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Maternal Medication Use and Risk of Hypospadias- An Exposure Spectrum Approach

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MATERNAL MEDICATION USE AND RISK OF HYPOSPADIAS- AN EXPOSURE SPECTRUM APPROACH

by

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APPROVAL PAGE

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ABSTRACT

Purpose To investigate associations between maternal use of selected medications during early pregnancy and the risk of 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 case infants with second or third degree isolated hypospadias and 4,314 male control infants born from 1997-2007. Exposure was based on reported use of any prescription or over-the-counter medication or herbal product, for which there were at least 5 exposed cases, from 1 month before to 4 months after conception, excluding topicals, vitamins, minerals, and products for which the components were unknown. Adjusted odds ratios (aORs) and 95% confidence intervals (CI) were estimated using multivariable logistic regression, adjusting for several confounders.

Results Of the 195 medication components with at least 5 exposed cases, 89 components met the inclusion criteria and were assessed-28 herbal and 61 non-herbal components. Hypospadias was associated with reported use of cephalexin (aOR 3.06; 95% CI 1.02, 9.18), phenylpropanolamine HCl (aOR 2.68; 95% CI 1.06, 6.80), and ibuprofen (aOR 1.16; 95% CI 1.00, 1.34), in primary analyses.

Conclusions We replicated a previously observed association between maternal exposure to phenylpropanolamine HCl and hypospadias. The associations with cephalexin and ibuprofen have not previously been reported. Given the exploratory nature of the analyses, these results should be considered hypothesis-generating. Better understanding of the potential fetal effects will allow clinicians and women of childbearing age to make more informed decisions regarding the use of medications during pregnancy.

INDEX WORDS: medications during pregnancy, hypospadias, birth defects, drug safety

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Lennard J, Lind J, Honeywell M. Advanced technology for fertility prediction. *US Pharmacist*. 2006 Dec;31(12):49-54.

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CHAPTER I
INTRODUCTION

1.1 Background

Birth defects are structural or functional abnormalities that are present at birth and cause physical or mental disability.[1] A structural birth defect results when some part of the body, internal or external, is missing or malformed.[2] Functional birth defects are related to a problem with how a body part or body system works and often lead to developmental disabilities.[1]

Birth defects affect approximately 3% of all live births in the United States and are an important public health issue.[3] Birth defects are a leading cause of infant mortality; in 2008 birth defects contributed to more than 5,600 infant deaths in the U.S., accounting for 20.1% of all infant deaths.[4] Furthermore, birth defects substantially impact health care costs. The cost of lifetime care for infants born in 1992, with one or more of 17 of the most clinically significant structural birth defects in the United States, was an estimated $6 billion.[5]

The causes of approximately 60-70% of birth defects are currently unknown; however genetic and environmental factors have been identified as potential risk factors for some birth defects.[2] Risk factors that have been identified for having a child with a birth defect include maternal age, certain medical conditions, and maternal use of certain medications, illicit drugs, cigarettes, or alcohol during pregnancy.[6]

Some medications are known or strongly suspected teratogens, including thalidomide, isotretinoin, valproic acid, and mycophenolate mofetil. Use of medications that are known to cause birth defects is at times necessary in the treatment of women of childbearing age, for conditions such as epilepsy and immune suppression after organ transplantation.[7] In the United States alone, women of childbearing age receive 11.7 million prescriptions for potentially teratogenic medications each year.[8]

In the United States, medication use is highly prevalent in women of childbearing age, with more than 80% of pregnant women taking over-the-counter (OTC) or prescription drugs during pregnancy, [9] despite the fact that little data exist on risks or safety of most medications used by pregnant women.[10–13] The overall prevalence of herbal use anytime during pregnancy was recently estimated at 9.4%.[14] Unlike prescription and newer OTC medications, herbal products are usually marketed without the benefit of clinical trials to demonstrate either efficacy or safety because under the Dietary Supplement Health and Education Act of 1994, the responsibility for ensuring safety before marketing belongs to manufacturers.[15]

Many pregnant women require drug therapy due to pregnancy-induced conditions such as nausea and vomiting, chronic conditions diagnosed before pregnancy, or acute conditions that develop during pregnancy. However, medication use during pregnancy poses a potential risk to both the mother and the fetus. Pregnancy is associated with physiologic and pharmacokinetic changes that potentially alter the dosing, effectiveness, and ultimately, the safety of many drugs.[11] Use of medications during pregnancy has been associated with an increased risk of many different types of birth defects, including hypospadias, a common birth defect in male offspring.[16–19]

1.2 Purpose of Study

The main objective of this study was to investigate associations between maternal use of selected medications, including prescription, over-the-counter, and herbal preparations, during the periconceptional period and early pregnancy and the risk of second- or third-degree hypospadias in male infants. This analysis will help to identify medications that may increase the risk of hypospadias in males. Identifying medications that may increase the risk of having a baby

with hypospadias will give researchers a better idea of what causes this birth defect and subsequently, findings may help inform directions for future preventive efforts.

1.3 Research Questions

1. Are there associations between maternal use of selected prescription, over-the-counter, and herbal preparations, during the periconceptional period and early pregnancy, and the risk of second- or third-degree hypospadias in male infants?
2. Are there associations between maternal use of prescription, over-the-counter, and herbal preparations, during the periconceptional period and early pregnancy, and the risk of second- or third-degree hypospadias in male infants, after adjusting for potential confounding factors?
3. Are there associations between maternal use of prescription, over-the-counter, and herbal preparations, during the periconceptional period and early pregnancy, and the risk of second- or third-degree hypospadias in male infants, after excluding infants with a positive family history of hypospadias?
4. Are there associations between maternal use of prescription, over-the-counter, and herbal preparations, during the periconceptional period and early pregnancy, and the risk of second- or third-degree hypospadias in male infants, after excluding low birth weight and multiple births?
5. Are there associations between maternal use of prescription, over-the-counter, and herbal preparations, during the periconceptional period and early pregnancy, and the risk of second- or third-degree hypospadias in male infants, after excluding mothers who reported illicit drug use?

CHAPTER II
REVIEW OF THE LITERATURE

In this chapter, support of this study's research questions and variables of interest are synthesized from the scientific literature. The literature review examines hypospadias, including a description of the condition, penile embryology, epidemiology, risk factors and etiology, and medication use during pregnancy and risk of hypospadias.

