Published in final edited form as:
J Pediatr. 2009 July ; 155(1): 39–44.e1. doi:10.1016/j.jpeds.2009.01.039.

Maternal Corticosteroid Use and Hypospadias

Suzan L. Carmichael, PhD, **Chen Ma, MD**, **Martha M. Werler, ScD**, **Richard S. Olney, MD**, and **Gary M. Shaw, DrPH National Birth Defects Prevention Study**
California Research Division, March of Dimes Foundation, Oakland, CA (S.C., C.M., G.S.); Slone Epidemiology Center, Boston, MA (M.W.); and National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control, Atlanta, GA (R.O.)

Abstract

Objective—To explore whether women who reported corticosteroid use during pregnancy were more likely to deliver an infant with hypospadias than women who did not.

Study design—The analysis encompassed data on deliveries with an estimated due date between 1997 and 2004 from the National Birth Defects Prevention Study, a large population-based, case-control study conducted in the United States. Included were 1165 cases of moderate to severe hypospadias and 3000 nonmalformed male controls.

Results—The mothers of 39 cases (3.3%) and 62 controls (2.1%) reported using a corticosteroid medication during the period extending from 4 weeks before conception to 14 weeks after conception. The odds ratio (OR) for any corticosteroid exposure versus no corticosteroid exposure was 1.6 (95% confidence interval [CI] = 1.1 to 2.5); after adjustment for maternal race/ethnicity, education, age, and study site, it was 1.3 (95% CI = 0.8 to 2.0). Analyses by route of administration and specific component suggest that elevated ORs occurred only for nasal spray/inhaled corticosteroids (OR = 1.5; 95% CI = 0.9 to 2.6).

Conclusions—Maternal use of corticosteroid medications was weakly associated with risk of hypospadias, but the association was negligible after adjustment for potential confounders.

Corticosteroids readily cross the placenta and cause various malformations in different animal models.[1,2] Evidence from human studies suggests that corticosteroid use in early pregnancy is associated with a 3- to 6-fold increased risk of orofacial clefts.[3] Few epidemiologic studies have explored the risk of other specific birth defects associated with corticosteroid use, however.

Hypospadias occurs at around 8 to 14 weeks after conception. It is one of the most common structural malformations in humans, occurring in approximately 4 to 6 per 1000 male births.[4-6] Corticosteroids (ie, glucocorticoids) affect several mechanisms that are critical to urethral development, including sex steroid synthesis, placental function, and epithelial–mesenchymal cell interactions.[7-14] A recent experimental study demonstrated that prednisone significantly affected urethral seam closure in mice.[15] Supraphysiologic doses of prednisone resulted in a more proximal urethral opening and thinner connective tissue around the urethral seam, and 25% of the male offspring had hypospadias. Experimental studies have also shown that administration of corticosteroids in utero results in reduced anogenital distance in male offspring, which is considered to be a measure of antiandrogenic exposure.[16-18] An

Reprint requests: Suzan L. Carmichael, PhD, March of Dimes, California Research Division, Children's Hospital Oakland Research Institute, 5700 Martin Luther King Jr Way, Oakland, CA 94609. scarmichael@marchofdimes.com.
*A list of National Birth Defects Prevention Study investigators is available at www.jpeds.com (Appendix).

The authors declare no potential conflicts of interest.

epidemiologic study in Denmark found that prescriptions for inhalation or systemic glucocorticoids in the period from 90 days before conception through the first trimester of pregnancy were not associated with hypospadias (odds ratio [OR] = 1.1; 95% confidence interval [CI] = 0.4 to 2.7),[19] A study in Sweden reported no association of hypospadias with anti-asthma medications, some of which were corticosteroids, in early pregnancy (OR 1.0, 95% CI 0.9, 1.3)[20], and a study in Hungary reported no increased risk associated with use of oral (OR 0.9, 95% CI 0.7, 1.3) or ointment (OR 0.4 95% CI 0.1, 1.2) corticosteroids at any time during pregnancy.[21]

The present study provides a detailed assessment of the association between corticosteroid use and hypospadias. Investigation of this hypothesis is important, given the biological plausibility and recent experimental evidence described above, along with limited previous epidemiologic studies. Specifically, using data from a recent large population-based, case-control study conducted in the United States, we explored whether women who reported corticosteroid use during pregnancy were more likely to deliver an infant with hypospadias compared with women who did not use corticosteroids during pregnancy.

