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Maternal Medication and Herbal Use and Risk for Hypospadias: Data from the National Birth Defects Prevention Study, 1997--2007

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Abstract

Purpose—Investigate associations between maternal use of common medications and herbals during early pregnancy and risk for hypospadias in male infants.

Methods—We used data from the National Birth Defects Prevention Study, a multi-site, population-based, case-control study. We analyzed data from 1,537 infants with second-or third-degree isolated hypospadias and 4,314 liveborn male control infants without major birth defects, with estimated dates of delivery from 1997–2007. Exposure was reported use of prescription or over-the-counter medications or herbal products, from 1 month before to 4 months after conception. Adjusted odds ratios (aORs) and 95% confidence intervals (CI) were estimated using multivariable logistic regression, adjusting for maternal age, race/ethnicity, education, pre-pregnancy BMI, previous live births, maternal sub-fertility, study site, and year.

Results—We assessed 64 medication and 24 herbal components. Maternal uses of most components were not associated with an increased risk of hypospadias. Two new associations were observed for venlafaxine (aOR 2.4; 95% CI 1.0, 6.0) and progestin only oral contraceptives (aOR 1.9, 95% CI 1.1, 3.2). The previously reported association for clomiphene citrate was

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Disclaimers:

- Coding of drug information in the National Birth Defects Prevention Study used the Slone Drug Dictionary under license from the Slone Epidemiology Center at Boston University.
- The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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confirmed (aOR 1.9, 95% CI 1.2, 3.0). Numbers were relatively small for exposure to other specific patterns of fertility agents, but elevated aORs were observed for the most common of them.

Conclusions—Overall, findings were reassuring that hypospadias is not associated with most medication components examined in this analysis. New associations will need to be confirmed in other studies. Increased risks for hypospadias associated with various fertility agents raises the possibility of confounding by underlying subfertility.

Article Keywords

medication; herbal; pregnancy; hypospadias; birth defects; drug safety

INTRODUCTION

Medication use is highly prevalent among pregnant women, despite the fact that few data exist on risks or safety of most medications.[1–5] In the United States, more than 80% of pregnant women reported taking over-the-counter (OTC) or prescription drugs during pregnancy,[3,6] and the overall prevalence of herbal use anytime during pregnancy was recently estimated at 9.4%.[7] While medications can be necessary during pregnancy, they can pose a potential risk to both mother and fetus. Pregnancy is associated with physiologic and pharmacokinetic changes that potentially alter the dosing, effectiveness, and ultimately, the safety of many drugs.[4]

Hypospadias, one of the most common birth defects in the United States (~5/1,000 live male births[8]), is a birth defect in male infants in which the urethral opening forms abnormally during weeks 8 to 14 following conception. Degrees of hypospadias range from minor (first degree) to severe (second or third degree). Hypospadias has been associated with a wide range of endocrine, genetic, and environmental factors (e.g. androgen metabolism abnormalities, chromosome abnormalities, single gene mutations, family history of hypospadias, low birth weight, maternal reproductive and demographic characteristics, maternal and paternal sub-fertility, and exposure to endocrine disruptors).[9,10] In addition, use of certain medications in pregnancy has been observed to be associated with risk for hypospadias in previous studies.[11–14]

The objective of this study was to conduct an exploratory analysis to assess associations between maternal use of common medication components and certain combinations, including prescription, over-the-counter, and herbal preparations, during the periconceptional period and early pregnancy and the risk for second- or third-degree hypospadias in male infants.

METHODS

Study Population and Data Collection

The National Birth Defects Prevention Study (NBDPS) is an ongoing, multi-site, population-based, case-control study coordinated by the Centers for Disease Control and Prevention (CDC) that seeks to identify risk factors associated with more than 30 selected

categories of major birth defects. Data have been contributed by 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah), using a standardized protocol. The study was approved by the institutional review boards of the participating study centers and by CDC, and participants provided informed consent. Detailed study methods[15] and description of case classification methods[16] have been published elsewhere.

NBDPS uses computer-assisted telephone interviews to collect information from women 6 weeks to 24 months after their estimated date of delivery (EDD). The interview covers a wide range of exposures including maternal health and reproductive characteristics, environmental exposures, and nutritional and behavioral factors.

NBDPS cases are identified through population-based birth defects surveillance. Controls are selected randomly from vital records or birth logs to represent the population from which the birth defects cases were ascertained. NBDPS includes infants with second- or third-degree hypospadias, defined as the urethral opening at the penile shaft, scrotum, or perineum and including modified versions of British Pediatric Association codes: 752.606, 752.607, 752.626, and 752.627; NBDPS excludes first-degree hypospadias. A clinical geneticist classifies eligible cases of hypospadias as isolated, if there was no concurrent major anomaly or only minor anomalies, or multiple, if there was at least one unrelated accompanying major anomaly in another organ system.[16]

