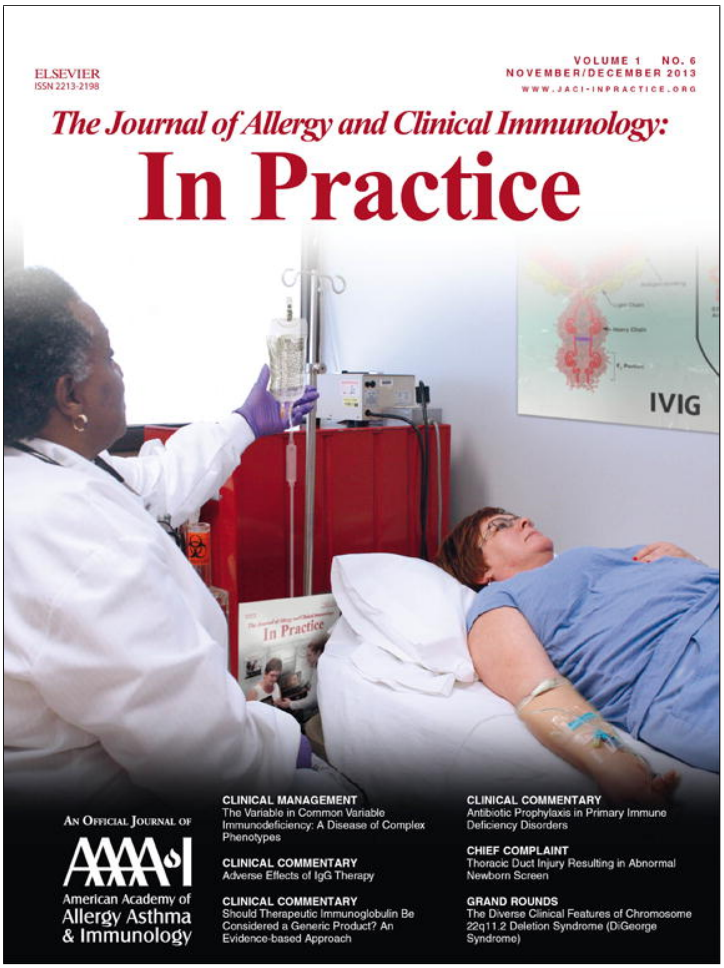

Original Article

Assessment of Antihistamine Use in Early Pregnancy and Birth Defects

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What is already known about this topic? Antihistamines are generally considered safe with respect to fetal risk. However, several studies have reported associations between specific antihistamines in early pregnancy and certain specific birth defects.

What does this article add to our knowledge? Findings from this study do not provide meaningful support for any strong associations between specific common antihistamines and specific major birth defects.

How does this study impact current management guidelines? This study provides reassurance that commonly used antihistamine medications appear to be relatively safe for women to take during pregnancy in terms of teratogenicity.

BACKGROUND: Several studies have reported an association between use of specific antihistamines in early pregnancy and certain specific birth defects.
OBJECTIVE: To test 16 previously hypothesized associations between specific antihistamines and specific birth defects, and to identify possible new associations.
METHODS: We used 1998-2010 data from the Slone Epidemiology Center Birth Defects Study, a multicenter case-control surveillance program of birth defects in North America. Mothers were interviewed within 6 months of delivery about demographic, reproductive, medical, and behavioral factors, and details on the use of prescription and nonprescription medications. We compared first trimester exposure to specific antihistamines between 13,213 infants with specific malformations and 6982 nonmalformed controls by using conditional logistic regression to estimate odds ratios and 95% confidence intervals (CIs), with adjustment for potential confounders, including indication for use.
RESULTS: Overall, 13.7% of controls were exposed to antihistamines during the first trimester. The most commonly used medications were diphenhydramine (4.2%), loratadine (3.1%), doxylamine (1.9%), and chlorpheniramine (1.7%). When estimates were stable, none supported the previously hypothesized associations. Among more than 100 exploratory comparisons of other specific antihistamine-defect pairs, 14 had odds ratios ≥1.5, of which 6 had 95% CI bounds excluding 1.0 before but not after adjustment for multiple comparisons.
CONCLUSION: Our findings do not provide meaningful support for previously posited associations between antihistamines and major congenital anomalies; at the same time, we identified associations that had not been previously suggested. We suspect that previous associations may be chance findings in the context of multiple comparisons, a situation that may also apply to our new findings. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2013;1:666-74)

Key words: *Antihistamines; Birth defects; First trimester; Maternal exposure*

Antihistamines are used for the symptomatic treatment of allergic rhinitis as well as the treatment of nausea and vomiting, motion sickness, dizziness, and insomnia.[1] Antihistamines are among the most commonly used drugs during pregnancy,[2] and most are considered US Food and Drug Administration category B (no evidence of human risk after *in utero* exposure) due to the scarce number of controlled studies in pregnant women.[3] Given

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Conflicts of interest: A. A. Mitchell has received a grant from the National Institute of Child Health and Human Development, consulted on one occasion for Duchesnay USA, had stock/stock options with Johnson & Johnson, and serves as a consultant to Biogen-Idec in his role as a member of the Tysabri Pregnancy Registry Advisory Committee. S. Hernández-Díaz has received a grant from the National Institutes of Health and has consulted for Novartis, AstraZeneca, and GSK Biologics. M. M. Werler has received a grant from the National Institute of Child Health and Human Development and has consultant arrangements with Amgen, Abbott, UCB, and Genentech. The rest of the authors declare that they have no relevant conflicts of interest.
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Abbreviations used
BDS- Slone Epidemiology Center Birth Defects Study
BMI- Body mass index
CI- Confidence interval
LMP- Last menstrual period
NSAID- Nonsteroidal anti-inflammatory drug
OR- Odds ratio
OTC- Over-the-counter

their wide use and availability without prescription (over-the-counter [OTC]), even a small increase in the risk of specific birth defects may have considerable clinical and public health implications. However, if these medications are relatively safe, then such information is important to diminish unwarranted fears of fetal damage secondary to exposure.