Methods

This study included data on deliveries with estimated due dates between October 1997 and December 2004 obtained from the National Birth Defects Prevention Study (NBDPS), a multistate case-control study of more than 30 different birth defects. The study design was approved by the institutional review boards of the participating study centers and by the Centers for Disease Control and Prevention. Details on the study methodology and the surveillance systems in the 10 states that contributed data to this analysis have been published previously.[22,23] In brief, 7 of the 10 states included liveborn, stillborn (fetal deaths at ≥ 20 weeks' gestation), and prenatally diagnosed and electively terminated cases (Arkansas, California, Georgia, Iowa, North Carolina, Texas, and Utah), 1 state included only liveborn and stillborn cases (Massachusetts), and 2 states included only liveborn cases (New Jersey and New York). Each state randomly selected approximately 100 nonmalformed liveborn controls per study year from birth certificates (Arkansas in 2000-2004, Georgia in 2001-2004, Iowa, Massachusetts, North Carolina, New Jersey, and Utah) or from birth hospitals (Arkansas in 1997-1999, California, Georgia in 1997-2000, New York, and Texas) to represent the population from which cases were derived. This analysis is restricted to all male controls. Case information obtained from multiple hospital reports and medical records was entered into a standardized database.

This study included only cases of second- or third-degree hypospadias, that is, with the urethral opening at the penile shaft, scrotum, or perineum (modified British Pediatric Association codes 752.606, 752.607, 752.626, and 752.627). Medical record information (including operative reports when available) with anatomic descriptions or diagrams by pediatricians, urologists, geneticists, pathologists, or other health care providers was reviewed by a clinical geneticist at each study center who determined whether to include or exclude cases in the NBDPS database. Cases described as chordee alone, mild hypospadias (ie, first-degree, coronal, or glandular), hypospadias not otherwise specified, epispadias, or ambiguous genitalia without further description were excluded. Infants with recognized single gene disorders, female karyotypes, or chromosomal abnormalities also were excluded. Each case received a final review by a single clinical geneticist (R.O.) to ensure that cases from each study center met standard eligibility criteria. This geneticist also classified each case as isolated, if there was no concurrent major anomaly or only a minor anomaly (eg, sacral/pilonidal dimple), or multiple, if there was at least 1 unrelated accompanying major anomaly and in another organ system.[24]

Maternal interviews were conducted using a standardized, computer-based telephone questionnaire in English or Spanish, no earlier than 6 weeks and no later than 24 months after the infant's estimated date of delivery (EDD). Final EDD was based on the mother's self-report; if this was not available, then EDD was estimated from information in the medical record (< 2% of subjects). Interviews were conducted with the mothers of 1165 cases (77% of eligibles) and 3000 controls. (The participation rate in the mothers of all controls was 75%; the rate in the mothers of male-only controls was not available.) The mean time from delivery to interview was 13.2 months in the mothers of cases and 8.9 months in the mothers of controls.

Exposure to corticosteroid medications was determined by asking the mothers whether they experienced various types of illnesses and injuries (eg, respiratory illness, infections) and what medications they used to treat them. The mothers were also asked to describe the specific illness or injury that they experienced. In a final section, the mothers reported the use of any other medications not reported in the preceding illness/injury-specific sections; indication was not recorded in this section. For each medication, information on start and stop dates of use and frequency of use was recorded. Those women who knew only either the start date or stop date of use, but not both, were asked about the duration of use. Medication exposure was assessed during the period extending from 4 weeks before conception through 18 weeks after conception. The date of conception was derived by subtracting 266 days from the EDD. A central coding facility assigned a drug code to each medication exposure, using the Slone Epidemiology Center Drug Dictionary. These codes were used to identify the primary components in each medication. Route of administration (eg, topical, systemic) was assigned based on exact wording from the mother's report or on the known formulation of the medication. Indication was assigned based on injury or illness reported in conjunction with the corticosteroid medication.

