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Environmental phenol associations with ultrasound and delivery measures of fetal growth

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ABSTRACT

Environmental phenols are used commonly in personal care products and exposure is widespread in pregnant women. In this study, we sought to assess the association between maternal urinary phenol concentrations in pregnancy and fetal growth. The study population included 476 mothers who participated in the prospective LIFECODES birth cohort between 2006 and 2008 at Brigham and Women's Hospital in Boston, Massachusetts, USA. Dichlorophenols (DCPs), benzophenone-3, parabens, triclosan, triclocarban, and bisphenol-S were measured in urine from three time points during pregnancy and averaged. Outcome measures were all standardized to create gestational-age specific z-scores and included: 1) birth weight; 2) ultrasound parameters measured at up to two time points in pregnancy (head and abdominal circumference and femur length); and 3) ultrasound estimates of fetal weight from two time points in combination with birth weight. Models were stratified to investigate sex differences. Inverse associations were observed between average 2,4- and 2,5-DCP concentrations and birth weight z-scores in males. For example, an interquartile range difference in 2,4-DCP was associated with a 0.18 standard deviation decrease in birth weight z-score (95% confidence interval [CI] = −0.33, −0.02). These associations were observed in models that included repeated ultrasound estimates of fetal weight during gestation as well. Also in males, we noted inverse associations between average triclosan exposure over pregnancy and estimated fetal weight combined with birth weight in repeated measures models. For females, associations were generally null. However, mothers with a detectable concentration of bisphenol-S at any of the study visits had lower weight females. In conclusion, we observed inverse associations between indicators of maternal phenol exposure during pregnancy and fetal growth, with several differences observed by sex.

1. Introduction

Suboptimal fetal growth during pregnancy is an important risk factor for stillbirth, neonatal death, and morbidity (Figueras and Gardosi, 2011). It is also a predictor of adverse health outcomes in adult life, including cardiovascular and metabolic disease (Barker, 2006). Distinguishing normal from abnormal growth in itself is a challenge, and thus understanding of the causes of fetal growth restriction remains limited. Maternal health complications and placental disorders are known risk factors (American College of Obstetricians and Gynecologists, 2013), but environmental factors are suspected to play a role as well.

Endocrine disrupting compounds (EDCs) may interfere with normal fetal growth by altering the maternal-fetal compartment hormonal milieu (Bigsby et al., 1999), or by interfering with normal implantation or nutrient transfer across the placenta (Robins et al., 2011). Persistent EDCs such as perfluorinated compounds, polybrominated diphenyl ethers, and polychlorinated biphenyls are associated with reduced fetal growth in humans (Zheng et al., 2016; Lopez-Espinosa et al., 2015; Lopez-Espinosa et al., 2016), but studies of non-persistent EDCs such as phthalates and phenols are fewer.

Phenols are used in numerous products that we come into contact

Abbreviations: EDCs, endocrine disrupting compounds; BWH, Brigham and Women's Hospital; 2,4-DCP, 2,4-dichlorophenol; 2,5-DCP, 2,5-dichlorophenol; BP3, benzophenone-3; SG, specific gravity; BMI, body mass index; IQR, interquartile range; CI, confidence interval

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with on a day to day basis, including pesticides, personal care products like makeups, sunscreen, hand soap, and toothpaste, and plastics (Darbre and Harvey, 2008; Agency for Toxic Substances and Disease Registry, 1999). Environmental exposure is common in the US and elsewhere, and has been linked to perturbations in endocrine activity in animals and humans, with commonly observed sex differences in associations (Darbre and Harvey, 2008; Koeppe et al., 2013). By endocrine disruption or other mechanisms, it has been hypothesized that maternal phenol exposure may adversely impact fetal growth. The studies that have investigated these associations in the past have been restricted to examining birth weight or other delivery parameters only, and are potentially missing changes occurring during pregnancy (Geer et al., 2017; Lassen et al., 2016; Philippat et al., 2014; Philippat et al., 2012; Tang et al., 2013; Wolff et al., 2008; Wu et al., 2016). Additionally, all but one of these studies have utilized a single spot urine sample to assess phenol exposure during gestation. This could be problematic because phenols have a short half-life in the human body, and one measurement may not accurately reflect maternal body burden over an extended period of time (Guidry et al., 2015; Meeker et al., 2013a).

Thus, we sought to examine the association between maternal urinary phenol concentrations measured at three time points in pregnancy in relation to fetal growth in a population of 476 pregnant women from Boston. To assess growth, we examined birth weight as well as longitudinal trajectories of anthropometric parameters measured by ultrasound, including head and abdominal circumference, femur length, and estimated fetal weight. Additionally, we examined effect modification by fetal sex as phenols may impact male and female growth differently.

