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Urinary phthalate and phthalate alternative metabolites and isoprostane among couples undergoing fertility treatment

Haotian Wu[a], Alexandra Olmsted[a], David E. Cantonwine[b], Shahin Shahsavari[a], Tayyab Rahil[c], Cynthia Sites[c], J. Richard Pilsner[a,*]

[a] Department of Environmental Health Sciences, School of Public Health and Health Sciences, University of Massachusetts, 686 North Pleasant Street, Amherst, MA 01003, United States

[b] Department of Obstetrics Gynecology and Reproductive Biology, Division of Maternal Fetal Medicine Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, United States

[c] Division of Reproductive Endocrinology and Infertility, Baystate Medical Center, 759 Chestnut Street, Springfield, MA 01199, United States

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ABSTRACT

Background: Epidemiological data suggest associations between phthalate exposures to a variety of adverse reproductive outcomes including reduced sperm quality and reproductive success. While mechanisms of these associations are not fully elucidated, oxidative stress has been implicated as a potential mediator. We examined associations of urinary metabolites of phthalates and phthalate alternative plasticizers with oxidative stress among couples seeking fertility treatment.

Methods: Seventeen urinary plasticizer metabolites and 15-F2t isoprostane, a biomarker of oxidative stress, were quantified in spot samples from 50 couples seeking fertility treatment who enrolled in the Sperm Environmental Epigenetics and Development Study during 2014–2015.

Results: In multivariable analyses, percent change in isoprostane was positively associated with interquartile range increases for the oxidative metabolites of di-2-ethylhexyl phthalate, [mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP; 20.0%, p=0.02), mono-2-ethyl-5-oxohexyl phthalate (MEOHP; 24.1%, p=0.01), and mono-2-ethyl-5-carboxypentyl phthalate (MECPP; 24.1%, p=0.004)], mono-isobutyl phthalate (MiBP; 17.8%, p=0.02), mono-hydroxyisobutyl phthalate (MHiBP; 27.5%, p=0.003), and cyclohexane-1,2-dicarboxylic acid mono-hydroxy-isononyl ester (MHINCH; 32.3%, p=0.002). Stratification of participants by sex revealed that isoprostane was positively associated with MHiBP (41.4%, p=0.01) and monocarboxy-isononyl phthalate (MCNP; 26.0%, p=0.02) among females and MEOHP (35.8%, p=0.03), MiBP (29.2%, p=0.01), MHiBP (34.7%, p=0.007) and MHINCH (49.0%, p=0.002) among males.

Conclusions: Our results suggest that exposure to phthalates and phthalate replacements are associated with higher levels of oxidative stress in a sex-specific manner. Additional studies are needed to replicate our findings and to examine the potential health implications of the use of phthalates and alternative phthalates in consumer end products.

1. Introduction

Phthalate diesters are a class of high-volume production synthetic organic chemicals used in industrial and consumer products. The classification of phthalate diesters can be divided by their carbon backbone alkyl chain into high molecular weight (HMW) and low molecular weight (LMW). HMW phthalates are used as plasticizers of polyvinyl chloride (PVC), which is manufactured in many consumer end products including medical equipment, food packaging, and building materials such as flooring and wallboard (Jurewicz and Hanke, 2011). LMW phthalates are typically included in personal care products, solvents, fixatives, or alcohol denaturants (Lyche et al., 2009; Meeker, 2012). Phthalates are not covalently bonded to products and are therefore easily released into the environment (Meeker et al., 2009). Because of this, human exposure is widespread, such that urinary phthalate metabolites have been detected in the majority of individuals from representative samples in the United States general population (CDC, 2015) and worldwide (Becker et al., 2009; Ha et al., 2014; Polanska et al., 2014).

Epidemiologic data suggest that exposure to some phthalates is

* Corresponding author.
E-mail address: rpilsner@umass.edu (J.R. Pilsner).

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adversely associated with a variety of reproductive outcomes including lower oocyte yield and lower proportion of cycles resulting in pregnancy as well as live birth (Hauser et al., 2015), poor sperm quality measures in the general population (Bloom et al., 2015b) as well as those seeking fertility treatment (Duty et al., 2003; Hauser et al., 2006; Wang et al., 2015), and longer time to pregnancy (Buck Louis et al., 2014). The direct mechanisms by which phthalates may induce these adverse reproductive outcomes are not clear but there is growing evidence that oxidative stress may be a contributing factor. Oxidative stress is implicated in adverse reproductive conditions including sperm DNA damage (Gavriliouk and Aitken, 2015), endometriosis (Mier-Cabrera et al., 2011; Sharma et al., 2010), and polycystic ovary syndrome (Palacio et al., 2006). Additionally, recent evidence suggests strong positive associations between urinary phthalate metabolite concentrations and biomarkers of oxidative stress among pregnant women (Ferguson et al., 2014, 2015; Holland et al., 2016), couples who were planning pregnancy (Guo et al., 2014), and the general US population (Ferguson et al., 2012). Most recently, oxidative stress was shown to partially mediate the association of phthalate exposure on preterm birth in Puerto Rico (Ferguson et al., 2016).

