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Antihistamine Use in Early Pregnancy and Risk of Birth Defects

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Abstract

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 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 six months of delivery about demographic, reproductive, medical, and behavioral factors, and details on use of prescription and non-prescription medications. We compared 1st trimester exposure to specific antihistamines between 13,213 infants with specific malformations and 6,982 non-malformed controls, using conditional logistic regression to estimate odds ratios (ORs) 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 1st trimester. The most commonly-used medications were diphenhydramine (4.2%), loratadine (3.1%), doxylamine (1.9%), and chlorpheniramine (1.7%). Where estimates were stable, none supported the previously-hypothesized associations. Among over 100 exploratory comparisons of other specific antihistamine/defect pairs, 14 had ORs 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-posed associations between antihistamines and major congenital anomalies; at the same time, we

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Conflict of interest disclosure:

The Pharmacoepidemiology Program at the Harvard School of Public Health is partially supported by training grants from Pfizer, Millennium and Asisa. The Slone Birth Defects Study receives support from a number of pharmaceutical manufacturers that may make products included in this study, but this analysis was not supported by commercial entities nor were they aware of it. Dr. Mitchell consulted on one occasion for Duchesnay, the manufacturer of Diclegis; while this product was not the subject of this analysis, one of its ingredients (doxylamine) was. Dr. Mitchell serves as a consultant to Biogen-Idec in his role as a member of the Tysabri Pregnancy Registry Advisory Committee. Dr. Hernández-Díaz has consulted for Novartis, AstraZeneca, and GSK_Biologics. Dr. Werler is on advisory boards of manufacturer-sponsored studies that evaluate pregnancy outcomes among women treated with medications for rheumatoid arthritis; No known conflict is identified. Ms.Li and Dr. Yau have no conflict of interest to report.

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 which may also apply to our new findings.

Keywords

Antihistamines; birth defects; first trimester; maternal exposure

INTRODUCTION

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 FDA category B (no evidence of human risk after *in utero* exposure) due to the scarce number of controlled studies in pregnant women.³ Given their wide use and availability without prescription (“over-the-counter”, or OTC), even a small increase in the risk of specific birth defects may have considerable clinical and public health implications. On the other hand, if these medications are relatively safe, 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 doxylamine in relation to oral clefts,³⁰ pyloric stenosis,^{31,32} hypoplastic left heart syndrome, spina bifida, and neural tube defects.²⁶

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/fetuses were identified as potential cases at regional centers around Boston (1976-present), Philadelphia (1977-present), Toronto (1979-2006), and San Diego (2001-present), and from birth defects registries in Massachusetts (1998-present) and New York State (2004-present); non-

malformed infants were identified as potential controls at participating hospitals (1993-present) and from a population-based sample of non-malformed infants in Massachusetts (1998-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 containing 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, hypoplastic left heart syndrome, and great veins anomalies. Major malformations are confirmed by the physicians of study subjects and by the mothers during interview; for subjects who provide medical record releases, diagnoses are 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 non-malformed infants enrolled in 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 to a secondary control group consisting of infants with all other structural malformations (including those with <100 subjects).

Exposure ascertainment and classification

Study nurses conducted standardized phone 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 are asked in a multilevel approach. First, women are asked whether they experienced any of a list of specific illnesses (e.g., 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 (e.g.,

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 highlighting key dates and events (e.g., LMP, Christmas, delivery date).

We studied the two generations of antihistamines, whether available by prescription or OTC – the older sedating products (e.g., chlorpheniramine, diphenhydramine, dimenhydrinate, doxylamine, promethazine), and the newer non-sedating products (e.g., 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 (i.e., 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 one day during the first trimester. 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’. While secular trend analyses used both definitions, etiologic comparisons compared only ‘likely exposed’ women to women without any use of the medication from 2 months before conception throughout delivery (i.e., 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 co-morbidities and the medications used concomitantly. Finally, we evaluated the associations between first-trimester exposure to specific antihistamines in relation 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 ≥ 100 cases; in the exploratory analyses, we restricted consideration to cells with ≥ 5 exposed cases. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (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 using Bonferroni³⁸ and Benjamini-Hochberg³⁹ approaches. For any positive associations found in the exploratory analyses, we assessed potential recall bias by conducting sensitivity analyses using our secondary control series (i.e., other malformed infants). To account for etiologic heterogeneity and provide analyses comparable to those conducted in the U.S. 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 6,982 non-malformed controls. Overall, 14.9% of cases and 13.7% of controls were exposed to antihistamines during first trimester. Among 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/vomiting, cold/flu, and insomnia. The prevalence of antihistamine use decreased from early to late pregnancy, except for diphenhydramine, where 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, making 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. On the other hand, 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.

