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Urinary concentrations of phthalate metabolites, bisphenols and personal care product chemical biomarkers in pregnant women in Israel

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ABSTRACT

Mounting evidence suggests possible adverse effects of intrauterine exposure to certain phenols and phthalates, two classes of endocrine disruptor chemicals, on the developing fetus, with consequences into later life. These findings have contributed to the replacement of some chemicals, such as di-2-ethylhexyl phthalate (DEHP) and bisphenol A (BPA), in consumer products. For the current study we quantified urinary concentrations of biomarkers of exposure among 50 pregnant women in Israel to several phthalates, bisphenols and personal care product chemicals, as well as DEHP and BPA alternatives. We detected 14 of the 31 biomarkers in more than 90% of the women. We detected biomarkers of 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH), bisphenol S, and bisphenol F not as frequently (27–56%). This study is the first to evaluate exposure to triclosan, bisphenols, parabens, and phthalates and BPA alternatives among Israeli pregnant women.

1. Introduction

Endocrine disruptor chemicals like phthalates and bisphenols are increasingly studied for their potential to produce adverse health effects in humans and animals. Indeed, human biomonitoring studies have detected many phthalate and bisphenol metabolites in the general population, suggesting widespread exposure (Katsikantami et al., 2016; Vandenberg et al., 2010).

Phthalates are a family of chemicals found in an array of consumer and industrial products. Low molecular weight phthalates, such as dimethyl phthalate (DMP), diethyl phthalate (DEP) and dibutyl phthalate (DBP), are typically found in medications, deodorants and lotions; high molecular weight phthalates, such as butyl-benzyl phthalate (BBzP) and di-2-ethylhexyl phthalate (DEHP), are used in the manufacturing of floor coverings, adhesives, medical devices and food packaging (Robinson and Miller, 2015). Phenols including bisphenol A, triclosan and benzophenone-3, and other chemicals are used in cosmetics and other personal care products, pharmaceuticals and food and beverage packaging (Ye et al., 2015).

In rodents, anti-androgenic effects of phthalates are the most well studied; other endocrine modulating effects include impaired mammary development and reductions in circulating levels of thyroid hormone (Erkekoglu et al., 2012; Macon and Fenton, 2013). In humans, exposure to some phthalates has been associated with low maternal thyroid hormone levels, reduced ano-genital distance in male infants, respiratory diseases, childhood obesity and effects on neurodevelopment in children (Robinson and Miller, 2015). Several phenols have shown estrogenic and anti-androgenic effects in animal studies, and there is evidence from human studies that bisphenol A (BPA) exposure might be associated with obesity, polycystic ovarian syndrome, recurrent miscarriage and male infertility (Rochester, 2013).

In recent years, restrictions and bans on the use of BPA and some phthalates in certain baby and child care products led to an increase in the production and use of alternatives, including 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH), bisphenol S (BPS), and bisphenol F (BPF) (Schutze et al., 2014; Silva et al., 2013; Silva et al., 2017; Ye et al., 2015). The effects of these substitutes are not well characterized, and their specific effects on pregnant women and the development fetus are still largely unexplored. While considered less toxic than DEHP, DINCH may have adverse effects on the liver, thyroid,

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Table 1
Detection frequencies and specific gravity-adjusted concentrations of triclocarban, bisphenols and BPA alternative metabolites (μg/L) in urine from 49 pregnant women before delivery.

Analyte name	Acronym	Percent Detected	Limit of Detection	50th percentile	90th percentile	95th percentile
Triclocarban	TCC	12%	0.1	< LOD	0.1	0.2
2,4-dichlorophenol	24-DCP	88%	0.1	0.4	3.3	3.8
2,5-dichlorophenol	25-DCP	100%	0.1	0.7	42.8	70.6
Benzophenone-3	BP-3	94%	0.4	16.3	214	480
Bisphenol A	BPA	98%	0.2	2.0	7.6	17.4
Bisphenol F	BPF	51%	0.2	0.4	1.6	3.3
Bisphenol S	BPS	27%	0.1	< LOD	0.4	0.7
Butyl paraben	B-PB	78%	0.2	0.4	19.2	44.8
Ethyl paraben	E-PB	55%	1.0	2.3	26.4	75.9
Methyl paraben	M-PB	96%	1.0	50.1	277	547
Propyl paraben	P-PB	98%	0.1	2.5	29.3	40.2
Triclosan	TCS	69%	1.7	4.4	122	293

kidneys and testes in animal studies (SCENIHR committee, 2016; Nardelli et al., 2017). BPS and BPF seem to have estrogenic activity, their potencies are in the same order of magnitude as the potency of BPA (Rochester and Bolden, 2015) and induce neurobehavioral disruption similar to BPA in experimental animals (Inadera, 2015).