2.1 Description of Hypospadias

Hypospadias is the result of abnormal development of the penis that leaves the urethral meatus proximal to its normal glanular position anywhere along the penile shaft, scrotum, or perineum.[20] Abnormalities commonly associated with hypospadias include ventral curvature of the penis known as chordee, a "hooded" incomplete prepuce, and an abortive corpora spongiosum.[21]

The term *hypospadias* stems from the Greek words *hypo*, which means "below," and *spadon*, which means "hole."[22] Hypospadias, as a congenital anomaly, was first documented in the medical literature by Heliodurus, Antyllus, and Galen in the 1st and 2nd centuries AD. Greek, Roman, and Egyptian texts from this time period have been found to contain references to hypospadias and hypospadias repairs, with the early writers documenting the abnormal urethral meatus below the corona of the glans and exhibiting concern regarding proper voiding and the ability to procreate.[23]

Hypospadias is classified by the location of the urethral meatus. Meatal position may be classified as anterior or distal, middle, and posterior or proximal, with more anatomically specific subgroups being applied further.[24] Anterior hypospadias is described as glandular, coronal, or distal. Glandular hypospadias is when the meatus is on the ventral surface of the glans penis, in coronal the meatus is in the balanopenile furrow, and distal is when the meatus is

in the distal third of the penile shaft. Middle hypospadias is along the middle third of the penile shaft and posterior hypospadias extends through the proximal third of the penile shaft to the perineum and is described as posterior penile, penoscrotal, scrotal, or perineal. Posterior penile hypospadias is when the meatus is at the base of the shaft, in penoscrotal it is at the base of the shaft in front of the scrotum, in scrotal it is on the scrotum or between the genital swellings, and in perineal it is behind the scrotum or behind the genital swellings.[25]

Hypospadias classification in terms of degrees was described by CK Smith in 1938, in which the first degree locates the meatus from the corona to the distal shaft, the second degree from the distal shaft to the penoscrotal junction, and the third degree is from the penoscrotal junction to the perineum.[26] Classification systems do not take into account the degree of penile curvature or other individual features or anomalies; therefore, they do not always correlate directly with the severity of the condition or extent of surgical repair that might be required.[27]

Treatment of hypospadias consists of surgical repair of the defect to construct a functional and cosmetically sound sexual organ, without penile curvature, and with a repositioned meatus to allow voiding while standing.[20,25,28] Repair can be performed in otherwise healthy infants between 4 -8 months of age as an outpatient procedure.[27] The majority of hypospadias cases can be repaired successfully in one-stage, however in some challenging cases with severe chordee and a proximal meatus, a two-stage repair is required.[20] Ultimately though, the technique used in the treatment of hypospadias is based upon glanular size, degree of chordee, and location of the meatus and must be tailored to the child.[23] Fistula formation, urethral stricture, a proximal meatus, residual curvature, and cosmetic abnormalities are all complications that can result from hypospadias surgery.[28]

2.2 Penile Embryology

The human penis goes through a natural state of hypospadias during its development from a primitive, undifferentiated structure into a fully differentiated penile urethra.[27] Penile and urethral development is a complex developmental process involving genetic programming, cell differentiation, hormonal signaling, enzyme activity, and tissue remodeling.[25]

The hindgut and future urogenital system reach the surface of the embryo at the cloacal membrane on the ventral surface by the end of the first month of gestation. The urorectal septum divides the cloacal membrane into two halves, a posterior or anal half and an anterior half called the urogenital membrane. Three protuberances appear around the urogenital membrane, with the most cephalad protruberance being the genital tubercle and the other two protruberances are the genital swellings that are located on each side of the urogenital membrane.[29]

At 8 weeks gestation, the external genitalia of both male and female embryos are indistinguishable, with both having the midline genital tubercle just above a urogenital membrane, flanked on each side by outer genital swellings and inner urethral folds. The male embryo urogenital system develops during weeks 8 to 14 following ovulation.[27] Masculinization of the external genitalia occurs under the influence of testosterone in response to a surge of luteinizing hormone from the pituitary gland and is signified by an increase in the distance between the anus and genital structures, followed by elongation of the genital tubercle which will become the penile shaft and glans, formation of the penile urethra from the urethral groove, and development of the prepuce.[29] The scrotum is formed when the genital swellings, also known as the labioscrotal folds, migrate caudally and fuse.[27] Fusion of the medial edges of the endodermal urethral folds forms the penile urethra [29] and creates an epithelial seam that is subsequently reabsorbed.[27] Fusion of the ectodermal edges of the urethral groove forms the median raphe.[29]

Two possible mechanisms have been proposed for the development of the distal, or glanular, urethra.[29] The standard theory is that the distal portion of the urethra develops as an ingrowth from the tip of the penis until it joins the proximal tubular urethra; however, recent evidence suggests that the entire urethra is formed from base to tip by continuous extension and fusion of the endodermal urethral groove.[27]

Proper formation of the urethral groove, urethral folds, and fusion of the folds with seam formation and seam removal is required in the development of a normal penile urethra with a meatus at the tip of the glans. Hypospadias results from failed seam formation during the fusion of the urethral folds and the final position of the urethral meatus is dictated by the site of failure.[27]

2.3 Hypospadias Epidemiology

Hypospadias is one of the most common birth defects in the United States. It is estimated that each year hypospadias occurs in approximately 1 in 250 newborns or about 1 out of 125 live male births.[25,30] Non-Hispanic whites appear to be at a higher risk than other racial-ethnic groups for most subgroups of hypospadias,[27] with hypospadias occurring at a reported incidence of 0.3% to 0.8% for white male live births and 0.05% to 0.4% for minority male live births.[31]

In previous years there were reports of increasing rates of hypospadias in industrialized countries. Congenital anomaly surveillance systems in Norway, Sweden, Denmark, England, and Hungary reported upward trends in the birth prevalence of hypospadias in the 1970s and 1980s. In 1997, Paulozzi and colleagues published a study examining data from the Metropolitan Atlanta Congenital Defects Program (MACDP) and the nationwide Birth Defects Monitoring Program (BDMP), to determine whether an increase in the birth prevalence of hypospadias had occurred in the United States. Data from both surveillance systems showed an approximate

doubling of hypospadias rates in the 1970s and 1980s, compared with immediately preceding decades.[30]

The reason that the hypospadias rates doubled over previous years is not known, but recent evidence suggests that the birth prevalence of hypospadias has stabilized in recent years.[27] A retrospective review of data from the New York State Congenital Malformations Registry, from 1992-2005, found no statistical change in hypospadias rates in New York State.[32] And no increase in prevalence of hypospadias was found in California in an analysis of data from the California Birth Defects Monitoring Program (CBDMP) from 1989-1997.[33] Similarly, a retrospective review of discharge records between 1990 and 1998 from 15 military treatment facilities reported no increase in overall incidence of hypospadias.[31]

2.4 Etiology and Risk Factors for Hypospadias

Hypospadias appears to be governed by a wide range of known and unknown endocrine, genetic, and environmental factors, however in the vast majority of individual cases, the specific etiology of hypospadias cannot be determined.[27]

Androgens are essential for normal urogenital development in males. Synthesized by the Leydig cells, androgenic steroids are first seen just before the onset of androgen-induced genital differentiation.[34] Human chorionic gonadotropin (hCG) stimulates the Leydig cells of the fetal testes to produce testosterone, which is then converted to the more active dihydrotestosterone (DHT) by the enzyme 5-α reductase type II.[27] Normal urethral closure is dependent on conversion of testosterone to DHT and proper androgen receptor signaling.[35] Even a partial deficiency of 5-α reductase type II can result in inadequate levels of DHT.[27] Hypospadias anatomy appears to be consistent with incomplete embryologic development due to abnormal androgen production by the fetal testis, limited androgen sensitivity in target tissues of the

developing genitalia, or premature cessation of androgenic stimulation due to early atrophy of the Leydig cells of the testes.[21] Fifty percent of boys with severe forms of hypospadias have defects in one or more of the enzymes required for the biosynthesis of testosterone and 9.7% of boys with isolated hypospadias have been found to have 5-α reductase type II mutations.[27] However, despite these finding, less than 5% of all patients with hypospadias can be explained by androgen metabolism abnormalities such as 5-α reductase type II deficiency, androgen receptor defects, or genetic defects, implying that other factors are responsible for hypospadias.[25,28]

