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Medications Used to Treat Nausea and Vomiting of Pregnancy and the Risk of Selected Birth Defects

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Abstract

Background—Nausea and vomiting of pregnancy (NVP) occurs in up to 80% of pregnant women, yet its association with birth outcomes is not clear. Several medications are used for the treatment of NVP; however, data are limited on their possible associations with birth defects.

Methods—Using data from the National Birth Defects Prevention Study (NBDPS), a multi-site population-based case-control study, we examined whether NVP or its treatment was associated with the most common non-cardiac defects in the NBDPS (non-syndromic cleft lip with or without cleft palate (CL/P), cleft palate alone (CP), neural tube defects (NTDs), and hypospadias) compared to randomly-selected non-malformed live births.

Results—Among the 4524 cases and 5859 controls included in this study, 67.1% reported first trimester NVP, and 15.4% of them reported using at least one agent for NVP. Nausea and vomiting of pregnancy was not associated with CP or NTDs, but modest risk reductions were observed for CL/P (aOR=0.87, 0.77–0.98), and hypospadias (OR=0.84, 0.72–0.98). In regards to treatments for NVP in the first trimester, the following adjusted associations were observed with an increased risk: proton pump inhibitors and hypospadias (aOR=4.36, 1.21–15.81), steroids and hypospadias (aOR=2.87, 1.03–7.97), and ondansetron and CP (aOR=2.37, 1.18–4.76), while antacids were associated with a reduced risk for CL/P (aOR=0.58, 0.38–0.89).

Conclusions—Nausea and vomiting of pregnancy was not observed to be associated with an increased risk of birth defects, but possible risks related to three treatments (i.e. proton pump inhibitors, steroids and ondansetron), which could be chance findings, warrant further investigation.

Keywords

hypospadias; medications; National Birth Defects Prevention Study; nausea and vomiting of pregnancy; neural tube defects; orofacial clefts

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Massachusetts Department of Public Health.

INTRODUCTION

Nausea and vomiting of pregnancy (NVP) occurs in up to 80 percent of pregnant women (Gill and Einarson, 2007). While there is consistency in reports about the association of NVP with reduction in risk of miscarriage, reports of the association of NVP with other pregnancy outcomes such as low birth weight and birth defects are conflicting (Weigel, 2000; Furneaux et al., 2001). It is most prevalent early in pregnancy, usually starting at about 4–9 weeks, peaking at about 7–12 weeks, and ceasing at by 16 weeks (Ebrahimi et al., 2010). Nausea and vomiting of pregnancy itself or its medication treatments, therefore, occur at a point in gestation when many embryologic systems are developing and thus are potentially susceptible to teratogenic effects of various exposures (Dilts, 1992).

For many years the mainstay of NVP treatment was Bendectin (Merrell Dow Pharmaceuticals, Kansas City, MO) (originally a combination of doxylamine succinate, dicyclomine and pyridoxine; a later formulation excluded the dicyclomine), the one medication in the United States approved for treatment of NVP. Following Bendectin's removal from the market in 1982 after allegations that it caused fetal damage (Brent, 1995), there has been limited information on what women in the US are using to treat NVP. While there is existing literature on the optimal management of NVP and the risk of some of these medications (Ebrahimi et al., 2010; ACOG, 2004; Arsenault et al., 2002; Asker et al., 2005; Borrelli et al., 2005; Einarson et al., 2007; Gill and Einarson, 2007; Koren et al., 2010; Portnoi et al., 2003), a number of them have not been adequately tested for safety in pregnancy.

We examined NVP experienced by women in the National Birth Defects Prevention Study (NBDPS), delineated medications used to treat NVP among these women, and investigated whether NVP itself or use of NVP medications in the first trimester of pregnancy was associated with selected birth defects.

METHODS

We used data from the NBDPS, a multi-site population-based case-control study, which seeks to identify risk factors associated with birth defects. Annually, each NBDPS site contributes maternal interviews of approximately 300 case subjects with any of over 30 selected birth defects and 100 control subjects without birth defects. All ten sites use a standardized protocol that was developed by the NBDPS collaborative. Case infants are identified from birth defects surveillance systems in the participating states. All infants with study-eligible birth defects who reside in the study areas are invited to participate. Controls are either randomly selected from birth certificates or selected from birth hospitals using a stratified random sampling design. Sites in the NBDPS during some or all of the study period were located in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas and Utah. The NBDPS has been described in detail elsewhere (Yoon et al, 2001; Rasmussen et al, 2003). All study sites obtained IRB approval and study participants provided informed consent.

Outcome Definition and Classification

The NBDPS collects information on cases with over 30 different birth defects diagnosed prenatally, at birth or during the first year of life. During at least some of the study period, 9 of the 10 participating sites also collected information on affected fetal deaths at 20 weeks gestation or greater and eight of the ten sites included pregnancies that were prenatally diagnosed and electively terminated. The NBDPS excludes cases with recognized or strongly suspected chromosome abnormalities or single-gene conditions.