U.S. biomonitoring data from 2001 to 2010 have highlighted temporal changes in the profiles of urinary biomarkers of phthalates as the use of alternative phthalates or phthalate substitutes meant to replace those with potential adverse effects on human health has increased (Zota et al., 2014). For example, the most common HMW phthalate plasticizer, di(2-ethylhexyl) phthalate (DEHP), is being replaced with other phthalates (e.g., di-isononyl phthalate (DiNP) and di-isodecyl phthalate (DiDP)), or non-phthalate plasticizers (e.g., di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH®)). Not surprisingly, urinary metabolite concentrations of these phthalate replacements have been reported to be increasing in recent years (CDC, 2015; Zota et al., 2014). Likewise, changes in LMW phthalate exposure profiles have also been observed, whereby use of di(isobutyl) phthalate (DiBP), an alternative to di(*n*-butyl) phthalate (DBP), also appeared to be on the rise in the past decade (Zota et al., 2014). Despite these changes, limited data are available in regard to the relationships of exposure to alternative phthalates or phthalate substitutes on oxidative stress. To gain a better understanding on the potential influence of current exposure profiles of phthalates on oxidative stress, we conducted a cross-sectional study among couples seeking reproductive assistance to determine whether preconception exposures to these compounds are associated with urinary isoprostane, a known biomarker of oxidative stress.

2. Methods

2.1. Study population

The Sperm Environmental Epigenetics and Developments Study (SEEDS) is a prospective cohort study aimed at investigating the associations of paternal preconception exposures to endocrine disrupting chemicals, such as phthalates, with sperm epigenetics and subsequent early-life development among couples undergoing fertility treatment at Baystate Medical Center located in Springfield, Massachusetts. Since 2014, the SEEDS cohort has been recruiting couples (men and women 18–55 and 18–40 years of age, respectively) who use their own gametes (sperm and oocytes) for in vitro fertilization. For the current study, we included data from the first 50 couples who enrolled in SEEDS. Attending physicians explained the study and obtained written consent from eligible males and females interested in participating. This study was approved by the institutional review boards at Baystate Medical Center and the University of Massachusetts Amherst.

2.2. Urinary biomarker measurements

Men and women who agreed to participate provided a spot urine sample in a sterile polypropylene collection cup on the same day of semen sample procurement and oocyte retrieval. Urine samples were vortexed, divided into several aliquots and stored at −80 °C. Urine samples were shipped overnight on dry ice to the National Center for Environmental Health of the Centers for Disease Control and Prevention (CDC), where quantification of urinary DINCH and phthalate metabolites was conducted via enzymatic deconjugation of the metabolites, solid-phase extraction, separation and detection using high performance liquid chromatography isotope dilution tandem mass spectrometry as described previously (Silva et al., 2013). Analytical standards, quality control (QC) materials prepared from spiked pooled urine, and reagent blank samples were included in each batch along with study samples. The QC concentrations—averaged to obtain one measurement of high-concentration QC and one of low-concentration QC for each batch—were evaluated by using standard statistical probability rules (Caudill et al., 2008). The coefficient of variations for the phthalate measurement of QC materials ranged from 6.7% to 11.7% (low concentration standard) and 5.0% to 9.3% (high concentration standard).

In total, seventeen urinary metabolites were quantified: mono(2-ethylhexyl) phthalate (MEHP); mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP); mono(2-ethyl-5-oxohexyl) phthalate (MEOHP); mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); monocarboxyisooctyl phthalate (MCOP); mono-isononyl phthalate (MNP); monobenzyl phthalate (MBzP); mono(3-carboxypropyl) phthalate (MCPP); monocarboxy-isononyl phthalate (MCNP); mono-n-butyl phthalate (MBP); mono-3-hydroxybutyl phthalate (MHBP); mono-isobutyl phthalate (MiBP); mono-hydroxyisobutyl phthalate (MHiBP); monoethyl phthalate (MEP); monomethyl phthalate (MMP); cyclohexane-1,2-dicarboxylic acid-monocarboxy isooctyl ester (MCOCH); and cyclohexane-1,2-dicarboxylic acid-mono(hydroxy-isononyl) ester (MHINCH). We calculated the molar sum of DEHP metabolites (ΣDEHP) by dividing each metabolite concentration by its molecular weight and then summing: [MEHP×(1/278)]+[MEHHP×(1/294)]+[MEOHP×(1/292)]+[MECPP×(1/308)]. The limits of detection (LODs) varied for each metabolite, ranging from 0.2 to 0.6 ng/mL. Concentrations below the LOD were assigned a value of LOD divided by the square root of 2. Specific gravity (SG) was measured at room temperature using a digital handheld refractometer (Atago Co., Ltd., Tokyo, Japan), which was calibrated prior to use with deionized water. For analyses utilizing SG-corrected metabolite concentrations, the following formula was used: Pc=P[(1.02-1)/(SG-1)] where Pc is the SG-corrected metabolite concentration (ng/mL), P is the observed metabolite concentration, 1.02 is the SG population median, and SG is the specific gravity of the urine sample.

2.3. Urinary isoprostane measurements

Urinary isoprostane (15-F2t-Isoprostane/8-epi-PGF2 alpha) was measured using a competitive enzyme-linked immunoassay (ELISA) kit according to the manufacturer's protocol (Cat #: EA85, Oxford Biomedical Research) and read on a SpectraMax M2 microplate reader (Molecular Devices). A significant amount of urinary isoprostane is excreted as glucuronide conjugates (Yan et al., 2010); therefore, urine samples were pretreated with beta-glucuronidase to allow for the measurement of total urinary isoprostane. All samples were run in duplicate with repeated analyses for duplicate results with a coefficient of variation (CV) > 15%. Final urinary isoprostane concentrations were SG-corrected as described above. Control urines were utilized to monitor plate-to-plate variations; intra-day and inter-day CVs were 5.1% and 6.5%, respectively.

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