Hypospadias is believed to have a complex genetic background in which gene expression acts along with environmental factors, suggesting a possible mechanism for the well-recognized familial tendency.[21,27] The exact mode of inheritance has not been well defined.[36] Familial clustering is seen in 4-25% of cases and the more severe the malformation of the index patient, the higher the recurrence risk for the next male sibling.[37] About 9% of fathers and 14% of brothers of boys with hypospadias have the condition, as well.[27] An increased incidence of hypospadias has also been seen in both monozygotic and dizygotic twins.[37]

Birth weight has also been found to be significantly associated with hypospadias when genetic effects are controlled.[38] Several epidemiological investigations from different countries have found that low birth weight is associated with approximately twice the risk of hypospadias.[39] In a study by Fredell and colleagues, published in 1998, results showed that in 16 out of 18 discordant monozygotic pairs, the twin with the lowest birth weight had hypospadias. The authors surmised that because hypospadias manifested or was worse in the smaller twin of discordant pairs that it suggests placental inadequacy to provide nutrients for both fetuses or insufficient hCG to meet the demand of two pairs of male gonads, which would affect the

smaller and more sensitive of the two male fetuses.[38] Additionally, hypospadias is 10 times more common among small-for-gestational-age infants in neonatal intensive care than in the general neonatal population[27] Hypospadias is significantly more common in infants with uniformly poor intrauterine growth (<10th percentiles), as measured by birth weight, length, or head circumference.[40]

There also appears to be an association between some maternal reproductive and demographic characteristics and hypospadias risk. Carmichael et al. found that maternal primiparity, age 35 years or older, and a pre-pregnancy BMI greater than 26 are associated with increased risk of hypospadias among offspring, especially when present in combination. It has been hypothesized that increased maternal estrogen levels may be associated with increased hypospadias risk and that maternal age, parity, and BMI may be predictive of the production and action of maternal estrogens.[35]

In addition, sub-fertility, both maternal and paternal, has been proposed to contribute to higher risk of hypospadias.[25,35] Low sperm motility and abnormal sperm morphology have been found to a greater degree in fathers of boys with hypospadias and it is speculated that hypospadias in some boys after intracytoplasmic sperm injection (ICSI) might reflect inheritance of the mutant genes that caused the paternal subfertility.[27] Likewise, assisted reproductive technology, such as in vitro fertilization (IVF), may contribute to the higher prevalence of hypospadias through a higher rate of twinning.[39]

Finally, there is growing concern that exposure to endocrine disruptors might be contributing to declining reproductive health in humans, particularly, males.[21,24,25,27–29] Endocrine disruptors are hormonally active agents in the environment that are synthetic or natural substances that can interfere with hormone systems by mimicking, blocking, or otherwise

altering the normal action of hormones during critical periods of embryonic or fetal development.[27] Humans and wild animals are constantly exposed to endocrine disruptors through insecticides used in crop production, natural plant estrogens, byproducts of plastic production, internal plastic coating used in the canned food industry inside metal cans, and pharmaceuticals.[29] It is theorized that exposure to anti-androgens, which are endocrine disruptors that inhibit androgen binding, androgen synthesis, and androgen-induced gene expression, during development of the urogenital tract can impede normal male differentiation and result in hypospadias.[27]

2.5 Medication Use during Pregnancy and Risk of Hypospadias

Statistically significant positive associations have been observed between maternal use of oral nystatin, valproic acid, progestins, proton pump inhibitors (PPIs), and steroids during pregnancy and hypospadias.[16–19]

In the population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities between 1980 and 1996, a teratogenic potential of nystatin was seen in the hypospadias case group for exposures during the critical period for the development of hypospadias. Results from the study indicated a higher maternal nystatin use during the third and fourth months of gestation among hypospadias cases, resulting in an adjusted odds ratio (aOR) of 4.0 with a 95% confidence interval (CI) of 1.1-14.2.[17]

Hypospadias is one of the most frequently described genital anomalies observed in infants prenatally exposed to valproic acid. Results from a case-control study, by Rodriguez-Pinilla et al., using data derived from the Spanish Collaborative Study of Congenital Malformations showed that the adjusted risk of hypospadias in infants prenatally exposed to valproic acid was 5.71 (95% CI 1.78-18.36, p=0.003).[18] Also, in a study using data from the

National Birth Defects Prevention Study (NBDPS) by Werler and colleagues, evaluating the use of specific antiepileptic drugs in pregnancy in relation to specific birth defects, an elevated adjusted odds ratio for hypospadias was observed for infants born to valproic acid-exposed mothers, although the lower confidence bounds were below 1.0 (aOR 2.4; 95% CI 0.62-9.0).[41]

In light of previous studies that have suggested that maternal intake of progestins during early pregnancy may be associated with an increased risk of hypospadias, Carmichael and colleagues examined the risk of hypospadias associated with periconceptional progestin intake using data from NBDPS. Case mothers in the study were 3.7 times more likely to be exposed to progestins during early pregnancy than control mothers (95% CI 2.3-6.0).[16]

Anderka et al. used NBDPS data to examine whether nausea and vomiting due to pregnancy or its treatment (i.e. antihistamine antiemetics, other antihistamines, prokinetics, 5HT3 antagonists, Emetrol (coke syrup), antacids, H2 blockers, proton pump inhibitors, pyridoxine, steroids, and herbal or natural products) was associated with the most common non-cardiac defects in the NBDPS, including hypospadias, compared with randomly selected non-malformed live births. Regarding treatments for nausea and vomiting due to pregnancy, the study found statistically significant positive associations with first-trimester use of PPIs and hypospadias (aOR 4.36, 95% CI 1.21-15.81) and steroids and hypospadias (aOR 2.87, 95% CI 1.03-7.97).[19]

In the current analysis, recently collected data from the National Birth Defects Prevention Study (NBDPS) was used to examine the relationship between maternal medication use during the periconceptional period and early pregnancy and the risk of severe hypospadias in male infants.

Chapter III
METHODOLOGY

3.1 Data Source and Study Population

The data used in this analysis were collected as part of the National Birth Defects Prevention Study (NBDPS). NBDPS is an ongoing, multi-site, population-based, case-control study which seeks to identify risk factors associated with more than 30 selected categories of major birth defects. The study is the result of a collaborative effort by the Centers for Birth Defects Research and Prevention (CBDRP), coordinated by the Centers for Disease Control and Prevention (CDC), and is the largest population-based U.S. study looking at the risk factors for and potential causes of birth defects. Annually, each study site contributes maternal interviews of approximately 300 case subjects with any of the selected birth defects and 100 liveborn control subjects without birth defects. Case infants are identified through population-based surveillance and all case records are reviewed by a clinical geneticist to ensure they meet the case definition, while control infants are randomly selected from either birth hospital or birth certificate records from the same geographic area and time period as the cases. Data have been contributed by 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah), all of which use a standardized protocol that was developed by the NBDPS collaborative. The study design was approved by the institutional review boards of the participating study centers and by the CDC, and study participants provided informed consent. Detailed study methods[42] and description of case classification methods[43] have been published elsewhere.

NBDPS uses computer-assisted telephone interviews to collect information from women. Mothers were contacted by telephone and interviewed 6 weeks to 24 months after their estimated date of delivery (EDD). The interviews take about one hour and are conducted in English or

Spanish. The interview covers a wide range of exposures, selected based on hypotheses about what causes birth defects and were broadly defined to include maternal health and reproductive characteristics, environmental exposures, and nutritional and behavioral factors.

