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Original article

Serum cotinine and whole blood folate concentrations in pregnancy

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ABSTRACT

Purpose: Prenatal tobacco smoke exposure may be associated with low maternal folate levels that increase the risk of adverse infant and child health outcomes by reducing folate availability during fetal development.
Methods: Using data from the Health Outcomes and Measures of the Environment Study, we examined the relationship between secondhand or active tobacco smoke exposure and whole blood folate concentrations in pregnant women from Cincinnati, Ohio ($n = 362$) at approximately 16-week gestation. We used multivariable linear regression to examine the association between continuous or categorical serum cotinine levels and whole blood folate levels, adjusting for sociodemographic, dietary, and perinatal variables.
Results: After adjustment for potential confounders, an interquartile range increases in serum cotinine concentration (0.012–0.224 ng/mL) was suggestively associated with decreased whole blood folate levels (β, −23 nmol/L; 95% confidence interval (CI), −49, 3; *P* value = .08). Compared with unexposed women, reductions in mean whole blood folate were observed among active smokers (β, −94, 95% CI, 195, 6 nmol/L; *P* value = .40); smaller reductions were observed among women with secondhand exposure (β, 26; CI, 84, 32 nmol/L; *P* value = .07).
Conclusions: Consistent with prior studies, active smoking was associated with reduced whole blood folate levels among these pregnant women. Secondhand tobacco smoke exposures were associated with small and imprecise reductions in whole blood folate levels.

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Introduction

Tobacco smoke exposure remains a prevalent and preventable cause of disease, disability, and death in the United States [1–3]. Smoking and secondhand tobacco smoke (SHS) exposure can cause adverse health effects across the lifespan, but the developing fetus may be particularly sensitive due to reduced nicotine detoxification capacity compared with adults [4,5]. Despite the well-known adverse health effects of tobacco smoke, approximately 14% of US women smoke during their pregnancy and at least 30% of US women experience SHS exposures before or during pregnancy [6–8]. Active and SHS exposures during pregnancy may increase the risk for numerous adverse maternal, fetal, infant, and child health outcomes. These include, but are not limited to placental abruption, intrauterine growth restriction, preterm birth, low birth weight, sudden infant death syndrome, neurodevelopmental disorders, and possibly neural tube defects (NTDs) [2,9–14].

Prenatal tobacco smoke exposures may increase infant or child disease risk by reducing folate bioavailability during the sensitive prenatal period of development [15–23]. Folate is an essential B-vitamin that functions as a coenzyme in single-carbon transfer reactions and is essential for DNA synthesis, methylation, and repair in cells [24]. Folate deficiency during pregnancy is associated with NTDs, such as spina bifida and anencephaly [25]. Although lower serum and red blood cell (RBC) folate concentrations have been

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observed in pregnant smokers compared with nonsmokers, we are not aware of prior studies examining the association between SHS exposure and folate status using validated biomarkers of SHS exposure (e.g., cotinine) while considering potential sociodemographic or nutritional confounders. Biomarkers of tobacco smoke exposure have several advantages over self-reported exposures: (1) pregnant women may not report active smoking because of social desirability, (2) questionnaires may not be sensitive enough to identify all relevant sources of SHS exposure, and (3) biomarkers of cumulative dose, like cotinine, can be used to examine dose-response relationships across the entire range of secondhand and active tobacco smoke exposures [26–28].

Since tobacco smoke exposures and low folate levels during pregnancy may increase the risk of subsequent disease, we examined the relationship between maternal serum cotinine and whole blood folate concentrations in pregnant women, while adjusting for sociodemographic and dietary factors.

Methods

Study sample

The data used in this study were collected from women participating in the Health Outcomes and Measures of the Environment (HOME) Study in Cincinnati, Ohio. The HOME Study has measured environmental chemical exposures and a variety of health outcomes in pregnant women and their children. Initial identification of participants was conducted at nine prenatal clinics affiliated with three hospitals between March 2003 and January 2006. Eligibility criteria included 18 years of age or older, living in a home built before 1978, 16 ± 3-week gestation at enrollment; residing in five counties in Southwest Ohio and one county in Northern Kentucky; intention to continue prenatal care and deliver at collaborating obstetric practices and hospitals; human immunodeficiency virus negative; and not receiving seizure or thyroid medications, or chemotherapy or radiation. Recruitment letters were mailed to 5512 women who were at least aged 18 years and lived in a home built before 1978. Of 1263 eligible women (23%), 468 (37%) enrolled in the study [26]. The HOME Study was approved by the Institutional Review Board at the Cincinnati Children's Hospital Medical Center and all subjects provided written informed consent before participation.

