OBSTETRICS

Associations between maternal periconceptional exposure to secondhand tobacco smoke and major birth defects

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BACKGROUND: While associations between secondhand smoke and a few birth defects (namely, oral clefts and neural tube defects) have been noted in the scientific literature, to our knowledge, there is no single or comprehensive source of population-based information on its associations with a range of birth defects among nonsmoking mothers.

OBJECTIVE: We utilized data from the National Birth Defects Prevention Study, a large population-based multisite case-control study, to examine associations between maternal reports of periconceptional exposure to secondhand smoke in the household or workplace/school and major birth defects.

STUDY DESIGN: The multisite National Birth Defects Prevention Study is the largest case-control study of birth defects to date in the United States. We selected cases from birth defect groups having >100 total cases, as well as all nonmalformed controls (10,200), from delivery years 1997 through 2009; 44 birth defects were examined. After excluding cases and controls from multiple births and whose mothers reported active smoking or pregestational diabetes, we analyzed data on periconceptional secondhand smoke exposure—encompassing the period 1 month prior to conception through the first trimester. For the birth defect craniosynostosis, we additionally examined the effect of exposure in the second and third trimesters as well due to the potential sensitivity to teratogens for this defect throughout pregnancy. Covariates included in all final models of birth defects with ≥5 exposed mothers were study site, previous live births, time between estimated date of delivery and interview date, maternal age at estimated date of delivery, race/ethnicity, education, body mass index, nativity, household income divided by number of people supported by this income, periconceptional alcohol consumption, and folic acid supplementation. For each birth defect examined, we used logistic regression analyses to estimate both crude and adjusted odds ratios and 95% confidence intervals for both isolated and total case groups for various sources of exposure (household only; workplace/school only; household *and* workplace/school; household *or* workplace/school).

RESULTS: The prevalence of secondhand smoke exposure only across all sources ranged from 12.9-27.8% for cases and 14.5-15.8% for controls. The adjusted odds ratios for any vs no secondhand smoke exposure in the household or workplace/school and isolated birth defects were significantly elevated for neural tube defects (anencephaly: adjusted odds ratio, 1.66; 95% confidence interval, 1.22—2.25; and spina bifida: adjusted odds ratio, 1.49; 95% confidence interval, 1.20—1.86); orofacial clefts (cleft lip without cleft palate: adjusted odds ratio, 1.41; 95% confidence interval, 1.10—1.81; cleft lip with or without cleft palate: adjusted odds ratio, 1.24; 95% confidence interval, 1.05—1.46; cleft palate alone: adjusted odds ratio, 1.31; 95% confidence interval, 1.06—1.63); bilateral renal agenesis (adjusted odds ratio, 1.99; 95% confidence interval, 1.05—3.75); amniotic band syndrome-limb body wall complex (adjusted odds ratio, 1.66; 95% confidence interval, 1.10—2.51); and atrial septal defects, secundum (adjusted odds ratio, 1.37; 95% confidence interval, 1.09—1.72). There were no significant inverse associations observed.

CONCLUSION: Additional studies replicating the findings are needed to better understand the moderate positive associations observed between periconceptional secondhand smoke and several birth defects in this analysis. Increased odds ratios resulting from chance (eg, multiple comparisons) or recall bias cannot be ruled out.

Key words: birth defects, congenital defects, congenital heart defects, environmental tobacco smoke, malformations, passive smoking, secondhand smoke

Introduction

The association between active maternal cigarette smoking and various birth defects has been recently reviewed.[1] The relationship between exposure to secondhand smoke (SHS) during pregnancy and birth defects, however, has been examined to a lesser extent.[2] SHS, also referred to as passive or environmental tobacco smoke, is formed from smoke emitted into the environment from a cigarette, mixed with smoke exhaled by the smoker.[3] SHS contains a complex mixture of >4000 chemicals[4] including known fetal developmental toxicants.[5] It remains an important public health concern, particularly in groups where exposure appears to be higher, such as those with lower incomes[6] and certain racial/ethnic groups.[3]

The Centers for Disease Control and Prevention reported that approximately 40% of US nonsmokers had a measured biomarker for SHS exposure between 2007 through 2008.[7] A recent analysis from the National Birth Defects Prevention Study (NBDPS) reported a slightly lower estimate with 30% of nonsmoking mothers of nonmalformed infants self-reporting exposure to SHS 3 months prior to conception through the pregnancy.[8]

Findings from the literature examining maternal SHS and birth defects have been mixed due to: (1) SHS being assessed at different stages of pregnancy; (2) quantity and source of SHS; and (3) etiologic heterogeneity across defects. Recent studies have reported positive associations between SHS and some defects: anorectal atresia,[9] neural tube

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defects (NTDs),[10-14] nonsyndromic atrioventricular septal defects,[15] limb defects,[16,17] orofacial clefts,[18-21] and omphalocoele[22]; but not others: hypospadias,[23] orofacial clefts,[24] craniosynostosis,[25] congenital heart defects (CHDs),[26] bilateral renal agenesis or hypoplasia,[27] esophageal atresia with or without tracheoesophageal fistula,[28] and diaphragmatic hernia (not otherwise specified).[29]

To our knowledge, however, there have been no comprehensive examinations of SHS during pregnancy and a range of birth defects among nonsmoking US mothers—and in the context of different sources of SHS. Given the current lack of spectrum analyses available on this important exposure, NBDPS data provide an excellent opportunity to explore these associations further.

