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Maternal Occupational Pesticide Exposure and Risk of Hypospadias in the National Birth Defects Prevention Study

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Abstract

BACKGROUND—Hypospadias is a common congenital malformation among men in which the urethral opening is ventrally displaced. Pesticide exposure has been suggested as a possible etiologic factor, but previous epidemiologic studies have produced inconsistent results.

METHODS—We used data from the National Birth Defects Prevention Study (NBDPS), a population-based case-control study, to examine maternal occupational exposure to fungicides, insecticides, and herbicides among 647 hypospadias case infants and 1496 unaffected male control infants with estimated delivery dates from October 1997 to December 2002. Periconceptional (1 month before conception through the first trimester of pregnancy) pesticide exposures were assigned by an expert rater, assisted by a job-exposure matrix (JEM), from a job history completed by mothers during a telephone interview. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with multivariable logistic regression, and adjusted for relevant covariates.

RESULTS—Maternal periconceptional occupational exposure to any pesticides (yes/no) was not associated with an increased risk of hypospadias (OR = 0.78; 95% CI = 0.61–1.01). Maternal occupational periconceptional pesticide exposure type (insecticides, fungicides, and herbicides) and estimated quantity also showed no significantly increased risk of hypospadias and no evidence of a dose-response relationship; however, the estimated pesticide exposure levels in this population were low.

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CONCLUSION—Using broad classes of insecticides, herbicides, and fungicides, we found no evidence that low intensity maternal periconceptional occupational pesticide exposure was a risk factor for hypospadias.

Keywords

hypospadias; pesticides; agrochemicals; birth defects; urogenital malformation; endocrine disruption

INTRODUCTION

Hypospadias is a congenital malformation in which the meatus, the urethral opening, is displaced along the underside of the penis. Hypospadias is classified as first, second, or third degree depending on the position of the meatus. A third degree hypospadias is the most severe and difficult to correct. Overall, hypospadias occurs in 0.3 to 1% of male live births (Manson and Carr, 2003; Kurzrock and Karpman, 2004; Stokowski, 2004). Uncorrected hypospadias can cause difficulties in urination, abnormal sexual function, and adverse psychological consequences; for this reason, the majority of hypospadias must be surgically corrected (Bubanj et al., 2004; Mieusset and Soulie, 2005). Severe hypospadias may require several surgeries and still have an improper appearance and function (Miller and Grant, 1997).

Because of their regulatory role in fetal genitourinary development, the disruption of endocrine hormones has been postulated to play a role in the development of hypospadias (Stoll et al., 1990; Akre et al., 1999; Moller and Weidner, 1999; Klip et al., 2002; Kurzrock and Karpman, 2004; Stokowski, 2004; Bianca et al., 2005; Carmichael et al., 2005; Palmer et al., 2005; Porter et al., 2005; Brouwers et al., 2006; Leung and Robson, 2007). Endocrine disrupting chemicals may have an estrogenic or androgen-antagonist effect (Sharpe and Skakkebaek, 1993; Baskin et al., 2001; Rittler and Castilla, 2002). Several common classes of pesticides have demonstrated potential to disrupt endocrine hormones in animal and in vitro studies (Steinhardt, 2004; Wang and Baskin, 2008) or to induce hypospadias in rats (Gray et al., 1999a; Gray et al., 1999b; Vilela et al., 2007).

Epidemiologic studies of pesticide exposure and hypospadias, however, have presented a conflicted picture. Few studies observed statistically significant changes in risk, with nearly equal numbers of studies having reported point estimates for reduced risks as increased risks. A meta-analysis of seven nonecologic studies on this topic noted a modest association between probable maternal pesticide exposure and hypospadias (pooled risk ratio = 1.36; 95% confidence interval [CI], 1.04–1.77; Rocheleau et al., 2009). Five of those studies relied on farm work as a proxy for pesticide exposure; however, this type of work is associated with many other exposures, including solvents, fertilizers, and animal wastes. The remaining two studies utilized a job-exposure matrix (JEM), which is more cost-effective but less sensitive and specific than expert industrial hygienist review of detailed work histories (Tielemans et al., 1999; Teschke et al., 2002). Small sample sizes or limited availability of exposure data in most of these studies also restricted the evaluation of confounders and effect modifiers. To improve the study of maternal occupational pesticide exposure and risk

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of hypospadias, we used an industrial hygienist-guided JEM to assess workplace exposures of mothers in the National Birth Defects Prevention Study (NBDPS).

METHODS

Study Design

The NBDPS is a population-based case-control study of more than 30 different birth defects initially conducted by eight state-based surveillance systems (Arkansas, California, Iowa, Georgia, Massachusetts, New Jersey, New York, and Texas) and the Centers for Disease Control and Prevention. The details of the study design and methods have been described elsewhere (Yoon et al., 2001). Briefly, the NBDPS began in 1997 and is one of the largest case-control studies of birth defects in the United States. Affected children and fetuses were identified through active case ascertainment by each surveillance program. Controls were a random sample of all unaffected live births in the areas covered by the state-based birth defects surveillance systems for the NBDPS. Controls were identified from hospital delivery logs (Arkansas, California, Georgia [1997–2000], New York, and Texas) or birth certificate files (Georgia [2001–2002], Iowa, Massachusetts, and New Jersey).