Biomarkers of tobacco smoke exposure

Serum and whole blood samples were obtained via venipuncture from women at approximately 16-week gestation. Samples were kept at less than −20°C or more before being shipped on dry ice to the Centers for Disease Control and Prevention laboratory. Serum was analyzed for cotinine, a sensitive and specific biomarker of SHS and active tobacco smoke exposure using high-performance liquid chromatography–tandem mass spectroscopy (HPLC-MS/MS) [29,30]. We used the actual measured cotinine concentrations for samples with results below the limit of detection (LOD = 0.015 ng/mL) rather than imputing values because this is statistically more efficient [31].

Using data from this cohort, we previously found that repeated serum cotinine concentrations collected during the latter two-thirds of pregnancy were highly correlated with each other (Pearson $r > 0.7$) and associated with self-reported secondhand and active tobacco smoke exposures [27]. Furthermore, women with no self-reported tobacco smoke exposures had serum cotinine concentrations consistent with SHS exposure, indicating that self-report may misclassify women's actual exposure [26].

Biomarkers of folate status

Whole blood samples were analyzed for folate vitamers by HPLC-MS/MS [32,33]. Whole blood (total) folate was calculated as the sum of five folate vitamers, with 5-methyltetrahydrofolate being the major folate form (~80% of total folate) (Supplemental Method 1). Whole blood folate is a specific measure of long-term folate status with a biological half-life of ~8 weeks [34]. Folate vitamer values less than LOD were substituted by the LOD/√2. To assess the between-run variability ($n = 14$), three known quality control (QC) pools (127–357 nmol/L whole blood [total] folate and 100–248 nmol/L whole blood 5-methyltetrahydrofolate) were analyzed in duplicate during each analytic run and two unknown QC pools (447–665 nmol/L whole blood [total] folate and 359–408 nmol/L whole blood 5-methyltetrahydrofolate) were analyzed as part of each analytic run at a rate of one unknown pool for every 20 study samples. The between-run variability for whole blood (total) folate for the three known and two unknown QC materials was 3.9%–6.7% and 1.5%–1.9%, respectively. The between-run variability for whole blood 5-methyltetrahydrofolate was 2.1%–3.6% and 2.0%–2.2%, respectively.

Potential confounders

Dietary folate intake, sociodemographic factors, and lifestyle are strong determinants of both serum cotinine and blood folate levels. Drawing on prior knowledge, we selected potential confounders based on whether they might be related to either serum cotinine or whole blood folate concentrations among pregnant women [3,8,35–37]. Trained research assistants collected sociodemographic, dietary, and perinatal variables using standardized, computer-assisted interviews at 20-week gestation and medical chart reviews after delivery. Sociodemographic covariates included maternal race, age, education, marital status, household income, and insurance status. Dietary variables included prenatal vitamin use frequency, food security (variety and quantity of food), and fresh fruit and vegetable consumption frequency. Perinatal variables included maternal depressive symptoms at 16-week gestation (Beck Depression Inventory-II) [38], maternal body mass index (BMI) at 16-week gestation, and parity.

Statistical analysis

We began our analysis by calculating the median and interquartile range (IQR) of serum cotinine and whole blood folate concentrations according to sociodemographic, dietary, and perinatal characteristics of the study participants.

We characterized tobacco smoke exposure at 16 weeks gestation using both continuous and categorical measures of serum cotinine concentrations. For analysis of continuous cotinine levels, we applied a Box–Cox transformation with a gamma value of 0.1 to serum cotinine levels to account for the right skew of the distribution [39]. For categorical analysis, prenatal serum cotinine concentrations were categorized into three levels: no exposure (<LOD), SHS exposure (LOD to 3 ng/mL), and active exposure (>3 ng/mL) [23]. Whole blood folate concentrations were approximately normal and not mathematically transformed.

In our primary analysis using linear regression, we examined the unadjusted and adjusted change in whole blood folate concentrations for an IQR increase in serum cotinine concentrations. We also estimated the unadjusted and adjusted mean whole blood folate concentrations according to the categories of maternal serum cotinine concentrations. We examined variance inflation factors and condition indices to determine whether there was multicollinearity among the variables in our adjusted model. Variance inflation

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