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Ultrasound gel as an unrecognized source of exposure to phthalates and phenols among pregnant women undergoing routine scan

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ABSTRACT

Background: Systemic absorption of phthalates and parabens has been demonstrated after dermal application of body lotion, and medical devices such as intravenous bags and tubing have been identified as a source of exposure to di(2-ethylhexyl) phthalate (DEHP). However, use of products during medical procedures such as aqueous gel applied during obstetrical ultrasound in pregnancy has not been investigated as a potential source of endocrine disrupting chemical (EDC) exposure. Human studies have associated EDCs with various adverse pregnancy outcomes. There is a need to identify sources of inadvertent exposure to EDCs especially during vulnerable developmental periods such as pregnancy.

Objectives: We conducted a pilot study to determine whether use of gel during routine obstetrical ultrasound increased urinary concentrations of phthalate and phenol biomarkers.

Methods: We recruited 13 women from the Massachusetts General Hospital who provided spot urine samples at the time of their second trimester anatomic survey. The first sample was collected prior to the procedure (pre-exposure, time 1), and two additional samples were obtained at approximately 1–2 h (time 2) and 7–12 h (time 3) post-exposure following the scan.

Results: Urinary concentrations of several DEHP metabolites and metabolite of diisononyl cyclohexane-1,2-dicarboxylate (DINCH) increased across time. For example, the geometric mean concentrations of mono(2-ethyl-5-hydroxyhexyl) phthalate increased from 3.1 ng/ml to 7.1 ng/ml (p-value = 0.03) between time 1 and time 3. We also observed significant differences in concentrations of metabolites of butylbenzyl phthalate (BBzP), di-n-butyl phthalate (DnBP), and di-isobutyl phthalate (DiBP). For example, mono-n-butyl phthalate (metabolite of DnBP) decreased from 3.5 ng/ml to 1.8 ng/ml (p-value = 0.04) between time 1 and time 2, but then increased to 6.6 ng/ml (p-value = 0.002) at time 3. Propylparaben concentrations increased from 8.9 ng/ml to 33.6 ng/ml between time 1 and time 2 (p-value = 0.005), followed by a decrease to 12.9 ng/ml at time 3 (p-value = 0.01). However, we cannot rule out the possibility that some of the observed differences are due to other sources of exposure to these compounds.

Conclusions: While additional research is needed, this pilot study potentially identifies a previously unknown source of phthalate and paraben exposure among pregnant women undergoing routine ultrasound examination.

Abbreviations: (MMP), mono-methyl phthalate; (MEP), monoethyl phthalate; (MBP), mono-n-butyl phthalate; (MiBP), mono-isobutyl phthalate; (MHBP), mono-3-hydroxy-n-butyl phthalate; (MHiBP), mono-hydroxyisobutyl phthalate; (MCPP), mono(3-carboxypropyl) phthalate; (MBzP), monobenzyl phthalate; (MEHP), mono(2-ethylhexyl) phthalate; (MEOHP), mono(2-ethyl-5-oxohexyl) phthalate; (MNP), monoisononyl phthalate; (MEHHP), mono(2-ethyl-5-hydroxyhexyl) phthalate; (MECPP), mono(2-ethyl-5-carboxypentyl) phthalate; (MCOP), monocarboxyisooctyl phthalate; (MCNP), monocarboxyisononyl phthalate; (DEHP), di(2-ethylhexyl) phthalate; (DINCH), Diisononyl cyclohexane-1,2-dicarboxylate; (MHiNCH), cyclohexane-1,2-dicarboxylic acid-mono(hydroxy-isononyl) ester; (MCOCH), cyclohexane-1,2-dicarboxylic acid-monocarboxy isooctyl ester; (MPB), methylparaben; (EPB), ethylparaben; (PPB), propylparaben; (BPB), butylparaben; (BPA), bisphenol A; (BPF), bisphenol F; (BPS), bisphenol S; (2,4-DCP), 2,4-dichlorophenol; (2,5-DCP), 2,5-dichlorophenol; (TCS), triclosan; (BP3), benzophenone-3

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1. Background

Phthalates, parabens, triclosan, and benzophenone-3 are endocrine disrupting chemicals (EDCs) with widespread use in many personal care products including cosmetics, lotions, creams, perfumes/cologne, and gels (Ferguson et al., 2017). Use of personal care products (PCPs) is an important route of exposure to some EDCs (Ferguson et al., 2017; Duty et al., 2005; Philippat et al., 2015). Systemic absorption of parabens and phthalates has been demonstrated after dermal application of body lotion (Janjua et al., 2007) and medical devices such as intravenous tubing and bags have been identified as a source of di(2-ethylhexl) phthalate (DEHP) exposure (Green et al., 2005; Latini et al., 2009). However, use of other products during medical examinations or procedures, such as aqueous gel used to facilitate trans-abdominal imaging during obstetrical ultrasound in pregnancy has not been investigated as a possible source of EDC exposure.

Both phthalates and parabens have properties appealing to manufacturers of personal care products. Low molecular weight phthalates are often used as solubilizing agents and are added to products containing fragrance or perfume as they help bind the scent and color. Parabens are widely used as preservatives to increase shelf life in moisturizers, skin lotions, and other personal care products. Ingredients listed by the manufacturers of aqueous ultrasound gel products used during ultrasound include propylparaben, fragrance, and dyes. Therefore, ultrasound gel used in gynecological and obstetric exams may be a potentially important yet unrecognized source of exposure given its use during vulnerable developmental periods such as pregnancy.

