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Maternal intake of pesticide residues from fruits and vegetables in relation to fetal growth☆

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ABSTRACT

Objectives: To examine the associations of maternal intake of fruits and vegetables (FVs), considering pesticide residue levels, with fetal growth.

Methods: We studied 1777 mothers (1275 white, 502 non-white) and their infants from Project Viva, a prospective pre-birth cohort (1999–2002). We categorized FVs as containing high or low pesticide residues using data from the US Department of Agriculture. We then used a food frequency questionnaire to estimate each participant's intake of high and low pesticide residue FVs in the first and second trimester. The primary outcomes were small-for-gestational-age (SGA; < 10th percentile in birth-weight-for-gestational-age), large-for-gestational-age (LGA; ≥10th percentile in birth-weight-for-gestational-age) and preterm birth (gestational age < 37 weeks). We also evaluated whether the associations between high pesticide residue FV intake and birth outcomes were modified by race/ethnicity.

Results: 5.5% of newborns were SGA, 13.7% were LGA, and 7.3% were preterm. Intakes of high or low pesticide residue FVs, regardless of pregnancy trimester, were not associated with risks of SGA, LGA, or preterm birth. In addition, the associations of high pesticide FV intake with SGA and LGA were not modified by race/ethnicity. However, we observed heterogeneity in the relationship between first trimester high pesticide FV intake and risk of preterm birth by race/ethnicity (P value for interaction = 0.01), although this relationship did not persist after correction for multiple comparisons (Bonferroni corrected level of significance: $P < 2.8 \times 10^{-3}$).

Conclusions: There were no clear associations between high or low pesticide FV intake during pregnancy with SGA, LGA or preterm birth.

Abbreviations: BMI, body mass index; CI, confidence interval; EPA, Environmental Protection Agency; FFQ, food frequency questionnaire; FV, fruit and vegetable; SGA, small for gestational age; LGA, large for gestational age; PON1, paraoxonase 1; PRBS, Pesticide Residue Burden Score

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1. Introduction

Fruits and vegetables (FVs) contain many important nutrients and are considered essential components of a healthy diet (Millen et al., 2016). According to the Dietary Guidelines for Americans 2015–2020, consumption of a variety of FVs is recommended throughout the lifespan including during pregnancy (Millen et al., 2016). Nonetheless, FVs can also serve as a source of exposure to pesticide residues. According to US Department of Agriculture (USDA) Pesticide Data Program, in 2015, 87% of FVs in U.S. markets had detectable pesticide residues, and 58% had detectable levels of three or more individual pesticides (USDA, 2015).

In the US, pesticide tolerances (i.e., amount of pesticide residues that are allowed to remain in or on food) are regulated by the Environmental Protection Agency under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Food Quality Protection Act (FQPA). Although the majority of US foods have residues below tolerance levels (USDA, 2015), it remains unclear whether long-term exposure through diet to low levels of pesticide residues below tolerance levels possess a risk. Pesticide metabolites can be detected in amniotic fluid collected at 15–18 weeks gestation (Bradman et al., 2003). The fetus, due to its rapid growth, immature metabolic pathways, and developing vital organ systems (Berkowitz et al., 2004), may exhibit greater susceptibility to the effects of pesticide residues than adults.

Fetal growth and preterm birth are not only indicators of fetal health but also predictors of long-term health outcomes. A growing number of studies suggest that preterm birth and higher or lower fetal growth are associated with adverse cardiometabolic health later in life (Frankel et al., 1996; Huxley et al., 2000; Irving et al., 2000; Newsome et al., 2003; Rich-Edwards et al., 1997; Rotteveel et al., 2008), although the underlying pathways with later outcomes may be different for preterm birth and fetal growth (Gillman, 2002). In the literature, a limited number of human studies have examined maternal prenatal urinary concentrations of organophosphate pesticide metabolites in relation to fetal growth and gestational age (Eskenazi et al., 2004; Harley et al., 2011; Naksen et al., 2015; Rauch et al., 2012; Whyatt et al., 2004). However, the results of these studies were mixed, possibly due to differences in timing of exposure (e.g., 1st trimester vs. 2nd trimester vs. 3rd trimester), sources of exposure (residential vs. dietary vs. agricultural exposure), high within-person variability of urinary biomarkers, and different frequencies of paraoxonase 1 (*PON1*) polymorphisms (an enzyme involved in detoxification of organophosphate pesticides (Costa et al., 2013)) across studies. Therefore, the objective of the study was to assess the associations of high and low pesticide residue FV intake during each of the first and second trimesters with fetal growth and preterm birth in a cohort of pregnant women from Eastern Massachusetts. We also examined whether the associations were modified by race/ethnicity, a proxy of frequency in *PON1* polymorphism (Chen et al., 2003; Draganov and La Du, 2004).