Eligible cases were defined as having a diagnosis of a second-degree or third-degree hypospadias, with or without chordee (modified British Pediatric Association codes 752.606, 752.607, 752.626, or 752.627). Abstracted medical records, including surgery reports where available, were reviewed at each study center by a clinical geneticist to identify potential cases. Records indicative of first-degree hypospadias (including coronal or glandular) were not collected, due to variable documentation in the medical records. Records of hypospadias without location information, epispadias, ambiguous genitalia with female karyotypes or without further description, and chordee alone were also not collected. All potential cases were reviewed by a second clinical geneticist (R.S.O.) to confirm that each case met eligibility and diagnosis criteria. Cases were further classified as isolated (no other major anomaly) or multiple (at least one major anomaly of another organ system, n = 34; Rasmussen et al., 2003). As hypospadias is specific to male infants, controls were also restricted to male infants.

Mothers of cases and controls were required to speak either English or Spanish and have access to a telephone. Computer-assisted telephone interviews were administered no sooner than 6 weeks and no later than 24 months after the estimated date of delivery (EDD; also referred to as ‘due date’) of the infant. The interview collected data on demographics, pregnancy characteristics, family history, medical and prenatal care, diet and lifestyle, and occupational history.

Study Variables

Subjects included in this analysis had an EDD (identified from abstracted medical records) from October 1, 1997 through December 31, 2002. During the interview, mothers were asked to provide information on all jobs worked for 1 month or more during the 3 months before pregnancy (B1–B3) through the end of the pregnancy (P1–P9 or EDD), including both full-time and part-time jobs and jobs worked at home, on a farm, or outside the home.

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For each job, the mother provided the name of the employer, a job title, descriptions of what the employer produced or the service it provided, main job activities or duties, and chemicals or substances handled or machines used on the job. Each mother also provided the month and year she started and, if applicable, ended each job. Additionally, mothers reported the usual number of days worked per week and hours worked per day (Yoon et al., 2001). When subjects reported ending a job in the same month and year as beginning a different job, the 15th day of the month was considered the end date for the preceding job, with the latter job assumed to begin on the 16th day of the month. Otherwise, jobs were assigned as beginning on the first day of a reported month and ending on the last day of a reported month. Although mothers reported jobs held in the 3 months before pregnancy and throughout the entire pregnancy, the critical period of exposure is believed to be the periconceptional period. Jobs were considered relevant to this critical period if they occurred 1 month before conception through the end of the first trimester (or termination of the pregnancy, if the pregnancy ended in <90 days from the date of conception).

Each job reported by the mother was assigned a North American Industry Classification System (U.S. Census Bureau, 2007) and 2000 Standard Occupational Classification (Bureau of Labor Statistics, 2000) code. A literature-based JEM (Samanic et al., 2008) was used to assign ‘typical’ pesticide exposures ratings to each job based on its 2000 Standard Occupational Classification and North American Industry Classification System (2007) codes; an industrial hygienist then used the job-specific information provided by the mother to modify these ratings. Exposure ratings estimated the probability (0, <1%, 1–33%, 34–66%, 67–89%, or 90% or greater) of someone with that job description having exposure to the pesticide classes of insecticides, herbicides, and/or fungicides. Jobs considered possibly exposed to any class of pesticides (probability >0) were also assigned a score for probable exposure intensity (<1, 1–9, 10–99, or 100+ mg/hour) and frequency in a typical work week (<2, 2–9, 10–19, and 20+ hours per week) for that pesticide class. Confidence scores were also assigned for each job (very low, low, moderate, or high), reflecting the rater’s confidence in the accuracy of his/her ratings based on familiarity with the job process and the availability of industrial hygiene data. Hours per week was calculated based on self-reported usual hours worked per day times the usual days per week worked. Observations exceeding 12 hours/day and 7 days/week were each reviewed for accuracy. When hours per day or days per week worked were unknown, an 8-hour day and/or a 5-day work week were assumed (<0.9% of jobs). Cumulative work exposure incorporated estimated exposure intensity, hours worked, and number of days worked during the critical period (B1–P3), and was calculated as:

$$\begin{aligned}&(\text{estimated exposure intensity in mg/hr})\\&\times[(\text{exposure frequency in hrs/week})/(40\,\text{hours/week})]\\&\times[(\text{hours worked/week})/7\,(\text{days/week})]\\&\times(\text{number of days worked in the exposure window})\,.\end{aligned}$$

Family history, advancing maternal age, and intrauterine growth retardation have all been suggested as risk factors for hypospadias (Akre et al., 1999; Moller and Weidner, 1999; Kurzrock and Karpman, 2004; Bianca et al., 2005; Porter et al., 2005), and the disorder may have a multifactorial origin (Stoll et al., 1990; Stokowski, 2004). In utero exposure to the