Epidemiologic studies that have examined antihistamines in the aggregate and birth defects overall are uninformative because of varied pharmacologic actions within the class of antihistamines and varied etiologies across the range of birth defects.[4] Most studies that have considered specific drugs in relation to specific defects have generally identified no associations between maternal use of antihistamines and major birth defects.[5-24] However, positive associations have been reported for diphenhydramine in relation to cleft palate,[25] cleft lip with or without cleft palate, neural tube defects, spina bifida, limb reduction defects, and gastroschisis[26]; loratadine in relation to hypospadias[27,28]; chlorpheniramine in relation to eye defects, ear defects,[29] spina bifida, and cleft lip with or without cleft palate[26]; and doxylamine in relation to oral clefts,[30] pyloric stenosis,[31,32] hypoplastic left heart syndrome, spina bifida, and neural tube defects.[26] By using data from the Slone Epidemiology Center Birth Defects Study (BDS) (also known as the Pregnancy Health Interview Study), we tested the previously reported associations between specific birth defects and first trimester exposure to antihistamines, and explored whether there might be associations between specific antihistamines and other common specific major congenital malformations.

METHODS

Study population

The BDS is an ongoing multicenter case-control surveillance program of birth defects in North America; details have been described elsewhere.[33-35] Malformed infants and fetuses were identified as potential cases at regional centers around Boston (1976 to present), Philadelphia (1977 to present), Toronto (1979-2006), and San Diego (2001 to present), and from birth defects registries in Massachusetts (1998 to present) and New York State (2004 to present); nonmalformed infants were identified as potential controls at participating hospitals (1993 to present) and from a population-based sample of nonmalformed infants in Massachusetts (1998 to present). The present analysis was based on data from subjects interviewed between 1998 and 2010. After exclusion of mothers who were ineligible and could not be contacted and invited to participate, the participation rate was 73% for mothers of cases and 68% for mothers of controls.[36] Oral informed consent was obtained from mothers, and the study has been approved by the institutional review boards of all relevant institutions and is fully compliant with requirements of the Health Insurance Portability and Accountability Act.

Cases and controls

Cases consisted of infants and fetuses with confirmed diagnoses of isolated or multiple major congenital malformations. Only categories with defects that contained more than 100 cases were considered; these included neural tube defects, spina bifida, eye defects, ear defects, oral clefts, cleft lip with or without cleft palate, cleft palate, tracheo-esophageal fistula, pyloric stenosis, small intestinal atresia/stenosis, anal atresia/stenosis, intestinal malrotation, clubfoot, limb reduction defects, gastroschisis, diaphragmatic hernia, renal agenesis/dysgenesis, cystic kidney disease, renal collecting system defects, extra or horseshoe kidney, undescended testis, hypospadias, conotruncal defects, tetralogy of Fallot, d-transposition of great arteries, aortic arch anomalies, ventricular septal defect, atrial septal defect, right ventricular outflow obstruction, pulmonary valve stenosis/atresia, left ventricular outflow obstruction, coarctation of aorta, hypolastic left heart syndrome, and great veins anomalies. Major malformations were confirmed by the physicians of the study subjects and by the mothers during the interview; for subjects who provide medical record releases, diagnoses were also validated via medical record review. We excluded infants with chromosomal defects, known Mendelian inherited disorders, syndromes, DiGeorge sequence, and amniotic bands, under the assumption that their etiologies are unlikely to be caused by antenatal exposures. Cases with more than one anomaly were considered in each defect category.

Our primary controls were nonmalformed infants enrolled in the BDS during the same time period. To address possible concerns about recall bias, we conducted sensitivity analyses, in which cases with a specific birth defect were compared with a secondary control group that consisted of infants with all other structural malformations (including those with <100 subjects).

Exposure ascertainment and classification

Study nurses conducted standardized telephone interviews of mothers within 6 months of delivery, with neither the nurses nor mothers aware of the various study hypotheses. Questions include maternal demographic, anthropometric, reproductive, medical, and life-style characteristics. Information is also obtained on all medications (prescription, OTC, vitamins and minerals, and herbal products) used at any time from 2 months before the last menstrual period (LMP) until the end of pregnancy. Medication-related questions were asked in a multilevel approach. First, women were asked whether they experienced any of a list of specific illnesses (eg, allergies) during pregnancy and the drugs they may have used to treat those conditions. Then they are asked about their use of categories of medications (eg, antihistamines) and finally about use of specific medications, including brand and generic names. Mothers who reported taking a medication were asked to identify the dates when use began and ended; recall was enhanced by a calendar that highlighted key dates and events (eg, LMP, Christmas, delivery date).