2. Materials and methods

2.1. Study population

Project Viva is a prospective pre-birth cohort which recruited women carrying a singleton pregnancy during their initial obstetric care visit at Atrius Harvard Vanguard Medical Associates between 1999 and 2002 in Eastern Massachusetts, USA. Details of the cohort have been described previously (Oken et al., 2015). Briefly, research assistants collected demographic and health history information including race/ethnicity, date of last menstrual period, maternal and paternal height and pre-pregnancy weight, and smoking history via interview and questionnaire. We also provided participants a take-home food frequency questionnaire (FFQ) at the first trimester (~10 weeks of gestation) and second trimester (~26–28 weeks of gestation) study visits. Of 2128 women who delivered a live-born infant, 1777 completed a first-trimester FFQ and 1666 completed a second-trimester FFQ. Compared to women who completed the first trimester FFQ, women who did not complete it were younger (mean 29.7 vs. 32.2 years), comprised a higher proportion of blacks (38.0% vs. 12.3%), never smokers (73.7% vs. 67.4%), had a higher mean pre-pregnancy BMI (26.3 vs. 24.6 kg/m^2) and were less educated (40.4% vs. 69.4% with at least college degree). However, they had similar maternal and paternal height. Institutional review boards of Harvard Pilgrim Health Care, Brigham and Women's Hospital, and Beth Israel Deaconess Medical Center approved the study protocols and all mothers provided written informed consent.

2.2. Dietary assessment

We assessed diet using a 140-item, self-administered FFQ based on a well-validated FFQ used in other cohorts (Yuan et al., 2017a, 2017b) and adapted for use among pregnant women (Fawzi et al., 2004). The first-trimester FFQ assessed diet intake since the last menstrual period and was completed by participants at enrollment. The second-trimester FFQ was self-completed at 26–28 weeks of gestation and assessed diet "during the past 3 months."

We used the FFQ to determine FV intake for each participant. We also used the FFQ to assign each participant to two dietary pattern scores derived by principal component factor analysis to summarize overall food choices (except for FVs) (Lange et al., 2010). The factor scores were standardized to have a mean of 0 and standard deviation of 1, with higher scores indicating higher adherence to Prudent (more poultry, fish, whole grains) or Western (more red meat, processed meat, refined grains, and desserts) dietary patterns.

2.3. Pesticide residue assessment

FVs were classified as having high versus low pesticide residues using the Pesticide Residue Burden Score (PRBS), a scoring system used to assess pesticide residue status in FVs. The PRBS has been described in greater details elsewhere (Chiu et al., 2015; Chiu et al., 2018). Briefly, the PRBS method couples the information from FFQ and pesticide residue surveillance data from US Department of Agriculture Pesticide Data Program (PDP) (USDA, 2013) and has been validated against urinary pesticide metabolites in two cohorts (Chiu et al., 2018; Hu et al., 2016). Specifically, we ranked the 36 FVs included in the FFQ according to each of the three contamination measures from Pesticide Data Program: (1) the percentage of samples with any detectable pesticide residues; (2) the percentage of samples with any pesticide residues above the tolerances; and (3) the percentage of samples with three or more different detectable pesticides. For each contamination measure, we assigned a score of 0 for FVs in the lowest tertile, 1 for FVs in the middle tertile, and 2 for FVs in the upper tertile. The PRBS for each FV was the sum of tertile scores across the three measures on a scale of 0 to 6. We classified FVs with a PRBS ≥ 4 as having high pesticide residues and those with a PRBS < 4 as having low pesticide residues (Supplemental Table S1). We summed the intake of high and low pesticide residue FVs, separately, for each participant. Of note, PDP data from 1999 to 2002 only cover 24 items in the FFQ. In order to maximize the available pesticide residue data for nearly all the FV items assessed in the FFQ, we created the PRBS using the PDP data from 1992 to 2013. Among the 24 items with overlap, the spearman correlation of the PRBS based on PDP data from1992 to 2013 and that based on PDP data from1999 to 2002 was 0.92.