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synthetic estrogen diethylstilbestrol is a recognized risk factor for hypospadias (Klip et al., 2002; Palmer et al., 2005; Brouwers et al., 2006), suggesting a possible role of estrogen in the etiology of hypospadias. Intake of synthetic estrogens and progestins, such as those used in oral contraceptives or assisted reproductive techniques, have also been associated with increased risk of hypospadias in some (but not all) studies (Carmichael et al., 2005; Leung and Robson, 2007). Based on these previously observed associations, we evaluated maternal age, parity, history of a miscarriage, singleton or multiple pregnancy, the gestational age and birth weight of the index infant, maternal alcohol consumption or cigarette smoking during the month before conception or any time during the first trimester of pregnancy, use of a folic acid-containing supplement, and maternal pre-pregnancy body mass index as potential covariates. Maternal and paternal race, income category, maternal and paternal highest education level attained, maternal and paternal birthplace outside the United States, language of the interview, and study center were also assessed. Because the study center reflects geography, and could relate to the types of agricultural products and chemicals used, interaction terms for the study center and pesticide type were assessed in logistic regression models. Use of progesterone or progestin-containing drugs has been suggested as a risk factor for hypospadias in a previous analysis of these data (Carmichael et al., 2005). All medications taken by month before pregnancy through the first trimester of pregnancy, for any indication, were classified as to whether or not they contained progesterone/progestins (yes/no). Because progestins used in contraceptives are typically of lower dose than those used for other indications, progestins were further categorized as being taken for contraception versus any other indication. A reported family history of hypospadias in a first-degree relative (father or full brother) was also examined.

Subjects with missing exposure or outcome data were excluded from all analyses. In the main analysis, subjects were limited to those with complete data for all included confounders and effect modifiers. To assess the impact of item nonresponse, a secondary analysis was also conducted in which a ‘missing’ category was created for all categorical confounding/effect modifying covariates with more than 10 missing responses (Miettinen, 1985). No continuous variables considered for inclusion in the models had more than 10 missing responses, thus imputation of missing continuous values was not performed.

It is unclear whether progesterone itself or the reason for taking progesterone might be the true risk factor. Progesterone and its synthetic analogues are primarily taken to prevent conception, to improve fertility, or to prevent pregnancy complications; the latter two indications (Carmichael et al., 2005) could be a consequence of a shared endocrine disrupting event that also led to development of hypospadias. As such, adjusting for the indication is inappropriate and would cause an attenuation of the observed effect. A subanalysis was conducted to examine the effects of separately adjusting for use of progestins and indication variables. Indication variables were the use of any fertility medication or procedure by either parent (yes/no), maternal use of any medication to prevent pregnancy complications (yes/no), or maternal use of oral or injected contraceptives (yes/no).

Birthweight has been previously associated with hypospadias, although it is unclear if the relationship is due to a true etiologic relationship or whether both are shared consequences

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of a separate risk factor. In the former condition, birthweight is an appropriate confounder to adjust for; in the latter condition, adjusting for birthweight would be inappropriate. Consequently, we did not adjust for birthweight in the main analysis but conducted a secondary analysis in which we adjusted for birthweight.

Some characteristics of mothers (e.g., maternal race/ethnicity or education level) tend to be highly correlated with the same characteristics of fathers (e.g., paternal race/ethnicity or education level); inclusion of both parents' terms may be unnecessary or introduce collinearity. When there was little difference between use of the maternal or paternal characteristic in the models, we chose to use maternal characteristics for consistency.

Statistical Analysis

All analyses were conducted using SAS 9.1.3 (SAS, Cary, NC). Crude odds ratios (ORs) and 95% CIs were calculated to determine the association between periconceptional maternal occupational pesticide exposure and hypospadias. Pesticide exposure was first evaluated as a bivariate variable (any pesticide exposure vs. none), then by pesticide exposure type (none; insecticides only; both herbicides and insecticides; both fungicides and insecticides; combined exposure to fungicides, herbicides, and insecticides); due to extensive overlap with insecticide exposure, it was not possible to evaluate fungicide and herbicide exposure separately. Finally, the cumulative exposure estimate (in total milligrams) to fungicides, insecticides, and herbicides, and total pesticides during the period of B1 to P3 was evaluated as both a continuous (linear, log-linear, quadratic) and categorical (quartiles among the exposed vs. no exposure; ≥90th percentile of exposure, <90th percentile of exposure, no exposure) variable.

To identify potential confounding variables, we used the chi-square test for categorical variables and linear regression for continuous variables. Variables that were related to both hypospadias and pesticide exposure terms ($\alpha \leq 0.10$) or that changed the OR estimate for the main effects (≥10%) were included in multivariable model selection. We evaluated biologically plausible interaction terms in the multivariable models; interaction terms whose inclusion changed the OR for the main effects (≥10%) were considered in the model selection process. A researcher-guided stepwise selection scheme was used to identify the most parsimonious model that adequately fit the data.