Materials and Methods

Study population: overview of the NBDPS

Mothers of cases and controls with estimated dates of delivery (EDD) from 1997 through 2009 were included. Briefly, the NBDPS was a multisite case-control study designed to better understand the risk factors for and potential causes of major birth defects.[30] Liveborn, stillborn, or electively terminated cases (with ascertainment varying by site) with ≥1 of 30 major structural birth defects were reviewed for eligibility by clinical geneticists, and cases with known etiology (ie, single gene conditions) were excluded.[31] Each case was classified as: (1) isolated—those with only 1 organ system affected by a major defect(s); (2) multiple—those with ≥2 major defects occurring in different organ systems; and (3) complex—those identified as a pattern of embryologically related defects thought to represent early problems in morphogenesis.[31] In addition, CHDs were classified as: (1) simple—those with either an isolated or well-defined single CHD; (2) associated—those with ≥2 CHDs; and (3) complex—those with ≥3 CHDs.[32]

Controls were liveborn infants with no major malformations selected from the same base population as cases.[30,33] They were selected as a stratified random sample[34] from either birth certificates or birth hospitals.[33]

Mothers of cases and controls who met study eligibility requirements (ie, had legal custody of the child at the time of interview, had informed consent to participate if <18 years old, and could speak English or Spanish) were administered a computer-assisted telephone interview from 6 weeks to 24 months after their child's EDD. The interview included a variety of demographic and pregnancy history questions,[30,33] as well as questions about exposure that, unless otherwise noted, covered the period from 3 months before conception to the date of index (case or control) birth (B3-DOIB).

Exposure collection

In the section of the computer-assisted telephone interview related to cigarette smoke exposure, mothers were asked whether they had ever smoked cigarettes any time during B3-DOIB, and about SHS in various settings, namely:

1. Whether anyone in the mother's household smoked cigarettes in her home between (B3-DOIB), and if *yes*, which months during this period someone smoked in her home.
2. Whether anyone near the mother in her workplace or school smoked cigarettes. If *yes*, which months, as above.

For this study, we restricted our analysis to mothers reporting exposure (yes/no) during the period 1 month prior to conception through the first trimester (B1T1)—corresponding to the critical sensitive period of embryonic development, where most defects are susceptible to teratogens.[35] Craniosynostosis, however, is thought to be sensitive to teratogenic exposures such as smoking throughout pregnancy.[25,36] For this reason, we additionally examined this defect for an effect in the second and third trimesters as well. Information on the amount of SHS was not collected.

The NBDPS was approved by individual institutional review boards at each site.[21,24]

Data analysis

We restricted our analyses to birth defects with ≥100 cases and further excluded cases and controls whose mothers reported any active cigarette smoking, prepregnancy diabetes type 1/2 (associated with a range of birth defects[37]), and plural births (also related to an increased risk of various congenital malformations[38]), as well as mothers missing EDD or information on SHS. Additional restrictions for specific cases and controls based on NBDPS protocol are described elsewhere.[33] The primary exposure of interest was any SHS exposure (B1T1) in the household or workplace/school. Subanalyses examined SHS separately for household and workplace/school exposures—where we restricted to mothers who reported they were employed or were students.

Covariates were selected based on a literature review (a priori), our descriptive analyses, and changes in the SHS main effect (>10% change when starting with all covariates in the individual birth defect models and removing 1 covariate at a time). Covariates assessed included maternal age at delivery (<20, 20-24, 25-29, 30-34, ≥35 years); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other); maternal education (<12, 12, >12 years completed); prepregnancy dietary folate equivalent intake (<600/≥600 μg/d); body mass index (underweight <18.5, normal 18.5-≤24.9, overweight 25.0-≤29.9, obese ≥30 kg/m^2)[28]; maternal alcohol intake during B1T1 (yes/no); folic acid intake from multivitamins/individual supplement 1 month prior to conception through the first month of pregnancy (yes/no); gestational diabetes during the index pregnancy (yes/no); previous live births (0, 1, ≥2); pregnancy intention (yes/no); parental nativity (US born/foreign born); household income/number of people in the home (≤median, >median); hypertension reported during the index pregnancy (yes/no); time to interview (≤12, >12 months); and study site.

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