This analysis included data on pregnancies with EDDs from October 1, 1997-December 31, 2007. The analysis was restricted to male infants with no major birth defects (controls) and male infants with isolated second- or third-degree hypospadias; isolated cases represented 90.6% of all hypospadias cases and are considered a more etiologically homogeneous group of defects than those associated with additional anomalies.[16–19] We defined exposure as any maternal medication or herbal use from 1 month (30 days) before to 4 months after conception (defined as 266 days before the estimated due date), to capture the period of development for the male urogenital system.[10] We did not require that the medication or herbal components be taken in isolation, and co-exposures were possible and in many cases likely. Because oral contraceptives (OC) and fertility treatments often comprise combinations of components, these combinations were considered rather than the individual components. Due to the way in which mothers were asked about OC, we were only able to consider these exposures through 3 months postconception. The Slone Epidemiology Center Drug Dictionary was used to assign codes for each reported product and to identify the components of each product. We assessed only medication or herbal components for which at least a minimum of one of the salts of the component had 5 exposed mothers of infants with isolated hypospadias. All salt forms for components with multiple salts were then combined. Topicals, vitamins, and minerals were not included in this analysis. If a multi-component product contained topical, vitamin, or mineral components, only the medication or herbal components were considered.

Statistical Analysis

Crude odds ratios (ORs) and adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression. We selected *a priori* the following

covariates to adjust for potential confounding: maternal age (<35/≥35 yr), race/ethnicity (Non-Hispanic White/Non-Hispanic Black/Hispanic/Other), education (<high school/high school/1–3 yr of college/≥4 yr of college), pre-pregnancy body mass index (BMI) (<18.5/18.5–24.9/25.0–29.9/≥30.0 kg/m^2),[20] previous live births (0 births/1 birth/≥2 births), maternal sub-fertility (any fertility-related treatments or procedures used by the mother/ none), study site, and year of due date in two year increments. Fertility agent analyses were not adjusted for maternal sub-fertility, except for progesterone use alone because the majority of reports were for pregnancy complications. Two sub-analyses were performed on elevated crude or adjusted ORs with a lower 95% CI ≥0.95 and on reduced crude or adjusted ORs with a corresponding upper bound ≤1.05 in the primary analyses (i.e. at least borderline statistically significant). The first sub-analysis excluded infants with a positive first degree family history of hypospadias (father, full sibling, or previous pregnancy), due to the increased risk for hypospadias in first-degree male relatives.[10,21,22] Also, given the hypothesis that placental insufficiency is associated with both fetal growth and hypospadias, the second sub-analysis excluded low birth weight infants and multiple births, as done in some previous analyses.[12,23–25] Data management and analysis were performed using the Statistical Package for the Social Sciences (SPSS) software, version 17.0.

RESULTS

There were 1,697 infants with second- or third-degree hypospadias with an EDD from October 1997 to December 2007 in NBDPS. Of these infants, 1,537 (90.6%) had isolated hypospadias. The control group consisted of 4,314 male infants with no major birth defects. One hundred and ninety-six medication or herbal components were identified for which at least one of the salts of the component had 5 exposed cases. Of the 196 medication or herbal components, 109 topicals, vitamins, and minerals were excluded. Thus, 88 components (64 from medication, including 4 combinations, and 24 from herbal products) were assessed for their association with hypospadias.

Comparing the case and control groups, there were many significant differences in maternal and infant characteristics (Table 1). Mothers of infants with isolated hypospadias were significantly more likely than control mothers to be Non-Hispanic White, 35 years of age or older at delivery, have 4 or more years of college, be obese, have pregestational diabetes, have a higher annual family income, have used alcohol during the periconceptional period, have used folic acid during the periconceptional period, be nulliparous, have given birth to multiples, and have used treatments or procedures for sub-fertility. Control mothers were significantly more likely than case mothers to be Hispanic and have used illicit drugs during the periconceptional period. Case infants were significantly more likely than control infants to be delivered preterm, have a low birth weight, and have a family history of hypospadias. There were also differences in the distribution of isolated hypospadias cases and controls by study site and EDD.

After adjusting for maternal age, race/ethnicity, education, pre-pregnancy BMI, previous live births, maternal sub-fertility, study site, and year of due date, most medication and herbal components were not associated with a risk for isolated hypospadias (Table 2). Of the seven analgesic agents examined, aORs were greater than 1.0 for uses of aspirin, meperidine

HCl, and ibuprofen, but only the aOR for ibuprofen was statistically significant (aOR 1.2; 95% CI 1.0, 1.3). Of the five antidepressant agents examined, aORs were close to 1.0 for all but venlafaxine (aOR 2.4; 95% CI 1.0, 6.0). Use of the most common OC, estrogen +progestin, was not associated with hypospadias, whereas use of progestin alone was associated with a nearly twofold increased risk (aOR 1.9; 95% CI 1.1, 3.2). There were 28 different combinations of six fertility agents (clomiphene citrate (CLO), follicle stimulating hormone (FSH), human chorionic gonadotropin (HCG), leuprolide (LEU), progesterone (PRO), and estrogen); six of them were reported frequently enough to estimate aORs. Use of clomiphene citrate alone and FSH+HCG+LEU+PRO were associated with hypospadias; aORs (and 95% CIs) were 1.9 (1.2, 3.0) and 2.2 (1.0, 4.8), respectively.