RESULTS

Comparison of Cases and Controls

Approximately 70% of eligible mothers participated in the NBDPS (cases, 71.6%; controls, 69.1%). Interview data were available on 1171 infants affected with hypospadias and 2980 unaffected male infants. Mothers who did not work any job in the month before pregnancy or at any time during the first trimester of pregnancy, or who could not be assigned occupational exposure due to missing or incomplete job information, were excluded (n = 2012). Birth mothers of 646 cases and 1493 controls that completed the NBDPS interview were evaluated in this study. As shown in Table 1, case mothers were more likely than control mothers to be older, have a higher household income, and be primiparous. Both

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fathers and mothers of case infants were more likely to have completed college, and less likely to be of Hispanic ethnicity. Preterm birth, low birth weight, and multiple gestations were more common among case infants than control infants. The proportion of cases also varied by study center.

Main Analysis

The main analysis excluded all subjects with a first-degree family history of hypospadias (n = 30) and multiple gestations (n = 105) or both family history and multiple gestations (n = 2). Most subjects who were estimated to be exposed to pesticides were either exposed only to insecticides or to all three types of pesticides (insecticides, herbicides, and fungicides; Table 2). Jobs held by mothers were very diverse. Farmers/agricultural laborers accounted for a large portion of jobs with high intensity exposure to fungicides, herbicides, and/or insecticides. Property managers/landlords also comprised a large portion of workers with low to moderate intensity (but infrequent) exposure to herbicides and insecticides. Teachers, child care workers, health care workers, and restaurant servers were the largest group of workers considered to have very low intensity insecticide exposure. Examples of jobs with very low intensity herbicide exposures include sales staff in garden and lawn supply centers and janitors. Among jobs rated as having very low fungicide exposure intensity, work in grocery stores and food preparation/food service were the most common.

Any maternal occupational pesticide exposure (yes/no) during the month before conception and during the first trimester of pregnancy suggested a reduced risk in the crude analysis (OR = 0.71; 95% CI = 0.57–0.88; Table 3). Adjusting for center, maternal race, maternal age, infant gestational age, and parity caused little change in the observed relationship between hypospadias and any maternal occupational pesticide exposure (adjusted OR = 0.78; 95% CI = 0.61–1.01).

Cumulative maternal occupational exposure to fungicides, insecticides, and herbicides during the periconceptional period was not associated with hypospadias, both before and after adjustment for center, maternal race, maternal age, gestational age of the infant, and parity (Table 3). There was no evidence of a dose-response effect among quartiles of estimated exposure. Restricting the analysis to third-degree (more severe) hypospadias did not cause a consistent increase or decrease in the observed ORs across categories of exposure to insecticides, herbicides, fungicides, or total pesticides (Table 3).

Secondary Analyses

Including subjects with a family history of hypospadias and multiple gestations resulted in some alterations in the point estimates and CIs, but no changes in the interpretation of the ORs (data not shown). Neither excluding subjects with a very low confidence score, excluding potentially exposed subjects with low exposure probability (<67%), nor excluding hypospadias cases with other birth defects caused >10% change in the ORs or CIs (data not shown). We could not stratify by peak exposure intensity because very few mothers had high intensity exposures. There was no evidence of a threshold effect comparing those at the 90th percentile of estimated exposure to unexposed subjects (data not shown).

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Substantial item nonresponse was noted for family income (9.8% missing) and use of medications to prevent pregnancy complications (23.0%, although all medication use was solicited in the interview, regardless of indication). In a secondary analysis, using a 'missing' category for these and any other variables with >10 missing responses (vs. restricting the analysis to subjects with complete response for all covariates in the model) altered the ORs slightly, but all CIs remained wide.

Because of the endocrine-disrupting potential of pesticides, confounding or interaction due to the use of progestin-containing drugs was a major concern. Previous work has shown an association between use of progestin-containing drugs and hypospadias, although it has been less clear whether the true risk factor was the medication or the indication for using the medication. Neither adjustment for the active medication ingredient (any progesterone/progestin [yes/no]) nor indication for medication use (fertility treatments or procedures by either parent [yes/no]; use of medications to prevent pregnancy complications [yes/no]; and use of any contraceptive [yes/no]) substantially altered the ORs for pesticide exposure and hypospadias risk.

DISCUSSION

Overall, we observed either no association or a decreased association between second-degree or third-degree hypospadias and maternal occupational exposure to pesticides during the month before conception through the first trimester of pregnancy. Point estimates less than unity may be the result of uncontrolled confounding (e.g., the 'healthy farmer effect') or because our study measured the prevalence of hypospadias at birth, rather than the true incidence of hypospadias. Previous studies have suggested an association between fetal exposure to pesticides and an increase in fetal death (Arbuckle and Sever, 1998; Settimi et al., 2008). Incident hypospadias occurring among fetuses that were spontaneously aborted would not be observed in this study because we were only able to observe prevalent hypospadias at birth.

