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Urinary phthalate metabolite and bisphenol A associations with ultrasound and delivery indices of fetal growth

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ABSTRACT

Growth of the fetus is highly sensitive to environmental perturbations, and disruption can lead to problems in pregnancy as well as later in life. This study investigates the relationship between maternal exposure to common plasticizers in pregnancy and fetal growth. Participants from a longitudinal birth cohort in Boston were recruited early in gestation and followed until delivery. Urine samples were collected at up to four time points and analyzed for concentrations of phthalate metabolites and bisphenol A (BPA). Ultrasound scans were performed at four time points during pregnancy for estimation of growth parameters, and birthweight was recorded at delivery. Growth measures were standardized to a larger population. For the present analysis we examined cross-sectional and repeated measures associations between exposure biomarkers and growth estimates in 482 non-anomalous singleton pregnancies. Cross-sectional associations between urinary phthalate metabolites or BPA and growth indices were imprecise. However, in repeated measures models, we observed significant inverse associations between di-2-ethylhexyl phthalate (DEHP) metabolites and estimated or actual fetal weight. An interquartile range increase in summed DEHP metabolites was associated with a 0.13 standard deviation decrease in estimated or actual fetal weight (95% confidence interval = −0.23, −0.03). Associations were consistent across different growth parameters (e.g., head circumference, femur length), and by fetal sex. No consistent associations were observed for other phthalate metabolites or BPA. Maternal exposure to DEHP during pregnancy was associated with decreased fetal growth, which could have repercussive effects.

1. Introduction

Reduced fetal growth is a well-recognized pregnancy endpoint of concern. While definitions and origins may differ, low birthweight, small for gestational age, and intrauterine growth restriction are all associated with increased risk of neonatal mortality and morbidity and have been linked to adverse health effects later in life (Barker et al., 2002; McCormick, 1985). The process of fetal development is highly sensitive to perturbations from environmental toxicant exposures (Wigle et al., 2008). Maternal behaviors such as smoking are clearly linked to reduced birthweight (Wang et al., 2002), and evidence also strongly suggests that some classic environmental exposures, such as lead and persistent organic pesticides, are associated with reductions in fetal growth (Wigle et al., 2008). Of emerging concern is the impact of non-persistent pollutants with widespread exposure, including a variety of chemicals found in plastics. Phthalate diesters and bisphenol-A (BPA) are used widely in these and other applications, and leach or are aerosolized into adjacent matrices which make for ready human exposure through ingestion or inhalation (Heudorf et al., 2007). Additionally, phthalates and occasionally BPA found in personal care products can be absorbed dermally. Despite rapid metabolism in the human body, contact is so frequent that phthalate metabolites and BPA in urine from pregnant mothers are detected almost ubiquitously in populations worldwide (Adibi et al., 2003; Casas et al., 2011; Ye et al., 2008)

A number of studies have examined the relationship between biomarkers of exposure to phthalates and BPA and fetal growth, with conflicting results (Casas et al., 2015; Philippat et al., 2012; Snijder et al.,

Abbreviations: BPA, bisphenol A; MEHP, mono-2-ethylhexyl phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MEOHP, mono-2-ethyl-5-oxohexyl phthalate; MECPP, mono-2-ethyl-5-carboxypentyl phthalate; MBzP, mono-benzyl phthalate; MBP, mono-*n*-butyl phthalate; MiBP, mono-isobutyl phthalate; MEP, mono-ethyl phthalate; MCPP, mono-3-carboxypropyl phthalate; HC, head circumference; AC, abdominal circumference; FL, femur length; EFW, estimated fetal weight; SD, standard deviation; LOD, limit of detection; BMI, body mass index; LME, liner mixed effects; IQR, interquartile range; CI, and confidence interval.

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2013; Veiga-Lopez et al., 2015a; Wolff et al., 2008a; Zhao et al., 2014). However, biologic plausibility exists for an impact of these chemicals on physical development. Phthalates and BPA have been shown to cause oxidative stress, hormonal disturbances, and epigenetic modifications that all could have deleterious effects on growth (Tetz et al., 2013; Hulak et al., 2013; Medici et al., 2012; Shields et al., 2011; Sant et al., 2015). Inconsistencies in previous studies of phthalate or BPA exposure and fetal growth may be due to the fact that the majority model associations with birthweight or other measures at delivery only (Wigle et al., 2008; Huang et al., 2009; Veiga-Lopez et al., 2015b; Wolff et al., 2008b; Zhang et al., 2009). Longitudinal studies with repeated ultrasound measurements taken during gestation have greater power to detect effects (Smarr et al., 2013). Additionally, specific to these non-persistent chemicals, most studies utilize single spot urine concentrations of phthalate metabolite and BPA as indices of exposure (Philippat et al., 2012; Huang et al., 2009; Wolff et al., 2008b; Huo et al., 2015; Lee et al., 2014); however, due to their short half-lives in the human body, measurements may not be representative of exposure over the course of pregnancy (Ferguson et al., 2014a). In the present analysis we investigated longitudinal associations between maternal exposure to phthalates and BPA in pregnancy and fetal growth in women from a prospective birth cohort. Notably, this study leverages a robust design including longitudinal exposure biomarker (up to 4 per subject) and growth assessments (up to 4 per subject).