The following covariates were considered for inclusion in multivariate models given a possible association with the risk of hypospadias or reported corticosteroid use: maternal education (less than high school diploma, high school diploma, 1 to 3 years of college, 4 or more years of college), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), age (< 25, 25 to 34, ≥ 35 years at the time of conception), number of previous live births (0, 1, 2 or more), folic acid–containing supplement intake (any vs none from 1 month before through 3 months after conception), smoking (any vs none from 1 month before through 3 months after conception), body mass index (underweight, normal weight, overweight, or obese),[25] subfertility (ie, any fertility-related treatments or procedures), and study site. The subfertility 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?”

We first examined the association between the risk of hypospadias and corticosteroid use versus no corticosteroid use during the periconceptional period (ie, 4 weeks before conception through 14 weeks after conception). We initially used this time window, which both precedes and includes the time of urethral and genital tubercle development, because some of the potential effects of corticosteroid medications extend beyond the actual period of use (eg, adrenal suppression). We then examined associations with more specific time windows of exposure, route of administration, and medication components. We also explored associations with corticosteroid use starting at 15 to 18 weeks after conception (i.e., after urethral closure would have been completed), to help identify possible reporting errors. ORs were estimated only if there were at least 2 exposed cases and 2 exposed controls in a particular comparison. To estimate relative risks, maximum likelihood estimates of ORs and their corresponding 95% CIs were calculated from logistic regression models using SAS version 9.1 (SAS Institute, Cary, North Carolina). Covariates were included in the models if their inclusion resulted in at

least a 10% change in the OR for the association of any corticosteroid use with hypospadias; they were tested one at a time because of the limited number of exposed subjects.

We also examined whether the association of corticosteroid use varied depending on whether or not the mother took folic acid–containing supplements during the periconceptional period, using a cross-product term in the logistic model.Most of the women who took supplements used a prenatal formulation.[26] Experimental studies have shown that vitamin B_6 and folic acid, both of which are contained in prenatal vitamin formulations, are protective against the teratogenic effects of corticosteroids,[27,28] possibly because they suppress the activity of glucocorticoid receptors.[29,30]

We reexamined final estimates separately for subjects with birth weight ≥ 2500 g, (because it is possible that infants with normal birth weight are etiologically distinct from those with low birth weight.[31,32]), cases that were isolated, cases from singleton births, and cases with no first-degree family history of hypospadias (ie, the father or any brothers).

Results

Mothers of cases were more likely to be non-Hispanic white than mothers of controls (70% versus 59%), and they were less likely to be Hispanic (9% versus 22%). The majority of the mothers of cases and controls had at least some college education (71% and 56%, respectively). Mothers of cases were more likely to be 35 or older (22% versus 14%) and nulliparous (55% versus 40%). In total, the mothers of 39 cases with hypospadias (3.3%) and of 62 controls (2.1%) reported corticosteroid medication use during the period extending from 4 weeks before conception through 14 weeks after conception (Table I). The odds ratio for any versus no corticosteroid exposure was 1.6 (95% CI 1.1, 2.5), and after adjustment for covariates the odds ratio was 1.3 (95% CI 0.8, 2.0) (Table I).

Analyses by route of administration and specific component found elevated ORs only for nasal spray/inhaled corticosteroids (Table I). As with the overall OR for any use, the ORs by route and component were reduced after adjustment for covariates, and all of the CIs included 1.

Analyses of more specific time windows of exposure found no elevated ORs for exposures occurring only during the 4 weeks before conception or the first 4 weeks after conception, after adjustment for potential confounders. The odds ratio for any exposure during weeks 5-14 after conception, which corresponds more closely to the actual time of genital tubercle and urethral development, was elevated (OR 1.8, 95% CI 1.1, 2.8), but closer to one after adjustment for covariates (OR 1.4, 95% CI 0.9, 2.4) (Table II). Separate analyses of exposures during weeks 5-8 versus weeks 9-14 yielded very similar results (data not shown). The OR for exposures starting in weeks 15 to 18 after conception (ie, after the completion of urethral development) was 1.0 (95% CI = 0.2 to 5.4), based on the exposures in 2 mothers of cases and 5 mothers of controls.