We studied the 2 generations of antihistamines, whether available by prescription or OTC, the older sedating products (eg, chlorpheniramine, diphenhydramine, dimenhydrinate, doxylamine, promethazine) and the newer nonsedating products (eg, loratadine, cetirizine, fexofenadine). For the timing of gestational exposure, the LMP date was determined by early ultrasound examination or maternal recall. We defined the estimated date of conception (ie, day 0) as 14 days after the LMP date and the first trimester of pregnancy as days 0-89. We considered "exposed" as maternal use of the antihistamine on at least 1 day during the

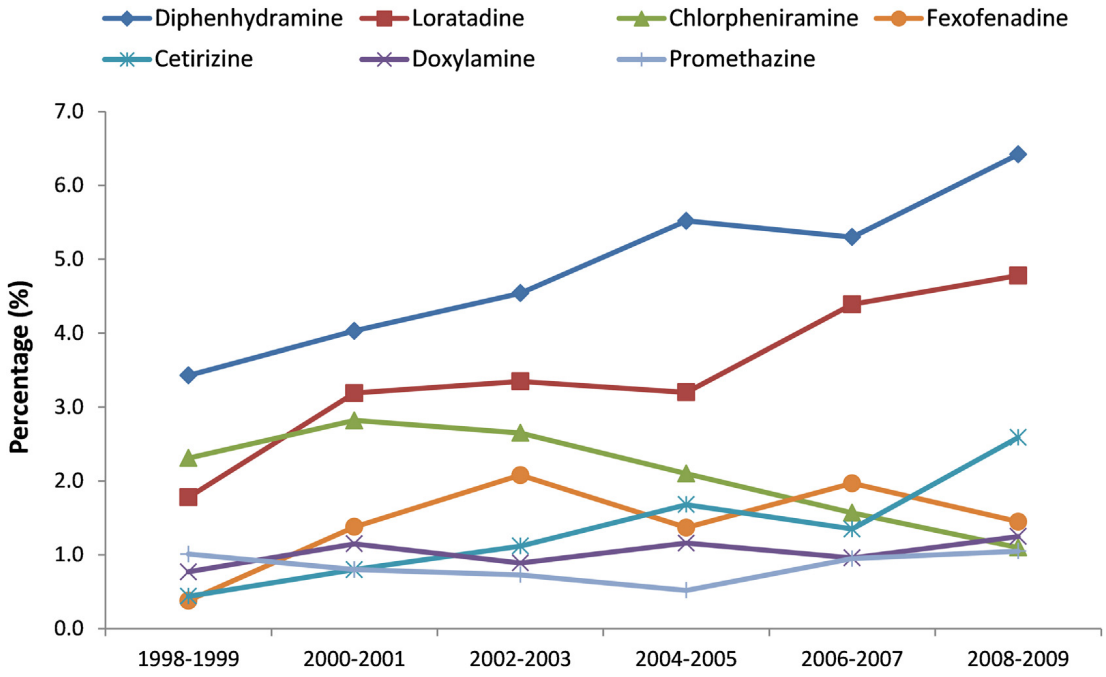

FIGURE 1. Temporal trend of first trimester antihistamine use, BDS, 1998-2009. **Figure legend**: Based on data only from Boston and Philadelphia, which have been participating in the BDS thoughout the study period; at the time of data extraction for this study, there were too few subjects interviewed in 2010 to include in this figure.

first trimester. By using a previously developed exposure classification algorithm that considers recall uncertainty in reported timing of medication exposure,[37] we classified antihistamines exposure in the first trimester into "likely exposed" and "possibly exposed." Whereas secular trend analyses used both definitions, etiologic comparisons compared only women "likely exposed" with women without any use of the medication from 2 months before conception throughout delivery (ie, the reference group).

Statistical analyses

We first characterized the trends of utilization patterns for specific antihistamines over time as well as by trimesters. To understand the risk factors associated with antenatal exposure to antihistamines, among controls, we compared first trimester-exposed women with unexposed women according to sociodemographic and life-style characteristics, prevalence of selected comorbidities, and the medications used concomitantly. Finally, we evaluated the associations between first-trimester exposure to specific antihistamines in relationship to (1) the risk of specific malformations previously hypothesized to be associated with each of these drugs, and (2) in exploratory analyses, the risk of other relatively common malformations. To obtain stable estimates, we only evaluated the most commonly used antihistamines in our population and considered only malformations with $\geq$100 cases; in the exploratory analyses, we restricted consideration to cells with $\geq$5 exposed cases. Conditional logistic regression was used to estimate odds ratios (OR) and 95% CIs for specific malformations associated with first-trimester exposure to each antihistamine. We matched controls to cases by stratifying on estimated conception year and study region, and adjusted for potential confounders by including terms in multivariable models. In the exploratory analyses, we adjusted for multiple comparisons by using Bonferroni and Benjamini-Hochberg approaches.[38,39] For any positive associations found in the exploratory analyses, we assessed potential recall bias by conducting sensitivity analyses by using our secondary control series (ie, other malformed infants). To account for etiologic heterogeneity and to provide analyses comparable with those conducted in the US National Birth Defects Prevention Study,[26] in secondary analyses, we restricted cases to those with isolated defects.

RESULTS

Utilization patterns of antihistamines in pregnancy

Between 1998 and 2010, our study population included 13,213 infants with malformations and 6982 nonmalformed controls. Overall, 14.9% of cases and 13.7% of controls were exposed to antihistamines during the first trimester. Among the controls, the most commonly used antihistamines were diphenhydramine (4.2%), loratadine (3.1%), doxylamine (1.9%), and chlorpheniramine (1.7%); the most common indications for antihistamine medications were allergy, followed by nausea and/or vomiting, cold or flu, and insomnia. The prevalence of antihistamine use decreased from early to late pregnancy, except for diphenhydramine, in which use slightly increased from 4.2% in the first trimester to 5.1% in the third trimester.