This analysis was limited to the most common non-cardiac NBDPS-eligible birth defect categories: orofacial clefts, neural tube defects (NTDs) and hypospadias. Cardiac defects will be the topic of a separate analysis. For analyses of clefts, we analyzed data on infants with cleft lip with or without cleft palate (CL/P) and cleft palate alone (CP) separately, given that these diagnoses are presumed to be pathogenetically and etiologically distinct (Genisca et al., 2009). Infants with clefts secondary to another defect (e.g., holoprosencephaly or amniotic band sequence) were excluded. For NTDs, we included infants with anencephaly, craniorachischisis, spina bifida, or encephalocele. Because of concern for incomplete ascertainment of first-degree hypospadias (urethral opening on the glans or corona), only infants with severe hypospadias (urethral opening at the penile shaft, scrotum or perineum) were included in the NBDPS. Orofacial clefts that were diagnosed prenatally, but not confirmed postnatally, were excluded from the NBDPS. Neural tube defects, diagnosed prenatally that did not have a postnatal examination to confirm the defect because a pregnancy termination was performed, were included if sufficient information was available to ensure that an NTD was the most likely diagnosis.

Clinical geneticists in each site reviewed information abstracted from medical records to ensure that case infants met the eligibility criteria and each infant was classified by clinical geneticists as having an isolated defect (if there was no other major anomaly or only minor anomalies) or multiple defects (one or more major, unrelated accompanying anomalies). More information on case eligibility criteria has been described in detail elsewhere (Rasmussen et al, 2003).

Study Population

This study included subjects from the NBDPS with expected dates of delivery between September 24, 1997 and December 31, 2004. The interview participation rates during this period were 76% for case mothers with CL/P, 75% for CP, 71% for NTDs, 69% for hypospadias and 69% percent for control mothers. Of subjects for whom complete interview data were available, 1546 had CL/P, 821 had CP, 1038 had an NTD, 1144 had 2nd or 3rd degree hypospadias and 5859 were control infants without birth defects. Hypospadias case infants were compared to the 2946 male control infants. The mean interval between birth and interview was 8.9 months for controls, and for cases, 10.4 months for CL/P, 10.9 months for CP, 11.7 months for NTDs and 13.1 months for hypospadias.

NVP Exposure and Treatment Measurement

We obtained histories of NVP and treatments from a standardized computer- assisted telephone interview with the mother, which asked if, when and how often women experienced NVP. The series of questions used to assess NVP in the NBDPS was developed by the collaborative based on a previous CDC questionnaire used for the Atlanta Birth Defects Case-Control Study (Boneva et al., 1999). These data were collected by month for the first trimester and by trimester for the second and third trimesters. Women who reported NVP were also asked about frequency, duration, timing and indication for any prescription or nonprescription medication use (including herbal products) to treat NVP. Medications were classified and coded according to the Slone Drug Dictionary of the Slone Epidemiology Center at Boston University. This analysis focused on medications used to treat NVP in the first trimester because that is considered the vulnerable time for development of the birth defects under study.

Description of NVP treatment

Among 22,381 women participating in the NBDPS during the study period, 75 different medications and a number of herbal products were reported as treatment for NVP. This count excludes intravenous fluids and replacement solutions, non-B6 vitamins and minerals,

and a few medications that were reported as being used for this condition but seemed implausible (e.g. narcotics, antiinfectives, cough/cold medications (mainly pseudoephedrine)). In producing the count of different medications reported for NVP, combination products (pharmaceuticals with two or more active ingredients) were counted only once.

A research pharmacist grouped medication exposures reported for NVP by women participating in the NBDPS into categories based on their therapeutic and pharmacologic class. Medication groups reported by more than 15 of the selected birth defect case and control women and for which at least 20 percent of use was reported by women with first trimester NVP treatment were included in the analysis. The medication groups meeting these criteria were antihistamine antiemetics, other antihistamines, antihistamine antiemetics plus B6 combinations, phenothiazines (other than promethazine), prokinetics, 5HT3 antagonists, emetrol/coke syrup, bismuth subsalicylate, antacids, histamine H2-receptor antagonists (H2 blockers), proton pump inhibitors (PPIs) (e.g. lansoprazole, omeprazole, esomeprazole), pyroxidine (vitamin B6), steroids and herbal/natural products. Categories not meeting the criteria, and which were therefore excluded from the analysis of relative risk were cannabinoids, antispasmodics, antidiarrheals, laxatives, analgesics and muscle relaxants.

Analysis

The main comparison was between women with NVP who used NVP medications in the first trimester versus those who did not. We included women who used these NVP medications regardless of indication for use. The women with no NVP permitted comparison of the effect of the condition itself regardless of medication use.. Measures of association were calculated for medication categories and individual medications or herbal products with at least four exposed cases.

