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Urinary triclosan concentrations during pregnancy and birth outcomes

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ABSTRACT

Background: Triclosan is an antimicrobial chemical used in consumer products, and exposure is ubiquitous among pregnant women in the United States. Triclosan may reduce the levels of thyroid hormones that are important for fetal growth and development.

Objective: We investigated the relationship of prenatal triclosan exposure with birth anthropometry and gestational duration.

Methods: We used data from 378 mother-child pairs participating in the Health Outcomes and Measures of the Environment (HOME) Study, a prospective pregnancy and birth cohort from Cincinnati, OH. We measured triclosan concentrations in maternal urine samples collected at 16 and 26 weeks of pregnancy. We abstracted information on neonatal anthropometry and gestational duration from medical records. We used multivariable linear regression to estimate the covariate-adjusted association between the average of the two urinary triclosan concentrations and gestational age standardized weight z-score, length, head circumference, and gestational age at birth.

Results: Median urinary triclosan concentrations were 16 ng/mL (range: < 2.4 to 1501 ng/mL). Each 10-fold increase in triclosan was associated with a predicted 0.15 standard deviation decrease (95% CI: −0.30, 0.00) in birth weight z-score, 0.4-cm decrease (95% CI: −0.8, 0.1) in birth length, 0.3-cm decrease (95% CI: −0.5, 0.0) in head circumference, and 0.3-week decrease (95% CI: −0.6, −0.1) in gestational age. Child sex did not modify the associations between triclosan and birth outcomes.

Conclusions: In this cohort, maternal urinary triclosan concentrations during pregnancy were inversely associated with infants' birth weight, length, head circumference, and gestational age.

1. Introduction

Triclosan is an antimicrobial chemical that is widely used in some toothpastes, mouthwashes, soaps, cosmetics, lotions, textiles, toys, and kitchenware. Dann and Hontela (2011) Exposure is ubiquitous among pregnant women in the United States. (Philippat et al., 2013; Wolff et al., 2008; Woodruff et al., 2011) The primary routes of exposure are oral and dermal, with the highest exposures hypothesized to be from dermally applied products. Rodricks et al. (2010) Oral care products, including some toothpastes, are another major source of exposure, particularly among children. Rodricks et al. (2010) The U.S. Food and Drug Administration banned over-the-counter consumer wash products that contain triclosan in September of 2016; however other potential sources of triclosan, such as some body lotions and toothpastes, remain in use. Safety and Effectiveness of Consumer Antiseptics (2016)

Triclosan may disrupt the actions within the hypothalamic-pituitary-thyroid axis (Brucker-Davis, 1998), and triclosan exposure reduces thyroxine concentrations in pregnant, fetal, and juvenile rats. (Paul et al., 2012; Paul et al., 2010; Johnson et al., 2016) Of particular concern is the potential for triclosan to disrupt thyroid hormone homeostasis during fetal development because thyroid hormones play a critical role in fetal growth and neurodevelopment; reduced thyroxine levels during gestation can have negative impacts on the developing fetus. (de Escobar et al., 2004; Gilbert et al., 2012; Ghassabian et al., 2011)

Triclosan has been associated with adverse birth outcomes in epidemiological studies. Maternal prenatal urinary triclosan concentrations have been inversely associated with newborn's head circumfer-

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ence, but not with weight or length at birth. (Philippat et al., 2014; Lassen et al., 2016) Another study found that prenatal urinary triclosan concentrations were inversely associated with birth weight and length among newborn boys, but not with head circumference. Wolff et al. (2008) However, prior studies were limited by having only one measure of prenatal urinary triclosan during pregnancy and this may have resulted in exposure misclassification.

The objective of this study was to investigate the relationship of prenatal urinary triclosan concentrations at 16 and 26 weeks of pregnancy with birth weight, length, head circumference, and gestational duration in a prospective pregnancy and birth cohort. Based on previous animal and epidemiologic studies, we hypothesized that urinary triclosan concentrations would be inversely associated with neonatal anthropometry and gestational duration.

2. Materials and methods

2.1. Study participants

We used data collected from women and children enrolled in The Health Outcomes and Measures of the Environment (HOME) Study, an ongoing prospective pregnancy and birth cohort in the greater Cincinnati, Ohio metropolitan area. The HOME Study was designed to investigate the impact of exposure to common environmental contaminants on child health and development. We previously described details of the study. Braun et al. (2016) Briefly, from March 2003 to January 2006 we recruited women living in the greater Cincinnati, Ohio metropolitan area who were: 18 years or older and 16 ± 3 weeks of gestation, spoke English, lived in a home built before 1978, and had no history of HIV infection or other medical conditions such as diabetes, bipolar disorder, schizophrenia or cancer that resulted in radiation treatment or chemotherapy. Of the 1263 eligible women we approached, 468 (37%) agreed to participate in our study. Of these, 67 dropped out before delivery leaving 401 women who delivered 389 singletons, 3 stillbirths, and 9 sets of twins.