NBDPS included only cases of second- or third-degree hypospadias, which was defined as the urethral opening at the penile shaft, scrotum, or perineum and included the modified British Pediatric Association codes 752.606, 752.607, 752.626, and 752.627. A clinical geneticist at each study center reviewed medical record information with anatomic descriptions or diagrams by pediatricians, urologists, geneticists, pathologists, or other health care providers to determine whether to include or exclude cases in the NBDPS database. A clinical geneticist further classified eligible cases of hypospadias into isolated, if there was no concurrent major anomaly or only a minor anomaly, or multiple, if there was at least one unrelated accompanying major anomaly in another organ system.

This study included data on deliveries with estimated dates of delivery (EDD) between October 1997 and December 2007. The analysis is restricted to all male controls and isolated hypospadias cases, as isolated cases represented 90.6% of all hypospadias cases and are considered a more etiologically homogeneous group of defects than those defects associated with additional anomalies.[43–46]

We considered maternal medication exposures from 1 month before to 4 months after conception, with the date of conception estimated by subtracting 266 days from the EDD. This window of exposure was defined to capture the periconceptional period and weeks 8-14 postconception, the latter of which is the period of development for the male embryo urogenital system.[27] Medications were broadly defined to include reported use of any prescription, over-the-counter, or herbal drug. The Slone Epidemiology Center Drug Dictionary was used by a central

coding facility to assign codes for each reported product and for the components of which these products were comprised. In this analysis only medication components for which there were at least 5 exposed cases were assessed. Topicals, vitamins, minerals, and not otherwise specified (NOS) components were excluded from the analysis. Equivalent medications, such as amoxicillin and amoxicillin trihydrate, were combined.

3.2 Statistical Analysis

The analysis assessed whether medication exposures differed among mothers of isolated hypospadias cases and mothers of male controls. Crude odds ratios (ORs) were estimated for each medication component exposure. Potential confounders for the adjusted analyses were selected *a priori* based on previous knowledge, and were maternal age (<35 yr/≥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) (underweight/normal/overweight/obese; defined below), parity (0 births/1 birth/≥2 births), maternal sub-fertility (any fertility-related treatments and procedures/none), study site, and year of due date in two year increments. The maternal sub-fertility variable was based on a positive response to any of the following 3 questions: 1) "Did you have any surgical procedures [to help you become pregnant]?"; 2) "In the 2 months before you became pregnant with [baby's name], did you take any medications to help you become pregnant?"; and 3) "Did you have any other procedures to help you become pregnant?" Pre-pregnancy BMI was based on standard BMI categories, with <18.5 for underweight, 18.5-24.9 for normal weight, 25.0-29.9 for overweight, and ≥30.0 for obese.[47] Adjusted odds ratios (aORs) and their corresponding 95% confidence intervals (CIs) were estimated using multivariable logistic regression. Sub-analyses were performed on associations for which the lower bound of the 95% CI was ≥0.95 for crude or

adjusted OR estimates >1 or the upper bound was ≤1.05 for crude or adjusted OR estimates <1 in the primary analyses (i.e. at least borderline statistically significant). Separate sub-analyses were conducted in which infants with a positive family history were excluded, low birth weight infants and multiple births were excluded, and mothers reporting illicit drug use were excluded, to evaluate whether these factors would make a difference in results. Data management and analysis were performed using the Statistical Package for the Social Sciences (SPSS) software, version 17.0. Throughout all analyses performed, a *P*-value less than 0.05 was considered statistically significant.

Chapter IV
RESULTS

Among infants in the NBDPS with an EDD from October 1997 through December 2007, 1,697 cases of second- or third-degree hypospadias were identified. Of the cases identified, 1,537 (90.6%) infants had isolated hypospadias. The control group consisted of 4,314 non-malformed male infants. One hundred and ninety-five medication components were identified for which there were at least 5 exposed cases. Of the 195 medication components, 104 components (topicals; vitamins; minerals; NOS components) were excluded and 2 equivalent component pairs (amoxicillin and amoxicillin trihydrate; albuterol and albuterol sulfate) were combined. Thus, 89 medication components were assessed for their association with hypospadias.

Table 1 gives the maternal and infant characteristics of the hypospadias cases and controls. Case mothers were significantly more likely than control mothers to be Non-Hispanic White, 35 years of age or older at delivery, to have 4 or more years of college, to be obese, to have an annual family income >$50,000, to have used alcohol during the periconceptional period, to have used folic acid during the periconceptional period, to be nulliparous, to have given birth to multiples, and to have used treatments or procedures for sub-fertility. Control mothers were significantly more likely than case mothers to be Hispanic and to have used illicit drugs during the periconceptional period. Case infants were significantly more likely than control infants to be delivered preterm, to have a low birth weight, and to have a family history of hypospadias. There were also differences in the distribution of cases and controls by study site and EDD.

Table 1: Descriptive Characteristics of Mothers of Case and Control Infants: National Birth Defects Prevention Study, October 1997 to December 2007

Characteristic	**Isolated Hypospadias 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%)	
Missing	1	2	
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 (7.7%)	756 (17.8%)	
High School	295 (19.5%)	1,047 (24.7%)	
1-3 yr of College	420 (27.8%)	1,125 (26.6%)	
≥4 yr of College	680 (45.0%)	1,309 (30.9%)	
Missing	25	77	
Pre-pregnancy Body Mass Index (kg/m^3)			.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%)	
Annual Family Income			< .001
<$10,000	149 (10.0%)	793 (19.6%)	
$10,000-$50,000	533 (35.7%)	1764 (43.5%)	
>$50,000	756 (50.7%)	1324 (32.7%)	
Missing	45	259	
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 Use[c]			.002
Yes	1,400 (91.6%)	3,813 (88.7%)	
No	129 (8.4%)	485 (11.3%)	
Missing	8	16	
Parity			< .001
0 births	816 (53.3%)	1,729 (40.2%)	
1 birth	454 (29.7%)	1,419 (33.0%)	
≥2 births	260 (17.0%)	1,157 (26.9%)	
Missing	7	9	
Plurality			< .001
Singleton	1,416 (92.2%)	4,182 (97.1%)	
Multiple	119 (7.8%)	123 (2.9%)	
Missing	2	9	
Maternal Subfertility Treatments and Procedures			< .001
None	1,373 (89.7%)	4,121 (95.8%)	
Any	157 (10.3%)	180 (4.2%)	
Missing	7	13	
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 (18.3%)	839 (19.5%)	
2000-2001	348 (22.7%)	853 (19.8%)	
2002-2003	250 (16.3%)	855 (19.8%)	
2004-2005	346 (22.6%)	894 (20.7%)	
2006-2007	310 (20.2%)	872 (20.2%)	
Missing	3	1	

Infant Characteristics			
Preterm Birth (<37 weeks)			< .001
Yes	375 (24.7%)	407 (9.4%)	
No	1141 (75.3%)	3,906 (90.6%)	
Missing	21	1	
Low Birthweight (<2,500 g)			< .001
Yes	380 (25.0%)	241 (5.6%)	
No	1,137 (75.0%)	4,055 (94.4%)	
Missing	20	18	
Family History of Hypospadias[d]			< .001
Yes	74/1537 (4.8%)	9/4314 (0.2%)	
No	1463/1537 (95.2%)	4305/4314 (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 (mother, father, full sibling) or previous pregnancy.