Of the 83 medication and herbal components and five component combinations considered in the primary analyses, 18 (acetaminophen, aspirin, azithromycin, barley grass, butalbital, progesterone alone, clomiphene citrate alone, FSH+HCG+LEU+PRO, CLO+PRO, FSH +HCG+PRO, FSH+PRO, herbal tea, ibuprofen, labetalol, levothyroxine sodium, phenylpropanolamine, progestin-only OC, and venlafaxine) had at least borderline statistically significant crude or adjusted OR estimates for their association with isolated hypospadias. Overall, sub-analyses in which infants with a positive first degree family history of hypospadias were excluded did not change aOR estimates appreciably (Table 3). Sub-analyses in which low birth weight infants and multiple births were excluded demonstrated results closer to the null relative to the primary analysis for several of the medication components (Table 4), particularly clomiphene citrate (aOR 1.6; 95% CI 0.9, 2.9) and progestin-only OCs. However, in this sub-analysis, the magnitude of the association of isolated hypospadias was much larger for maternal use of venlafaxine (aOR 3.7; 95% CI 1.4, 9.7).

DISCUSSION

The results of this analysis suggest an association between second- or third-degree hypospadias and maternal use during the period of 1 month before to 4 months after conception of ibuprofen, venlafaxine, progestin-only OC, clomiphene citrate alone, and FSH +HCG+LEU+PRO. While findings for the fertility medications are consistent with other studies,[26,27] the progestin-only OC and venlafaxine findings are novel and should be explored in other data sources.

Although only a weak statistically significant association was observed for ibuprofen, future studies could investigate this association because it is a common medication. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that works by decreasing the activity of the enzyme cyclooxygenase (COX), resulting in the inhibition of prostaglandin synthesis.[28] Animal models suggest that the action of testosterone on embryonic genitalia involves prostaglandins and that prenatal exposure to COX inhibitors inhibits masculinization of male genitalia.[29] In another study utilizing NBDPS data from 1997–2004,[30] NSAID use during the first trimester and the risk of birth defects was evaluated; no association was observed for 2nd and 3rd degree hypospadias. There were, however, fewer cases classified as exposed to ibuprofen in that study (n=99) compared to this one (n=423), due to their shorter exposure window, the separation of women who could not characterize the frequency of

NSAID use in the first trimester into a separate “as needed” category, and different exclusion criteria. Excluding the “as needed” exposures from our data did not substantially affect our findings. Our observation of an elevated odds ratio for maternal use of ibuprofen, although statistically significant, is close to the null and, therefore, minor bias or misclassification of exposure could account for the observed slightly increased odds ratio. Although statistically significant, ibuprofen is a more common medication and therefore has higher power (i.e. a modest departure from the null is more likely to be statistically significant).

With the exception of progesterone alone, elevated aORs were observed for the five most common patterns of fertility agent exposures, but numbers were small and lower 95% CIs included 1.0 for all but one. The elevated ORs for exposure to different patterns of fertility agents may be confounded by underlying subfertility, which we were unable to evaluate because these agents are rarely taken for other indications. Subfertility, both maternal and paternal, has been proposed to contribute to a higher risk for hypospadias.[31, 32] In previous analyses of NBDPS data, hypospadias was similarly associated with maternal use of clomiphene citrate alone [27] and use of assisted reproductive technologies overall, but further refinement of fertility agent exposures were not examined.[33] An earlier subset of NBDPS data showed no association for progestin exposure from OCs.[12] That study did not separate OCs comprised of estrogen and progestin from those comprised of progestin alone; the latter formulations were less popular during those years, and their null finding likely corresponds to the present null finding for estrogen/progestin combination OCs. That same study also reported an approximately two-fold increased OR for progesterone taken for sub-fertility or pregnancy complications for women with and without exposure to other fertility agents. In contrast, the OR in the present study was not elevated for progesterone taken without other fertility agents, but ORs were elevated for the five most common combinations of progesterone and other fertility agents.

Another consideration for fertility medications and risk of hypospadias is the possible role for fetal growth, multiple births, and placental insufficiency. Ovulation induction medications are associated with an increased risk for multiple births.[34–37] An increased prevalence of hypospadias has been previously observed in both monozygotic and dizygotic twins.[21] After excluding low birth weight infants and multiple births, ORs were generally similar to those for the primary analysis, suggesting that any effect of these exposures on hypospadias risk is through another pathway than one shared with fetal growth or multiple gestations.

Venlafaxine is a serotonin-norepinephrine reuptake inhibitor used in the treatment of depression and anxiety.[28] Serotonin and norepinephrine play a role in embryologic signaling pathways, and it is therefore plausible that a medication that interacts with these neurotransmitters may affect embryogenesis.[29–30] Despite evidence that there is substantial transfer of venlafaxine across the placenta,[40] there are few published reports describing its use during pregnancy.[41] No association was observed in two small case series (N<40).[42–43] A study by Einarson and colleagues reported that among 150 women exposed to venlafaxine during pregnancy, two babies were born with major malformations, of which one had hypospadias; drug-specific ORs were not estimated.[42] None of these studies was sufficiently

powered to detect an association of the magnitude we observed here (aOR = 2.4; 95% CI = 1.0, 6.0). A recently-published NBDPS analysis reported an association between hypospadias and any periconceptional exposure to venlafaxine, but this association did not remain when concurrent medications were excluded [43].