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 1). As expected, first trimester antihistamine use was related to conditions that are indications for antihistamine medications, which included allergy, asthma, nausea/vomiting, sleeping problems, respiratory infection and cold/flu. Medications associated with first trimester antihistamine use included oral corticosteroids, decongestants, acetaminophen, aspirin, non-steroidal 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 use of specific antihistamines were confined to the four most commonly-used agents – diphenhydramine, loratadine, chlorpheniramine, and doxylamine. As reflected in Table 2, 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 involving a total of 107 comparisons, six exposure-outcome pairs had elevated ORs with lower 95% CI bounds exceeding 1.0 (Table 3): diphenhydramine and D-transposition of great arteries (OR: 2.3, 1.1-5.0); doxylamine and cystic kidney disease (OR: 2.7, 1.3-5.6); and chlorpheniramine and neural tube defects (OR: 2.6, 1.1-6.1),

tetralogy of Fallot (OR: 3.1, 1.2-8.4), hypoplastic left heart syndrome (OR: 4.9, 1.6-14.9), and great veins anomalies (OR: 3.3, 1.1-10.0). Loratadine use was inversely associated with oral clefts (OR: 0.5, 0.3-0.9). Another 8 exposure-outcome ORs were ≥ 1.5 but 95% CIs were wide and included 1.0. In the sensitivity analyses using secondary malformed controls in each comparison, the OR estimates generally changed little (see Table E1 in the Online Repository). However, all CIs included 1.0 after adjustment for multiple comparisons 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 between 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. On the other hand, in our exploratory analyses that involved 107 comparisons, we identified 14 associations that had ORs ≥ 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 CIs included 1.0 when we employed two widely-used multiple-comparison adjustment approaches, supporting 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 are 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, which included the antihistamine doxylamine along with vitamin B6, caused birth defects, leading its manufacturer to voluntarily withdraw it from the market in 1983.⁴⁰ As Figure 1 reveals, the prevalence of doxylamine use in pregnant women was quite low during the period of our study. Extensive studies of Bendectin, including two 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 supporting the relative safety of doxylamine. Of note, in April 2013, the U.S. FDA approved Diclegis, having the same ingredients as Bendectin, for treating nausea and vomiting in pregnant women.⁴³

Werler et al previously described trends of diphenhydramine, loratadine, doxylamine, and chlorpheniramine use among women in the BDS through 2004.² In the present analysis, the previously-reported increases in use of diphenhydramine and loratadine appeared to continue to 2009, while 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 (0.6-5.3), and in the exploratory analyses, we observed an elevated risk for any neural tube defects (OR: 2.6, 1.1-6.1), due to a very large but unstable risk for encephalocele

(OR: 20.4, 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 datasets 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 involving both nonmalformed and malformed control groups, and conducting multivariate adjustment and sensitivity/secondary analyses.

On the other hand, 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 involving malformed controls yielded similar elevations in risk, reducing 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 where inclusion of diverse subtypes is 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 which may also apply to the findings in the current study. Therefore, it is important that others test the hypotheses generated from our exploratory analyses. In conclusion, accumulated epidemiological evidence does not provide meaningful support for any strong associations between common specific antihistamines and major congenital malformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

OTC	over-the-counter
BDS	Birth Defects Study
LMP	last menstrual period
OR	odds ratio
CI	confidence interval
BMI	body mass index
NSAID	non-steroidal anti-inflammatory drug

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Highlights box

- 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.
- Findings from this study do not provide meaningful support for any strong associations between specific common antihistamines and specific major birth defects.
- This study provides reassurance that commonly-used antihistamine medications appear to be relatively safe for women to take during pregnancy in terms of teratogenicity.

