Prenatal exposure to organophosphate flame retardants and children's growth and development

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Introduction

Obesity among children continues to be a major public health concern. According to a recent population-based survey, 10% of American children under the age of 2 are obese (1). Children with higher body mass index (BMI) are more likely to become overweight or obese adults, and are at increased risk of many chronic conditions, including diabetes, cardiovascular disease, and some cancers (2). Although the imbalance between energy intake and energy expenditure is certainly a key determinant of weight, emerging evidence supports the hypothesis that environmental exposures, particularly those occurring in early-life, may interfere with homeostatic controls and induce or exacerbate obesity.

Organophosphate flame retardants (PFRs) are commonly used in residential furniture, electronics, and baby products as flame retardants and are also used in other consumer products as plasticizers (3-6). PFRs have been detected with high frequency in studies of the indoor environment and data indicate that human exposure is likely ubiquitous (e.g. 4, 7). Although the human health effects of exposure to PFRs are largely unexplored, animal studies provide compelling evidence that PFR exposure may impact growth and development as well as other health endpoints.

The goals of our present work are twofold: 1) to evaluate individual characteristics associated with higher levels of exposure to PFRs, and 2) to evaluate impacts of in utero PFRs exposure on children's prenatal and early-life growth measures using data from the Pregnancy Infection and Nutrition (PIN) Study.

Materials and methods

The PIN study enrolled a cohort of central North Carolina women in early pregnancy and conducted follow-up through delivery and early childhood (8). The current analyses are limited to mothers recruited 2002-2005, whose children participated in follow-up through age 3 years (n=349). Self-administered questionnaires, telephone interviews and a brief questionnaire at the hospital after delivery were used to collect health and lifestyle information during the pregnancy. In-home study visits collected children's height and weight at 12 and 36 months of age. Growth information was also collected from pediatric well-child doctor's visits, resulting in over 4000 measures of children's height and weight. All study protocols and procedures were approved by the Institutional Review Board at the University of North Carolina-Chapel Hill.

During the late-second or early-third trimester, PIN women collected a spot urine samples in which 6 PFR metabolites were assessed (BDCIPP, BCIPP, DPHP, ip-PPP, tb-PPP and BCIPHIPP) using previously

described methods. Briefly, samples were extracted using enzyme deconjugation and solid phase extraction (SPE) techniques described in Van den Eede 2013 and Butt 2016 (9, 10).

Preliminary analyses indicated that urinary PFR metabolite levels were positively skewed. Accordingly, we used non-parametric analyses or log10-transformed metabolite concentrations in statistical analyses investigating predictors of urinary metabolites. Assessed predictors included age, race, education, pre-pregnancy BMI, parity and, gestational duration at the time of sample collection date of sample collection and season of collection. We then assessed relationships between maternal PFR metabolites and birth outcomes (e.g. birthweight, gestational duration, and birthweight for gestational age percentile) and children's growth using multivariable regression and mixed models.

Results and discussion

PFR metabolites were detected in every urine sample, with BDCIPP, DHPH, ip-PPP and BCIPHIPP detected in >80% of samples. Geometric mean concentrations were higher than what has been reported previously for similarly-timed cohorts. Women with higher pre-pregnancy BMI tended to have higher levels of urinary metabolites. For example, those classified as obese at the start of pregnancy had ip-PPP levels that were 1.52 times as high as normal weight range women (95% confidence interval (CI): 1.23, 1.89). Women in their first pregnancy also tended to have higher urinary levels of DPHP, but lower levels of ip-PPP. In addition, we saw strong evidence of seasonal trends in metabolite concentrations (e.g. higher DPHP, BDCIPP, and BCIPHIPP in summer, and evidence of increasing ip-PPP 2002 to 2005).

The median birthweight for infants in the cohort was 3353 g (range 1422-4760 g) and infants were born at a median of 39 weeks gestation (range 29-42 weeks). Relationships between prenatal exposures to PFRs and birth outcomes differed based on the sex of the infant. On average, women with the highest quartile of urinary ip-PPP concentration delivered girl babies 1 week earlier than women with the lowest quartile ip-PPP levels (95% CI: -1.9, -0.2). Similarly, high prenatal ip-PPP exposure was associated with lower birth weight (-348 g, 95% CI: -601, -94, comparing quartile 4 to quartile 1 of urinary ip-PPP). However, birth weight for gestational age percentiles were not associated with ip-PPP, suggesting that exposure may impact gestation duration, but not growth. Similar, although less precisely estimated, patterns of association were observed between gestational age and BDCIPP and DPHP among female infants. Conversely, among males, prenatal TPHP exposure (as indicated by maternal urinary DPHP) tended to be associated with increased gestation duration (mean difference of 0.7 weeks comparing quartile 4 to quartile 1, 95% CI: -0.1, 1.5). Although prenatal PFR exposures, as indicated by metabolite concentrations in maternal urine, were generally not related to BMI at 36 months of age, additional analyses investigating growth trajectories are currently ongoing.

Cumulatively, our results indicate ubiquitous exposure to PFRs among NC women in the early 2000s. Additionally, our work suggests that individual characteristics are related to exposure and that temporal variation, both seasonal and annual, may exist. With respect to birth outcomes, our results indicate that prenatal exposure to PFRs may impact timing of birth, specifically earlier birth among female infants. Because pre-term birth is associated with later risks for children, further investigation is warranted to explore potential implications for long-term health and development.

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