Several analyses using NBDPS data have been published on the association of a specific medication or herbal and hypospadias. The findings in this analysis are consistent with several other studies in which no significant association between risk for hypospadias and exposure to loratadine,[44] certain antibiotics,[45] certain SSRIs,[46] ephedra,[47] certain antihistamines,[48] acetaminophen,[49] bupropion,[50] certain opioid analgesics,[51] certain corticosteroids,[23] or certain antihypertensives[50] were observed. Our results are also consistent with the positive association reported for hypospadias and proton pump inhibitors, which included lansoprazole and ompeprazole.[11] We examined each agent separately, producing greater than 2.8-fold increased aORs with lower 95% CIs that included 1.0.

This study had several strengths. The data came from a large, population-based study that allowed for sufficient statistical power to analyze numerous medication and herbal exposures during the critical period for male urethral development. The multi-center study design provided geographic diversity. There was consistent and detailed case ascertainment, with cases reviewed and classified by clinical geneticists, allowing for exclusion of defects with genetic etiologies and restriction to isolated hypospadias cases.

The study has several limitations. Maternal medication and herbal use was not exclusive and mothers may have been using multiple medications or herbals concurrently. Many of the medication and herbal exposures were in multiple component products; however the analysis was on the component level, not combined product level other than for fertility agents and some OCs, for which nearly all use is in a combination. Furthermore, confounding by indication is a potential limitation, due to our inability to separate effects of the underlying conditions from those of the medications used. Inability to examine dose of medications or herbals is a limitation. While overall this was a large study, there were a small number of exposed infants for some medication and herbal components, which could affect the robustness of results. Medication and herbal exposures were determined by maternal report; hence exposure misclassification is another potential limitation of the study. To improve recall, NBDPS mothers were provided with a pregnancy calendar before the interview to help them respond to questions about the timing of exposure more accurately. Some medications and herbals were specifically queried, while others were reported as treatment for reported maternal medical conditions. With 88 different medication and herbal components and combinations examined in this analysis, another limitation is multiple testing. Given the exploratory nature of the analyses, the aim of these results is to help generate hypotheses for future analyses. Also, there are still many medications and herbals that were not evaluated and these results therefore cannot be used to make generalized statements about the overall risk of maternal medication and herbal use on hypospadias. In addition, there were some substantial differences in rates of second -degree hypospadias by study site. Definitive descriptions of the type of hypospadias were often not available at the time of initial case ascertainment. The extent of clinical follow-up information from

providers and referral hospitals was variable across study sites, therefore infants whose type of hypospadias was not specified were excluded from NBDPS more frequently at some sites. We attempted to address the differences in hypospadias ascertainment by adjusting for study site in the analyses. A sub-analysis in which the study sites were stratified into two groups, high ascertainment and lower ascertainment, resulted in numbers too small to interpret any differences. Finally, because the study population was limited to infants with isolated second- or third-degree hypospadias it was not possible to examine potential associations between specific medication or herbal exposures and milder forms of hypospadias.

In conclusion, most of the medication and herbal components examined in this analysis were not associated with an increased risk for isolated second- or third-degree hypospadias in male infants, with the exception of progestin-only OCs, clomiphene citrate alone, FSH +HCG+LEU+PRO, ibuprofen, and venlafaxine. Future studies on the associations observed here, on combinations of medications not assessed in this analysis, and on medications and herbals not included in this study are warranted. Further investigation into medications and herbals associated with a risk for hypospadias will allow clinicians and women of childbearing age to make more informed decisions regarding clinical management of maternal conditions.

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Key Points

- Most of the medication and herbal components examined in this analysis were not associated with an increased risk for second- or third-degree hypospadias in male infants after adjustment for appropriate confounders.
- Future studies on the associations observed here, between subfertility and its treatments, progestin-only oral contraceptives, and venlafaxine during the periconceptional period and an increased risk for second- or third-degree hypospadias in male infants, are warranted.

Table 1

Descriptive Characteristics of Mothers of Infants with Isolated Second- and Third-Degree Hypospadias (cases) and Male Infants with No Major Birth Defects (controls): National Birth Defects Prevention Study, October 1997 to December 2007

Maternal Characteristic	Cases (*n*= 1537)	Controls (*n*= 4314)	P Value[a]
		N (%)	
Race/Ethnicity			< .001
Non-Hispanic White	1,125 (73.2%)	2,513 (58.3%)	
Non-Hispanic Black	194 (12.6%)	479 (11.1%)	
Hispanic	122 (7.9%)	1,019 (23.6%)	
Other	95 (6.2%)	301 (7.0%)	
Age at Delivery			< .001
<35 yr	1,224 (79.6%)	3,721 (86.3%)	
≥35 yr	313 (20.4%)	593 (13.7%)	
Education			< .001
< High School	117 (7.6%)	756 (17.5%)	
High School	295 (19.2%)	1,047 (24.3%)	
1–3 yr of College	420 (27.3%)	1,125 (26.1%)	
≥4 yr of College	680 (44.2%)	1,309 (30.3%)	
Pre-pregnancy Body Mass Index (kg/m^2)			.003
Underweight (<18.5)	80 (5.2%)	238 (5.5%)	
Normal (18.5–24.9)	824 (53.6%)	2,272 (52.7%)	
Overweight (25.0–29.9)	341 (22.2%)	938 (21.7%)	
Obese (≥30.0)	257 (16.7%)	674 (15.6%)	
Pregestational Diabetes			.03
Yes	16 (1.0%)	22 (0.5%)	
No	1411 (91.8%)	3983 (92.3%)	
Annual Family Income			< .001
<$10,000	149 (9.7%)	793 (18.4%)	
$10,000–$50,000	533 (34.7%)	1764 (40.9%)	
>$50,000	756 (49.2%)	1324 (30.7%)	
Cigarette Smoking[b]			.42
Yes	265 (17.2%)	809 (18.8%)	
No	1248 (81.2%)	3,441 (79.8%)	
Alcohol Use[b]			< .001
Yes	656 (42.7%)	1583 (36.7%)	
No	847 (55.1%)	2644 (61.3%)	
Maternal Illicit Drug Use[b]			.02
Yes	50 (3.3%)	202 (4.7%)	
No	1487 (96.7%)	4,112 (95.3%)	
Folic Acid-Containing Supplement Use[c]			.002