Potential confounders for the adjusted analyses were selected a priori and included maternal age, race-ethnicity, education, parity, smoking in the month before conception through the first trimester, plurality, previous miscarriage, infant sex, use of multivitamin with folic acid anytime between the month before conception through the first trimester, body mass index (BMI), study site, and year of expected date of delivery. Adjusted odds ratios and their corresponding 95 percent confidence intervals were estimated using unconditional logistic regression. Subjects with a parent, sibling or half sibling with the same birth defect were excluded because their birth defects may be etiologically different from subjects without such a family history.

Where an association was observed between first trimester medication use and a birth defect, medication exposure was further examined according to month of pregnancy and the intensity of nausea and vomiting (average frequency of NVP in months 1, 2 and 3 of pregnancy). These analyses were repeated excluding women with pre-existing diabetes and excluding infants with more than one major birth defect.

RESULTS

Prevalence of NVP and NVP Treatment

The prevalence of NVP was 68.6% among controls, and among them, the prevalence of treatment was 15.4%. The percent of controls treated for NVP according to maternal characteristics is shown in Table 1. Treatment was less likely for Hispanic compared to white, non-Hispanic women and was more likely for women with the highest BMIs and for women with unknown folic acid use compared with women reporting any use of folic acid in the month before conception through the first trimester. The percent of mothers reporting treatment also varied by study site, ranging from 8.9 to 23.5 percent.

Relation of NVP to Birth Defects

As shown in Table 2, adjusted analyses revealed that cases were less likely than controls to experience NVP for CL/P and hypospadias, but not for CP and NTDs. Adjusted effect measures ranged from 0.84 to 1.00.

Relationship of specific first trimester NVP treatments and selected birth defects

As reflected in Table 3, antacid use, primarily calcium carbonate, was associated with a lower relative odds for CL/P (aOR=0.58; CI, 0.38–0.89).

Table 4 presents measures of effect between CP and medication use in the first trimester. We observed a higher odds ratio among women exposed to ondansetron (aOR=2.37; CI, 1.18–4.76). There was also higher odds among women exposed to PPIs, in the crude analysis, but the confidence interval of the adjusted association included 1.0 (aOR=2.59; CI, 0.88–7.63).

Table 5 presents measures of effect between NTDs and medication use in the first trimester. Women exposed to bismuth subsalicylate were at higher odds for developing NTDs in the crude analysis, but the confidence interval of the adjusted association included 1.0 (aOR=2.37; CI, 0.90–6.21), based on 7 and 15 exposed case and control mothers, respectively. Results were similar when the exposure period was defined as one month before and after conception (aOR=2.27; CI, 0.79–6.48), based on 6 and 13 exposed case and control mothers, respectively.

Table 6 presents measures of association between hypospadias and medication use in the first trimester. An association was observed between hypospadias and maternal use of PPIs (aOR=4.36; CI, 1.21–15.81), based on 7 exposed cases and 5 exposed controls. Steroids were also associated with hypospadias (aOR=2.87; CI, 1.03–7.97), based on 10 exposed cases and 8 exposed controls.

Excluding women with pre-existing diabetes and cases with other than an isolated defect did not meaningfully change the associations, nor did controlling for intensity of NVP.

DISCUSSION

This study found that after controlling for covariates, mothers of infants with CL/P and hypospadias had a reduced odds of experiencing NVP relative to controls. Treatment of NVP with a wide variety of different agents was relatively frequent - over 15% among women who reported NVP and about 10% of all women. The majority of medication groups and specific medications were not associated with the four birth defects studied, but numbers of exposed subjects were sometimes small. We did find, however, some positive associations with first trimester use of these medications: PPIs and hypospadias, steroids and hypospadias, ondansetron and CP. We also saw positive associations between PPIs and CP, and bismuth subsalicylate and NTDs; although the confidence intervals in the adjusted analyses included 1. The one inverse association was antacids and CL/P.

Our results show that pregnant women are currently taking a wide range of agents for treatment of NVP. While there is existing literature on the optimal management of NVP, much of the literature on the safety of the wide range of medications used by pregnant women is based on samples that are too small to assess risks for specific birth defects, and the large majority of teratogenic effects in humans have been shown to affect specific defects rather than increase the risk of birth defects overall. Thus, a major strength of the NBDPS case-control approach is our ability to evaluate the risks and safety of various exposures with respect to specific birth defects that have been clinically validated. The wide

variety of medications reported resulted in relatively small cell sizes, limiting our ability to investigate the risk or safety of individual medications.