Unadjusted (OR) and adjusted (aOR) odds ratios were estimated for 89 medication exposures (Table 2). Statistically significant positive associations with isolated hypospadias were observed for maternal use of phenylpropanolamine HCl (OR 2.82; 95% CI 1.17, 6.80), labetalol (OR 4.24; 95% CI 1.51, 11.93), acetaminophen (OR 1.19; 95% CI 1.05, 1.35), ibuprofen (OR 1.36; 95% CI 1.19, 1.55), aspirin (OR 1.42; 95% CI 1.10, 1.84), butalbital (OR 2.82; 95% CI 1.06, 7.53), lutein (OR 1.48; 95% CI 1.06, 2.07), lycopene (OR 1.65; 95% CI 1.00, 2.71), barley grass (OR 2.82; 95% CI 1.17, 6.80), progesterone (OR 2.62; 95% CI 1.97, 3.48), iodine (OR 1.34; 95% CI 1.16, 1.54), and levothyroxine sodium (OR 1.81; 95% CI 1.24, 2.64), in the unadjusted analysis.

In analyses adjusted for maternal age, race/ethnicity, education, pre-pregnancy BMI, parity, maternal sub-fertility, study site, and year of due date, statistically significant associations with isolated hypospadias were observed only for maternal use of phenylpropanolamine HCl (aOR 2.68; 95% CI 1.06, 6.80), ibuprofen (aOR 1.16; 95% CI 1.00, 1.34), and cephalexin (aOR 3.06; 95% CI 1.02, 9.18) (Table 2).

Table 2: Association of Isolated Hypospadias with Maternal Medication Use,[a] National Birth Defects Prevention Study, October 1997 to December 2007.

Medication Exposure	Exposed Cases	Exposed Controls	OR (95% CI)	Adjusted OR[b] (95% CI)
Antihistamines, First Generation				
Diphenhydramine HCl	38	98	1.09 (0.75, 1.60)	1.01 (0.67, 1.51)
Doxylamine Succinate	27	68	1.12 (0.71, 1.75)	0.98 (0.61, 1.60)
Chlorpheniramine Maleate	37	78	1.35 (0.91, 2.00)	1.35 (0.88, 2.09)
Promethazine	8	23	0.98 (0.44, 2.19)	0.97 (0.40, 2.36)
Promethazine HCl	38	126	0.84 (0.58, 1.22)	0.77 (0.52, 1.13)
Antihistamines, Second Generation				
Cetirizine HCl	21	46	1.29 (0.77, 2.17)	0.99 (0.57, 1.71)
Fexofenadine HCl	22	39	1.60 (0.94, 2.70)	1.13 (0.65, 1.97)
Loratadine	46	98	1.33 (0.93, 1.90)	1.11 (0.76, 1.62)
Antibiotics				
Cephalexin	6	8	2.11 (0.73, 6.10)	**3.06 (1.02, 9.18)**
Azithromycin	19	70	0.76 (0.46, 1.27)	0.61 (0.35, 1.05)
Amoxicillin Trihydrate	85	233	1.03 (0.80, 1.33)	1.01 (0.77, 1.33)
Sulfamethoxazole	15	38	1.11 (0.61, 2.03)	1.06 (0.55, 2.02)
Antibiotics, Urinary				
Nitrofurantoin	28	67	1.18 (0.76, 1.84)	1.27 (0.79, 2.06)
Nitrofurantoin Monohydrate	25	58	1.22 (0.76, 1.95)	1.24 (0.74, 2.08)
Trimethoprim	15	38	1.11 (0.61, 2.03)	1.06 (0.55, 2.02)
Alpha/Beta Agonists				
Ephedra	8	28	0.80 (0.37, 1.76)	1.03 (0.45, 2.35)
Phenylpropanolamine HCl	10	10	**2.82 (1.17, 6.80)**	**2.68 (1.06, 6.80)**
Pseudoephedrine HCl	144	380	1.07 (0.88, 1.31)	0.92 (0.73, 1.14)
Pseudoephedrine Sulfate	6	13	1.30 (0.49, 3.43)	1.18 (0.42, 3.33)
Alpha-Adrenergic Agonists				
Phenylephrine HCl	7	13	1.52 (0.60, 3.81)	1.70 (0.64, 4.52)
Beta$_2$-Adrenergic Agonists				
Albuterol Sulfate	49	122	1.13 (0.81, 1.59)	1.13 (0.78, 1.62)
Salmeterol Xinafoate	12	20	1.69 (0.83, 3.47)	1.66 (0.77, 3.62)
Antilipemics				
Niacin	158	432	1.03 (0.85, 1.25)	0.85 (0.69, 1.05)
Cardiovascular Agents				
Labetalol	9	6	**4.24 (1.51, 11.93)**	2.58 (0.86, 7.74)
Atenolol	5	10	1.41 (0.48, 4.12)	1.01 (0.31, 3.27)
Methyldopa	9	21	1.21 (0.55, 2.64)	1.05 (.44, 2.47)

Analgesics				
Acetaminophen	956	2514	**1.19 (1.05, 1.35)**	0.96 (0.84, 1.10)
Ibuprofen	423	945	**1.36 (1.19, 1.55)**	**1.16 (1.00, 1.34)**
Naproxen Sodium	76	176	1.23 (0.93, 1.62)	0.99 (0.74, 1.33)
Aspirin	93	187	**1.42 (1.10, 1.84)**	1.25 (0.94, 1.66)
Codeine Phosphate	14	39	1.01 (0.55, 1.87)	0.86 (0.45, 1.68)
Meperidine HCl	8	21	1.07 (0.47, 2.42)	1.05 (0.45, 2.45)
Oxycodone HCl	11	17	1.83 (0.85, 3.91)	1.13 (0.50, 2.57)
CNS Stimulants				
Caffeine	27	52	1.47 (0.92, 2.35)	1.08 (0.66, 1.78)
Barbiturates				
Butalbital	8	8	**2.82 (1.06, 7.53)**	2.07 (0.74, 5.77)
Antidepressants				
Bupropion HCl	12	26	1.30 (0.65, 2.58)	1.32 (0.65, 2.70)
Venlafaxine	9	11	2.31 (0.96, 5.58)	2.38 (0.95, 5.96)
Fluoxetine HCl	13	42	0.87 (0.47, 1.63)	0.88 (0.45, 1.74)
Paroxetine HCl	9	29	0.87 (0.41, 1.85)	1.00 (0.45, 2.20)
Sertraline HCl	22	48	1.29 (0.78, 2.15)	1.22 (0.71, 2.10)
GI, Antiemetics				
Ondansetron HCl	23	45	1.44 (0.87, 2.39)	0.97 (0.57, 1.65)
GI, Antiflatulants				
Simethicone	12	33	1.02 (0.53, 1.99)	0.68 (0.33, 1.39)
GI, Antiulcer Agents and Acid Suppressants				
Ranitidine HCl	11	27	1.15 (0.57, 2.32)	0.91 (0.43, 1.92)
Lansoprazole	6	6	2.82 (0.91, 8.76)	2.81 (0.80, 9.83)
Omeprazole	5	5	2.82 (0.82, 9.75)	2.87 (0.73, 11.29)
GI, Cathartics and Laxatives				
Docusate Sodium	190	516	1.04 (0.87, 1.24)	0.94 (0.78, 1.14)
GI, Digestants				
Betaine HCl	5	20	0.70 (0.26, 1.87)	0.65 (0.23, 1.80)
GI, Prokinetic Agents				
Metoclopramide HCl	9	17	1.49 (0.66, 3.35)	1.06 (0.45, 2.49)
Herbals				
Bioflavonoid Compound	19	47	1.14 (0.67, 1.95)	0.84 (0.47, 1.48)
Hesperidin Complex	5	6	2.35 (0.72, 7.70)	2.06 (0.60, 7.09)
Rutin	9	30	0.84 (0.40, 1.78)	0.66 (0.30, 1.42)
Spirulina	11	26	1.19 (0.59, 2.42)	0.87 (0.41, 1.83)
Lutein	54	104	**1.48 (1.06, 2.07)**	1.16 (0.81, 1.66)
Lycopene	25	43	**1.65 (1.00, 2.71)**	1.31 (0.77, 2.22)
Alfalfa	7	22	0.89 (0.38, 2.10)	0.67 (0.27, 1.62)
Allium Sativum, Herb	9	25	1.01 (0.47, 2.17)	0.92 (0.41, 2.07)
Angelica Polymorpha	8	22	1.02 (0.45, 2.30)	0.78 (0.33, 1.84)
Barley Grass	10	10	**2.82 (1.17, 6.80)**	2.13 (0.84, 5.38)