2. Methods

2.1. Study population

Pregnant women were recruited in Boston as part of the LIFECODES birth cohort study. Individuals were eligible for participation if they were <15 weeks pregnant, were carrying a singleton non-anomalous fetus, and were planning to deliver at Brigham and Women's Hospital. At the initial study visit subjects provided informed consent and completed questionnaires detailing demographic information, personal and family health histories, and characteristics of pregnancy. Gestational age was calculated based on protocol established by the American College of Obstetricians and Gynecologists (Gynecologists ACoOa, 2014). Spot urine samples were collected at four time points (visits 1–4) during pregnancy, at median 10, 18, 26, and 35 weeks gestation, in polypropylene cups. Approximately 65% of urine samples were obtained in the morning (8 am to 1 pm) and the other 35% were collected in the afternoon or evening (after 1 pm). At delivery (visit 5), birthweight was recorded. We selected 130 cases of singleton preterm birth, defined as delivery prior to 37 weeks completed gestation, as well as 352 random singleton term controls from the participants recruited between 2006 and 2008 to examine the relationship between urinary phthalate metabolites and BPA and preterm birth. Institutional Review Board approval for the case-control study was obtained from the University of Michigan and from Brigham and Women's Hospital.

2.2. Fetal growth measurements

At the visit 1 ultrasound fetuses received a crown-rump length as part of the screen for aneuploidy. At visit 2 ultrasound scans were routinely performed for all study subjects for standard clinical assessments of fetal morphology. At visits 3 and 4, ultrasounds were not part of the study protocol. However, additional ultrasounds scans were also performed in cases where there was suspected abnormality of pregnancy (e.g., growth restriction, gestational diabetes, etc.) or at the patient's request. For all ultrasounds, measurements were abstracted from scans by board certified sonologists in the departments of Radiology and Maternal-Fetal Medicine. We used the following measurements for this analysis: head circumference (HC); abdominal circumference (AC); and femur length (FL). Additionally, measurements were combined using the following formula of Hadlock to create estimates of fetal weight (EFW) at visits 2–4 (Hadlock et al., 1985).

In order to combine growth measurements across different time points during pregnancy for longitudinal models, we created z-scores of each ultrasound measurement. We used mean and standard deviation (SD) ultrasound measurements available on all non-anomalous singleton pregnancies with delivery at Brigham and Women's Hospital from 2006 to 2012 (N = 18.904) as our standard (Cantonwine et al., 2016).

2.3. Exposure assessment

Urine samples collected during pregnancy were analyzed for a panel of nine phthalate metabolites as well as total urinary BPA by NSF International (Ann Arbor, MI, USA) (Lewis et al., 2013). Briefly, urine samples undergo enzymatic deconjugation of glucuronidated metabolites, solid phase extraction, liquid chromatographic separation, and tandem mass spectrometry (Lewis et al., 2013). Concentrations below the limit of detection (LOD) were kept as is if reported, and otherwise were replaced with the LOD divided by the square root of 2. Urinary specific gravity was measured using a digital handheld refractometer (Atago Company Ltd., Tokyo, Japan) as an indicator of urine dilution. In addition to individual phthalate metabolites, we also examined a molar sum of the di-2-ethyl-hexyl (DEHP) metabolites, including mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), and mono-2-ethyl-5-carboxypentyl phthalate (MECPP). For modeling purposes, we calculated cumulative pregnancy exposure to phthalate metabolites or BPA defined as the geometric average of urinary biomarker concentrations collected up until the time of ultrasound for visits 1–4. Cumulative exposure at visit 5 (delivery) was identical to the exposure metric from visit 4, since urine samples were not collected for analysis at birth.

2.4. Statistical analysis

All analyses were performed in R version 3.2.1. All analyses using the combined case-control sample were weighted using inverse probability weights indicative of the probability of preterm birth case and control selection from the base cohort population (Jiang et al., 2006). Thus, the results do not over represent associations within cases of preterm birth. We examined distributions of demographic characteristics within the study population using these weights. We also calculated percentiles of specific gravity corrected (Ferguson et al., 2014a) urinary phthalate metabolite measurements to present distributions.

To examine relationships between exposure and growth, we first used a cross-sectional approach to estimate associations between cumulative exposure at visit 5 (delivery) and birthweight alone. Crude models were adjusted for cumulative urinary specific gravity as well as gestational age at delivery. The fully adjusted model (Model 2) additionally included covariates that were associated with both exposures and outcome, and that impacted effect estimates by >10%. These included maternal age, race/ethnicity (White, African American, Other), visit 1 body mass index (BMI; continuous), health insurance provider (private, public), and infant gender. Finally, we examined adjusted models stratified by infant sex as previous studies have identified sex differences in these relationships (Models 3 and 4 for males and females, respectively) (Zhao et al., 2014). Differences in coefficient estimates from male vs. female models were tested using a z statistic. We additionally created cross-sectional models with z-scored growth measures from visits 2–4 with the corresponding cumulative exposure metrics.

Our second modeling approach was to create linear mixed effects (LME) models of the relationship between repeated measures of cumulative exposure and each indicator of fetal growth using the R nlme package (Pinheiro et al., 2015). As with cross-sectional models, these were created in crude, adjusted, and sex-stratified manners.

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