2. Methods

2.1. Study population

The LIFECODES birth cohort is an ongoing prospective study begun in 2006 at Brigham and Women's Hospital (BWH) in Boston, Massachusetts. Under the study design, mothers are recruited prior to 15 weeks gestation at BWH or affiliated academic practices. Gestational age is estimated according to American College of Obstetricians and Gynecologists (ACOG) guidelines (American College of Obstetricians and Gynecologists, 2014). Women approached for participation are included in the study if they are carrying non-anomalous fetuses and plan to deliver at BWH. At the first study visit the mother provides informed consent and is asked to provide spot urine and blood samples as well as questionnaire information pertaining to demographic characteristics and medical history. At subsequent visits, targeted at 18, 26, and 35 weeks gestation, she provides additional spot urine and blood samples. At delivery, detailed information on any complications as well as gestational age and birth weight are recorded. This study protocol was approved by the Institutional Review Board at BWH.

In accordance with the ACOG guidelines, all pregnancies receive a first trimester aneuploidy screening, as well as a 16–22 week ultrasound for assessing fetal anatomy. From the latter ultrasound, measurements of head circumference (mm), femur length (mm), and abdominal circumference (mm) are recorded, and estimated fetal weight is calculated based on the formula of Hadlock (Hadlock et al., 1985). Additional ultrasound measurements from scans taken later in pregnancy are collected on many subjects, either for a medically indicated purpose or at the patient's request, and also include each of these parameters. All scans were performed and reviewed by board-certified sonologists.

For the present analysis, we included participants with singleton deliveries between 2006 and 2008 from LIFECODES. These subjects were part of a case control study designed to assess the relationship between environmental exposures and preterm birth (Ferguson et al., 2014). All singleton preterm cases (delivery < 37 weeks gestation) were selected for this study (n = 130) and controls (delivery ≥ 37 weeks gestation) were selected randomly in an approximately 3:1 ratio (n = 352). Of these participants, we drew unthawed urine aliquots from -80 °C freezer storage for analysis of phenol concentrations. Phenols were measured in urine samples from at least one of the first three study visits in 476 participants (n = 30 with 1 sample; n = 106 with two samples; n = 340 with three samples), which was the final sample size for the present analysis. To adjust for the study design, inverse probability weightings were applied to all analyses so that the results would be generalizable to the base LIFECODES birth cohort (Jiang et al., 2006).

2.2. Fetal growth measures

We excluded from analysis ultrasound measurements from the fetal anatomy screening as the variability in measurements is low at this time point (median 18 weeks gestation) and the likelihood of measurement error is high, which would skew our results toward the null (Casas et al., 2016; Hindmarsh et al., 2002). Subsequent ultrasound measurements (including head circumference, femur length, abdominal circumference, and the summary measure of estimated fetal weight) were available from 321 of the participants (67%). Participants had 0 (n = 155), 1 (n = 175), or 2 (n = 146) measurements in pregnancy for each participant, collected from median 32.9 (range 19.9–40.3) weeks gestation. All subjects had birth weight measured at delivery (N = 476), and delivered at median 39.0 (range 24.3–42.7) weeks gestation (weighted estimates). For statistical analyses, all parameters (i.e., head circumference, femur length, etc.) were standardized to gestational age specific z-scores from the base BWH population as described elsewhere (Cantonwine et al., 2016). Means and standard deviations that were used to calculate these z-scores can be used for interpretation of effect estimates in repeated measures models, although the interpretation will change based on which gestational age is selected. We present interpretations for repeated measures of estimated fetal weight or birth weight at delivery based on the mean (standard deviation) of birth weight at 40 weeks gestation in grams: 3565 (426) (Cantonwine et al., 2016). Means and standard deviations in mm for head circumference (304, 13), abdominal circumference (298 20), and femur length (65, 3.3) from 33 weeks gestation (the median time of ultrasound scan) may also be used for interpretation purposes (Cantonwine et al., 2016).

On a subset of the population placental weight (n = 91) and newborn length (n = 389) were measured at delivery. The placenta was weighed within 12–24 h of delivery after being trimmed of its cord (within 2 cm of the insertion) per published guidelines (Driscoll and Langston, 1991). No attempt was made to control for the blood drained from the placental vasculature. These outcomes were not standardized and were examined in relation to phenols separately as an exploratory analysis.

2.3. Urinary phenol concentrations

Ten phenols were measured in previously unthawed urine samples by NSF International (Ann Arbor, MI) using isotope dilution–liquid chromatography–tandem mass spectrometry (ID–LC–MS/MS): 2,4-dichlorophenol (2,4-DCP); 2,5-dichlorophenol (2,5-DCP); benzophenone-3 (BP3); butyl, ethyl, methyl, and propyl parabens; triclosan; bisphenol-S; and triclocarban. An in-house method was developed, based on the Centers for Disease Control and Prevention (CDC) Laboratory Procedure Manuals for BPA and Other Environmental Phenols in urine (Centers for Disease Control and Prevention, 2009). The methods were validated in accordance with Food and Drug Administration Guidance for Industry: Bioanalytical Method Validation (Food and Drug Administration, 2001). Samples underwent enzymatic deconjugation of glucuronidated species, online solid phase extraction, and analysis using a Thermo Scientific (Waltham, MA, USA) Quantiva triple quadrupole mass spectrometer using multiple reaction monitoring in negative ionization APCI mode.