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# Hypospadias in Washington State: Maternal Risk Factors and Prevalence Trends

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**ABSTRACT.** *Objective.* Maternal risk factors for hypospadias are poorly defined, and there is debate about temporal trends in hypospadias prevalence. We examined select maternal characteristics as possible risk factors for hypospadias among male offspring and evaluated yearly prevalence rates in Washington State.

*Methods.* We performed a population-based, case-control study using linked birth-hospital discharge data from Washington State for 1987–1997 and prevalence data for 1987–2002. All cases of hypospadias were identified on the basis of *International Classification of Diseases, Ninth Revision*, codes from the birth hospitalization ( $N = 2155$ ). Five control subjects were randomly selected for each case subject from the remaining singleton births, frequency matched according to year of birth ( $N = 10\,775$ ). Maternal and infant characteristics were ascertained from the birth certificate. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Yearly prevalence was determined by dividing the total number of hypospadias cases by the number of male singleton live births for each year.

*Results.* The risk of delivering an affected male infant increased with advancing maternal age; relative to women <20 years of age, those >40 years of age were at greatest risk (OR: 1.70; 95% CI: 1.17–2.48). Infants of nonwhite women were generally at decreased risk. Infants born to women with preexisting diabetes mellitus were at greater risk than those born to women without diabetes (OR: 2.18; 95% CI: 1.03–4.60); however, this was not observed for infants born to women with gestational diabetes. The birth prevalence of hypospadias in 2002 was 5.0 cases per 1000 male births, not significantly different from that in 1987.

*Conclusion.* Older maternal age, white race, and preexisting diabetes were associated with increased risk of hypospadias among male offspring. The prevalence of hypospadias in Washington State did not increase significantly between 1987 and 2002. *Pediatrics* 2005; 115:e495–e499. URL: [www.pediatrics.org/cgi/doi/10.1542/peds.2004-1552](http://www.pediatrics.org/cgi/doi/10.1542/peds.2004-1552)

*peds.2004-1552; hypospadias, age, race, diabetes mellitus, prevalence.*

ABBREVIATIONS. OR, odds ratio; CI, confidence interval; ICD-9, *International Classification of Diseases, Ninth Revision*.

Hypospadias is one of the most common congenital anomalies in the United States, with an estimated prevalence of 3 to 8 cases per 1000 male births.<sup>1,2</sup> The malformation is the result of incomplete fusion of the urethral folds, which usually occurs between 9 and 12 weeks of gestation. Although the success rate for surgical repair is high,<sup>3</sup> the high prevalence of hypospadias translates into a significant financial burden on the health care system. When rare complications do occur, the resultant morbidity of corrective procedures, psychologic stress, and potential loss of function can be devastating to the patient and family.

Although hypospadias is common, risk factors for this birth defect are relatively poorly defined. Familial aggregation is well recognized.<sup>4</sup> It has been established that low birth weight and shorter gestation are associated with hypospadias,<sup>5–7</sup> but other risk factors are more controversial. At least 2 studies have suggested that older maternal age may be a risk factor for hypospadias,<sup>1,8</sup> but both of those studies relied on data from the same birth defects registry. Studies that examined race as a potential risk factor have yielded conflicting results.<sup>1,9</sup> Diabetes mellitus was implicated in at least 1 study.<sup>10</sup> Finally, at least 1 large study suggested that the prevalence of hypospadias in the United States is increasing,<sup>11</sup> a conclusion not shared by others.<sup>1,8</sup>

The goal of this study was to evaluate the extent to which maternal age, race/ethnicity, and diabetes are associated with hypospadias among male offspring. We also calculated yearly prevalence rates, to determine whether the prevalence of hypospadias is increasing in Washington State.

## METHODS

We conducted a population-based, case-control study using linked birth certificate-hospital discharge data from Washington State. Information available for this study included variables from the birth certificates (which use a check-box format to record maternal, pregnancy, and infant characteristics), as well as *International Classification of Diseases, Ninth Revision* (ICD-9) codes and administrative and billing data for the birth hospitalization of the mother and infant. Data used for analysis of potential risk factors

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included linked records, which were available for 1987–1997; data used for prevalence estimates were available through 2002.

Case subjects were defined as male singleton infants with an ICD-9 code for hypospadias/epispadias (752.6), ie, any 1 of up to 9 birth hospitalization discharge diagnosis codes available. In 1996, the ICD-9 code for hypospadias/epispadias was expanded to include a specific subcategory for hypospadias (752.61), and this code was used to identify cases after 1996. Control subjects were randomly selected from the remaining male singleton infants, at a relative frequency of 5 control subjects per case subject. Control subjects were frequency-matched to case subjects according to year of birth.