Although some point estimates were elevated, none were statistically significant; these results may be spurious due to multiple comparisons. There was no evidence of a dose-response relationship across quartiles of estimated exposure to any pesticide, insecticides, herbicides, or fungicides; nor did we see a threshold effect in the main analysis, although our estimates were imprecise as shown by the wide CIs. When we restricted our analysis to controls and more severe cases (third-degree hypospadias) we did not observe any consistent increase or decrease within quartiles of estimated exposure to any pesticide, insecticides, or herbicides.

The estimated cumulative periconceptional pesticide exposure levels among study participants were generally quite low; these results may not be applicable to higher pesticide levels. To reduce potential exposure misclassification, we conducted two separate analyses in which we excluded subjects (1) for whom the expert raters' had low confidence of exposure assessment, and (2) whose jobs might have been exposed, although with low (<67%) probability. Neither analysis revealed any significantly increased association

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between maternal occupational pesticide exposure and hypospadias, although these comparisons were imprecise.

Our finding of no increased risk of hypospadias associated with maternal pesticide exposure is consistent with two previous studies using a JEM to assign maternal pesticide exposure (Pierik et al., 2004; Carbone et al., 2007); to our knowledge, however, this is the first study to evaluate maternal occupational pesticide exposure based on a JEM, modified as needed by an expert rater, in a population-based setting. Exposure assessments performed by industrial hygienists are thought to be more accurate than self-reported exposure or assigning exposure based on job title alone (McGuire et al., 1998). We used a rater with broad industry experience and expertise in coding retrospective exposure histories, combining rater expertise with a data-driven JEM.

Previous studies of the potential association between pesticide exposure and hypospadias have faced several methodological limitations, including small sample sizes or very limited data due to the use of existing records. Five of seven studies evaluated in a recent meta-analysis (Rocheleau et al., 2009) relied on farm work as a proxy for pesticide exposure. The remaining two studies utilized a JEM. Small sample sizes or limited availability of exposure data in most of these studies also restricted the evaluation of confounders and effect modifiers. Our data-set provided a relatively large sample size and detailed information, which allowed us to adjust for relevant factors such as parity and maternal age.

In our bivariate analysis, we observed several positive associations with hypospadias that have been identified elsewhere: advancing maternal age (Porter et al., 2005), low parity (Weidner et al., 1999; Aschim et al., 2004; Morera et al., 2006), low birth weight (Weidner et al., 1999; Aschim et al., 2004; Morera et al., 2006), multiple gestation (Weidner et al., 1999), family history of hypospadias (Weidner et al., 1999; Aschim et al., 2004; Morera et al., 2006), and parental subfertility (Fritz and Czeizel, 1996; Swan et al., 2003; Swan, 2006; Asklund et al., 2007; Roeleveld and Bretveld, 2008). Hispanic ethnicity was also associated with reduced risk of hypospadias in our analysis, as previously described in the literature (Kirby et al., 2000). This consistency with other research in describing these associations supports our overall findings.

Our study benefited from the systematic collection of interview and outcome data. In particular, the NBDPS used a computer-assisted telephone interview with preprogrammed probes to elicit detailed responses from subjects in a systemized manner. These steps may reduce variations in data quality (Clavel and Hemon, 1993; Stewart and Stewart, 1995). Since creating a timeline may improve subjects' recall (Bradburn et al., 1987), a pregnancy calendar was created for all NBDPS participants at the beginning of their interview.

Despite the strengths of this study, these data must be interpreted cautiously. Most pesticide-exposed women in the population were only exposed to very low estimated pesticide levels. The lack of an association between pesticides and hypospadias at the low levels observed in our study does not indicate the lack of a relationship between higher maternal doses of pesticides and hypospadias. Also, due to inconsistency with animal data at a range of exposure levels, we must consider that our negative findings may reflect exposure

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misclassification rather than a lack of association between maternal pesticide exposure and hypospadias. Animal studies indicate that maternal exposure to certain pesticides at critical periods in urogenital development can induce hypospadias, possibly through an endocrine disruption mechanism (Gray et al., 1999a; Gray et al., 1999b; Gray et al., 2001; Kang et al., 2004). Hypospadias occurs when fusion of the urogenital urethral folds, primarily occurring between weeks 8 and 14 of gestation in humans, is interrupted; the fusion process is largely controlled by endocrine hormones produced by the fetal testes (Baskin et al., 2001; Kurzrock and Karpman, 2004). Exposure to other endocrine-disrupting chemicals, such as progestins (Calzolari et al., 1986; Carmichael et al., 2005) and diethylstilbestrol (Klip et al., 2002; Brouwers et al., 2006), are also associated with hypospadias.

Although expert assessments have been shown to be more accurate than self-reports or JEMs alone, they are still subject to exposure misclassification (Kauppinen, 1994; Mannetje et al., 2003); such misclassification of exposure will generally bias results toward the null (Kromhout et al., 1987; Benke et al., 1997; Blair et al., 2007). A case-control study design, although efficient for rare outcomes like hypospadias, generally precludes the collection of more accurate direct monitoring data. We were also unable to account for exposure modifiers such as the use of personal protective equipment, hygiene, ventilation during exposed tasks, or changes in job tasks during pregnancy. Because data were based on recall, we were also not able to examine specific pesticides or functional classes of pesticides. The broad categories of fungicides, insecticides, and herbicides each contain a diverse array of chemicals that are unlikely to all exhibit similar properties. Less specific measures of exposure generally dilute any observed associations (Friesen et al., 2007), as they tend to mix effects.