Maternal Characteristic	Cases (*n*= 1537)	Controls (*n*= 4314)	P Value[a]
Yes	1,400 (91.1%)	3,813 (88.4%)	
No	129 (8.4%)	485 (11.2%)	
Previous Live Births			< .001
0 births	816 (53.1%)	1,729 (40.1%)	
1 birth	454 (29.5%)	1,419 (32.9%)	
≥2 births	260 (16.9%)	1,157 (26.8%)	
Plurality			< .001
Singleton	1,416 (92.1%)	4,182 (96.9%)	
Multiple	119 (7.7%)	123 (2.9%)	
Maternal Subfertility Treatments and Procedures			< .001
None	1,373 (89.3%)	4,121 (95.5%)	
Any	157 (10.2%)	180 (4.2%)	
Study Site			< .001
Arkansas	209 (13.6%)	539 (12.5%)	
California	68 (4.4%)	523 (12.1%)	
Georgia	212 (13.8%)	459 (10.6%)	
Iowa	84 (5.5%)	473 (11.0%)	
Massachusetts	335 (21.8%)	534 (12.4%)	
New Jersey	286 (18.6%)	258 (6.0%)	
New York	92 (6.0%)	383 (8.9%)	
North Carolina	124 (8.1%)	312 (7.2%)	
Texas	28 (1.8%)	530 (12.3%)	
Utah	99 (6.4%)	303 (7.0%)	
Year of Due Date			.01
1997–1999	280 (18.2%)	839 (19.4%)	
2000–2001	348 (22.6%)	853 (19.8%)	
2002–2003	250 (16.3%)	855 (19.8%)	
2004–2005	346 (22.5%)	894 (20.7%)	
2006–2007	310 (20.2%)	872 (20.2%)	
Infant Characteristics			
Preterm Birth (<37 weeks)			< .001
Yes	375 (24.4%)	407 (9.4%)	
No	1141 (74.2%)	3,906 (90.5%)	
Low Birth Weight (<2,500 g)			< .001
Yes	380 (24.7%)	241 (5.6%)	
No	1,137 (74.0%)	4,055 (94.0%)	
Family History of Hypospadias[d]			< .001
Yes	74 (4.8%)	9 (0.2%)	
No	1463 (95.2%)	4305 (99.8%)	

[a] P values were calculated by Pearson's chi-square test.

[b] Any time 1 month preconception through month 3 postconception.

[c] Any time 1 month preconception through month 4 postconception.

[d] Family history of hypospadias in a first degree relative (father or full sibling) or mother's previous pregnancy.

Table 2

Association of Isolated Second- or Third-Degree Hypospadias with Periconceptional Maternal Medication Use[a], National Birth Defects Prevention Study, October 1997 to December 2007.