Separate analyses by indication were not conducted, because indication was not specified in a majority of the exposed cases (19/39) and controls (23/33), and also because the reported indications were diverse, especially within subgroups based on timing.

The association of any versus no corticosteroid use was examined separately in women who began taking vitamin supplements during the month before conception or the first month after conception (early intake), during the second or third month after conception (later intake), or not at all during this time period (no periconceptional intake). The results suggest an association between corticosteroid use and increased risk of hypospadias in those with later or no periconceptional supplement intake (OR = 3.0 and 2.9, respectively) but not in those with early supplement intake (OR = 1.1) (Table III). The *P* value for the interaction term included in the

logistic regression model was .091. The stratum-specific ORs were similar after adjustment for the covariates.

Results from analyses that excluded subjects with birth weight < 2500 g (331 cases and 173 controls), cases with multiple anomalies (110 cases), multiple births (92 cases and 70 controls), or subjects with a family history of hypospadias in the father or a brother (52 cases and 6 controls) were similar to the results without these exclusions. For example, the unadjusted odds ratios for any versus no corticosteroid use from 4 weeks before through 14 weeks after conception ranged from 1.6 to 1.8 after making each of these exclusions (data not shown), which is similar to the odds ratio of 1.6 observed before making any exclusions.

Discussion

Maternal use of corticosteroids was weakly associated with the risk of hypospadias, but this association was negligible after adjustment for potential confounders. Our findings do not provide support for a recent experimental study indicating an association between prednisone and hypospadias. [15] They are in agreement with other recent epidemiologic studies that attempted to examine this hypothesis.[19-21]

Our findings suggest that the use of nasal spray/inhaled corticosteroids may be associated with a moderately increased risk of hypospadias, but that systemic corticosteroids are not associated with increased risk. One possible explanation for this difference is the longer duration of use for nasal spray/inhaled medications; However, the half-life and absorption of these medications tend to be less than systemic medications. Frequency of exposure tended to be daily for both medications and thus is an unlikely explanation for the findings.

Although we found no strong association between corticosteroid use and hypospadias overall, we did find a possible association between corticosteroid and increased risk of hypospadias in the mothers who did not take folic acid—containing supplements around the time of conception. In other words, early supplement intake may be protective against potential negative effects of corticosteroid intake. However, it is unclear why supplement intake during the second or third month of pregnancy, which would cover the time of urethral development, was not also protective. As noted earlier, experimental studies have demonstrated that vitamin B_6 and folic acid, which are contained in prenatal vitamin preparations, are protective against the teratogenic effects of corticosteroids,[27,28] and that these effects may result from the suppressed activity of glucocorticoid receptors. [29,30] A limitation of our stratified analysis is we analyzed corticosteroid exposure only overall, that is, without regard to specific time windows or route of administration. We did not pursue further classification of corticosteroid use based on timing, because of the relatively small numbers of exposed women and variable patterns of use during the designated time period. We categorized supplement use based on timing because maternal characteristics have been shown to vary among women who start taking supplements at different times relative to pregnancy.[26]

Strengths of our study include its population-based design, large size, geographic diversity, and ability to examine corticosteroid medication use based on specific time periods related to urethral development. It was also advantaged by its thorough case ascertainment from medical records, precise case definition, and differentiation of isolated and multiple cases. But even in this large study, certain comparisons were limited by small sample size, including comparisons based on type of medication and comparisons of ORs within the stratum of vitamin supplement use. Other limitations include the inability to examine dose of medications and underlying maternal conditions or indication. Recall bias (i.e., differential accuracy of reporting by case and control mothers) is possible, although the popular belief is that mothers of cases would tend to more accurately report exposures than mothers of controls, leading to spuriously strong

results. The longer recall period among cases than controls could also contribute to recall bias. Given that about 25% of study subjects were not interviewed, selection bias is a potential concern, and the generalizability of our findings to the larger study population is uncertain. For example, it is possible that non-participation could have selectively removed corticosteroid-exposed cases and therefore incurred some bias in our results, but we cannot determine whether this occurred. In addition, given that our study was limited to moderate/severe cases, an association with milder forms of hypospadias (the majority of cases) is possible, but this was not examined.