Secular patterns for first trimester use, based on data from the Boston and Philadelphia study sites, which have been participating in the BDS throughout the study period (Figure 1), revealed that diphenhydramine use has been increasing, which makes it the most commonly used antihistamine, reaching a prevalence of 6.4% by 2009. Use of loratadine also increased appreciably, to almost 5% in the late 2000s. However, chlorpheniramine use has decreased over the years and was most recently reported by only 1% of women. Use of antihistamine medications not shown in Figure 1 was not appreciable.

TABLE I. Characteristics associated with antihistamine use in the first trimester among mothers of nonmalformed infants, BDS, 1998-2010

Characteristic	Users, no. (%) (N = 723)	Nonusers, no. (%) (N = 5357)*	Crude matched OR and 95% CI†
Study center			
Boston	375 (51.9)	2949 (55.1)	Referent
Philadelphia	149 (20.6)	989 (18.5)	1.2 (0.9-1.4)
Toronto	94 (13.0)	511 (9.5)	1.5 (1.1-1.9)
San Diego	75 (10.4)	701 (13.1)	0.8 (0.6-1.1)
New York	30 (4.2)	207 (3.9)	1.1 (0.7-1.6)
Maternal age			
<25 y	125 (17.3)	1184 (22.1)	Referent
25-29 y	180 (24.9)	1372 (25.6)	1.2 (1.0-1.6)
30-33 y	229 (31.7)	1475 (27.5)	1.5 (1.2-1.8)
≥34 y	189 (26.1)	1306 (24.4)	1.4 (1.1-1.7)
Unknown	0	20 (0.4)	—
Maternal race/ethnicity			
White (non-Hispanic)	579 (80.1)	3660 (68.3)	Referent
Black (non-Hispanic)	46 (6.4)	436 (8.1)	0.6 (0.5-0.9)
Hispanic	54 (7.5)	838 (15.6)	0.4 (0.3-0.6)
Other	44 (6.1)	417 (7.8)	0.6 (0.5-0.9)
Unknown	0	6 (0.1)	—
Maternal pre-pregnancy BMI			
<18.5 kg/m^2	39 (5.4)	304 (5.7)	1.0 (0.7-1.4)
18.5-24.9 kg/m^2	427 (59.1)	3352 (62.6)	Referent
25.0-29.9 kg/m^2	154 (21.3)	994 (18.6)	1.2 (1.0-1.5)
≥30.0 kg/m^2	94 (13.0)	573 (10.7)	1.3 (1.0-1.6)
Unknown	9 (1.2)	134 (2.5)	0.6 (0.3-1.1)
Maternal education			
<13 y	140 (19.4)	1580 (29.5)	Referent
13-15 y	189 (26.1)	1219 (22.8)	1.8 (1.4-2.2)
≥16 y	394 (54.5)	2555 (47.7)	1.8 (1.4-2.1)
Unknown	0	3 (0.1)	—
Household annual income, US$			
<45,000	162 (22.4)	1606 (30.0)	Referent
≥45,000	519 (71.8)	3263 (60.9)	1.6 (1.3-1.9)
Unknown	42 (5.8)	488 (9.1)	0.9 (0.6-1.2)
Maternal smoking			
Never	401 (55.5)	3095 (57.8)	Referent
Only before pregnancy	188 (26.0)	1208 (22.6)	1.2 (1.0-1.5)
During pregnancy	117 (16.2)	835 (15.6)	1.1 (0.9-1.3)
Unknown	17 (2.4)	219 (4.1)	0.5 (0.3-0.8)
Maternal alcohol drinking			
Never	224 (31.0)	2261 (42.2)	Referent
Only before pregnancy	117 (16.2)	868 (16.2)	1.4 (1.1-1.8)
During pregnancy	382 (52.8)	2228 (41.6)	1.7 (1.5-2.1)
Maternal coffee drinking			
Never	204 (28.2)	1715 (32.0)	Referent
Only before pregnancy	11 (1.5)	91 (1.7)	1.0 (0.6-2.0)
During pregnancy	288 (39.8)	1930 (36.0)	1.3 (1.1-1.6)
Unknown	220 (30.4)	1621 (30.3)	0.9 (0.6-1.4)
Maternal conditions and medication use‡			
Allergy during pregnancy	426 (58.9)	407 (7.6)	19.3 (16.0-23.2)
Nausea and/or vomiting in the first trimester	545 (75.4)	3421 (63.9)	1.7 (1.5-2.1)
Sleeping problems in the first trimester	86 (11.9)	26 (0.5)	29.4 (18.7-46.2)
Asthma during pregnancy	115 (15.9)	266 (5.0)	3.7 (2.9-4.7)
Respiratory infection, cold or flu in the first trimester	302 (41.8)	1629 (30.4)	1.7 (1.4-2.0)

(continued)

TABLE I. *(Continued)*

Characteristic	Users, no. (%) (N = 723)	Nonusers, no. (%) (N = 5357)*	Crude matched OR and 95% CI†
Pregestational diabetes	6 (0.8)	64 (1.2)	0.7 (0.3-1.6)
Oral corticosteroids use in the first trimester	118 (16.3)	180 (3.4)	5.6 (4.3-7.1)
Decongestant use in the first trimester	248 (34.3)	293 (5.5)	10.0 (8.2-12.2)
Acetaminophen use in the first trimester	475 (65.7)	2235 (41.7)	2.8 (2.4-3.3)
Aspirin use in the first trimester	60 (8.3)	307 (5.7)	1.5 (1.1-2.0)
NSAIDs use in the first trimester§	213 (29.5)	990 (18.5)	1.9 (1.6-2.3)
Antibiotics use in the first trimester	54 (7.5)	248 (4.6)	1.7 (1.2-2.3)
Periconceptional folic acid supplementation‖	508 (70.3)	3470 (64.8)	1.3 (1.1-1.5)

NSAID, Nonsteroidal anti-inflammatory drug.
*No use of any antihistamine during 2 mo before the LMP through the end of pregnancy.
†Matched on the calendar year of conception for the analysis of "study center" and on the calendar year of conception and study center for the analyses of all other variables.
‡Reference category for each variable is "no occurrence or use" during the specific time frame indicated.
§Eighty-five percent being ibuprofen.
‖During the period from 1 mo before to 1 mo after conception.