We observed an elevated risk for hypospadias and CP among women exposed to PPIs in the first trimester. PPI medications to which women were exposed included lansoprazole, omeprazole and esomerprazole magnesium. The number of subjects exposed to specific PPI medications was small, which made it difficult to consider relationships with the specific PPIs. While cohort studies (Lalkin et al., 1998; Ruigomez et al., 1999; Kallen 2001; Kallen 1998) and two meta-analyses (Nikfar et al., 2002; Gill et al., 2009) did not suggest an increased risk of birth defects overall among women who ingested PPIs in the first trimester, none had the power to rule out even modest increases in risk of specific defects. A recent study found no risk of major birth defects overall with use of PPIs in the first trimester, but did not have sufficient power to consider the risk of specific birth defects (Pasternak and Hviid, 2010; Mitchell, 2010).

Ondansetron is an anti-nausea medication primarily used to treat nausea and vomiting in patients receiving chemotherapy. However, women are also using this medication for treatment of NVP. Two previous studies (Asker et al, 2005; Einarson et al, 2004) found no association with use of this medication in pregnancy and major birth defects overall, but the sample sizes were quite small and insufficient to consider risks of specific defects. Our data were compatible with their findings except for CP, for which we observed a doubling in odds.

Bismuth subsalicylate, a combination of bismuth salts and sodium salicylate, can be a source of a large amount of salicylate (262 mg for original strength and 525 mg for maximum strength per tablespoon) and thus is not recommended for use in pregnancy (Black and Hill, 2003). In previous human studies, salicylates have been associated with gastroschisis (Martinez-Frias et al., 1997) and holoprosencephaly (Croen et al, 2000), but our finding of an association of borderline significance with neural tube defects has not been seen before. In this analysis, steroids were associated with increased risk of hypospadias A previous analysis, which used NBDPS data to assess the odds of hypospadias after use of any corticosteroid through the 18^{th} week of pregnancy, found a weak association which decreased in magnitude (and had a lower 95% CI below 1.0) after adjustment for confounders (Carmichael et al, 2009). Two previous case control studies reported a moderately increased risk for CL/P with use of steroids in the first trimester (Carmichael et al., 2007; Pradat et al, 2003) and a meta-analysis showed a greater than threefold risk of oral clefts with such exposure (Park-Wylllie et al., 2000). We did not find an increased risk of CL/P based on 6 exposed cases and 15 exposed controls; there were not enough exposed cases with CP to calculate a measure of association.

We found an odds ratio of 2.36 for metoclopramide for CP, based on 5 exposed cases and 18 exposed controls, with a lower confidence bound that did not exclude 1.0. While a recent study of over 3000 exposed pregnancies found no increase in risk of major birth defects overall, the study had insufficient power to consider risks associated with specific birth defects (Matok et al., 2009).

A previous paper used NBDPS data to study the association between use of antihistamines in early pregnancy and risk of a spectrum of birth defects (Gilboa et al., 2009). That study found associations between certain antihistamines and birth defects that we did not observe in this study. Specifically, they saw and increased risk for NTDs with use of diphenhydramine, doxylamine and promethazine; for CL/P with use of diphenhydramine; and, for CP with use of meclizine. Four of these five associations were weak to moderate (OR < 2.5) and one was stronger (OR > 6) but was imprecise. The present study differed

from that study in that we used an additional year of NBDPS data and our study population was limited to women with NVP in the first trimester, a subset of women in the NBDPS.

Our study has a number of limitations including the potential for exposure misclassification due to incomplete recall or recall/reporting bias and selection bias as well as sparse data for some analyses. We obtained both NVP and NVP treatment information via a maternal interview conducted between six weeks and 24 months after the estimated date of delivery. Since on average, control mothers were interviewed three months sooner than cases, NVP and/or medication use could have been differentially recalled. If cases more often underreported their use of medication, the observed risk might be underestimated. We used as controls infants with no major birth defects. Studies have shown that recall of exposure information can depend on disease status (Khoury et al., 1994). If mothers of cases recalled NVP and its treatment differently from controls, recall bias could result. To improve recall, we provided NBDPS subjects with a pregnancy calendar in advance of the interview to help them more accurately respond to questions about the exposure timing.

Interpretation is limited due to the small number of women exposed to specific medications or medication groups. Further, residual confounding could exist due to uncontrolled factors that differed between women who used and did not use NVP treatment (e.g. genetic factors). Of course, those factors would have to be associated with risk of the defects under study.

Since the analyses of the relationship between NVP medications and birth defects were limited to subjects with NVP who were either exposed or not exposed to treatments, confounding by NVP was unlikely to play a role; however, confounding by severity of NVP could have influenced the observed results. Though key analyses were repeated controlling for frequency of nausea and vomiting, this process is unlikely to control fully for confounding by indication.

Perhaps of most importance is the possibility of chance as an explanation for the statistically significant associations that we observed. There were 70 comparisons made which would suggest that three to four such associations would be expected by chance alone. Nevertheless, this is the first study with extensive medication and defect-specific data and the observed associations deserve further research.