As noted earlier, several previous human epidemiologic studies have suggested that the use of corticosteroid medications during early pregnancy is associated with a 3- to 6-fold increased risk of orofacial clefts.[3] Few studies have explored associations with other structural malformations. Investigations of associations with other birth defects— especially defects with strong biological plausibility, such as hypospadias—will provide more insight into the potential teratogenicity of corticosteroids. In turn, this knowledge will allow clinicians and pregnant women to make more informed decisions regarding the intake of these important, commonly prescribed drugs during pregnancy.

Acknowledgments

Funding information is available at www.jpeds.com (Appendix). The findings and conclusions presented in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, the National Institute of Child Health and Human Development, the National Institutes of Health, or the California Department of Public Health.

We thank the California Department of Public Health, Maternal Child and Adolescent Health Division for providing surveillance data from California for this study.

Appendix

This research was supported by a grant from the National Institute of Child Health and Human Development (R03HD058873) and a cooperative agreement with the Centers for Disease Control and Prevention (Centers of Excellence Award U50/CCU925286). Coding of drug information in the NBDPS was done using the Slone Epidemiology Center Drug Dictionary, under license from the Slone Epidemiology Center at Boston University. We thank the California Department of Public Health, Maternal, Child and Adolescent Health Division for providing surveillance data from California for this study.

The following centers and investigators participated in the NBDPS:

University of Arkansas for Medical Sciences, Little Rock, Arkansas (Charlotte Hobbs, MD; U50/CCU613236); California March of Dimes, Oakland, California (Gary Shaw, DrPH; U50/CCU913241); University of Iowa, Iowa City, Iowa (Paul Romitti, PhD; U50/CCU713238); Massachusetts Department of Public Health, Boston, Massachusetts (Marlene Anderka, PhD; U50/CCU113247); New York State Department of Health, Albany, New York (Charlotte Druschel, MD; U50/ CCU223184); University of North Carolina, Chapel Hill, Raleigh, North Carolina (Andy Olshan, PhD and Robert Meyer, PhD; U50/CCU422096); Texas Department of State Health Services, Austin, Texas (Mark Canfield; PhD and Peter Langlois, PhD; U50/CCU613232); Utah Department of Health, Salt Lake City, Utah (Marcia Feldkamp, MSPH; U50/CCU822097).