Characteristics of first trimester antihistamine users

Among controls, factors associated with first trimester use of antihistamines included older maternal age, white race/ethnicity, higher pre-pregnancy body mass index, higher education level and income, and alcohol and coffee drinking (Table I). As expected, first trimester antihistamine use was related to conditions that are indications for antihistamine medications, which included allergy, asthma, nausea and/or vomiting, sleeping problems, respiratory infection, and cold or flu. Medications associated with first-trimester antihistamine use included oral corticosteroids, decongestants, acetaminophen, aspirin, nonsteroidal anti-inflammatory drugs, and antibiotics. All these factors were considered as potential confounders in subsequent analyses.

Risk of major malformations associated with first-trimester antihistamine use

The 16 previously hypothesized associations between specific major malformations and the use of specific antihistamines were confined to the 4 most commonly used agents: diphenhydramine, loratadine, chlorpheniramine, and doxylamine. As reflected in Table II, none of these associations had lower 95% CIs that excluded 1.0. However, some of the estimates were based on small numbers, and the 95% CIs were very wide. For example, use of chlorpheniramine in relation to ear defects and spina bifida showed positive associations based on only 3 and 4 exposed cases, respectively. However, where cells included at least 5 exposed cases, none had adjusted estimates with upper CIs that exceeded 3.0.

In exploratory analyses that involve a total of 107 comparisons, 6 exposure-outcome pairs had elevated ORs with lower 95% CI bounds that exceeded 1.0 (Table III): diphenhydramine and D-transposition of great arteries (OR 2.3 [95% CI, 1.1-5.0]); doxylamine and cystic kidney disease (OR 2.7 [95% CI, 1.3-5.6]); and chlorpheniramine and neural tube defects (OR 2.6 [95% CI, 1.1-6.1]), tetralogy of Fallot (OR 3.1 [95% CI, 1.2-8.4]), hypoplastic left heart syndrome (OR 4.9 [95% CI, 1.6-14.9]), and great veins anomalies (OR 3.3 [95% CI, 1.1-10.0]). Loratadine use was inversely associated with oral clefts (OR 0.5 [95% CI, 0.3-0.9]). Another 8 exposure-outcome ORs were $\geq$1.5, but the 95% CIs were wide and included 1.0. In the sensitivity analyses when using secondary malformed controls in each comparison, the OR estimates generally changed little (see Table E1 in this article's Online Repository at www.jaci-inpractice.org.). However, all 95% CIs included 1.0 after adjustment for multiple comparisons when using Bonferroni or Benjamini-Hochberg approaches. Secondary analyses restricted to cases with isolated defects did not reveal meaningful changes in the above findings (data not shown).

DISCUSSION

The findings from our study did not replicate any of the 16 previously reported associations among specific antihistamines and major congenital malformations. Many of the previous studies involved multiple comparisons and small numbers of cases. Therefore, we posit that many if not all of these hypothesized associations could be explained by chance. However, in our exploratory analyses that involved 107 comparisons, we identified 14 associations that had ORs $\geq$1.5, of which 6 had 95% CI bounds excluding 1.0; these 6 associations either had not been previously reported or were reported as null.[26] All the 95% CIs included 1.0 when we used 2 widely used multiple-comparison adjustment approaches, which supported the possibility of false-positive associations. Further, by restricting the exploratory analyses to cases with at least 5 exposed subjects, among the case groups with small numbers, we were selecting those with higher prevalence of exposure and, therefore, preferentially identifying positive associations. Thus, findings from our exploratory analyses should be considered only to have generated hypotheses.

In the early 1980s, many lawsuits alleged that Bendectin (Wm S. Merrell Company, Cincinnati, Ohio), which included the antihistamine doxylamine along with vitamin B6, caused birth defects, which led its manufacturer to voluntarily withdraw it from the market in 1983.[40] As revealed in Figure 1, the prevalence of doxylamine use in pregnant women was quite low during the period of our study. Extensive studies of Bendectin, including 2 of our own, found no evidence to support earlier concerns and, in fact, established the relative safety of this medication.[33,41,42] Our current findings provide additional evidence that supports the relative safety of doxylamine. Of note, in April 2013, the US Food and Drug Admninstration approved Diclegis (Duchesnay USA Inc, Rosemont, Pa), which has the same ingredients as Bendectin, for treating nausea and vomiting in pregnant women.[43]

Werler et al[2] previously described trends of diphenhydramine, loratadine, doxylamine, and chlorpheniramine use among

TABLE II. For *a priori* hypotheses: associations between first trimester exposure to antihistamines and specific malformations, BDS, 1998-2010*