Bee Pollen	11	29	1.07 (0.53, 2.14)	1.05 (0.50, 2.17)
Cranberry Concentrate	6	9	1.88 (0.67, 5.29)	1.58 (0.55, 4.58)
Echinacea	11	22	1.41 (0.68, 2.91)	1.23 (0.57, 2.65)
Ginger	17	43	1.11 (0.63, 1.96)	1.02 (0.56, 1.86)
Ginkgo Biloba Extract	8	13	1.73 (0.72, 4.19)	1.60 (0.59, 4.36)
Ginseng	10	20	1.41 (0.66, 3.02)	1.42 (0.64, 3.19)
Herbal Tea	17	35	1.37 (0.77, 2.45)	1.84 (0.96, 3.52)
Hydrastis Canadensis	6	12	1.41 (0.53, 3.76)	1.61 (0.57, 4.53)
Hypericum Perforatum	5	6	2.35 (0.72, 7.71)	1.70 (0.49, 5.87)
Peppermint	5	13	1.08 (0.39, 3.04)	0.75 (0.25, 2.25)
Raspberry Leaf	18	33	1.54 (0.87, 2.74)	0.94 (0.51, 1.75)
Sarsaparilla Root	5	8	1.76 (0.58, 5.39)	2.25 (0.67, 7.57)
Siberian Ginseng	5	13	1.08 (0.39, 3.04)	1.17 (0.39, 3.51)
Thea Sinesis	12	32	1.06 (0.54, 2.05)	0.85 (0.42, 1.75)
Vitis Vinifera	8	10	2.26 (0.89, 5.73)	1.94 (0.70, 5.34)
Glucosamine	6	0	---	---
Royal Jelly	10	31	0.91 (0.44, 1.85)	0.81 (0.38, 1.72)
Lactobacillus Acidophilus	5	14	1.00 (0.36, 2.79)	0.70 (0.24, 2.02)
Steroids, Glucocorticoids				
Budesonide	6	8	2.11 (0.73, 6.10)	1.23 (0.41, 3.73)
Fluticasone Propionate	21	39	1.52 (0.89, 2.59)	1.13 (0.64, 2.01)
Prednisone	5	15	0.94 (0.34, 2.59)	0.59 (0.20, 1.72)
Triamcinolone Acetonide	5	8	1.76 (0.58, 5.39)	1.88 (0.57, 6.22)
Antidiabetic Agents, Biguanide				
Metformin HCl	7	12	1.64 (0.65, 4.18)	0.92 (0.34, 2.52)
Progestins				
Progesterone	93	104	**2.62 (1.97, 3.48)**	1.25 (0.89, 1.76)
Progesterone Gel	8	1	---	---
Thyroid and Antithyroid Agents				
Iodine	363	813	**1.34 (1.16, 1.54)**	1.17 (1.00, 1.37)
Levothyroxine Sodium	45	71	**1.81 (1.24, 2.64)**	1.33 (0.88, 2.01)
Potassium Iodide	67	176	1.07 (0.81, 1.43)	0.81 (0.59, 1.11)
Respiratory Agents				
Dextromethorphan HBR	50	113	1.25 (0.89, 1.76)	1.02 (0.71, 1.47)
Guaifenesin	41	120	0.96 (0.67, 1.37)	0.82 (0.55, 1.21)
Miscellaneous Therapeutic Agents				
Potassium Clavulanate	8	18	1.25 (0.54-2.88)	1.16 (0.48, 2.79)

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, parity, sub-fertility, study site, and year of due date.
--- Odds ratios were not estimated for medication components with fewer than 5 exposed controls.

Of the 89 medication components considered in the primary analyses, 17 had at least borderline statistically significant crude or adjusted OR estimates for their association with isolated hypospadias. Overall, the results of sub-analyses in which infants with a positive family history of hypospadias were excluded did not change adjusted OR estimates appreciably (Table 3). Associations of isolated hypospadias with cephalexin (aOR 3.29; 95% CI 1.10, 9.87) and venlafaxine (aOR 2.52; 95% CI 1.01, 6.31) were stronger when infants with a positive family history were excluded. The association of phenylpropanolamine HCl with isolated hypospadias was slightly attenuated when infants with a positive family history were excluded (aOR 2.58; 95% CI 0.99, 6.73).

Table 3: Association of Isolated Hypospadias with Maternal Use of Specific Medications, Excluding Infants with a Positive Family History, National Birth Defects Prevention Study, October 1997 to December 2007.[a,b]

Medication Exposure	**Exposed Cases**	**Exposed Controls**	**aOR[c] (95% CI) Sub-Analysis**	**aOR (95% CI) Primary Analysis**
Cephalexin	6	8	**3.29 (1.10, 9.87)**	**3.06 (1.02, 9.18)**
Azithromycin	19	70	0.65 (0.37, 1.11)	0.61 (0.35, 1.05)
Phenylpropanolamine HCl	9	10	2.58 (0.99, 6.73)	**2.68 (1.06, 6.80)**
Niacin	143	430	0.81 (0.65, 1.01)	0.85 (0.69, 1.05)
Labetalol	9	6	2.65 (0.88, 7.96)	2.58 (0.86, 7.74)
Acetaminophen	895	2507	0.93 (0.81, 1.07)	0.96 (0.84, 1.10)
Ibuprofen	403	942	**1.16 (1.00, 1.35)**	**1.16 (1.00, 1.34)**
Aspirin	90	186	1.27 (0.95, 1.68)	1.25 (0.94, 1.66)
Butalbital	8	8	2.20 (0.79, 6.13)	2.07 (0.74, 5.77)
Venlafaxine	9	11	**2.52 (1.01, 6.31)**	2.38 (0.95, 5.96)
Lutein	50	104	1.12 (0.77, 1.62)	1.16 (0.81, 1.66)
Lycopene	23	43	1.27 (0.74, 2.19)	1.31 (0.77, 2.22)

Barley Grass	8	10	1.65 (0.62**,** 4.41)	2.13 (0.84, 5.38)
Herbal Tea	16	35	1.81 (0.94**,** 3.51)	1.84 (0.96, 3.52)
Progesterone	89	104	1.26 (0.90**,** 1.78)	1.25 (0.89, 1.76)
Iodine	334	813	1.12 (0.95**,** 1.31)	1.17 (1.00, 1.37)
Levothyroxine Sodium	43	71	1.34 (0.88**,** 2.03)	1.33 (0.88, 2.01)

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 (mother, father, full sibling) or previous pregnancy.
[c] Odds ratios were adjusted for maternal age, race/ethnicity, education, pre-pregnancy BMI, parity, sub-fertility, study site, and year of due date.