References

1. Rowland J, Hendrickx A. Corticosteroid teratogenicity. Adv Vet Sci Comp Med 1983;27:99–128. [PubMed: 6359839]

2. Montenegro MA, Palomino H, Palomino HM. The influence of earthquake-induced stress on human facial clefting and its simulation in mice. Arch Oral Biol 1995;40:33–7. [PubMed: 7748110]
3. Carmichael SL, Shaw GM, Ma C, Rasmussen SA, Lammer EJ. Maternal corticosteroid use and orofacial clefts. Am J Obstet Gynecol 2007;197:585.e1–7. [PubMed: 18060943]
4. Paulozzi LJ. International trends in rates of hypospadias and cryptorchidism. Environ Health Perspect 1999;107:297–302. [PubMed: 10090709]
5. Paulozzi LJ, Erickson JD, Jackson RJ. Hypospadias trends in two US surveillance systems. Pediatrics 1997;100:831–4. [PubMed: 9346983]
6. Dolk H, Vrijheid M, Scott JE, Addor MC, Botting B, de Vigan C, et al. Toward the effective surveillance of hypospadias. Environ Health Perspect 2004;112:398–402. [PubMed: 14998760]
7. Sirianni R, Rehman KS, Carr BR, Parker CR Jr, Rainey WE. Corticotropin-releasing hormone directly stimulates cortisol and the cortisol biosynthetic pathway in human fetal adrenal cells. J Clin Endocrinol Metab 2005;90:279–85. [PubMed: 15494460]
8. Sirianni R, Mayhew BA, Carr BR, Parker CR Jr, Rainey WE. Corticotropin-releasing hormone (CRH) and urocortin act through type 1 CRH receptors to stimulate dehydroepiandrosterone sulfate production in human fetal adrenal cells. J Clin Endocrinol Metab 2005;90:5393–400. [PubMed: 16014403]
9. Negulescu RI, Strecker JR, Lauritzen C, Pal S. The influence of betamethasone on the feto-placental unit: a preliminary report. J Perinat Med 1977;5:120–32. [PubMed: 578813]
10. Ajayi GO, Fadiran EO. The effect of combined iron therapy (Chemiron) and single iron therapy on the dexamethasone-estriol reaction test for placenta insufficiency during normal pregnancy. Clin Exp Obstet Gynecol 1999;26:27–30. [PubMed: 10412619]
11. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. Arch Intern Med 1999;159:941–55. [PubMed: 10326936]
12. Reinisch JM, Simon NG, Karow WG, Gandelman R. Prenatal exposure to prednisone in humans and animals retards intrauterine growth. Science 1978;202:436–8. [PubMed: 705336]
13. Salomon DS, Pratt RM. Involvement of glucocorticoids in the development of the secondary palate. Differentiation 1979;13:141–54. [PubMed: 232045]
14. Kurzrock EA, Baskin LS, Cunha GR. Ontogeny of the male urethra: theory of endodermal differentiation. Differentiation 1999;64:115–22. [PubMed: 10234808]
15. Yucel S, Desouza A, Baskin LS. In utero prednisone exposure affects genital development. J Urol 2004;172:1725–30. [PubMed: 15371800]
16. Weinstock M. The potential influence of maternal stress hormones on development and mental health of the offspring. Brain Behav Immun 2005;19:296–308. [PubMed: 15944068]
17. Williams MT, Hennessy MB, Davis HN. CRF administered to pregnant rats alters offspring behavior and morphology. Pharmacol Biochem Behav 1995;52:161–7. [PubMed: 7501659]
18. Wise LD, Vetter CM, Anderson CA, Antonello JM, Clark RL. Reversible effects of triamcinolone and lack of effects with aspirin or L-656,224 on external genitalia of male Sprague-Dawley rats exposed in utero. Teratology 1991;44:507–20. [PubMed: 1771593]
19. Sorensen HT, Pedersen L, Norgaard M, Wogelius P, Rothman KJ. Maternal asthma, preeclampsia and risk of hypospadias. Epidemiology 2005;16:806–7. [PubMed: 16222172]
20. Kallen B, Olausson PO. Use of anti-asthmatic drugs during pregnancy, 3: congenital malformations in the infants. Eur J Clin Pharmacol 2007;63:383–8. [PubMed: 17279357]
21. Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology 1997;56:335–40. [PubMed: 9451758]
22. Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, et al. The National Birth Defect Prevention Study. Public Health Rep 2001;116(Suppl 1):32–40. [PubMed: 11889273]
23. National Birth Defects Prevention Network. Congenital malformations surveillance report: a report from the National Birth Defects Prevention Network. Teratology 2000;61:33–158. [PubMed: 10603201]
24. Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol 2003;67:193–201. [PubMed: 12797461]

25. Institute of Medicine, Committee on Nutritional Status During Pregnancy and Lactation, Food and Nutrition Board. Nutrition during pregnancy Part I: weight gain; part II: nutrient supplements. Washington, DC: National Academy Press; 1990.

26. Carmichael SL, Shaw GM, Yang W, Laurent C, Herring A, Royle M, et al. National Birth Defects Prevention Study. Correlates of intake of folic acid–containing supplements among pregnant women. Am J Obstet Gynecol 2006;194:203–10. [PubMed: 16389033]

27. Peer LA, Bryan WH, Strean LP, Walker JC, Bernhard WG, Peck GC. Induction of cleft palate in mice by cortisone and its reduction by vitamins. J Int Coll Surg 1958;30:249–54. [PubMed: 13575880]

28. Yoneda T, Pratt RM. Vitamin B6 reduces cortisone-induced cleft palate in the mouse. Teratology 1982;26:255–8. [PubMed: 7163974]

29. McCarty MF. High-dose pyridoxine as an “anti-stress” strategy. Med Hypotheses 2000;54:803–7. [PubMed: 10859691]

30. Allgood VE, Powell-Oliver FE, Cidlowski JA. The influence of vitamin B6 on the structure and function of the glucocorticoid receptor. Ann N Y Acad Sci 1990;585:452–65. [PubMed: 2192624]

