Environmental Research 150 (2016) 52–58

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Prenatal phthalate exposure and infant size at birth and gestational duration

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ARTICLE INFO

Article history:
Received 22 February 2016
Received in revised form
17 May 2016
Accepted 18 May 2016

Keywords:
Phthalate
Endocrine disrupting chemicals
Prenatal
Exposure
Birth outcomes

ABSTRACT

Background: Phthalate exposure is widespread. Prior research suggests that prenatal phthalate exposure may influence birth size and gestational duration, but published results have been inconsistent.
Objective: We quantified the relationship between maternal urinary phthalate concentrations and infant birth weight z-scores, length, head circumference, and gestational duration.
Methods: In a cohort of 368 women from the HOME Study, based in Cincinnati, OH, we measured nine phthalate metabolites representing exposure to six parent phthalate diesters in urine collected at approximately 16 and 26 weeks gestation. Infant birth size and gestational duration were abstracted from medical records. We used multivariable linear regression to estimate covariate adjusted associations between urinary phthalate metabolite concentrations and infant outcomes.
Results: In unadjusted models, we observed a negative association between monoethyl phthalate (MEP) and birth weight z-scores, while mono-3-carboxypropyl phthalate (MCPP) was positively associated with gestational duration. After covariate adjustment, phthalate metabolite concentrations were no longer associated with birth size or gestational duration.
Conclusions: In this cohort, urinary phthalate metabolite concentrations during pregnancy were not associated with infant birth size or gestational duration. Additional research is needed to determine if exposures during earlier periods of fetal development are associated with infant health.

1. Introduction

Phthalic acid diesters, or phthalates, are found in a wide variety of consumer products. Phthalates like diethyl phthalate (DEP), di-n-butyl phthalate and di-iso-butyl phthalate are used to retain scents in personal care products, such as lotions and perfumes (Braun et al., 2013; Koo and Lee, 2004). Other phthalates, namely di(2-ethylhexyl) phthalate (DEHP) and benzylbutyl phthalate, are used as plasticizers in polyvinyl chloride plastics, food processing equipment, adhesives, and rainwear (Calafat et al., 2006; Hauser and Calafat, 2005). Phthalate exposure is widespread, including among pregnant women (Braun et al., 2012; Philippat et al., 2012). Phthalate diesters are metabolized quickly into hydrolytic and/or oxidative monoester metabolites, conjugated to glucuronide or sulfate, and excreted in urine. Urinary concentrations of phthalate monoester metabolites can be used to assess exposure to phthalates. However, exposures are variable over time, possibly leading to exposure misclassification (Braun et al., 2012).

Phthalate monoester metabolites have been detected in amniotic fluid, umbilical cord blood, and meconium (Latini et al., 2003; Silva et al., 2004; Zhang et al., 2003). Some phthalates have well documented anti-androgenic activity in rats and the potential to affect other hormonal pathways like the hypothalamic-pituitary-adrenal axis and thyroid axis, which are important for growth and development (Boas et al., 2012; Howdeshell et al., 2008; Ma et al., 2011).

Prenatal phthalate exposure has been reported to have an effect on birth size in some animal studies (Sharpe, 2005; Tanaka, 2002, 2003, 2005; Tyl et al., 2004) but not in others (Arcadi et al., 1998; Hoshino et al., 2005). Similarly, associations between prenatal phthalate exposure and infant size at birth or gestational duration in humans have been inconsistent. Some studies reported that increased prenatal phthalate exposure was associated with smaller size at birth and shorter gestation (Ferguson et al., 2014b;

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http://dx.doi.org/10.1016/j.envres.2016.05.033
0013-9351/

Meeker et al., 2009; Whyatt et al., 2009), while others reported that exposure was associated with longer gestation (Adibi et al., 2009; Wolff et al., 2008).

The purpose of this study was to examine the relation between prenatal phthalate exposure and infant size at birth (birth weight z-score, length, and head circumference) and gestational duration using a population-based prospective cohort of pregnant women from Cincinnati, OH, who provided up to two urine samples during the 2nd and 3rd trimesters of pregnancy.

2. Methods

2.1. Study participants

We analyzed data collected from an ongoing prospective pregnancy and birth cohort, the Health Outcomes and Measures of the Environment (HOME) Study. Eligibility requirements included that women were ≥ 18 years of age, less than 19 weeks of gestation, living in the Cincinnati, OH area, and living in a home built before 1978 (Braun et al., 2010, 2016). Women in this study were recruited from seven prenatal care clinics affiliated with three Cincinnati, OH hospitals between 2003 and 2006. Our analysis included women who gave birth to a live singleton infant. Our final sample size was 368 mother-infant pairs after excluding two infants with genetic or chromosomal abnormalities and women missing covariate information (n = 18).

