007), adult women (Svensson et al., 2011), and lactating women (Hines et al., 2009) support associations between phthalate metabolite urinary concentrations, insulin resistance and diabetes mellitus. Widespread phthalate exposure and its potential for substantial public health impact have led to studies that describe exposure among vulnerable subgroups such as pregnant women and women of reproductive age (Adibi et al., 2008; Braun et al., 2013; Peck et al., 2010). While there is concern about the endocrine disrupting properties of phthalates, studies have yet to examine whether phthalate exposure during pregnancy is associated with metabolic endpoints such as blood glucose levels. Pregnancy naturally induces an insulin-resistant state in order to direct maternal metabolism to provide enough nutrition to support the growth and development of the fetus. This insulin-resistant state results in higher circulating levels of glucose. An insufficient pancreatic insulin response to lower blood glucose into the normal range can lead to gestational diabetes mellitus (GDM) (Ryan, 2003).

Given emerging evidence that phthalates may disrupt insulin or glucose action in human populations (Hauser and Calafat, 2005), we examined whether phthalate exposure is associated with blood glucose alterations during pregnancy, a window when both maternal and fetal health are susceptible to changes in glucose action or uptake. We evaluated this hypothesis by measuring urinary concentrations of phthalate metabolites during early pregnancy and examining associations with blood glucose levels obtained at the time of prenatal GDM screening.

Materials and methods

Study population

Pregnant women ($n = 110$) were recruited for a pilot study of environmental chemical exposures during their first prenatal care visit at the University of Oklahoma Medical Center Women's Clinic between February and June 2008. Women were eligible to participate in the study if their first prenatal care visit occurred before the 22nd week of pregnancy, they were 18 years of age or older, and spoke either English or Spanish. Women were ineligible to participate if at the time of enrollment they presented with a medically threatened pregnancy, multiple gestation, or if they had a history of diabetes (type 1 or type 2), preeclampsia, preterm rupture of membranes, or preterm labor.

For purposes of this analysis, women were excluded if they reported having a history of gestational diabetes ($n = 6$). Patients were administered a one hour 50 g oral glucose challenge test as part of routine GDM screening (median gestational age at screen: 26.3 weeks; range: 10.3–35.4 weeks). Blood glucose concentrations (mg/dl) were obtained from the electronic medical record. Pregnant women with an elevated screening value of ≥135 mg/dl received further testing (oral glucose tolerance tests) for diagnosis of GDM (Carpenter and Coustan, 1982; Metzger and Coustan, 1998). Our analyses were restricted to 72 pregnant women for whom glucose challenge test results were available in the medical record. Reasons for missing glucose challenge test results included experiencing a pregnancy loss ($n = 10$), transferring care to another facility ($n = 6$) or not returning to the clinic for prenatal care ($n = 16$) prior to GDM screening. The demographic characteristics of women who were excluded from analyses did not statistically differ from women whose data were available (Table 1).

This study was approved by the University of Oklahoma Health Sciences Center Institutional Review Board. The analysis of blinded specimens by the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

Biomarkers of phthalate exposure

Upon enrollment, women provided a urine spot sample to measure biomarkers of exposure to environmental contaminants and cotinine. Sterile urine collection containers were provided by the CDC laboratory. Following collection, urine specimens were temporarily refrigerated in the clinic, until they could be aliquotted for storage (−20 °C) at the end of each recruitment day. After the enrollment period ended, in 2011, samples were shipped to the CDC laboratory on dry ice.

Urinary concentrations of nine phthalate metabolites and creatinine were measured. The metabolites and their respective parent diesters are listed in Appendix A. Phthalate metabolites were measured using online solid phase extraction coupled with high performance liquid chromatography isotope dilution tandem mass spectrometry as described elsewhere (Kato et al., 2005). Creatinine was measured using an enzymatic reaction on a Roche Hitachi 912 chemistry analyzer (Roche Hitachi, Basel Switzerland).

Limits of detection (LODs) ranged from 0.2 μg/l for monocarboxypropyl phthalate (MCPP) to 1.2 μg/l for mono-2-ethylhexyl phthalate (MEHP). Reported concentrations, including the LOD of monoethyl phthalate (MEP) and monobenzyl phthalate (MBzP), were multiplied by 0.66 and 0.72, respectively, to account for the purity of the analytical standards used (Centers for Disease Control and Prevention National Center for Environmental Health Divsion of Laboratory Sciences, 2012). All but three of the nine phthalate metabolites were detectable in 100% of urine specimens analyzed. MBzP and MCPP were detectable in 98% and 99% of urine specimens,