Even if maternal occupational exposure were perfectly measured, other sources of pesticide exposure may not be adequately accounted for. Mothers can be exposed to pesticides through pesticide drift or community-wide sprayings, through residential applications of pesticides in and around the home, through carry home exposures from other household members who may be exposed to pesticides, and from pesticide residues on food. We were only able to collect self-reports of another household member working with pesticides, but proxy reports of occupational exposures are not usually accurate (Johnson et al., 1993; Fryzek et al., 2000; Campbell et al., 2007). Paternal occupational exposure may also be linked to hypospadias risk by exerting effects during spermatogenesis. We were unable to account for paternal pesticide exposure in our study; this prevents us from examining paternally mediated risk through sperm damage or carry home exposures. Future work can attempt to reduce exposure misclassification by measuring all sources of potential pesticide exposure – occupational and residential, of both parents.

Future work is also needed to examine the relationship between first-degree hypospadias and periconceptional pesticide exposure. Our study was limited to second-degree and third-degree hypospadias; different forms of hypospadias might have different etiologies. We were also unable to examine interactions with genetic factors, such as those that influence pesticide metabolism. Future work should also examine gene and environment interactions.

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Finally, although previous work has identified an increased risk of hypospadias in the sons of women who work in agriculture (Rocheleau et al., 2009), agricultural workers experience a number of unique exposures that are not limited to pesticides; these include fertilizers, diesel fuel, animal wastes, solvents, and hormones. Hormones are often mixed with livestock feed to promote growth, enhance milk or egg production, or influence the development of lean muscle mass. An association between maternal agricultural work and hypospadias could be due to agricultural exposures other than pesticides. In our study, few women worked in agriculture; we were not able to stratify pesticide exposure by agricultural versus nonagricultural work. Given that endocrine disruption is believed to play a causal role in the development of hypospadias, potential hormone exposures among agricultural workers deserves further study. Also, agricultural workers tend to have greater pesticide exposures than the generally low exposed population in our study.

In conclusion, this study found no consistent association between estimated low-dose maternal occupational pesticide exposure and hypospadias. This study was not able to address the health effects of higher doses of pesticide exposure, the potential contribution of paternal pesticide exposure to hypospadias risk, the effects of nonoccupational pesticide exposures, the effects of specific pesticides, or the effect of other agricultural exposures (such as hormones). We also could not assess the likelihood or magnitude of potential exposure misclassification. Future studies should focus on improving study designs to address these shortcomings.

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Table 1

Demographic Characteristics of Hypospadias Case and Control Families, NBDPS 1997 to 2002

		Hypospadias n (%)[a] n = 646	Controls n (%)[a] n = 1493
Maternal characteristics	Age at conception[b]		
	Less than 20 years old	28 (4.3)	129 (8.6)
	20–24 years old	109 (16.9)	323 (21.6)
	25–29 years old	148 (22.9)	403 (27.0)
	30–34 years old	228 (35.3)	413 (27.7)
	More than 35 years old	133 (20.6)	225 (15.1)
	Education level[b]		
	Did not complete high school	39 (6.0)	144 (9.6)
	Completed high school	309 (47.8)	837 (56.1)
	Completed college or higher	298 (46.1)	509 (34.1)
	Missing	0 (0.0)	3 (0.2)
	Race and ethnicity[b]		
	White, non-Hispanic	461 (71.4)	985 (66.0)
	Black, non-Hispanic	93 (14.4)	178 (11.9)
	Hispanic	54 (8.4)	245 (16.4)
	Other	34 (5.3)	82 (5.5)
	Missing	4 (0.6)	3 (0.2)
	Household income[b]		
	Less than $10,000 annually	45 (7.0)	178 (11.9)
	$10,000–$29,999 annually	122 (18.9)	357 (23.9)
	$30,000–$49,999 annually	108 (16.7)	255 (17.1)
	$50,000 or more annually	332 (51.4)	532 (35.6)
	Missing	39 (6.0)	171 (11.5)
	Pre-pregnancy BMI		
	<18.5 (under weight)	29 (4.5)	82 (5.5)
	18.5–24.9 (normal weight)	350 (54.2)	839 (56.2)
	25.0–29.9 (over weight)	149 (23.1)	341 (22.8)
	≥30 (obese)	109 (16.9)	202 (13.5)
	Missing	9 (1.4)	29 (1.9)
	Smoked cigarettes during periconceptional period		
	Yes	122 (18.9)	324 (21.7)
	No	524 (81.1)	1169 (78.3)
	Drank alcohol during periconceptional period		
	Yes	304 (47.1)	667 (44.7)
	No	337 (52.2)	818 (54.8)
	Missing	5 (0.8)	8 (0.5)