Phthalates and bisphenols can cross the placenta (Jensen et al., 2015; Philippat et al., 2013), and the developing fetus (Philippat et al., 2012) may be especially sensitive to the adverse effects of these chemicals. In addition, there may be behavioral factors during pregnancy, such as dietary changes or increased use of personal care products that may affect exposure to phthalates and bisphenols. Therefore, it is important to assess exposure to these contaminants in populations of pregnant women.

Previous studies in Israel have reported exposure to phthalates in a small sample of pregnant women (Berman et al., 2009), to phthalates and BPA in the general population (Berman et al., 2013) and in vegetarians (Tordjman et al., 2016), and to phthalates and phthalate alternatives among women undergoing IVF (Machtinger et al., 2018). However, data on population exposure to triclosan, benzophenone-3 and other bisphenols as well as to BPA alternatives (BPF, BPS) in Israel do not exist. The objective of the current study was to characterize exposure to phthalates, bisphenols, chemicals in personal care products and some of their alternatives in 50 pregnant women in Israel.

2. Material and methods

The study was approved by Sheba Medical Center institutional review board (1717-14). All patients provided written informed consent.

2.1. Patients and sample collection

Data were collected between July 2015 and December 2016 as part of a study designed to evaluate associations between prenatal exposure to endocrine disrupting chemicals (EDCs) and epigenetic alterations in twin pregnancies. Inclusion criteria for twin pregnancies were dichorionic diamniotic (DC/DA) twins. Inclusion criteria for singletons were patients at term. We excluded cases of monochorionic diamniotic (MC/DA) and monochorionic mono-amniotic (MC/MA) twin pregnancies. Pregnant women provided a spot urine sample on the same day or the day before scheduled elective cesarean section or upon admission to the delivery room, and were asked to complete a questionnaire regarding their consumer habits during pregnancy.

Women collected urine into a 120-mL polypropylene urine container before any intravenous line was used, and patients were advised not to use any wipes before collection to avoid contamination with certain chemicals (e.g., parabens). For each sample, we used a handheld reflectometer to measure specific gravity (SG); we used SG to adjust for urine dilution. Urine samples were aliquoted to 1-mL tubes and stored at −80 °C before shipping to the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA, for analysis. The involvement of the CDC laboratory was determined not to constitute engagement in human subject research.

2.2. Quantification of chemical biomarkers

Samples were shipped on dry ice to the CDC for the quantification of 17 phthalate metabolites: monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-hydroxybutyl phthalate (MHBP), mono-isobutyl phthalate (MiBP), mono-hydroxyisobutyl phthalate (MHiBP), monobenzyl phthalate (MBzP), mono-3-carboxypropyl phthalate (MCPP), 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), mono-2-ethyl-5-hydroxyhexyl terephthalate (MEHHTP), mono-2-ethyl-5-carboxypentyl terephthalate (MECPTP), mono-isononyl phthalate (MNP), monooxononyl phthalate (MONP), mono(carboxy-isooctyl) phthalate (MCOP), mono(carboxy-isononyl) phthalate (MCNP); two metabolites of the phthalate alternative DINCH: cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester (MHiNCH), and cyclohexane-1,2-dicarboxylic acid monocarboxyisooctyl ester (MCOCH); triclocarban, and 11 phenols: 2,4-dichlorophenol, 2,5-dichlorophenol, benzophenone-3, BPA, BPF, BPS, methyl paraben, propyl paraben, ethyl paraben, butyl paraben and triclosan. Researchers at the CDC had no access to participants' personal private information. We quantified biomarkers of DINCH and phthalates in 50 samples (MEHHTP and MECPTP were measured in only 40 of them), and measured bisphenols and personal care product chemical biomarkers in 49 samples (one sample had insufficient volume for all analyses).

The analytical approaches used were based on solid-phase extraction coupled online with high performance liquid chromatography-isotope dilution tandem mass spectrometry, following standard quality assurance/quality control procedures as previously explained (Silva et al., 2013; Silva et al., 2017; Ye et al., 2005; Zhou et al., 2014). Limits of detection (LODs) for all biomarkers measured are shown in Tables 1 and 2.

2.3. Data analysis

For metabolite concentrations below the limit of detection (LOD), LOD were replaced with the LOD divided by the square root of 2 (Hornung and Reed, 1990).

To control for urinary dilution, urinary concentrations were adjusted according to specific gravity (SG), which is less likely to change in various stages of pregnancy (Duty et al., 2005; Cunningham et al., 2005) compared to urinary creatinine. We calculated SG-corrected metabolite concentrations using the following formula: $P_c = P [(1.011 - 1)/(SG - 1)]$, where P_c is the SG-corrected biomarker concentration (μg/L), P is the measured biomarker concentration (μg/L),