Accumulating epidemiologic evidence has associated EDCs with adverse reproductive health outcomes in humans, including infertility, implantation failure, pregnancy loss, reduced clinical pregnancy rates, preterm birth, preeclampsia, and poorer child development (Gore et al., 2015; Woodruff et al., 2008). Studies have shown that the developing embryo and fetus are particularly sensitive to potential adverse effects of EDCs (Gore et al., 2015; Wittassek et al., 2009). Preterm neonates in intensive care units have substantially higher urinary concentrations of DEHP, di-isononyl phthalate (DiNP), butylbenzyl phthalate (BBzP) and bisphenol A compared to full term infants, suggesting higher exposure and potentially differential metabolism by gestational age at birth (Green et al., 2005; Calafat et al., 2009; Weuve et al., 2006; Huygh et al., 2015). Phthalates and phenols can cross the placenta and have been detected in amniotic fluid, cord blood, and newborn meconium (Wittassek et al., 2009; Philippat et al., 2013). Furthermore, several phthalate metabolites have been detected in the urine of both preterm and full-term infants at post-natal day 7(Frederiksen et al., 2014).

Despite widespread use of phthalates, parabens, and other phenols in cosmetics and PCPs, there are limited data on systemic human absorption of these compounds through the skin (Janjua et al., 2007). To our knowledge no study has investigated whether ultrasound gel products used during routine obstetric ultrasound scans are a source of exposure to these chemicals. A better understanding of potentially unknown sources of exposure during critical developmental windows such as periconception and pregnancy is important and provides data that may be used to reduce exposure. The objective of this study was to determine whether exposure to gel during routine obstetrical ultrasound examinations increased urinary concentrations of 17 individual phthalate metabolites, 2 metabolites of diisononyl cyclohexane-1,2-dicarboxylate (DINCH), and 11 phenols.

2. Methods

2.1. Study cohort

The Environment and Reproductive Health (EARTH) Study is a prospective preconception cohort of couples from the Massachusetts General Hospital (MGH) Fertility Center. The study was designed to evaluate the effects of environmental exposures and diet on fertility and pregnancy outcomes. The EARTH Study has been ongoing since 2004 and has recruited approximately 800 women and 500 men to date. Women 18–46 years are eligible to participate and may enroll independently or as a couple. Participants are followed from study entry throughout their fertility care, pregnancy, and delivery. At enrollment, participants completed a study staff-administered sociodemographic, lifestyle, and medical history questionnaire. They also completed a more comprehensive questionnaire on family, medical, reproductive and occupational history, stress, product use, smoking history, and physical activity.

2.2. Pilot study design

EARTH Study participants who were pregnant and scheduled for their routine 20-week anatomic survey ultrasound between December 2014 and December 2015 were approached to take part in this pilot study at the MGH obstetrical outpatient unit. The pilot was designed to investigate potential exposure at the time of participant's routine ultrasound at approximately 17–20 weeks gestation. Participants provided a total of three spot urine samples: the first two were obtained following trained study staff instructions on the obstetrical unit at the MGH. Sample 1 (S1) was collected immediately prior to the start of the ultrasound scan (pre-exposure, time 1) and sample 2 (S2) 1–2 h after the commencement of the scan (post-exposure, time 2). Participants used a home urine collection kit that we provided to collect the third sample (S3) at 7–12 h post ultrasound (post-exposure, time 3). The kit included instructions, a collection cup, ice packs, questionnaire, and pre-paid overnight mail back labels. All participants also completed self-reported questionnaires at the time of each urine collection to identify product use and food/beverage consumption. The ultrasound technician conducting the scan also completed a brief form identifying the length of the ultrasound, the products used (manufacturer name and product), whether the ultrasound was only trans-abdominal or if transvaginal imaging was also necessary, the number of fetuses, and approximate gestational age. Technicians additionally collected a sample of the gel applied during the procedure, which was stored for future analyses. Trained study staff described the study protocol to all participants in detail and answered questions, and participants provided written informed consent. The study was approved by the Institutional Review Boards of MGH, Harvard T.H. Chan School of Public Health, and the Centers for Disease Control and Prevention (CDC).

2.3. Phthalate and phenol measurement

All urine samples were collected in a polypropylene specimen cup and analyzed for specific gravity with a handheld refractometer (National Instrument Company, Inc., Baltimore, MD, USA), divided into aliquots, and frozen for long-term storage at −80 °C. Samples were shipped on dry ice overnight to the CDC (Atlanta, GA, USA) for quantification of urinary phthalate and phenol biomarker concentrations, as well as metabolites of diisononyl cyclohexane-1,2-dicarboxylate (DINCH, a replacement chemical for DEHP), using online solid phase extraction coupled with high performance liquid chromatography-isotope dilution tandem mass spectrometry (Silva et al., 2007; Ye et al., 2005). The urinary concentrations of the following 19 biomarkers were measured: monomethyl phthalate (MMP), primary metabolite of dimethyl phthalate (DMP); monoethyl phthalate (MEP), primary metabolite of diethyl phthalate (DEP); mono-*n*-butyl phthalate (MBP) and mono-3-hydroxy-*n*-butyl phthalate (MHBP), metabolites of di-*n*-butyl phthalate (DBP); mono-isobutyl phthalate (MiBP) and mono-hydroxyisobutyl phthalate (MHiBP), metabolites of DiBP, monoisononyl phthalate (MNP) and monocarboxyisooctyl phthalate (MCOP), metabolites of DiNP; mono(3-carboxypropyl) phthalate (MCPP), metabolite of di-*n*-octyl phthalate (DOP) and of other high molecular weight phthalates; monobenzyl phthalate (MBzP), metabolite of BBzP; mono