The Cincinnati Children's Hospital Medical Center (CCHMC) and participating delivery hospitals' Institutional Review Boards (IRB) approved the HOME Study. After research assistants explained study protocols, all women provided written informed consent for themselves and their children. Brown University relinquished IRB authority to CCHMC through an Interagency Agreement. The Centers for Disease Control and Prevention (CDC) also relied on CCHMC IRB.

2.2. Urinary triclosan biomarkers

Women provided two urine samples at an average of 16.0 (range: 10.4–22.6) and 26.5 (range: 19.1–34.6) weeks of gestation. We collected urine in polypropylene containers and stored them at −20 °C until shipped to the CDC for analysis. We measured total (conjugated + free) urinary triclosan concentrations using online solid phase extraction coupled with high performance liquid chromatography-isotope dilution tandem mass spectrometry as previously described. Ye et al. (2005) Concentrations below the limit of detection (LOD) of 2.3 ng/mL were given a value of LOD/√2 for the statistical analysis. Urinary triclosan concentrations were creatinine-standardized (μg/g creatinine) to control for individual variation in urine dilution. Because creatinine-standardized urinary triclosan concentrations were right skewed, we $\log_{10}$-transformed them to reduce the influence of extreme observations before taking the mean of the 16 and 26-week $\log_{10}$-transformed creatinine-standardized urinary triclosan concentrations. Ninety-four percent of women had triclosan measurements at 16 and 26 weeks; for those who had only one measure, we used that in place of the mean.

2.3. Birth outcomes

We extracted birth weight, length, and head circumference, gestational duration, and the method for determining gestational age (last menstrual period, n = 368; antenatal ultrasound, n = 6; or Ballard Maturational Assessment, n = 3) from newborn medical charts. We calculated sex and gestational age standardized birth weight z-scores using United States Natality datasets. Oken et al. (2003)

2.4. Covariates

We considered adjusting for potential confounders that might be associated with both gestational triclosan concentrations and fetal growth or gestational duration using a directed acyclic graph (DAG) (Supplemental Fig. S1). We collected information about sociodemographic factors including maternal race and ethnicity, age, education, marital status, and household income using a computer-assisted questionnaire administered by trained research staff during the second trimester of pregnancy. Depressive symptoms were measured with the Beck Depression Inventory (BDI-II) at 20 weeks of pregnancy Beck and Brewn (1996). We measured perinatal factors, including delivery method, parity, weight at 16 weeks gestation, and prenatal vitamin use using standardized interviews or medical chart reviews. We assessed tobacco smoke exposure using the average of serum cotinine concentrations taken at 16 and 26 weeks of pregnancy. Benowitz et al. (2009)

2.5. Statistical analysis

Of the 389 women in the HOME Study who gave birth to singletons, we excluded women who had offspring with congenital or chromosomal abnormalities (n = 2), were missing the method used to determine gestational age (n = 1), or were missing covariate data (n = 8). This left 378 mother-neonate pairs for analysis of birth weight z-score and gestational age. Eight children were missing the head circumference measurements and 9 children were missing the birth length measurements, leaving 370 and 369 mother-neonate pairs for the analysis of head circumference and birth length, respectively.

We started our statistical analysis by calculating the geometric mean of the average prenatal triclosan concentrations and the mean birth weight z-score by covariates. Next, we calculated intraclass correlation coefficients (ICCs) between the 16 and 26 week $\log_{10}$-transformed creatinine-standardized urinary triclosan concentrations to estimate the reproducibility of the repeated urinary triclosan concentrations. Rosner (1982)

We then determined whether there were non-linear relationships between urinary triclosan concentrations and birth outcomes using restricted cubic splines. Desquilbet and Mariotti (2010) Because we observed a linear association (non-linearity p-values > 0.3), we estimated the unadjusted and adjusted difference in birth weight z-score, gestational age, birth head circumference, and birth length associated with a 10-fold increase in gestational urinary triclosan concentration using multivariable linear regression. To enhance interpretability of the results, we also examined the adjusted mean value in birth outcomes across quartiles of prenatal urinary triclosan concentrations. We examined whether child sex modified the association between triclosan and birth outcomes in our multivariable model by including child sex and a product interaction term between triclosan concentrations and child sex. Finally, we used Poisson regression with robust standard errors to calculate the relative risk of low-birth weight (< 2500 g), preterm birth (< 37 weeks gestation), and small for gestational age (SGA, < 10th birth weight z-score percentile) for a 10-fold increase in prenatal triclosan concentrations. Zou (2004) We used SAS version 9.4 (SAS Institute, Inc. Cary, NC) and R version 3.2 for statistical analysis.