Sub-analyses in which low birth weight infants and multiple births were excluded demonstrated attenuated results relative to the primary analysis for several of the medications, including cephalexin (aOR 1.37; 0.27, 6.95) (Table 4). However, in this sub-analysis, the association of isolated hypospadias was much stronger with maternal use of venlafaxine (aOR 3.67; 95% CI 1.39, 9.70) and slightly stronger with phenylpropanolamine HCl, although only marginally significant (aOR 2.83; 95% CI 0.98, 8.16).

Table 4: Association of Isolated Hypospadias with Maternal Use of Specific Medications, Excluding Low Birth Weight Infants and Multiple Births, National Birth Defects Prevention Study, October 1997 to December 2007.[a]

Medication Exposure	**Exposed Cases**	**Exposed Controls**	**aOR[b] (95% CI) Sub-Analysis**	**aOR (95% CI) Primary Analysis**
Cephalexin	2	7	1.37 (0.27, 6.95)	**3.06 (1.02, 9.18)**
Azithromycin	18	66	0.73 (0.42, 1.28)	0.61 (0.35, 1.05)
Phenylpropanolamine HCl	7	9	2.83 (0.98, 8.16)	**2.68 (1.06, 6.80)**
Niacin	122	408	0.87 (0.69, 1.10)	0.85 (0.69, 1.05)
Labetalol	4	5	1.63 (0.40, 6.61)	2.58 (0.86, 7.74)
Acetaminophen	701	2318	0.97 (0.83, 1.14)	0.96 (0.84, 1.10)
Ibuprofen	309	873	1.16 (0.98, 1.37)	**1.16 (1.00, 1.34)**
Aspirin	61	164	1.21 (0.87, 1.69)	1.25 (0.94, 1.66)
Butalbital	5	8	1.51 (0.47, 4.81)	2.07 (0.74, 5.77)

Venlafaxine	9	9	**3.67 (1.39, 9.70)**	2.38 (0.95, 5.96)
Lutein	40	93	1.21 (0.81, 1.82)	1.16 (0.81, 1.66)
Lycopene	22	38	1.72 (0.98, 3.05)	1.31 (0.77, 2.22)
Barley Grass	6	10	1.65 (0.56, 4.84)	2.13 (0.84, 5.38)
Herbal Tea	10	32	1.69 (0.77, 3.73)	1.84 (0.96, 3.52)
Progesterone	51	76	1.44 (0.95, 2.18)	1.25 (0.89, 1.76)
Iodine	258	753	1.14 (0.95, 1.37)	1.17 (1.00, 1.37)
Levothyroxine Sodium	31	61	1.38 (0.86, 2.23)	1.33 (0.88, 2.01)

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, parity, sub-fertility, study site, and year of due date.

In the final sub-analysis the association between isolated hypospadias and maternal use of specific medications, excluding mothers who reported illicit drug use was evaluated (Table 5). Overall, results from the sub-analysis were similar to the aORs from the primary analysis, presented in Table 2. The aORs for cephalexin (aOR 3.50; 95% CI 1.13, 10.87), phenylpropanolamine HCl (aOR 2.85; 95% CI 1.10, 7.38), and ibuprofen (aOR 1.20; 95% CI 1.03, 1.39) were stronger in the sub-analysis than the primary analysis.

Table 5: Association of Isolated Hypospadias with Maternal Use of Specific Medications, Excluding Mothers Reporting Illicit Drug Use, National Birth Defects Prevention Study, October 1997 to December 2007.[a,b]

Medication Exposure	**Exposed Cases**	**Exposed Controls**	**aOR[c] (95% CI) Sub-Analysis**	**aOR (95% CI) Primary Analysis**
Cephalexin	6	7	**3.50 (1.13, 10.87)**	**3.06 (1.02, 9.18)**
Azithromycin	18	66	0.61 (0.35, 1.07)	0.61 (0.35, 1.05)
Phenylpropanolamine HCl	10	9	**2.85 (1.10, 7.38)**	**2.68 (1.06, 6.80)**
Niacin	154	414	0.86 (0.69, 1.06)	0.85 (0.69, 1.05)
Labetalol	8	5	2.51 (0.76, 8.25)	2.58 (0.86, 7.74)
Acetaminophen	918	2381	0.95 (0.82, 1.09)	0.96 (0.84, 1.10)

Ibuprofen	406	870	**1.20 (1.03, 1.39)**	**1.16 (1.00, 1.34)**
Aspirin	90	177	1.23 (0.92, 1.64)	1.25 (0.94, 1.66)
Butalbital	8	8	2.06 (0.74, 5.75)	2.07 (0.74, 5.77)
Venlafaxine	9	10	2.51 (0.99, 6.37)	2.38 (0.95, 5.96)
Lutein	52	103	1.10 (0.76, 1.58)	1.16 (0.81, 1.66)
Lycopene	24	43	1.23 (0.72, 2.10)	1.31 (0.77, 2.22)
Barley Grass	9	10	1.93 (0.74, 5.00)	2.13 (0.84, 5.38)
Herbal Tea	16	31	1.91 (0.97, 3.77)	1.84 (0.96, 3.52)
Progesterone	93	103	1.26 (0.90, 1.77)	1.25 (0.89, 1.76)
Iodine	354	773	1.17 (1.00, 1.37)	1.17 (1.00, 1.37)
Levothyroxine Sodium	44	71	1.30 (0.86, 1.98)	1.33 (0.88, 2.01)

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] Mothers reporting illicit drug use any time 1 month preconception through month 3 postconception were excluded.

[c] Odds ratios are adjusted for maternal age, race/ethnicity, education, pre-pregnancy BMI, parity, sub-fertility, study site, and year of due date.

Chapter V
DISCUSSION AND CONCLUSION

5.1 Discussion

After adjusting for potential confounders, the results of this analysis suggested an increased risk of second- or third-degree hypospadias among infants delivered to women who took cephalexin, phenylpropanolamine HCl, ibuprofen, and venlafaxine during the period of 1 month before to 4 months after conception.

This analysis illustrates that the association between isolated hypospadias and medication exposure during the periconceptional period and early pregnancy is sensitive to confounding by the factors we considered. The majority of the 89 odds ratios estimated in the crude analysis were attenuated in the adjusted analysis. Restricting analyses based on a potentially confounding factor is an alternative method to multivariable models for controlling confounding. Relative to the primary analysis, associations between hypospadias and maternal use of cephalexin and venlafaxine became stronger, and for phenylpropanolamine HCl were attenuated, in sub-analyses in which infants with a positive family history of hypospadias were excluded, though overall, estimates did not change appreciably. In sub-analyses excluding low birth weight infants and multiple births, the associations with venlafaxine and phenylpropanolamine HCl were stronger; attenuated results were observed for several of the medications including cephalexin. Excluding mothers who reported illicit drug use resulted in aOR estimates similar overall to those observed in the primary analysis, although stronger associations were observed for cephalexin, phenylpropanolamine HCl, and ibuprofen.