Medication	Outcome	No. (%) exposed	Crude matched OR (95% CI)†	Adjusted OR (95% CI)‡
Diphenhydramine	Nonmalformed (n = 6982)	202 (2.9)	Referent	Referent
	Cleft palate (n = 452)	21 (4.7)	1.6 (1.0-2.6)	1.5 (0.9, 2.6)
	Cleft lip with or without cleft palate (n = 776)	22 (2.8)	1.0 (0.7-1.7)	0.9 (0.5, 1.5)
	Neural tube defects (n = 292)	9 (3.1)	1.2 (0.6-2.5)	1.5 (0.7, 3.1)
	Spina bifida (n = 213)	6 (2.8)	1.0 (0.5-2.4)	1.2 (0.5, 3.0)
	Limb reduction defects (n = 179)	7 (3.9)	1.3 (0.6-2.9)	1.2 (0.5, 2.8)
	Gastroschisis (n = 235)	7 (3.0)	0.9 (0.4-2.0)	0.8 (0.3-2.2)
Loratadine	Nonmalformed males (n = 3448)	74 (2.2)	Referent	Referent
	Hypospadias (n = 632)§	13 (2.1)	1.0 (0.5-1.9)	0.8 (0.4-1.7)
Chlorpheniramine	Nonmalformed (n = 6982)	76 (1.1)	Referent	Referent
	Eye defects (n = 164)	2 (1.2)	1.2 (0.3-5.2)	0.9 (0.2-4.1)
	Ear defects (n = 142)	3 (2.1)	2.2 (0.7-7.1)	3.0 (0.8-11.8)
	Spina bifida (n = 213)	4 (1.9)	1.9 (0.7-5.3)	1.7 (0.6-5.3)
	Cleft lip with or without cleft palate (n = 776)	13 (1.7)	1.7 (0.9-3.2)	1.3 (0.6-2.5)
Doxylamine	Nonmalformed (n = 6982)	110 (1.6)	Referent	Referent
	Oral clefts (n = 1228)	23 (1.9)	0.8 (0.5-1.2)	0.7 (0.5-1.2)
	Pyloric stenosis (n = 583)	15 (2.6)	0.7 (0.4-1.3)	0.6 (0.3-1.1)
	Hypoplastic left heart syndrome (n = 174)	4 (2.3)	0.7 (0.3-2.0)	0.7 (0.2-1.9)
	Spina bifida (n = 213)	7 (3.3)	1.2 (0.5-2.6)	1.1 (0.5-2.5)
	Neural tube defect (n = 292)	8 (2.7)	0.8 (0.4-1.8)	0.8 (0.4-1.7)

*Comparison of "likely exposed" in the first trimester to nonuse between 2 mo before the LMP through the end of pregnancy.
†Matched on calendar year of conception and study region.
‡Additionally adjusted for potential confounders, including maternal age, race or ethnicity, education, household annual income, alcohol consumption, allergy and asthma during pregnancy, nausea and/or vomiting, sleeping problems, respiratory infection (cold or flu), oral corticosteroids, decongestants, acetaminophen, aspirin, NSAIDs, and antibiotics use in the first trimester.
§Comparison restricted to male infants.

women in the BDS through 2004. In the present analysis, the previously reported increases in use of diphenhydramine and loratadine appeared to continue to 2009, whereas use of doxylamine remained infrequent and use of chlorpheniramine continued to decrease.

We did not have sufficient power to provide stable risk estimates for the previously hypothesized association of chlorpheniramine and ear defects, but a 3-fold risk was observed. For the hypothesized association between chlorpheniramine and spina bifida, the OR was 1.7 (95% CI, 0.6-5.3), and, in the exploratory analyses, we observed an elevated risk for any neural tube defects (OR 2.6 [95% CI, 1.1-6.1]), due to a very large but unstable risk for encephalocele (OR 20.4 [95% CI, 2.5-166.2). We also found 3 additional positive associations with ORs > 3 in the exploratory analyses for chlorpheniramine. However, for reasons noted above, these findings should be interpreted with caution.

Our study has several strengths. First, BDS contains comprehensive information on OTC drug use in contrast to data sets that are largely limited to prescription drugs. In addition, the interview-based data collection obtains critical covariates such as maternal reproductive history, smoking, alcohol, periconceptional folate and multivitamin use, and treatment indications. These variables are rarely directly available in administrative databases, and it is of particular value that the BDS included information on important potential confounders. Second, we gave special consideration to reducing potential biases in our study design and analysis; these included detailed and structured data collection, outcome validation, comparisons that involved both nonmalformed and malformed control groups, and conducted multivariate adjustment and sensitivity and/or secondary analyses.

However, there were several limitations in our study. First, despite the large number of subjects, we had sufficient power only to evaluate associations between the most common antihistamine medications and relatively common malformations. Capacity to examine the potential dose effect (dose or days of exposure) was limited. Second, our data were collected retrospectively by maternal reporting. Although many approaches are in place to improve the accuracy of maternal recall and reporting in the BDS, recall bias[44,45] and exposure misclassification remain possible. With respect to recall bias, the mother of a normal infant may search her memory less thoroughly than the mother of a malformed infant and thus might underreport antenatal exposures, which would lead to an overestimation of the true risk. Because recall bias is unlikely to be defect-specific, our use of malformed infants as a secondary control group maximized the likelihood of symmetrical recall in cases and controls. Sensitivity analyses that involved malformed controls yielded similar elevations in risk, which reduced the likelihood that recall bias accounts for positive findings. With regard to exposure misclassification, the detailed information about medication use collected by the BDS allowed us to create separate categories of subjects who varied in their likelihood of exposure. By restricting our definition of exposure to only those women considered most likely to have been exposed, we sought to minimize exposure misclassification. Third, although we considered specific malformations rather than defects by organ system or birth defects overall, there might still be etiologic heterogeneity within some specific case groups in which inclusion of diverse subtypes is

