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Maternal periconceptional occupational exposure to pesticides and selected musculoskeletal birth defects

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ABSTRACT

This population-based U.S. study investigated the association between major musculoskeletal malformations and periconceptional maternal occupational pesticide exposure for a wide range of occupations. We conducted a multi-site case–control analysis using data from the National Birth Defects Prevention Study among employed women with due dates from October 1, 1997 through December 31, 2002. Cases included 871 live-born, stillborn, or electively terminated fetuses with isolated craniosynostosis, gastroschisis, diaphragmatic hernia, or transverse limb deficiencies. Controls included 2857 live-born infants without major malformations. Using self-reported maternal occupational information, an industrial hygienist used a job-exposure matrix and expert opinion to evaluate the potential for exposure to insecticides, herbicides or fungicides for each job held during one month pre-conception through three months post-conception. Exposures analyzed included any exposure (yes/no) to pesticides, to insecticides only, to both insecticides and herbicides (I + H) and to insecticides, herbicides and fungicides (I + H + F). We used logistic regression to evaluate the association between exposures and defects, controlling for infant and maternal risk factors. Occupational exposure to I + H + F was associated with gastroschisis among infants of women aged 20 years or older (adjusted odds ratio [aOR] = 1.88; 95% confidence interval [CI]: 1.16–3.05), but not for women under age 20 (aOR = 0.48; 95% CI: 0.20–1.16). We found no significant associations for the other defects. Additional research is needed to validate these findings in a separate population.

Introduction

Major musculoskeletal birth defects, including craniosynostosis, gastroschisis, diaphragmatic hernia, and transverse limb reduction deficiencies, are an important public health issue of largely unknown etiology with evidence of increased prevalence for gastroschisis. Gastroschisis, a congenital abdominal wall fissure causing herniation of abdominal organs into the amniotic cavity, has increased in prevalence worldwide (Di Tanna et al., 2002) and in the United States (Canfield et al., 2006; Parker et al., 2010). Craniosynostosis, the premature closing of cranial sutures which can result in neurocognitive deficits (Kapp-Simon et al., 2007), occurs in 3–5/10,000 U.S. births (Cohen and MacLean, 2000). Diaphragmatic hernia, in which the abdominal organs enter the chest cavity, constricting the heart and lungs, is a severe defect found in about 2.6/10,000 U.S. births (Parker et al., 2010). Transverse limb deficiencies, the absence of distal limb structures, are the most common type of limb reduction deficiency, occurring in about 4 cases per 10,000 (Stoll et al., 1996).

The role of maternal occupational pesticide exposure in the etiology of these defects is important to assess in light of the prevalence of pesticide use, the large numbers of women in

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the workforce, and the generally higher exposures encountered in occupational settings. Pesticides may be categorized by their target organism, as insecticides, herbicides, or fungicides. Animal studies have found associations between diaphragmatic hernia and specific herbicides (Costlow and Manson, 1981), limb deficiencies and craniofacial defects and dithiocarbamate fungicides (Larsson et al., 1976; Varnagy et al., 2000), and skeletal abnormalities and organophosphate insecticides (Farag et al., 2003). In epidemiologic studies, various types of limb deficiencies have been investigated primarily in relation to parental agricultural occupation, with mixed results (Engel et al., 2000; Kristensen et al., 1997; Lin et al., 1994; Schwartz et al., 1986; Schwartz and LoGerfo, 1988), and one study of maternal occupations in general did not find associations (Shaw et al., 1999). A study of birth defects and farming found no significant elevations in either gastroschisis or craniosynostosis in farming families compared to non-farming families (Kristensen et al., 1997), a study of craniosynostosis and maternal occupations (Bradley et al., 1995) found no associations, but did not specifically assess pesticide exposure, and no human studies were found for diaphragmatic hernia.

In summary, most previous research focused on agricultural work as a proxy for occupational pesticide exposure, which primarily reflects herbicide exposure, and few epidemiologic studies have examined maternal occupational pesticide exposure in relation to gastroschisis, craniosynostosis or diaphragmatic hernia. Additionally, most studies combined cases of isolated defects with cases having additional defects, and most limb reduction studies combined sub-types, which can have different etiologies. Using self-reported interview data from the National Birth Defects Prevention Study (NBDPS) and expert review by an industrial hygienist, this multi-center population-based study assessed the potential for periconceptional maternal insecticide, herbicide, and fungicide exposure in non-agricultural and agricultural occupations, and examined whether isolated craniosynostosis, gastroschisis, diaphragmatic hernia and transverse limb deficiencies are associated these exposures.