31. van der Werff JFA, Nievelstein RAJ, Brands E, Luijsterburg AJM, Vermeij-Keers C. Normal development of the male anterior urethra. Teratology 2000;61:172–83. [PubMed: 10661906]

32. Carmichael SL, Shaw GM, Nelson V, Selvin S, Torfs CP, Curry CJ. Hypospadias: trends and descriptive epidemiology in a California population. Epidemiology 2003;14:701–6. [PubMed: 14569186]

Glossary

CI
: Confidence interval

EDD
: Estimated date of delivery

NBDPS
: National Birth Defects Prevention Study

OR
: Odds ratio

Table I

Association of hypospadias with maternal use of corticosteroid medications from 4 weeks before through 14 weeks after conception, by route of administration and component corticosteroid, NBDPS, 1997-2004

Route and component	Exposed cases	Exposed controls	OR (95% CI)*	Adjusted OR (95% CI)†
Any use	39	62	1.6 (1.1-2.5)	1.3 (0.8-2.0)
Any systemic use	7	19	1.0 (0.4-2.3)	0.6 (0.2-1.5)
Prednisone	5	11	1.2 (0.4-3.4)	0.7 (0.2-2.2)
Any nasal spray/ inhaled use	26	37	1.8 (1.1-3.0)	1.5 (0.9-2.6)
Beclomethasone	1	3	-	-
Budesonide	3	4	2.0 (0.4-8.8)	1.0 (0.2-4.6)
Fluticasone	13	18	1.9 (0.9-3.9)	1.5 (0.7-3.3)
Triamcinolone	6	7	2.2 (0.8-6.7)	2.1 (0.7-6.5)
Any topical use	3	9	0.9 (0.2-3.2)	0.6 (0.2-2.4)
Other/not otherwise specified use	3	0	-	-

*The reference group for these comparisons included 1126 hypospadias cases and 2938 male controls with no exposure from 4 weeks before through 14 weeks after conception.

†The reference groups for these comparisons included 1101 hypospadias cases and 2881 male controls with no exposure from 4 weeks before through 14 weeks after conception; ORs were adjusted for maternal race/ethnicity, education, age, and study site.

Table II

Association of hypospadias with maternal use of corticosteroid medications from 4 weeks before through 14 weeks after conception, by timing of exposure, NBDPS, 1997-2004

Exposure period	Exposed cases	Exposed controls	OR (95% CI)*	Adjusted OR (95% CI)†
Any exposure 4 weeks before conception through 14 weeks after conception	39	62	1.6 (1.1-2.5)	1.3 (0.8-2.0)
Any exposure during weeks 5-14 after conception	31	46	1.8 (1.1, 2.8)	1.4 (0.9, 2.4)
Exposure only during 4 weeks before conception or weeks 1-4 after conception	8	16	1.3 (0.6, 3.1)	0.9 (0.3, 2.1)

*The reference group for the comparisons included 1126 hypospadias cases and 2938 male controls with no exposure from 4 weeks before through 14 weeks after conception.

†The reference group for these comparisons included 1101 hypospadias cases and 2881 male controls with no exposure from 4 weeks before through 14 weeks after conception; ORs were adjusted for maternal race/ethnicity, education, and age and study site.

Table III

Association of hypospadias with maternal use of corticosteroid medications from 4 weeks before through 14 weeks after conception, stratified by maternal periconceptional intake of folic acid–containing supplements, NBDPS, 1997-2004

	Cases, n	Controls, n	OR (exact 95% CI)	Adjusted odds ratio (95% CI)*
Supplement intake began in the month before pregnancy or the first month of pregnancy				
Corticosteroid use	24	44	1.1 (0.7-1.9)	0.9 (0.5, 1.6)
No use	693	1432	Reference*	Reference
Supplement intake began in the second or third month of pregnancy				
Corticosteroid use	11	12	3.0 (1.3-6.8)	2.6 (1.1, 6.5)
No use	325	1052	Reference	Reference
No periconceptional supplement intake				
Corticosteroid use	4	6	2.9 (0.8-10.5)	2.9 (0.6, 13.1)
No use	101	440	Reference	Reference

*Odds ratios were adjusted for maternal race-ethnicity, education, age, and study site.