Figure 1.

Temporal Trend of First Trimester Antihistamine Use, Slone Epidemiology Center Birth Defect Study (BDS), 1998-2009

Based on data only from Boston and Philadelphia which have been participating in the BDS throughout 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.

Table 1
 Characteristics Associated with Antihistamine Use in First Trimester among Mothers of Non-malformed Infants, Slone Epidemiology Center Birth Defect Study, 1998-2010

Characteristic	Users (N=723) n (%)	Non-users ^a (N=5,357) n (%)	Crude matched ^b odds ratio and 95% confidence interval
Study center			
Boston	375 (51.9)	2,949 (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, years			
<25	125 (17.3)	1,184 (22.1)	Referent
25-29	180 (24.9)	1,372 (25.6)	1.2 (1.0, 1.6)
30-33	229 (31.7)	1,475 (27.5)	1.5 (1.2, 1.8)
34	189 (26.1)	1,306 (24.4)	1.4 (1.1, 1.7)
Unknown	0	20 (0.4)	-
Maternal race/ethnicity			
White (non-Hispanic)	579 (80.1)	3,660 (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, kg/m ²			
<18.5	39 (5.4)	304 (5.7)	1.0 (0.7, 1.4)
18.5-24.9	427 (59.1)	3,352 (62.6)	Referent
25.0-29.9	154 (21.3)	994 (18.6)	1.2 (1.0, 1.5)
30.0	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, years			
<13	140 (19.4)	1,580 (29.5)	Referent
13-15	189 (26.1)	1,219 (22.8)	1.8 (1.4, 2.2)

Characteristic	Users (N=723) n (%)	Non-users ^a (N=5,357) n (%)	Crude matched ^b odds ratio and 95% confidence interval
16	394 (54.5)	2,555 (47.7)	1.8 (1.4, 2.1)
Unknown	0	3 (0.1)	-
Household annual income, dollars			
<45,000	162 (22.4)	1,606 (30.0)	Referent
45,000	519 (71.8)	3,263 (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)	3,095 (57.8)	Referent
Only before pregnancy	188 (26.0)	1,208 (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)	2,261 (42.2)	Referent
Only before pregnancy	117 (16.2)	868 (16.2)	1.4 (1.1, 1.8)
During pregnancy	382 (52.8)	2,228 (41.6)	1.7 (1.5, 2.1)
Maternal coffee drinking			
Never	204 (28.2)	1,715 (32.0)	Referent
Only before pregnancy	11 (1.5)	91 (1.7)	1.0 (0.6, 2.0)
During pregnancy	288 (39.8)	1,930 (36.0)	1.3 (1.1, 1.6)
Unknown	220 (30.4)	1,621 (30.3)	0.9 (0.6, 1.4)
Maternal conditions and medication use ^c			
Allergy during pregnancy	426 (58.9)	407 (7.6)	19.3 (16.0, 23.2)
Nausea and/or vomiting in 1 st trimester	545 (75.4)	3,421 (63.9)	1.7 (1.5, 2.1)
Sleeping problems in 1 st 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/flu in 1 st trimester	302 (41.8)	1,629 (30.4)	1.7 (1.4, 2.0)
Pre-gestational diabetes	6 (0.8)	64 (1.2)	0.7 (0.3, 1.6)
Oral corticosteroids use in 1 st trimester	118 (16.3)	180 (3.4)	5.6 (4.3, 7.1)
Decongestant use in 1 st trimester	248 (34.3)	293 (5.5)	10.0 (8.2, 12.2)
Acetaminophen use in 1 st trimester	475 (65.7)	2,235 (41.7)	2.8 (2.4, 3.3)

Characteristic	Users (N=723) n (%)	Non-users ^a (N=5,357) n (%)	Crude matched ^b odds ratio and 95% confidence interval
Aspirin use in 1 st trimester	60 (8.3)	307 (5.7)	1.5 (1.1, 2.0)
NSAIDs use in 1 st trimester	213 (29.5)	990 (18.5)	1.9 (1.6, 2.3)
Antibiotics use in 1 st trimester	54 (7.5)	248 (4.6)	1.7 (1.2, 2.3)
Periconceptional ^d folic acid supplementation	508 (70.3)	3,470 (64.8)	1.3 (1.1, 1.5)

BMI: body mass index

NSAIDs: non-steroidal anti-inflammatory drugs, 85% being ibuprofen

^aNo use of any antihistamine during 2 months before last menstrual period through the end of pregnancy

^bMatched on calendar year of conception for the analysis of “study center”, and on calendar year of conception and study center for the analyses of all other variables

^cReference category for each variable is “no occurrence or use” during the specific time frame indicated.