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Abbreviations

aOR	adjusted odds ratio
BMI	body mass index
CI	confidence interval
CL/P	cleft lip with or without palate
cOR	crude odds ratio

CP	cleft palate alone
H2 blockers	histamine H2-receptor antagonists
NBDPS	National Birth Defects Prevention Study
NTD	neural tube defect
NVP	nausea and vomiting of pregnancy
OR	odds ratio
PPIs	proton pump inhibitors
US	United States

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Table 1

Distribution of treatment for nausea and vomiting of pregnancy in the first trimester by selected characteristics among mothers of live born control infants without major birth defects, National Birth Defects Prevention Study 10/97–12/04

Character	# T1NVP	# Treatment for T1NVP	% Treated	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Total	4021	621	15.4	-	-
Age in years					
< 25	1311	195	14.9	Reference	Reference
25–34	2163	346	16.0	1.09 (0.90–1.32)	1.14 (0.91–1.43)
35+	547	80	14.6	0.98 (0.74–1.30)	1.11 (0.79–1.54)
Race					
White, non-Hispanic	2475	417	16.8	Reference	Reference
Black, non-Hispanic	423	75	17.7	1.06 (0.81–1.39)	1.02 (0.76–1.38)
Hispanic	890	101	11.3	0.63 (0.50–0.80)	0.64 (0.47–0.87)
Other	222	28	12.6	0.71 (0.47–1.07)	0.72 (0.47–1.10)
Unknown	11	0	0.0	-	-
Education (completed years)					
< 12	640	79	12.3	0.77 (0.58–1.03)	0.92 (0.67–1.26)
12	990	153	15.5	Reference	Reference
13+	2388	389	16.3	1.07 (0.87–1.31)	1.08 (0.86–1.35)
Unknown	3	0	0.0	-	-
Parity					
Primaparous	1517	236	15.6	Reference	Reference
Multiparous 1	1423	230	16.2	1.05 (0.86–1.28)	0.98 (0.80–1.21)
Multiparous 2+	1081	155	14.3	0.91 (0.73–1.13)	0.83 (0.65–1.05)
Plurality					
Singleton	3870	601	15.5	Reference	Reference
Multiple	108	15	13.9	0.88 (0.51–1.52)	0.95 (0.54–1.68)
Unknown	43	5	11.6	0.72 (0.28–1.83)	1.40 (0.52–3.77)
Previous miscarriage					
Yes	931	147	15.8	1.04 (0.85–1.27)	1.04 (0.84–1.28)
No	3090	474	15.3	Reference	Reference

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Character	# T1NVP	# Treatment for T1NVP	% Treated	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Any smoking B1–T1					
Yes	715	116	16.2	1.07 (0.86–1.34)	1.03 (0.81–1.31)
No	3305	505	15.3	Reference	Reference
Unknown	1	0	0.0	-	-
BMI					
< 18.5	216	30	13.9	0.92 (0.62–1.38)	0.95 (0.63–1.43)
18.5 ≤ BMI < 25	2181	325	14.9	Reference	Reference
25 ≤ BMI < 30	845	132	15.6	1.06 (0.85–1.32)	1.07 (0.85–1.33)
> 30	618	118	19.1	1.35 (1.07–1.70)	1.32 (1.04–1.68)
Unknown	161	16	9.9	0.63 (0.37–1.07)	0.85 (0.48–1.52)
Infant sex					
Female	2056	323	15.7	Reference	Reference
Male	1962	298	15.2	0.96 (0.81–1.14)	0.95 (0.80–1.13)
Unknown	3	0	0.0	-	-
Any use of folic acid B1–T1					
Yes	3480	530	15.2	Reference	Reference
No	461	70	15.2	1.00 (0.76–1.31)	1.16 (0.87–1.54)
Unknown	80	21	26.3	1.98 (1.19–3.29)	2.24 (1.33–3.77)
Study site					
Arkansas	476	112	23.5	1.58 (1.14–2.20)	1.50 (1.06–2.13)
California	539	73	13.5	0.81 (0.57–1.15)	0.98 (0.67–1.43)
Georgia	436	71	16.3	Reference	Reference
Iowa	454	70	15.4	0.94 (0.65–1.34)	0.84 (0.57–1.24)
Massachusetts	490	65	13.3	0.79 (0.55–1.13)	0.72 (0.49–1.05)
New Jersey	383	34	8.9	0.50 (0.32–0.77)	0.52 (0.33–0.83)
New York	365	40	11.0	0.63 (0.42–0.96)	0.60 (0.39–0.92)
Texas	470	73	15.5	0.95 (0.66–1.35)	1.21 (0.82–1.79)
North Carolina[b]	204	40	19.6	1.26 (0.82–1.93)	1.12 (0.70–1.78)
Utah[b]	204	43	21.1	1.37 (0.90–2.09)	1.14 (0.71–1.82)
Year of due date					