Cephalexin, a first generation cephalosporin antibiotic used frequently during pregnancy, is indicated for the treatment of susceptible bacterial infections including respiratory tract infections, otitis media, skin and skin structure infections, bone infections, and genitourinary

tract infections.[48,49] The observation of a statistically significant association between cephalexin and hypospadias risk in this study differs from several older published reports which found no association between use of cephalexin and congenital defects or toxicity in newborns.[50] More recently published studies have reported an association between cephalexin and cephalosporin use and risk of certain birth defects.[48,50,51] However, an association with hypospadias has not been previously reported.

Phenylpropanolamine HCl, also known as PPA, is a synthetic sympathomimetic amine that was historically used frequently in many OTC weight loss products and as a decongestant in cough and cold medications. Since November 2000, the United States Food and Drug Administration (FDA) has been working to remove PPA from all drug products and requested that all drug companies discontinue marketing products containing PPA, as a result of the FDA Nonprescription Drugs Advisory Committee's determination of an association between PPA and hemorrhagic stroke.[52,53] Heinonen et al. evaluated the association between prenatal PPA exposure and congenital malformations in the Collaborative Perinatal Project, which monitored 50,282 mother-child pairs. There were 4 observed hypospadias cases among 726 pregnant women who had PPA exposure during their first trimester, resulting in a standardized relative risk of 1.63 (95% CI 0.44-4.13).[54] Blood vessels of the uterus, which are normally fully dilated, contain alpha-adrenergic receptors.[50] It is possible then that use of PPA, which stimulates alpha- and beta-adrenergic receptors, could cause constriction of uterine vessels and reduce uterine blood flow, potentially resulting in poor intrauterine growth, a risk factor for hypospadias.[27,40,50]

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), works by decreasing the activity of the enzyme cyclooxygenase (COX), which results in the inhibition of prostaglandin synthesis.[49] 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.[55] Additionally, COX inhibitors, including ibuprofen, have been found to be endocrine disruptors, as well as to affect steroid hormone synthesis in rainbow trout.[56] Studies have also shown that another COX inhibitor, aspirin, inhibits androgen response to hCG stimulation in normal human adult males.[57] Therefore, exposure to COX inhibitors during critical periods of gestation could affect normal urogenital development in males.[58] In another study utilizing NBDPS data from 1997-2004,[59] NSAID use during the first trimester and the risk of birth defects was evaluated, and they found no association between first trimester ibuprofen use and hypospadias. There were, however, fewer cases classified as exposed to ibuprofen in that study (n=99) compared to this one (n=423), due to them having fewer years of data, an exposure window defined as the estimated day of conception through 3 months afterward, their exclusion of mothers with preexisting diabetes mellitus, and their separation of women who could not characterize their frequency of NSAID use in the first trimester into a separate "as needed" category. While an association between hypospadias and maternal use of ibuprofen has not been previously reported, an association has been observed between prenatal use of the mild analgesics acetaminophen, aspirin, and ibuprofen and risk of congenital cryptorchidism, [60] a genital abnormality commonly observed with hypospadias.[27]

Venlafaxine is a serotonin-norepinephrine reuptake inhibitor used in the treatment of depression and anxiety.[49] Despite evidence that there is substantial transfer of venlafaxine across the placenta,[61] there are very few published reports describing the use of venlafaxine during human pregnancy.[50] In a review by Salvatore Gentile, no malformations were observed in data obtained from the UK Drug Safety Research Unit that reported the outcomes of 39 women who took venlafaxine during pregnancy.[62] Likewise, in a prospective study in which there were ten

cases exposed to venlafaxine during pregnancy, all obstetrical findings were normal during each of the pregnancies and no congenital abnormalities were diagnosed in the infants in their first 12 months.[63] Yet, concurring with the association between venlafaxine exposure and hypospadias found here, in a study by Einarson and colleagues, in which data on 150 women exposed to venlafaxine during pregnancy in seven pregnancy counseling centers were compared with data from studies of pregnant women who were exposed to selective serotonin-reuptake inhibitors (SSRIs) and to women who received non-teratogenic drugs, it was observed that among the women exposed to venlafaxine during pregnancy, two babies were born with major malformations, one of which was hypospadias; drug-specific ORs were not estimated in the study.[64]

Several analyses using NBDPS data have been published on the association of a specific medication and the spectrum of birth defects included in the NBDPS. The findings in this analysis coincide with several of these other studies that observed no significant association between risk of hypospadias and exposure to loratadine, [65] certain SSRIs,[66] ephedra,[67] certain antihistamines,[68] acetaminophen,[69] bupropion,[70] certain opioid analgesics,[71] certain corticosteroids,[72] or certain antihypertensives.[73]

This analysis did not replicate the findings reported by Anderka and colleagues regarding an association of hypospadias with proton pump inhibitors (PPIs) or steroids used in the treatment of nausea and vomiting in pregnancy. It should be noted, however, that in their study, PPIs and steroids were analyzed as combined medication groups and drug-specific ORs were not calculated.[19]

5.2 Study Strengths and Limitations

This study had numerous strengths. The data came from a large, population-based study that allowed for sufficient statistical power to analyze numerous medication exposures during the critical period for male urethral development. The multi-center study design also provided geographic diversity. In addition, there was consistent and detailed case ascertainment, with cases reviewed and classified by clinical geneticists, and differentiation of isolated and multiple hypospadias cases.

However, the study is not without potential limitations. Maternal medication use in the analyses was not exclusive and mothers may have been using multiple medications at the same time. Therefore, there is potential for confounding from concurrent medication use. Inability to examine the dose of medications is another limitation. Also, while overall this was a large study, there were a relatively small number of exposed infants for some of the medication components, which could potentially affect analyses results. Medication exposures were determined by maternal report during the interview; hence recall bias is another potential limitation of the study. However, 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, in the way that they best remember, such as by date, month of pregnancy, or trimester. Some medications were specifically queried, while others were reported in response to treatment for reported maternal medical conditions. With 89 different medication components examined in this analysis, another limitation is multiple testing. Therefore, these results should be considered hypothesis-generating rather than hypothesis-testing, with the aim to help generate justification for future analyses. Furthermore, while numerous medications were examined in this analysis, there are still many medications that were not evaluated and these results do not provide

definitive information on the overall association between maternal medication use and risk of hypospadias. Finally, because the study population was limited to second- and third-degree isolated hypospadias cases it was not possible to examine if there may be an association between specific medication exposures and milder forms of hypospadias.

5.3 Conclusion and Recommendations

In conclusion, the findings presented here suggest there may be an association between maternal use of cephalexin, phenylpropanolamine HCl, ibuprofen, and venlafaxine during the periconceptional period and early pregnancy and an increased risk of second- or third-degree hypospadias in male infants. Future studies on the associations observed here and on medications not included in this study are warranted. Further investigation into medications associated with a risk of hypospadias will allow clinicians and women of childbearing age to make more informed decisions regarding the prescribing and intake of certain medications, by adding to the body of knowledge on the effects of medication use during pregnancy.

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