Medication Exposure	Exposed Cases (*Total cases*=1537)	Exposed Controls (*Total controls*=4314)	OR (95% CI)	Adjusted OR[b] (95% CI)
Antihistamines, First Generation				
Chlorpheniramine	37	78	1.4 (0.9, 2.0)	1.4 (0.6, 2.1)
Diphenhydramine	38	99	1.1 (0.7, 1.6)	1.0 (0. 7, 1.5)
Doxylamine succinate	27	68	1.1 (0.7, 1.8)	1.0 (0.6, 1.6)
Promethazine	46	148	0.9 (0.6, 1.2)	0.8 (0. 6, 1.1)
Antihistamines, Second Generation				
Cetirizine HCl	21	46	1.3 (0.8, 2.2)	1.0 (0.6, 1.7)
Fexofenadine HCl	22	39	1.6 (0.9, 2.7)	1.1 (0.7, 2.0)
Loratadine	46	98	1.3 (0.9, 1.9)	1.1 (0.8, 1.6)
Antibiotics				
Amoxicillin trihydrate	85	233	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)
Azithromycin	19	70	0.8 (0.5, 1.3)	0.6 (0.4, 1.1)
Cephalexin	10	34	0.8 (0.4, 1.7)	0.9 (0.4, 1.8)
Nitrofurantoin	28	68	1.2 (0.8, 1.8)	1.3 (0.8, 2.1)
Sulfamethoxazole	15	38	1.1 (0.6, 2.0)	1.1 (0.6, 2.0)
Trimethoprim	15	38	1.1 (0.6, 2.0)	1.1 (0.6, 2.0)
Alpha/Beta Agonists				
Phenylpropanolamine	11	14	**2.2 (1.0, 4.9)**	2.0 (0.9, 4.8)
Pseudoephedrine	148	392	1.1 (0.9, 1.3)	0.9 (0.7, 1.1)
Alpha-Adrenergic Agonists				
Phenylephrine	8	14	1.6 (0.7, 3.9)	1.6 (0.6, 4.1)
Analgesics				
Acetaminophen	956	2514	**1.2 (1.1, 1.4)**	1.0 (0.8, 1.1)
Aspirin	93	187	**1.4 (1.1, 1.8)**	1.3 (0.9, 1.7)
Codeine	14	42	0.9 (0.5, 1.7)	0.9 (0.4, 1.6)
Ibuprofen	423	945	**1.4 (1.2, 1.6)**	**1.2 (1.0, 1.3)**
Meperidine HCl	9	21	1.2 (0.6, 2.6)	1.2 (0.5, 2.6)
Naproxen sodium	77	179	1.2 (0.9, 1.6)	1.0 (0.7, 1.3)
Oxycodone	12	21	1.6 (0.8, 3.3)	1.0 (0.5, 2.3)
Antidepressants				
Bupropion HCl	12	26	1.3 (0.7, 2.6)	1.3 (0.7, 2.7)
Fluoxetine HCl	13	42	0.9 (0.5, 1.6)	0.9 (0.5, 1.7)
Paroxetine	9	29	0.9 (0.4, 1.9)	1.0 (0.5, 2.2)
Sertraline HCl	22	48	1.3 (0.8, 2.2)	1.2 (0.7, 2.1)
Venlafaxine	9	11	**2.3 (1.0, 5.6)**	**2.4 (1.0, 6.0)**
Antidiabetic Agents				
Insulin	12	19	1.8 (0.9, 3.7)	2.1 (0.9, 4.7)

Medication Exposure	Exposed Cases (*Total cases*=1537)	Exposed Controls (*Total controls*=4314)	OR (95% CI)	Adjusted OR[b] (95% CI)
Metformin	7	13	1.5 (0.6, 3.8)	0.8 (0.3, 2.2)
Barbiturates				
Butalbital	8	8	**2.8 (1.1, 7.5)**	2.1 (0.7, 5.8)
Beta$_2$-Adrenergic Agonists				
Albuterol sulfate	49	122	1.1 (0.8, 1.6)	1.1 (0.8, 1.6)
Salmeterol xinafoate	12	20	1.7 (0.8, 3.5)	1.7 (0.8, 3.6)
Cardiovascular Agents				
Atenolol	5	10	1.4 (0.5, 4.1)	1.0 (0.3, 3.3)
Labetalol	9	6	**4.2 (1.5, 11.9)**	2.6 (0.9, 7.7)
Methyldopa	9	21	1.2 (0.6, 2.6)	1.1 (0.4, 2.5)
CNS Stimulants				
Caffeine	27	52	1.5 (0.9, 2.4)	1.1 (0.7, 1.8)
Fertility Agents				
Progesterone only*	46	71	**1.8 (1.3, 2.7)**	1.1 (0.7, 1.7)
Clomiphene only	38	43	**2.5 (1.6, 3.9)**	**1.9 (1.2, 3.0)**
FSH+HCG+LEU+PRO	17	11	**4.4 (2.1, 9.4)**	**2.2 (1.0, 4.8)**
Clomiphene+PRO	10	10	**2.8 (1.2, 6.8)**	2.0 (0.8, 5.0)
FSH+HCG+PRO	10	7	**4.0 (1.5, 10.6)**	1.7 (0.6, 4.7)
FSH+PRO	7	6	**3.3 (1.1, 9.8)**	1.7 (0.5, 5.4)
GI, Antiemetics				
Ondansetron HCl	23	45	1.4 (0.9, 2.4)	1.0 (0.6, 1.7)
GI, Antiflatulants				
Simethicone	12	33	1.0 (0.5, 2.0)	0.7 (0.3, 1.4)
GI, Antiulcer Agents and Acid Suppressants				
Lansoprazole	6	6	2.8 (0.9, 8.7)	2.8 (0.8, 9.8)
Omeprazole	5	5	2.8 (0.8, 9.8)	2.9 (0.7, 11.3)
Ranitidine HCl	11	27	1.2 (0.6, 2.3)	0.9 (0.4, 1.9)
GI, Digestants				
Betaine	5	20	0.7 (0.3, 1.9)	0.7 (0.2, 1.8)
GI, Prokinetic Agents				
Metoclopramide	10	21	1.3 (0.6, 2.9)	1.0 (0.5, 2.3)
Herbals				
Alfalfa	7	22	0.9 (0.4, 2.1)	0.7 (0.3, 1.6)
Allium sativum, herb	9	25	1.0 (0.5, 2.2)	0.9 (0.4, 2.1)
Angelica polymorpha	8	22	1.0 (0.5, 2.3)	0.8 (0.3, 1.8)
Barley grass	10	10	**2.8 (1.2, 6.8)**	2.1 (0.8, 5.4)
Bee pollen	11	29	1.1 (0.5, 2.1)	1.1 (0.5, 2.2)
Bioflavonoid	19	47	1.1 (0.7, 2.0)	0.8 (0.5, 1.5)
Compound				
Cranberry Concentrate	6	9	1.9 (0.7, 5.3)	1.6 (0.6, 4.6)
Echinacea	11	22	1.4 (0.7, 2.9)	1.2 (0.6, 2.7)