Character	# T1NVP	# Treatment for T1NVP	% Treated	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
1997	78	14	17.9	0.85 (0.46–1.57)	0.95 (0.51–1.79)
1998	499	66	13.2	0.59 (0.43–0.82)	0.66 (0.47–0.94)
1999	576	78	13.5	0.61 (0.45–0.83)	0.68 (0.49–0.94)
2000	594	73	12.3	0.55 (0.40–0.75)	0.60 (0.43–0.84)
2001	539	76	14.1	0.64 (0.47–0.87)	0.73 (0.52–1.02)
2002	486	82	16.9	0.79 (0.58–1.08)	0.90 (0.65–1.25)
2003	632	106	16.8	0.79 (0.59–1.05)	0.76 (0.57–1.02)
2004	617	126	20.4	Reference	Reference

NVP=nausea and vomiting of pregnancy, B1= month before conception, T1=trimester one, BMI=body mass index

[a] Adjusted for the variables in the table.

[b] North Carolina and Texas joined the NBDPS in 2002.

Table 2

Relationship between nausea and vomiting of pregnancy in the first trimester and selected birth defects, National Birth Defects Prevention Study 10/97–12/04

Defect	N[a]	% T1 NVP	Crude OR (CI)	Adjusted OR[b] (CI)
CL/P	1,546	64.5	0.83 (0.74–0.93)	0.87 (0.76–0.98)
CP	821	67.0	0.93 (0.79–1.08)	0.93 (0.80–1.09)
NTD	1,038	69.1	1.02 (0.89–1.18)	1.00 (0.86–1.16)
Controls	5,859	68.6	Reference	Reference
Hypospadias[c]	1,144	60.5	0.77 (0.67–0.88)	0.84 (0.72–0.98)
Male controls	2,946	66.6	Reference	Reference

NVP=nausea and vomiting of pregnancy, T1=trimester 1, CL/P=cleft lip with or without cleft palate, CP=cleft palate only, NTD=neural tube defect

[a] Number of subjects with completed interviews and data on NVP and medication use.

[b] Adjusted for maternal age, race/ethnicity and education, parity, plurality, previous miscarriage, any smoking in the month before conception through the first trimester, body mass index, any use of folic acid in the month before conception through the first trimester, expected year of delivery and site. CL/P, CP, and NTDs are also adjusted for infant sex.

[c] Hypospadias analysis uses only male controls.

Table 3

Odds ratios of cleft lip with or without cleft palate in offspring exposed to selected medications in the first trimester among women with first trimester nausea and vomiting of pregnancy, National Birth Defects Prevention Study 10/97–12/04

	Exposed		Unexposed		Crude		Adjusted[b]	
Medication Exposure[a]	**Cases**	**Controls**	**Cases**	**Controls**	**OR**	**95% CI**	**OR**	**95% CI**
Antihistamine Antiemetics	45	212	888	3797	0.91	0.65–1.26	1.02	0.72–1.44
Promethazine	38	162	885	3847	1.01	0.70–1.45	1.11	0.76–1.63
Other Antihistamine	22	97	911	3912	0.97	0.61–1.56	0.95	0.59–1.55
Diphenhydramine	17	68	916	3941	1.08	0.63–1.84	1.03	0.59–1.79
Cetirizine	6	30	927	3979	0.86	0.36–2.07	0.90	0.36–2.22
Phenothiazines (other than Promethazine)	5	16	928	3993	1.34	0.49–3.68	1.44	0.51–4.12
Prochlorperazine	5	16	928	3993	1.34	0.49–3.68	1.44	0.51–4.12
Prokinetetics	5	18	928	3991	1.19	0.44–3.23	1.44	0.52–4.03
Metoclopramide	4	18	929	3991	0.95	0.32–2.83	1.23	0.40–3.72
5HT3 antagonists	7	46	926	3963	0.65	0.29–1.45	0.83	0.37–1.90
Ondansetron	7	44	926	3965	0.68	0.31–1.52	0.88	0.38–2.00
Antacids	27	198	906	3811	0.57	0.38–0.86	0.58	0.38–0.89
Calcium Carbonate	21	153	912	3856	0.58	0.37–0.93	0.59	0.37–0.96
H2 Blockers	4	29	929	3980	0.59	0.21–1.69	0.57	0.19–1.67
Pyridoxine	19	99	914	3910	0.82	0.50–1.35	1.02	0.61–1.71
Steroids	6	15	927	3994	1.72	0.67–4.45	1.72	0.64–4.59
Herbal/Natural products	22	117	911	3892	0.80	0.51–1.27	0.86	0.53–1.39
Ginger	5	18	928	3991	1.19	0.44–3.23	1.49	0.54–4.15

[a] Used alone or in combination with other agents; categories are not mutually exclusive. Missing data on medication exposure (<0.7% of subjects) were grouped with the unexposed.