Methods

Study design and participants

We analyzed data from the NBDPS, a U.S. multisite population-based study of risk factors for birth defects (Yoon et al., 2001). The NBDPS collects environmental, clinical, nutritional, behavioral, employment and sociodemographic information via maternal computer-assisted telephone interview. NBDPS cases are live-born infants (all centers), stillborn infants (all centers except New Jersey and New York), or electively terminated fetuses (all centers except New Jersey, New York, and Massachusetts), identified using active surveillance systems, and whose medical record data are abstracted and reviewed by clinical geneticists. Defects classified as part of a known or strongly suspected chromosomal or single gene disorder are excluded. NBDPS controls are live-born infants with no major birth defects identified, randomly selected from birth certificates (Centers for Disease Control and Prevention (CDC)-Atlanta [2001–2002], Iowa, Massachusetts, and New Jersey) or hospital records (Arkansas, California, CDC-Atlanta [1997–2000], New York, Texas).

The current analysis used data from eight NBDPS study sites (Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, and CDC-Atlanta) for mothers of case and control infants with due dates or birth dates from October 1, 1997 to December 31, 2002. The study sample was restricted to infants whose mothers were employed at any time during the periconceptional period (1 month prior to conception to 3 months post-conception) to avoid confounding by factors that may be associated with employment, such as maternal health and family structure. All cases of isolated (i.e., no additional major malformations) craniosynostosis, gastroschisis, diaphragmatic hernia, and transverse limb deficiencies ascertained by the NBDPS were included. Transverse limb deficiencies were selected because it was the only limb reduction sub-type with sufficient numbers in our dataset. Due to small numbers, mothers of infants having multiple defects were excluded from the main analysis. A detailed description of these types of defects can be found in Rasmussen et al. (2003).

Exposure assessment

The telephone interview contained questions about each job held by participating mothers during the periconceptional period, including job title, employer name, employer products and/or services, primary job duties, and substances handled. An industrial hygienist blinded to case or control status reviewed this information and assigned codes based on North American Industry Classification System (U.S. Census Bureau, 2007) and 2000 Standard Occupational Classification (Bureau of Labor Statistics, 2000). These codes were used together with a literature-based job exposure matrix to assign the potential for exposure for each job (yes/no) to insecticides, herbicides, and fungicides. Also assessed were (1) the probability of exposure associated with each job (0, <1–33%, 34–66%, 67–89%, 90% or greater), and (2) a confidence rating (very low, low, moderate, high) summarizing the hygienist's assessment of the quality of the pesticide exposure assessment, similar to a method used previously by Samanic et al. (2008).

Four exposure measures were identified for each job held during the periconceptional period: (1) exposure to any of the three pesticide types; (2) exposure to insecticides only; (3) exposure to insecticides and herbicides (I + H); and (4) exposure to insecticides, herbicides and fungicides (I + H + F). The comparison group for each measure consisted of those not exposed to any pesticide type. For each of the above measures, mothers reporting more than one job held during the periconceptional period were classified as exposed if at least one job was so classified. Because of extensive overlap between exposure to the three pesticide types, few or no mothers were exposed to herbicides only, fungicides only, insecticides and fungicides only, and herbicides and fungicides only; therefore, these additional exposures could not be assessed in this analysis.

Statistical analysis

The most commonly reported jobs classified as having the potential for exposure to one or more pesticides were enumerated using their assigned standard occupational classification (SOC) codes. Distributions of the exposure variables, birth defects, and potential confounders were assessed and bivariable analysis of exposures and outcomes was conducted to compare the prevalence of exposure among the control mothers to that among the case mothers. To assess potential confounding, we examined both the association of the covariables with the exposures among the controls and with the outcomes among the unexposed using chi-square analysis. Covariables assessed as being potential confounders ($p < 0.15$) were incorporated into multivariable models. The following variables were assessed: infant sex; maternal age at delivery (<20 vs 20–34 (ref), ≥35); pre-pregnancy body mass index (≥25 kg/m^2 vs <25 kg/m^2); gravidity (any prior pregnancies vs nulliparous); singleton vs multiple birth; maternal race/ethnicity (black non-Hispanic vs white non-Hispanic, Hispanic, and other race; Hispanic vs non-Hispanic); maternal education (high school or less vs >high school); folic acid use from one month prior to conception through 1 month post-conception; and maternal smoking and alcohol use from 1 month prior to conception through three