Medication Exposure	Exposed Cases (*Total cases*=1537)	Exposed Controls (*Total controls*=4314)	OR (95% CI)	Adjusted OR[b] (95% CI)
Ephedra	8	28	0.8 (0.4, 1.8)	1.0 (0. 5, 2.4)
Ginger	17	43	1.1 (0.6, 2.0)	1.0 (0.6, 1.9)
Ginkgo biloba extract	8	13	1.7 (0.7, 4.2)	1.6 (0.6, 4.4)
Ginseng	10	20	1.4 (0.7, 3.0)	1.4 (0.6, 3.2)
Herbal tea	17	35	1.4 (0.8, 2.5)	**1.8 (1.0, 3.5)**
Hesperidin Complex	5	6	2.4 (0.7, 7.7)	2.1 (0.6, 7.1)
Hydrastis canadensis	6	12	1.4 (0.5, 3.8)	1.6 (0.6, 4.5)
Hypericum perforatum	5	6	2.4 (0.7, 7.7)	1.7 (0.5, 5.9)
Peppermint	5	13	1.1 (0.4, 3.0)	0.8 (0.3, 2.3)
Raspberry leaf	18	33	1.5 (0.9, 2.7)	0.9 (0.5, 1.8)
Rutin	9	30	0.8 (0.4, 1.8)	0.7 (0.3, 1.4)
Sarsaparilla root	5	8	1.8 (0.6, 5.4)	2.3 (0.7, 7.6)
Siberian ginseng	5	13	1.1 (0.4, 3.0)	1.2 (0.4, 3.5)
Spirulina	11	26	1.2 (0.6, 2.4)	0.9 (0.4, 1.8)
Thea sinesis	12	32	1.1 (0.5, 2.1)	0.9 (0.4, 1.8)
Vitis vinifera	8	10	2.3 (0.9, 5.7)	1.9 (0.7, 5.3)
Hormonal Contraceptive Medications				
Estrogen+Progestin[c,d]	70	212	1.0 (0.6, 1.5)	1.0 (0.7, 1.5)
Progestin only[c,e]	29	95	1.1 (0.8, 1.5)	**1.9 (1.1, 3.2)**
Respiratory Agents				
Dextromethorphan	51	113	1.3 (0.9, 1.8)	1.1 (0.7, 1.5)
Guaifenesin	41	120	1.0 (0.7, 1.4)	0.8 (0.6, 1.2)
Steroids, Glucocorticoids				
Budesonide	6	8	2.1 (0.7, 6.1)	1.2 (0.4, 3.7)
Fluticasone	21	39	1.5 (0.9, 2.6)	1.1 (0.6, 2.0)
Prednisone	5	15	0.9 (0.3, 2.6)	0.6 (0.2, 1.7)
Triamcinolone	5	9	1.6 (0.5, 4.7)	1.5 (0.5, 4.9)
Thyroid and Antithyroid Agents				
Levothyroxine sodium	45	71	**1.8 (1.2, 2.7)**	1.3 (0.9, 2.0)
Potassium iodide	67	176	1.1 (0.8, 1.4)	0.8 (0.6, 1.1)
Miscellaneous Therapeutic Agents				
Lactobacillus acidophilus	5	14	1.0 (0.4, 2.8)	0.7 (0.2, 2.0)
Glucosamine	6	3	---	---
Potassium clavulanate	8	18	1.3 (0.5, 2.9)	1.2 (0.5, 2.8)
Royal jelly	10	31	0.9 (0.4, 1.9)	0.8 (0.4, 1.7)

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index.

[a] Medication exposure is reported for the period from 1 month before to 4 months after conception.

[b] Odds ratios are adjusted for maternal age, race/ethnicity, education, pre-pregnancy BMI, previous live births, sub-fertility, study site, and year of due date. Fertility agents other than progesterone alone were not adjusted for sub-fertility.

[*] Progesterone use was reported either for subfertility or for pregnancy complications.

[c] Progestin and estrogen compound exposures are in response to questions during the maternal interview about oral contraceptives only and include only exposures through month 3 postconception.

[d] Progestin and estrogen compounds include combinations of the following estrogen compounds: ethinyl estradiol, estradiol cypionate, and NOS-estrogen; and the following progestin compounds: desogestrel, drosperinone, etonogestrel, levonorgestrel, medroxyprogesterone, norelgestromin, norethnidrone, norgestimate, and progestin NOS

[e] Progestin only medications include levonorgestrel, medroxyprogesterone, norethindrone, and progestin NOS

--- Odds ratios were not estimated for medication components with fewer than 5 exposed controls.