[b] Adjusted for maternal age, race/ethnicity and education, parity, plurality, previous miscarriage, any smoking in the month before conception through the first trimester, body mass index, infant sex, any folic acid use in the month before conception through the first trimester, use of unknown antiemetic, site, and expected year of delivery. N=933 CL/P cases (833 (89.3%) isolated and 100 (10.7%) multiple defects) and 4009 controls.

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Table 4

Odds ratios of cleft palate in offspring exposed to selected medications in the first trimester among women with first trimester nausea and vomiting of pregnancy, National Birth Defects Prevention Study 10/97–12/04

	Exposed		Unexposed		Crude		Adjusted[b]	
Medication Exposure[a]	**Cases**	**Controls**	**Cases**	**Controls**	**OR**	**95% CI**	**OR**	**95% CI**
Antihistamine Antiemetics	24	212	501	3797	0.86	0.56–1.32	0.92	0.58–1.44
Promethazine	17	162	508	3847	0.79	0.48–1.32	0.80	0.47–1.36
Other Antihistamine	14	97	511	3912	1.10	0.63–1.95	1.20	0.67–2.14
Diphenhydramine	10	69	515	3941	1.11	0.57–2.17	1.19	0.60–2.36
Cetirizine	4	30	521	3979	1.02	0.36–2.90	1.17	0.40–3.43
Prokinetetics	5	18	520	3991	2.13	0.79–5.77	2.36	0.85–6.55
Metoclopramide	5	18	520	3991	2.13	0.79–5.77	2.36	0.85–6.55
5HT3 antagonists	11	46	514	3963	1.84	0.95–3.58	2.29	1.14–4.58
Ondansetron	11	44	514	3965	1.93	0.99–3.76	2.37	1.18–4.76
Antacids	21	198	504	3811	0.80	0.51–1.27	0.70	0.44–1.12
Calcium Carbonate	16	153	509	3856	0.89	0.47–1.34	0.69	0.40–1.17
H2 Blockers	5	29	520	3980	1.32	0.51–3.42	1.04	0.39–2.75
Ranitidine	5	21	520	3988	1.83	0.69–4.86	1.33	0.49–3.61
Proton Pump Inhibitors	5	13	520	3996	2.96	1.05–8.32	2.59	0.88–7.63
Pyridoxine	10	99	515	3910	0.77	0.40–1.48	0.95	0.48–1.87
Herbal/Natural products	15	117	510	3892	0.98	0.57–1.69	0.98	0.56–1.71

[a] Used alone or in combination with other agents; categories are not mutually exclusive. Missing data on medication exposure (<0.7% of subjects) were grouped with the unexposed.

[b] Adjusted for maternal age, race/ethnicity and education, parity, plurality, previous miscarriage, any smoking in the month before conception through the first trimester, body mass index, infant sex, any folic acid use in the month before conception through the first trimester, use of unknown antiemetic, site, and expected year of delivery. N=525 CP cases (421 (80.2%) isolated and 104 (19.8%) multiple defects) and 4009 controls.

Table 5

Odds ratios of neural tube defects in offspring exposed to selected medications in the first trimester among women with first trimester nausea and vomiting of pregnancy, National Birth Defects Prevention Study 10/97–12/04

	Exposed		Unexposed		Crude		Adjusted[b]	
Medication Exposure[a]	**Cases**	**Controls**	**Cases**	**Controls**	**OR**	**95% CI**	**OR**	**95% CI**
Antihistamine Antiemetics	43	211	668	3805	1.16	0.83–1.63	1.24	0.87–1.78
Doxylamine	7	38	704	3978	1.04	0.46–2.34	1.05	0.46–2.43
Promethazine	35	161	676	3855	1.24	0.85–1.80	1.39	0.94–2.06
Other Antihistamine	17	97	694	3919	0.99	0.59–1.67	0.99	0.58–1.71
Diphenhydramine	16	68	695	3947	1.32	0.76–2.28	1.32	0.74–2.34
antihistamine antiemetics plus B6 combinations:								
Doxylamine plus pyridoxine	6	19	705	3997	1.78	0.71–4.45	1.84	0.71–4.78
Phenothiazines (other than Promethazine)	4	16	707	4000	1.41	0.47–4.24	1.59	0.51–4.96
Prochlorperazine	4	16	707	4000	1.41	0.47–4.24	1.59	0.51–4.96
5HT3 antagonists	4	46	707	3970	0.49	0.18–1.36	0.58	0.21–1.64
Ondansetron	4	44	707	3972	0.51	0.18–1.43	0.60	0.21–1.68
Emetrol/Coke syrup	5	22	706	3994	1.29	0.49–3.41	1.46	0.54–3.94
Phosphorated Carbohydrate Solution	5	21	706	3995	1.34	0.51–3.58	1.53	0.57–4.16
Bismuth subsalicylate	7	15	704	4001	2.65	1.08–6.53	2.37	0.90–6.21
Antacids	29	198	682	3818	0.82	0.55–1.22	0.92	0.61–1.39
Calcium Carbonate	20	153	691	3863	0.73	0.46–1.17	0.87	0.54–1.42
Aluminum Magnesium Hydroxide/Simethicone	4	29	707	3987	0.78	0.27–2.22	0.61	0.19–1.96
H2 Blockers	8	29	703	3987	1.56	0.71–3.44	1.80	0.80–4.05
Ranitidine	4	21	707	3995	1.08	0.37–3.14	1.28	0.43–3.82
Pyridoxine	14	98	697	3918	0.80	0.46–1.41	0.75	0.42–1.34
Herbal/Natural products	22	119	689	3897	1.05	0.66–1.66	1.14	0.70–1.83