Initially, stratified analyses were conducted with Mantel-Haenszel methods to obtain odds ratio (OR) estimates of the relative risk and 95% confidence intervals (95% CIs). Subsequently, logistic regression was used. The main exposure variables obtained from the birth certificates were maternal age (<20, 20–24, 25–29, 30–34, 35–39, 40–44, or 45–49 years), race/ethnicity (white, black, Hispanic, Asian, other, or missing), and diabetes status (none, preexisting, or gestational). Missing data were not included in the analyses. In addition to these variables, other potential confounding variables considered were paternal age (<20, 20–29, 30–39, or >39 years or missing), maternal prenatal smoking and alcohol use (yes, no, or missing), number of prior births and pregnancies (0, 1, 2, 3, or >3), and infant gestational age (20–37, 38–42, or >42 weeks or missing) and birth weight (grams, as a continuous variable). Only covariates that changed the risk estimate by  $\geq 10\%$  were retained in the model.

Crude yearly birth prevalence rates were determined by dividing the total number of cases that occurred during a calendar year by the total number of male singleton births during the same year. Robust linear regression analysis was used to test the trend of yearly prevalence rates.

## RESULTS

Infants with hypospadias were slightly more likely to be delivered at gestational age of <37 weeks, and their mothers were slightly less likely to have had

**TABLE 1.** Maternal and Infant Characteristics of Hypospadias Case and Control Subjects, Washington State, 1987–1997

Characteristic	No. (%)	
	Hypospadias (N = 2155)	Control (N = 10 775)
Gestational age		
$\leq 37$ wk	268 (15.0)	1036 (11.6)
38–42 wk	1514 (84.7)	7842 (88.1)
>42 wk	5 (0.3)	24 (0.3)
Prior pregnancies		
1	1334 (61.9)	6554 (60.8)
2	392 (18.2)	1938 (18.0)
3	231 (10.7)	1073 (10.0)
$\geq 4$	198 (9.2)	1210 (11.2)
Prior births		
0	967 (44.9)	4390 (40.7)
1	657 (30.5)	3485 (32.3)
2	315 (14.6)	1610 (14.9)
3	111 (5.2)	596 (5.5)
$\geq 4$	105 (4.9)	694 (6.4)
Paternal age		
<20 y	63 (3.3)	301 (3.2)
20–29 y	842 (44.3)	4510 (47.6)
30–39 y	853 (44.9)	3993 (42.1)
>39 y	143 (7.5)	680 (7.2)
Maternal smoking		
Yes	360 (16.7)	1923 (17.9)
No	1646 (76.4)	8161 (75.7)
Missing	149 (6.9)	691 (6.4)
Maternal alcohol use		
Yes	31 (1.4)	145 (1.4)
No	1539 (71.4)	7828 (72.7)
Missing	585 (27.2)	2802 (26.0)

Numbers may not add up to totals because of missing data.

prior births (Table 1). Most other characteristics examined were similar for case and control subjects.

The risk of hypospadias increased with increasing maternal age, ranging from an OR of 1.12 (95% CI: 0.94–1.34) for infants of mothers 20 to 24 years of age to an OR of 1.70 (95% CI: 1.17–2.48) for infants of mothers >40 years of age (Table 2). The linear trend was statistically significant ( $P < .001$ ). Relative to infants of white women, infants born to nonwhite women were consistently at decreased risk of hypospadias, with the lowest risk being observed for infants of Hispanic women (OR: 0.46; 95% CI: 0.37–0.58). Infants of women with preexisting diabetes (OR: 2.18; 95% CI: 1.03–4.60), but not gestational diabetes (OR: 1.18; 95% CI: 0.88–1.59), were at increased risk.

Overall, the birth prevalence of hypospadias neither increased nor decreased between 1987 and 2002 ( $P$  for linear trend = .17) (Fig 1). In 1987, the prevalence of hypospadias was 4.6 cases per 1000 male singleton births; in 2002, the prevalence was 5.0 cases per 1000 births.

## DISCUSSION

Our reliance on hospital discharge data for the birth hospitalization might have resulted in some underreporting of hypospadias, although the use of these data allowed a longer window of observation for birth conditions and anomalies that might not be reported on birth certificates alone. Even birth defect registries might not identify milder forms of hypospadias.<sup>1,12</sup> In our analyses, underreporting of hypospadias, resulting in misclassification of case subjects as control subjects, would have had the effect of biasing results toward the null hypothesis.