Table 3

Association of Isolated Second- or Third-Degree Hypospadias with Maternal Periconceptional Use of Specific Medications, Excluding Infants with a Positive First Degree Family History, National Birth Defects Prevention Study, October 1997 to December 2007.[a,b]

Medication/Herbal Exposure	Exposed Cases (*Total cases* =1463)	Exposed Controls (*Total cases*=4305)	aOR[c] (95% CI) Sub-Analysis	aOR (95% CI) Primary Analysis
Acetaminophen	895	2507	0.9 (0.8, 1.1)	1.0 (0.8, 1.1)
Aspirin	90	186	**1.3 (1.0, 1.7)**	1.3 (0.9, 1.7)
Azithromycin	19	70	0.7 (0.4, 1.1)	0.6 (0.4, 1.1)
Barley grass	8	10	1.7 (0.6, 4.4)	2.1 (0.8, 5.4)
Butalbital	8	8	2.2 (0.8, 6.1)	2.1 (0.7, 5.8)
Progesterone only[d]	42	71	1.1 (0.7, 1.6)	1.1 (0.7, 1.7)
Clomiphene only	35	43	**1.7 (1.1, 2.8)**	**1.9 (1.2, 3.0)**
FSH+HCG+LEU+PRO	17	11	**2.3 (1.0, 5.0)**	**2.2 (1.0, 4.8)**
CLO+PRO	10	10	2.1 (0.8, 5.3)	2.0 (0.8, 5.0)
FSH+HCG+PRO	10	7	1.8 (0.7, 5.0)	1.7 (0.6, 4.7)
FSH+PRO	6	6	1.6 (0.5, 5.4)	1.7 (0.5, 5.4)
Herbal tea	16	35	1.8 (0.9, 3.5)	**1.8 (1.0, 3.5)**
Ibuprofen	403	942	**1.2 (1.0, 1.4)**	**1.2 (1.0, 1.3)**
Labetalol	9	6	2.7 (0.9, 8.0)	2.6 (0.9, 7.7)
Levothyroxine sodium	43	71	1.3 (0.9, 2.0)	1.3 (0.9, 2.0)
Phenylpropanolamine	10	14	1.9 (0.8, 4.7)	2.0 (0.9, 4.8)
Progestin-only oral contraceptives	29	95	**2.0 (1.2, 3.4)**	**1.9 (1.1, 3.2)**
Venlafaxine	9	11	**2.5 (1.0, 6.3)**	**2.4 (1.0, 6.0)**

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval

[a] Medication exposure is reported for the period from 1 month before to 4 months after conception.

[b] Family history of hypospadias in a first degree relative (father or full sibling) or mother's previous pregnancy.

[c] Odds ratios were adjusted for maternal age, race/ethnicity, education, pre-pregnancy BMI, previous live births, sub-fertility, study site, and year of due date. Fertility agents were not adjusted for sub-fertility.

[d] Progesterone use was reported either for subfertility or for pregnancy complications.

Table 4

Association of Isolated Second- or Third-Degree Hypospadias with Maternal Periconceptional Use of Specific Medications, Excluding Low Birth Weight Infants and Multiple Births, National Birth Defects Prevention Study, October 1997 to December 2007.[a]

Medication/Herbal Exposure	Exposed Cases (Total *cases*=1108)	Exposed Controls (*Total cases*=3978)	aOR[b] (95% CI) Sub-Analysis	aOR (95% CI) Primary Analysis
Acetaminophen	701	2318	1.0 (0.8, 1.1)	1.0 (0.8, 1.1)
Aspirin	61	164	1.2 (0.9, 1.7)	1.3 (0.9, 1.7)
Azithromycin	18	66	0.7 (0.4, 1.3)	0.6 (0.4, 1.1)
Barley grass	6	10	1.7 (0.6, 4.8)	2.1 (0.8, 5.4)
Butalbital	5	8	1.5 (0.5, 4.8)	2.1 (0.7, 5.8)
Progesterone only[c]	33	59	1.3 (0.8, 2.1)	1.1 (0.7, 1.7)
Clomiphene only	20	34	1.6 (0.9, 2.9)	**1.9 (1.2, 3.0)**
FSH+HCG+LEU+PRO	3	4	---	**2.2 (1.0, 4.8)**
CLO+PRO	6	8	1.6 (0.5, 4.9)	2.0 (0.8, 5.0)
FSH+HCG+PRO	5	3	---	1.7 (0.6, 4.7)
FSH+PRO	2	5	---	1.7 (0.5, 5.4)
Herbal tea	10	32	1.7 (0.8, 3.7)	**1.8 (1.0, 3.5)**
Ibuprofen	309	873	**1.2 (1.0, 1.4)**	**1.2 (1.0, 1.3)**
Labetalol	4	5	---	2.6 (0.9, 7.7)
Levothyroxine sodium	31	61	1.4 (0.9, 2.2)	1.3 (0.9, 2.0)
Phenylpropanolamine	7	13	2.0 (0.7, 5.4)	2.0 (0.9, 4.8)
Progestin-only oral contraceptives	16	89	1.3 (0.7, 2.6)	**1.9 (1.1, 3.2)**
Venlafaxine	9	9	**3. 7 (1.4, 9.7)**	**2.4 (1.0, 6.0)**

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Medication exposure is reported for the period from 1 month before to 4 months after conception.

[b] Odds ratios are adjusted for maternal age, race/ethnicity, education, pre-pregnancy BMI, previous live births, sub-fertility, study site, and year of due date. Fertility agents were not adjusted for sub-fertility.

--- Odds ratios were not estimated for medication components with fewer than 5 exposed cases.

[c] Progesterone use was reported either for subfertility or for pregnancy complications