[a] Used alone or in combination with other agents; categories are not mutually exclusive. Missing data on medication exposure (<0.7% of subjects) were grouped with the unexposed.

[b] Adjusted for maternal age, race/ethnicity and education, parity, plurality, previous miscarriage, any smoking in the month before conception through the first trimester, body mass index, infant sex, any folic acid use in the month before conception through the first trimester, use of unknown antiemetic, site, and expected year of delivery. N=711 NTD cases (634 (89.2%) isolated, 76 (10.7%) multiple, and 1 (0.1%) complex defects) and 4016 controls.

Table 6

Odds ratios of hypospadias in offspring exposed to selected medications in the first trimester among women with first trimester nausea and vomiting of pregnancy, National Birth Defects Prevention Study 10/97–12/04

	Exposed		Unexposed		Crude		Adjusted[b]	
Medication Exposure[a]	**Cases**	**Controls**	**Cases**	**Controls**	**OR**	**95% CI**	**OR**	**95% CI**
Antihistamine Antiemetics	26	107	629	1849	0.71	0.46–1.11	0.68	0.43–1.09
Promethazine	21	78	634	1878	0.80	0.49–1.30	0.78	0.46–1.31
Other Antihistamine	19	54	636	1902	1.05	0.62–1.79	1.05	0.59–1.85
Diphenhydramine	11	37	644	1919	0.89	0.45–1.75	1.00	0.49–2.07
Cetirizine	8	17	647	1939	1.41	0.61–3.28	1.12	0.44–2.84
Prokinetetics	6	9	649	1947	2.00	0.71–5.65	1.17	0.39–3.55
Metoclopramide	6	9	649	1947	2.00	0.71–5.65	1.17	0.39–3.55
5HT3 antagonists	5	19	650	1937	0.78	0.29–2.11	0.55	0.19–1.53
Ondansetron	5	18	650	1938	0.83	0.31–2.24	0.57	0.20–1.60
Emetrol/Coke syrup	6	15	649	1941	1.20	0.46–3.10	1.05	0.38–2.87
Phosphorated Carbohydrate Solution	5	15	650	1941	1.00	0.36–2.75	0.94	0.32–2.72
Antacids	40	90	615	1866	1.35	0.92–1.98	0.66	0.43–1.02
Calcium Carbonate	34	68	621	1888	1.52	1.00–2.32	0.73	0.45–1.18
H2 Blockers	7	15	648	1941	1.40	0.57–3.44	1.07	0.41–2.83
Ranitidine	4	11	651	1945	1.09	0.34–3.42	0.70	0.20–2.41
Proton Pump Inhibitors	7	5	648	1951	4.22	1.33–13.33	4.36	1.21–15.81
Pyridoxine	8	48	647	1908	0.49	0.23–1.04	0.56	0.25–1.24
Steroids	10	8	645	1948	3.78	1.48–9.61	2.87	1.03–7.97
Herbal/Natural products	30	50	625	1906	1.83	1.15–2.90	1.52	0.92–2.52
Ginger	4	9	651	1947	1.33	0.41–4.33	0.89	0.23–3.36
Herbal/Folk remedy	4	5	651	1951	2.40	0.64–8.96	2.26	0.56–9.10

[a] Used alone or in combination with other agents; categories are not mutually exclusive. Missing data on medication exposure (<0.7% of subjects) were grouped with the unexposed.

[b] Adjusted for maternal age, race/ethnicity and education, parity, plurality, previous miscarriage, any smoking in the month before conception through the first trimester, body mass index, any folic acid use in the month before conception through the first trimester, use of unknown antiemetic, site, and expected year of delivery. N=655 hypospadias cases (599 (91.5%) isolated and 56 (8.5%) multiple defects) and 1956 male controls.