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		Hypospadias n (%)[a] n = 646	Controls n (%)[a] n = 1493
	Used folic acid supplements during periconceptional period		
	Yes	396 (61.3)	776 (60.0)
	No	250 (38.7)	717 (40.0)
	Parous[b]		
	Yes	264 (40.9)	838 (56.1)
	No	382 (59.1)	654 (43.8)
	Missing	0 (0.0)	1 (0.1)
	Used progesterone/progestin during periconceptional period		
	Yes	100 (15.5)	181 (12.1)
	No	546 (84.5)	1312 (87.9)
	Household member worked with pesticides[c]		
	Yes	6 (0.9)	31 (2.1)
	No	636 (98.5)	1458 (97.7)
	Missing/unknown	4 (0.6)	3 (0.2)
Paternal characteristics	Education level[d]		
	Did not complete high school	234 (36.2)	649 (43.5)
	Completed high school	134 (20.7)	321 (21.5)
	Completed college or higher	259 (40.1)	493 (33.0)
	Missing	19 (2.9)	30 (2.0)
	Race and ethnicity[b]		
	White, non-Hispanic	372 (57.6)	899 (60.2)
	Black, non-Hispanic	91 (14.1)	174 (11.7)
	Hispanic	45 (7.0)	205 (13.7)
	Other	41 (6.3)	94 (6.3)
	Missing	97 (15.0)	121 (8.1)
Infant characteristics	Gestational age[b]		
	Very preterm (<32 weeks)	55 (8.5)	23 (1.5)
	Preterm (32–36 weeks)	125 (19.3)	106 (7.1)
	Term (37–45 weeks)	466 (72.1)	1364 (91.4)
	Birth weight[b]		
	<2500 g	175 (27.1)	89 (6.0)
	≥2500 g	465 (72.0)	1395 (93.4)
	Missing	6 (0.9)	9 (0.6)
	Plurality[b]		
	Singleton	588 (91.0)	1444 (96.7)
	Two or more	56 (8.7)	47 (3.1)
	Missing	2 (0.3)	2 (0.1)
	Conceived during/after fertility treatments or procedures[b]		

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	Hypospadias n (%)[a] n = 646	Controls n (%)[a] n = 1493
Yes	81 (12.5)	77 (5.2)
No	565 (87.5)	1415 (94.8)
Missing	0 (0.0)	1 (0.1)
First-degree relative with hypospadias[b]		
Yes	30 (4.6)	2 (0.1)
No	616 (95.4)	1491 (99.9)
Study center[b]		
Arkansas	74 (11.5)	183 (12.3)
California	23 (3.6)	172 (11.5)
Georgia	115 (17.8)	188 (12.6)
Iowa	18 (2.8)	220 (14.7)
Massachusetts	108 (16.7)	220 (14.7)
New Jersey	237 (36.7)	185 (12.4)
New York	54 (8.4)	181 (12.1)
Texas	17 (2.6)	144 (9.7)

[a] Percentages may not total 100 because of rounding.

[b] p value < 0.0001.

[c] p value < 0.05.

[d] p value < 0.001.

NBDPS, National Birth Defects Prevention Study; BMI, body mass index.

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Table 2

Reported Patterns of Estimated Periconceptional Exposure to Pesticides among Case and Control Mothers, NBDPS 1997 to 2002

	Hypospadias	Controls
	n[a] (%)	n[a] (%)
Total pesticide exposure[b]		
Any	140 (25.0)	464 (32.2)
None	419 (75.0)	979 (67.8)
Pesticide exposure, by class		
None	419 (75.0)	979 (67.8)
Insecticides only	102 (18.2)	318 (22.0)
Herbicides only	0 (0.0)	2 (0.1)
Fungicides only	0 (0.0)	0 (0.0)
Both insecticides and herbicides	9 (1.6)	28 (1.9)
Both insecticides and fungicides	2 (0.4)	4 (0.3)
Both herbicides and fungicides	0 (0.0)	0 (0.0)
Insecticides, herbicides, and fungicides	27 (4.8)	112 (7.8)

[a] Subjects restricted to singleton births without a reported first-degree family history of hypospadias.

[b] p value < 0.0001.

NBDPS, National Birth Defects Prevention Study.