We found a strong positive association between advancing maternal age and risk of hypospadias. Until recently, multiple studies investigating hypospadias did not report an association with maternal age.<sup>6,13–15</sup> In 2001, however, Fisch et al<sup>8</sup> reported a 50% higher risk of hypospadias among women >35 years of age, compared with women <20 years of age, in California and a 20% higher risk for this age group in New York. In 2003, Carmichael et al<sup>1</sup> reported similar results for California. Both of these studies relied on registry data, and both used the same California registry. Our results are consistent with those findings. However, we were also able to demonstrate a linear relationship between maternal age and hypospadias risk, with risk nearly doubling by the time women were >40 years of age.

It is not known why maternal age may be a risk factor for hypospadias. It is clear, however, that older women are at higher risk of having children with genetic defects.<sup>16</sup> It is therefore plausible that the risk is mediated via underlying genetic defects associated with aging. Some authors have suggested that subfertility is a potential mechanism linking hypospadias with maternal age, because subfertile women often are older at the time of first conception.<sup>17</sup> We did not have sufficient data to pursue this as a potential confounding factor or as an independent risk factor for hypospadias, although our results were

**TABLE 2.** Hypospadias in Relation to Selected Maternal Characteristics, Washington State, 1987–1997

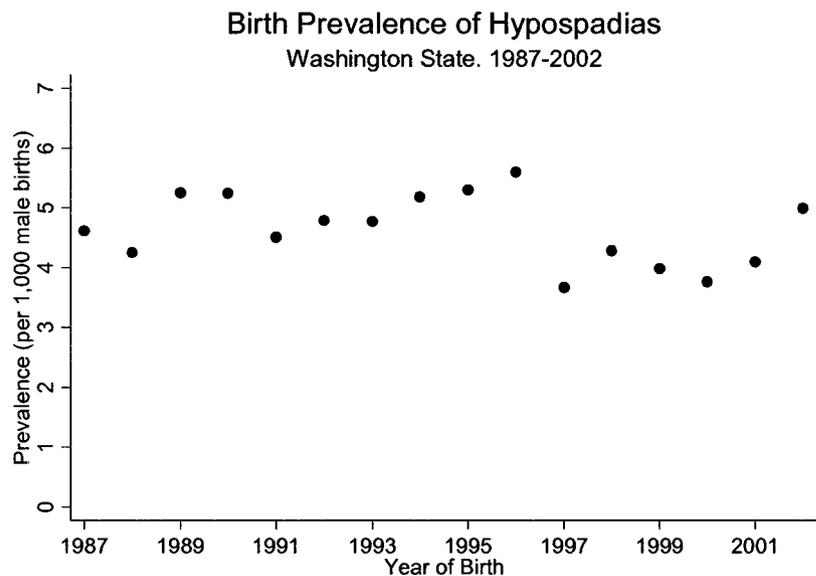
Characteristic	No. (%)		OR (95% CI)
	Hypospadias (N = 2155)	Control (N = 10 775)	
Age*			
<20 y	205 (9.5)	1174 (10.9)	1.00 (referent)
20–24 y	514 (23.9)	2774 (25.7)	1.12 (0.94–1.34)
25–29 y	624 (29.0)	3245 (30.1)	1.20 (1.01–1.43)
30–34 y	536 (24.9)	2408 (22.4)	1.43 (1.19–1.71)
35–39 y	234 (10.9)	1001 (9.3)	1.54 (1.25–1.91)
≥40 y	42 (2.0)	173 (1.2)	1.70 (1.17–2.48)†
Race/ethnicity			
White	1838 (85.3)	8405 (78.0)	1.00 (referent)
Black	59 (2.7)	401 (3.7)	0.67 (0.51–0.89)
Hispanic	85 (3.9)	839 (7.8)	0.46 (0.37–0.58)
Asian	72 (3.3)	594 (5.5)	0.55 (0.43–0.71)
Other	39 (1.8)	239 (2.2)	0.75 (0.53–1.05)
Diabetes status			
None	1914 (88.8)	9617 (89.3)	1.00 (referent)
Preexisting	10 (0.5)	23 (0.2)	2.18 (1.03–4.60)
Gestational	55 (2.6)	234 (2.2)	1.18 (0.88–1.59)

Numbers may not add up to totals because of missing data.

\* Adjusted for parity.

† Trend test,  $P < .001$ .

**Fig 1.** Reported prevalence of hypospadias in linked birth-hospital discharge records for male singletons born in Washington State, 1987–2002 (trend test,  $P = .17$ ).



generally not affected by maternal parity or gravidity. Alternatively, it is possible that age is the underlying reason for subfertility, making maternal age the proximal risk factor for hypospadias.