^dDuring the period from 1 month before to 1 month after conception

For *a priori* Hypotheses: Associations Between First Trimester Exposure to Antihistamines and Specific Malformations^a, Slone Epidemiology Center Birth Defect Study, 1998-2010

Table 2

Medications	Outcomes	Numbers exposed (%)	Crude matched ^b OR (95% CI)	Adjusted ^c OR (95% CI)
Diphenhydramine	Non-malformed (n=6,982)	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)
Loratadine	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)
	Non-malformed males (n=3,448)	74 (2.2)	Referent	Referent
Chlorpheniramine	Hypospadias ^d (n=632)	13 (2.1)	1.0 (0.5, 1.9)	0.8 (0.4, 1.7)
	Non-malformed (n=6,982)	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)
Doxylamine	Cleft lip with or without cleft palate (n=776)	13 (1.7)	1.7 (0.9, 3.2)	1.3 (0.6, 2.5)
	Non-malformed (n=6,982)	110 (1.6)	Referent	Referent
	Oral clefts (n=1,228)	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)

OR: odds ratio; CI: confidence interval

^aComparison of 'likely exposed' in the first trimester to nonuse between 2 months before last menstrual period through the end of pregnancy

^bMatched on calendar year of conception and study region

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

^dComparison restricted to male infants

Table 3

Exploratory Analyses^a: Associations Between First Trimester Exposure to Antihistamines and Specific Malformations in Slone Epidemiology Center Birth Defect Study, 1998-2010

Outcome	Loratadine			Diphenhydramine			Chlorpheniramine			Doxylamine		
	N	%	Adjusted OR ^b (95% CI)	N	%	Adjusted OR ^b (95% CI)	N	%	Adjusted OR ^b (95% CI)	N	%	Adjusted OR ^b (95% CI)
No malformations (n=6,982)	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 ^c	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 ^d	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=1,440)	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)
Hypoplastic 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=1,228)	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)	7	1.6	0.7 (0.3, 1.5)
Cleft palate alone (n=452)	7	1.6	0.5 (0.2, 1.2)			Tested	7	1.6	1.4 (0.6, 3.4)	16	2.1	0.8 (0.5, 1.4)
Cleft lip with or without cleft palate (n=776)	10	1.3	0.5 (0.3, 1.0)			Tested			Tested	6	3.3	1.1 (0.4, 2.7)
Tracheo-esophageal fistula (n=182)			N/A	6	3.3	1.2 (0.5, 3.0)			N/A			Tested
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)			N/A
Small intestinal atresia/stenosis (n=196)			N/A	6	3.1	0.6 (0.2, 1.7)			N/A	7	3.3	1.2 (0.5, 2.7)
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	5	2.6	1.4 (0.5, 3.6)
Intestinal malrotation (n=190)			N/A	6	3.2	0.9 (0.4, 2.5)			N/A	10 ^c	4.9	2.7 (1.3, 5.6)
Cystic kidney disease ^e (n=204)			N/A									

Outcome	Loratadine			Diphenhydramine			Chlorpheniramine			Doxylamine		
	N	%	Adjusted OR ^b (95% CI)	N	%	Adjusted OR ^b (95% CI)	N	%	Adjusted OR ^b (95% CI)	N	%	Adjusted OR ^b (95% CI)
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)
Non-malformed males only (n=3,448)	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)

OR: odds ratio; CI: confidence interval

^a Comparison of 'likely exposed' in the first trimester to nonuse between 2 months before last menstrual period through the end of pregnancy; limited to at least 5 exposed defects in any given category.

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

^c Tested: The *a priori* hypothesis-based associations were presented in the previous Table 2.

^d N/A: Not estimated due to <5 exposed cases

^e 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.