Maternal Corticosteroid Use and Hypospadias

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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. *(J Pediatr 2009;155:39-44)*.

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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 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.

CI	Confidence interval
EDD	Estimated date of delivery
NBDPS	National Birth Defects Prevention Study
OR	Odds ratio

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*A list of National Birth Defects Prevention Study investigators is available at www.jpeds.com (**Appendix**).

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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