TABLE III. Exploratory analyses: associations between first trimester exposure to antihistamines and specific malformations in BDS, 1998-2010*

	Loratadine		Diphenhydramine		Chlorpheniramine		Doxylamine	
Outcome	No. (%)	Adjusted OR (95% CI)†	No. (%)	Adjusted OR (95% CI)†	No. (%)	Adjusted OR (95% CI)†	No. (%)	Adjusted OR (95% CI)†
No malformations (n = 6982)	163 (2.3)	Referent	202 (2.9)	Referent	76 (1.1)	Referent	110 (1.6)	Referent
Any neural tube defects (n = 292)	6 (2.1)	1.0 (0.4-2.5)		Tested‡	8 (2.7)	2.6 (1.1-6.1)		Tested
Spina bifida (n = 213)	6 (2.8)	1.5 (0.6-3.9)		Tested		Tested		Tested
Any conotruncal defect (n = 718)	19 (2.7)	1.2 (0.7-2.1)	26 (3.6)	1.4 (0.8-2.2)	9 (1.3)	1.3 (0.6-2.7)	20 (2.8)	1.0 (0.6-1.7)
Tetralogy of Fallot (n = 277)	7 (2.5)	1.0 (0.4-2.3)	10 (3.6)	1.1 (0.5-2.3)	6 (2.2)	3.1 (1.2-8.4)	7 (2.5)	1.2 (0.5-2.8)
D-Transposition of great arteries (n = 195)	6 (3.1)	1.7 (0.7-4.2)	11 (5.6)	2.3 (1.1-5.0)		N/A	5 (2.6)	1.2 (0.4-3.0)
Aortic arch anomalies (n = 223)	7 (3.1)	1.3 (0.6-3.0)	5 (2.2)	0.6 (0.2-1.5)		N/A		N/A
Ventricular septal defect (n = 1440)	31 (2.2)	0.9 (0.6-1.4)	42 (2.9)	0.9 (0.6-1.3)	17 (1.2)	1.0 (0.6-1.8)	24 (1.7)	0.8 (0.5-1.3)
Secundum atrial septal defect (n = 241)		N/A	5 (2.1)	0.6 (0.2-1.6)		N/A	7 (2.9)	1.1 (0.5-2.5)
Right ventricular outflow obstruction (n = 557)	11 (2.0)	0.9 (0.4-1.7)	24 (4.3)	1.6 (1.0-2.7)		N/A	14 (2.5)	0.8 (0.5-1.5)
Pulmonary valve stenosis/atresia (n = 287)	7 (2.4)	1.1 (0.5-2.6)	14 (4.9)	1.6 (0.8-3.1)		N/A	7 (2.4)	0.9 (0.4-2.0)
Left ventricular outflow obstruction (n = 623)	12 (1.9)	1.0 (0.5-2.0)	21 (3.4)	1.1 (0.6-2.0)	7 (1.1)	1.4 (0.6-3.3)	16 (2.6)	0.9 (0.5-1.5)
Coarctation of aorta (n = 247)	5 (2.0)	1.0 (0.4-2.6)	10 (4.1)	1.3 (0.6-2.8)		N/A	6 (2.4)	0.8 (0.3-2.0)
Hypolastic left heart syndrome (n = 174)		N/A	5 (2.9)	0.8 (0.3-2.4)	5 (2.9)	4.9 (1.6-14.9)		Tested
Great veins anomalies (n = 194)		N/A		N/A	5 (2.6)	3.3 (1.1-10.0)		N/A
Oral clefts (n = 1228)	17 (1.4)	0.5 (0.3-0.9)	43 (3.5)	1.1 (0.7-1.7)	20 (1.6)	1.3 (0.7-2.4)		Tested
Cleft palate alone (n = 452)	7 (1.6)	0.5 (0.2-1.2)		Tested	7 (1.6)	1.4 (0.6-3.4)	7 (1.6)	0.7 (0.3-1.5)
Cleft lip with or without cleft palate (n = 776)	10 (1.3)	0.5 (0.3-1.0)		Tested		Tested	16 (2.1)	0.8 (0.5-1.4)
Tracheo-esophageal fistula (n = 182)		N/A	6 (3.3)	1.2 (0.5-3.0)		N/A	6 (3.3)	1.1 (0.4-2.7)
Pyloric stenosis (n = 583)	13 (2.2)	1.0 (0.6-2.0)	15 (2.6)	1.0 (0.5-1.8)	10 (1.7)	1.2 (0.6-2.5)		Tested
Small intestinal atresia/stenosis (n = 196)		N/A	6 (3.1)	0.6 (0.2-1.7)		N/A		N/A
Anal atresia/stenosis (n = 213)	6 (2.8)	1.1 (0.4-2.7)	7 (3.3)	1.0 (0.4-2.5)		N/A	7 (3.3)	1.2 (0.5-2.7)
Intestinal malrotation (n = 190)		N/A	6 (3.2)	0.9 (0.4-2.5)		N/A	5 (2.6)	1.4 (0.5-3.6)
Cystic kidney disease (n = 204)§		N/A				N/A	10 (4.9)	2.7 (1.3-5.6)
Renal collecting system anomalies (n = 919)	25 (2.7)	1.1 (0.7-1.8)	43 (4.7)	1.5 (1.0-2.2)	12 (1.3)	1.2 (0.6-2.4)	22 (2.4)	1.3 (0.8-2.2)
Extra or horseshoe kidney (n = 148)		N/A	8 (5.4)	1.5 (0.6-3.5)		N/A		N/A
Clubfoot (n = 495)	7 (1.4)	0.6 (0.3-1.4)	13 (2.6)	0.9 (0.5-1.8)	6 (1.2)	1.1 (0.4-2.7)	12 (2.4)	1.2 (0.6-2.3)
Limb reduction defects (n = 179)	5 (2.8)	1.1 (0.4-2.9)		Tested		N/A	5 (2.8)	1.2 (0.5-3.2)
Diaphragmatic hernia (n = 150)		N/A		N/A		N/A	6 (4.0)	1.3 (0.5-3.2)
Nonmalformed males only (n = 3448)	74 (2.2)	Referent	108 (3.1)	Referent	36 (1.0)	Referent	56 (1.6)	Referent
Undescended testicle (males only) (n = 561)	7 (1.3)	0.7 (0.3-1.7)	18 (3.2)	0.9 (0.5-1.7)		N/A	14 (2.5)	1.5 (0.7-3.0)
Hypospadias (males only) (n = 632)		Tested	23 (3.6)	1.3 (0.7-2.3)	10 (1.6)	1.9 (0.8-4.7)	14 (2.2)	0.9 (0.4-1.7)