At least 3 recent studies investigated race as a potential risk factor for hypospadias in the United States. Two of those studies, which were hospital based, found no association.<sup>7,9</sup> However, using the population-based California Birth Defects Registry, Carmichael et al<sup>1</sup> observed that “non-Hispanic white” women were at greater risk of having a child with hypospadias, with the exception of nonisolated severe cases. Our results are consistent with those findings. We found that mothers classified as white were at greatest risk, compared with other identified racial groups, whereas those classified as Hispanic had the lowest risk. The reason for this association is unclear. It is possible that race-related susceptibility

genes or different exposures to environmental risk factors are responsible for the observed differences in risk. It is also possible that ascertainment bias accounts for the observed difference, with accurate diagnosis occurring less often among racial minorities. However, all patients in our study (mothers and infants) were hospitalized at birth (home births were not included), making it less likely that nondiagnosis occurred because of race-related differences in access to care.

Greater-than-expected rates of several different congenital malformations, including hypospadias, were reported in a Swedish registry-based study of women with preexisting diabetes.<sup>10</sup> However, this was not observed in a hospital-based analysis of NICU admissions.<sup>7</sup> Consistent with the findings of the earlier study, we observed an association with preexisting but not gestational diabetes. An in-

creased risk of congenital malformations among women with diabetes has been well established,<sup>18</sup> but the mechanism by which diabetes might affect the developing urethra is unclear. Normal development of the urethra occurs under the influence of androgens, which are synthesized in response to fetal surges of luteinizing hormone at the gestational age of ~8 to 14 weeks.<sup>17</sup> It is possible that diabetes interferes with the normal fetal endocrine axis, resulting in a greater likelihood of abnormal urethral development. The observation that gestational diabetes is not associated with a higher risk of hypospadias is consistent with this idea, because gestational diabetes usually develops after these key steps in urethral development have been completed.<sup>19</sup>

Finally, in contrast to a previously published report that indicated that the prevalence of hypospadias in the United States was increasing,<sup>11</sup> we observed relatively stable rates of hypospadias in Washington State from 1987 through 2002. However, as noted previously, the ICD-9 classification of hypospadias changed in 1996, which might in part account for the dip in prevalence between 1996 and 1997 (Fig 1). After the ICD-9 code was changed from 752.6 (hypospadias/epispadias) to 752.61 (hypospadias), we used the new code to define prevalent cases. It is possible that before the code expansion physicians coded other congenital abnormalities affecting the penis as 752.6 because of the lack of a more specific code. After the code was expanded to include more accurate subcategories, the prevalence of hypospadias determined by our method might have decreased, with previous misclassification of nonhypospadias cases being replaced by assignment to appropriate diagnostic subcategories. To investigate the effect this might have had on the prevalence trends, we performed several subanalyses. When we considered cases before 1997 and after 1997 separately, there was not a statistically significant trend for either time period. When we considered all cases with the ICD-9 categories 752.6 and 752.6x as prevalent cases, there was a statistically significant increase with time. However, increasing proportions of women bearing children each year were in older age groups, and the trend became nonsignificant after adjustment for maternal age. Taken as a whole, the evidence from this study does not suggest that the prevalence of hypospadias is increasing significantly in Washington State.

This study has several potential limitations. First, the case ascertainment relied on available ICD-9 codes, which likely resulted in some of the cases before 1996 having the diagnosis of epispadias (a distinct, severe, penile abnormality that is associated with bladder extrophy). Fortunately, epispadias is rare, and review of the data available after 1996 demonstrated that the mean frequency of epispadias in Washington State was 2.3 cases per year from 1996 to 2002, making it unlikely that misclassification biased the results. However, as mentioned above, it is possible that congenital anomalies other than hypospadias and epispadias (eg, congenital chordee) were coded as such because of the lack of a more appropriate

ICD-9 code. There is no way to determine whether, and at what frequency, this occurred. It is likely, though, that this was a relatively rare event and therefore had minimal effects on our results. Second, our method of case ascertainment did not allow us to classify hypospadias according to severity, ie, first, second, or third degree. If this accepted classification scheme is a clinical continuum with a common set of risk factors, then our inability to subclassify the cases should not have affected our results. However, if more severe forms have distinct causes, then the associations we identified might not be generalizable to all categories of severity. Because ~80% of hypospadias cases are classified as first or second degree,<sup>17</sup> our results are likely to be most generalizable to these categories of severity. Finally, our study was not able to ascertain data for infants born at home. It has been estimated that home births represent only 1% of all births in Washington State,<sup>20</sup> however, and it is unlikely that excluding this subset of infants significantly biased our results.

## CONCLUSIONS

Advanced maternal age, white maternal race, and preexisting diabetes mellitus were associated with hypospadias among offspring. Additional research is needed to establish the biologic link between hypospadias and these risk factors. Furthermore, the prevalence of hypospadias in Washington State did not increase significantly between 1987 and 2002.

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