2.2. Prenatal phthalate exposure assessment

Participants provided two spot urine samples at approximately 16 (range: 10.4–22.6) and 26 (range: 19.1–34.6) weeks gestation. Urine was collected into polypropylene specimen cups, refrigerated until processing, and stored at or below $-20\,^{\circ}C$ until chemical analysis. Nine urinary phthalate metabolites were measured using previously described analytic methods; the limits of detection ranged from 0.1 to 1.0 ng/mL (Silva et al., 2004). To account for urine dilution, phthalate metabolite concentrations were creatinine-standardized by dividing metabolite concentrations (ng/mL) by creatinine concentrations (mg/dL) and multiplying by 100. These creatinine-standardized values were then $\log_{10}$-transformed. If more than one urine sample was provided, as was the case for 353 women (96%), the $\log_{10}$-transformed creatinine-standardized values from the 16- and 26-week samples were averaged. We created a summary measure for the four monoester metabolites of DEHP by dividing each metabolite by its molar mass and summing the metabolite concentrations, such that ($\sum$**DEHP**) was the molar sum of mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP).

2.3. Infant anthropometrics and gestational duration

We abstracted infant birth anthropometry, including birth weight (g), length (cm), and head circumference (cm), from medical records. Gestational duration (weeks) was calculated using mothers' self-report of last menstrual period (n = 360), ultrasound (n = 6), or Ballard scores (n = 2). We calculated birth weight z-scores, a standardized measure of birth weight for gestational age, from United States reference data (Oken et al., 2003).

2.4. Covariates

A directed acyclic graph (DAG) was drawn *a priori* to assess potential confounders associated with both phthalate exposure and birth outcomes (Supplemental Fig. 1) (Greenland et al., 1999; Textor et al., 2011). We considered socio-demographic, nutritional, environmental, and perinatal factors. Socio-demographic factors including maternal age, race, income, marital status, and insurance status were assessed using standardized interviews administered by trained research assistants. Nutritional factors were assessed during the 2nd or 3rd trimester of pregnancy using standardized interviews and included maternal food security, prenatal vitamin use, and frequency of fruit, vegetable, and fish consumption. Serum cotinine, a sensitive and specific marker of active and secondhand tobacco smoke exposure, was measured using previously described methods (Bernert et al., 1997; Braun et al., 2010). Perinatal factors including parity and maternal mid pregnancy body mass index (BMI) at $\sim$16 weeks gestation were abstracted from medical records. Depressive symptoms at 20 weeks gestation were assessed using the Beck Depression Inventory-II (Beck, 1996). Our final adjusted models included maternal race, age, income, education, marital status, insurance status, parity, cotinine, food security, BMI, prenatal vitamin use, fish consumption, fruit/vegetable consumption, and depressive symptoms. When assessing head circumference, mode of delivery was added to the model.

2.5. Statistical analysis

We described mean birth weight z-scores according to covariates. We then examined univariate characteristics of urinary phthalate metabolite concentrations, calculated Spearman correlations between repeated measures at 16 and 26 weeks gestation for all phthalate metabolites, and examined correlations between different phthalate metabolites. We used linear regression to estimate the unadjusted and adjusted difference in size at birth or gestational duration for each ten-fold increase in urinary phthalate metabolite concentration. We also considered preterm birth (gestational duration <37 weeks) as a dichotomous outcome. We evaluated the presence of non-linear relationships of phthalate metabolites with birth weight z-score and gestational duration using restricted cubic splines (Desquilbet and Mariotti, 2010).

We performed additional analyses removing nutritional exposures and only including socio-demographic covariates in our multivariable models. We also examined whether maternal smoking (serum cotinine ≥ 3 ng/mL vs. <3 ng/mL) (Benowitz et al., 2009), infant sex, or race (Black vs. White) modified the association between urinary phthalate metabolite concentrations and birth outcomes by including product interaction terms between urinary phthalate metabolite concentrations and these potential modifiers. We examined the magnitude and precision of associations within strata, as well as the product interaction term p-value.

2.6. Sensitivity analyses

We performed several sensitivity analyses to examine the robustness of results to various assumptions and adjustments. First, we excluded 49 women with one or more of the following medical conditions that could possibly affect phthalate metabolite excretion and fetal growth: gestational diabetes (n = 10), pregnancy induced hypertension (n = 18), preeclampsia (n = 21), chorioamnionitis (n = 5), placenta previa (n = 2), or placental abruption (n = 9). Then we performed analyses using birth weight, instead of birth weight z-scores, both with and without adjusting for gestational duration in the model. Next, we conducted analyses without creatinine-standardizing phthalate metabolite concentrations, instead adding creatinine to the model as a covariate. We also reconducted our analyses restricting to women with urinary creatinine levels between 30 and 300 mg/dl. We ran analyses adjusting for maternal weekly weight gain during pregnancy. We also