N/A, Not estimated due to <5 exposed cases.

*Comparison of "likely exposed" in the first trimester with nonuse between 2 mo before the LMP through the end of pregnancy; limited to at least 5 exposed defects in any given category.

†Additionally adjusted for potential confounders, including maternal age, race/ethnicity, education, household annual income, alcohol consumption, allergy and asthma during pregnancy, nausea and/or vomiting, sleeping problems, respiratory infection (cold or flu), oral corticosteroids, decongestants, acetaminophen, aspirin, NSAIDs, and antibiotics use in the first trimester.

‡The *a priori* hypothesis-based associations were presented in Table II.

§Seventy-four percent of the cystic kidney diseases were multicystic dysplastic kidneys in our population; all the 10 doxylamine-exposed cystic kidney disease cases had multicystic dysplastic kidneys.

likely[46,47] or when cases with isolated or multiple defects were considered together. However, when we restricted the analyses to cases with isolated defects only, findings did not materially change.

We suspect that many if not all previously reported associations between antihistamines and birth defects may be chance findings observed in the context of multiple comparisons, a situation that may also apply to the findings in the current study. Therefore, it is important that other researchers test the hypotheses generated from our exploratory analyses. In conclusion, accumulated epidemiologic evidence does not provide meaningful support for any strong associations between common specific antihistamines and major congenital malformations.

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TABLE E1. Sensitivity analyses by using malformed controls: associations between first trimester exposure to antihistamines and specific malformations, Slone Epidemiology Center Birth Defect Study, 1998-2010*

Medication	Outcome	no. (%)	Crude matched OR (95% CI)†	Adjusted OR (95% CI)‡
Diphenhydramine	D-transposition of great arteries (n = 195)	11 (5.6)	2.0 (1.1-3.9)	2.1 (1.0-4.4)
	Right ventricular outflow obstruction (n = 557)	24 (4.3)	1.7 (1.1-2.6)	1.7 (1.1-2.8)
	Pulmonary valve stenosis/atresia (n = 287)	14 (4.9)	1.8 (1.1-3.2)	1.7 (0.9-3.2)
	Renal collecting system anomalies (n = 919)	43 (4.7)	1.5 (1.1-2.1)	1.5 (1.0-2.2)
	Extra or horseshoe kidney (n = 148)	8 (5.4)	1.8 (0.9-3.7)	1.6 (0.7-3.7)
Doxylamine	Cystic kidney disease (n = 204)	10 (4.9)	2.2 (1.1-4.3)	2.4 (1.2-4.8)
	Undescended testicle (males only) (n = 561)	14 (2.5)	1.5 (0.8-2.7)	1.6 (0.9-3.0)
Chlorpheniramine	Neural tube defects (n = 292)	8 (2.7)	2.2 (1.0-4.7)	2.4 (1.1-5.5)
	Tetralogy of Fallot (n = 277)	6 (2.2)	1.7 (0.8-4.0)	2.3 (0.9-6.0)
	Hypoplastic left heart syndrome (n = 174)	5 (2.9)	2.3 (1.0-5.6)	3.2 (1.2-9.4)
	Great veins anomalies (n = 194)	5 (2.6)	2.3 (0.9-5.7)	3.0 (1.1-8.6)
	Hypospadias (males only) (n = 632)	10 (1.6)	1.5 (0.8-3.0)	1.4 (0.7-3.0)
Loratadine	Spina bifida (n = 213)	6 (2.8)	1.5 (0.7-3.5)	1.8 (0.7-4.4)
	D-Transposition of great arteries (n = 195)	6 (3.1)	1.6 (0.7-3.7)	1.8 (0.7-4.4)

OR, Odds ratio.

*Comparison of "likely exposed" in the first trimester with nonuse between 2 mo before the last menstrual period through the end of pregnancy.

†Matched on the calendar year of conception and study region.

‡Additionally adjusted for potential confounders, including maternal age, race/ethnicity, education, household annual income, alcohol consumption, allergy and asthma during pregnancy, nausea and/or vomiting, sleeping problems, respiratory infection (cold or flu), oral corticosteroids, decongestants, acetaminophen, aspirin, nonsteroidal anti-inflammatory drugs, and antibiotics use in the first trimester.