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Table 3

Crude and Adjusted Odds Ratios for Estimated Maternal Periconceptional Pesticide Exposure, by Pesticide Type, NBDPS 1997 to 2002

	Per any estimated periconceptional exposure (vs. none)					
	Type II and III hypospadias[a]				Type III hypospadias[a]	
	Exposed subjects (n)	Crude OR (95% CI)	Base[b] OR (95% CI)	Adjusted[c] OR (95% CI)	Exposed subjects (n)	Adjusted[c] OR (95% CI)
Insecticides	602	0.71 (0.57–0.89)	0.76 (0.59–0.98)	0.76 (0.57–1.00)	493	0.90 (0.52–1.54)
Herbicides	178	0.63 (0.43–0.92)	0.83 (0.40–1.73)	0.99 (0.47–2.10)	149	1.05 (0.27–4.14)
Fungicides	145	0.63 (0.41–0.95)	0.92 (0.42–2.03)	1.25 (0.56–2.83)	121	0.59 (0.12–2.83)
All pesticides	604	0.71 (0.57–0.88)	N/A	0.78 (0.61–1.01)	495	0.81 (0.49–1.33)
Per 1.0 gram increase in estimated periconceptional exposure						
Insecticides	602	1.00 (0.94–1.07)	1.02 (0.86–1.21)	1.03 (0.86–1.23)	493	1.21 (0.49–2.99)
Herbicides	178	1.01 (0.95–1.08)	1.07 (0.93–1.24)	1.05 (0.90–1.23)	149	0.69 (0.10–4.67)
Fungicides	145	0.98 (0.89–1.08)	0.89 (0.73–1.09)	0.93 (0.76–1.14)	121	not calculated[d]
All pesticides	604	1.00 (0.98–1.03)	N/A	1.01 (0.98–1.03)	495	0.74 (0.38–1.41)
Per quartile of estimated cumulative periconceptional exposure						
Insecticides (grams)						
0 (ref)	1400	1.0 (ref)	1.0 (ref)	1.0 (ref)	1067	1.0 (ref)
>0 to <0.030	145	0.61 (0.40–0.93)	0.61 (0.38–0.99)	0.62 (0.36–1.08)	121	not calculated[d]
0.030 to <0.075	155	0.79 (0.54–1.15)	0.84 (0.57–1.24)	0.74 (0.47–1.16)	127	not calculated[d]
0.075 to <0.160	143	0.79 (0.53–1.17)	0.86 (0.57–1.31)	0.93 (0.58–1.52)	114	not calculated[d]
0.160+	159	0.66 (0.45–0.98)	0.71 (0.45–1.12)	0.71 (0.41–1.22)	131	not calculated[d]
Herbicides (grams)						
0 (ref)	1824	1.0 (ref)	1.0 (ref)	1.0 (ref)	1411	1.00 (ref)
0 to <0.017	45	0.71 (0.35–1.45)	0.92 (0.38–2.28)	1.24 (0.48–3.21)	37	not calculated[d]
0.017 to <0.050	43	0.48 (0.21–1.09)	0.34 (0.08–1.34)	0.29 (0.07–1.26)	39	not calculated[d]
0.050 to <0.160	43	0.66 (0.31–1.38)	0.77 (0.17–3.57)	0.90 (0.18–4.48)	35	not calculated[d]
0.160+	47	0.67 (0.33–1.36)	1.46 (0.44–4.90)	1.30 (0.35–4.85)	38	not calculated[d]
Fungicides (grams)						
0 (ref)	1857	1.0 (ref)	1.0 (ref)	1.0 (ref)	1439	1.0 (ref)

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	Per any estimated periconceptional exposure (vs. none)					
	Type II and III hypospadias[a]				Type III hypospadias[a]	
	Exposed subjects (n)	Crude OR (95% CI)	Base[b] OR (95% CI)	Adjusted[c] OR (95% CI)	Exposed subjects (n)	Adjusted[c] OR (95% CI)
>0 to <0.035	37	0.69 (0.31–1.52)	1.49 (0.51–4.34)	2.05 (0.65–6.49)	31	not calculated[d]
0.035 to <0.072	38	0.78 (0.37–1.65)	1.79 (0.45–7.08)	3.05 (0.72–12.85)	32	not calculated[d]
0.072 to <0.135	37	0.69 (0.31–1.52)	0.96 (0.21–4.48)	1.47 (0.29–7.42)	29	not calculated[d]
0.135+	33	0.35 (0.12–0.99)	0.33 (0.07–1.56)	0.59 (0.11–3.06)	29	not calculated[d]
All pesticides (grams)						
0 (ref)	1398	1.0 (ref)	N/A	1.0 (ref)	1065	1.00 (ref)
>0 to <0.033	149	0.67 (0.44–1.00)	N/A	0.71 (0.45–1.11)	123	0.79 (0.33–1.93)
0.033 to <0.096	145	0.77 (0.52–1.14)	N/A	0.75 (0.48–1.17)	120	1.33 (0.62–2.86)
0.96 to <0.210	155	0.66 (0.44–0.98)	N/A	0.75 (0.47–1.18)	127	0.53 (0.20–1.43)
0.210+	155	0.73 (0.50–1.08)	N/A	0.96 (0.61–1.51)	125	0.64 (0.26–1.59)

[a] Limited to singleton births and subjects without a reported first-degree family history of hypospadias.

[b] Base model is adjusted for all other pesticide classes.

[c] Limited to subjects with complete data for included covariates; adjusted for exposure to all other pesticide classes, parity, maternal race, maternal age, infant gestational age, and center.

[d] Not calculated due to small cell sizes.

NBDPS, National Birth Defects Prevention Study; OR, odds ratio; CI, confidence interval; N/A, not applicable.

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