

Maternal Hypertension, Antihypertensive Medication Use, and the Risk of Severe Hypospadias

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BACKGROUND: Hypertensive disorders occur in an estimated 5–10% of pregnancies, but few studies have examined birth defects in relation to high blood pressure and antihypertensive medication use. The objective of this study was to investigate the relationship between high blood pressure, antihypertensive medication use, and severe hypospadias. **METHODS:** We used data from the National Birth Defects Prevention Study, a population-based, multicenter, case-control study of birth defects to assess risks for severe hypospadias in relation to self-reported high blood pressure and prenatal exposures to antihypertensive drugs in 758 male infants with severe hypospadias and 2,058 male controls born between 1997 and 2002. Logistic regression analyses estimated ORs and 95% CIs, adjusted for potential confounders. **RESULTS:** We observed slight to moderate elevations in the risk of severe hypospadias for maternal untreated hypertension (adjusted OR 2.1; 95% CI: 1.6–2.9) and antihypertensive medication use during 1 month preconception through pregnancy month 4 (adjusted OR 1.4; 95% CI: 0.7–2.9). The association was strongest for subjects initiating medications after the fourth month (adjusted OR 5.0; 95% CI: 1.9–12.9). **CONCLUSIONS:** We observed an association between hypertension, antihypertensive medication use, and the risk of severe hypospadias, particularly when medication use began late in pregnancy. Because hypospadias occurs in early pregnancy, the data suggest that hypertension and its morphologic/physiologic precursors play an etiologic role, perhaps via compromised uteroplacental perfusion. *Birth Defects Research (Part A) 82:34–40, 2008.* © 2007 Wiley-Liss, Inc.†

Key words: hypospadias; maternal hypertension; antihypertensive medications

INTRODUCTION

Hypertensive disorders occur in 5–10% of pregnancies and are the leading cause of maternal and perinatal mortality worldwide (Afifi and Churchill, 2003). In women with severe hypertension, antihypertensive medications are administered in the hospital to prevent stroke, death, and eclampsia in the mother (Afifi and Churchill, 2003; Magee, 2001; Mulrow et al., 2000; NHBPEP, 2000, 2004; Sibai, 2002). However, there is no consensus on treating mild to moderate hypertension during pregnancy, and antihypertensive medications are often used.

Six major classes of drugs are used to treat hypertension, based on site of action: antiadrenergic agents, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers, calcium channel blockers, diuretics, and direct vasodilators (Afifi and Churchill,

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2003; Magee, 2001; Mulrow et al., 2000; NHBPEP, 2004; Sibai, 2002). Information on the use of antihypertensive medications during pregnancy and the risk of birth defects is limited. Clinical trials enrolling women with hypertension have not detected birth defects associated with the commonly used antihypertensive medications, but sample sizes in these trials have been too small to draw firm conclusions (Afifi and Churchill, 2003; Magee, 2001; Mulrow et al., 2000; NHBPEP, 2004; Sibai, 2002). ACE inhibitors and angiotensin II receptor blockers, two classes with a similar mechanism of action, are contraindicated during pregnancy because of a well-known fetopathy associated with second and third trimester use (Quan, 2006). The safety of the beta blocker atenolol has been questioned due to an increased risk of small for gestational age births (Briggs et al., 2003; Lydakis et al., 1999).

Hypospadias is a male urogenital anomaly that results from the abnormal development of the urethra (Manson and Carr, 2003; Hussain et al., 2002). It is one of the most common congenital malformations in males and has been increasing in the United States and Europe since the 1970s. Some epidemiologic studies have suggested an increased risk of severe hypospadias in infants of women exposed to beta blockers (Briggs et al., 2003; Czeizel, 1989) or diuretics (Briggs et al., 1998), while other studies have failed to demonstrate increased risks in infants of women exposed to any antihypertensive medication (Heinonen et al., 1977) or calcium channel blockers (Sorensen et al., 2001). Recent studies have suggested an association between preeclampsia and severe hypospadias (Akre et al., 1999; Sorensen et al., 2005), but other studies have failed to show such a relationship with chronic hypertension, gestational hypertension, or preeclampsia (Aschim et al., 2004; Heinonen et al., 1977; Hussain et al., 2002). In addition to these inconsistent findings, it is difficult to separate the effects of maternal hypertension from those of medication (Kallen, 2005; Mitchell, 2000; Ward, 2001). Such concern is particularly relevant because hypertension (Kliman, 2000; Mayhew et al., 2004) or iatrogenic hypotension (Afifi and Churchill, 2003; Magee, 2001; NHBPEP, 2004; von Dadelszen and Magee, 2002) may cause adverse birth outcomes by altering perfusion in the placenta during early pregnancy.

Because approximately half of the pregnancies in the United States are unplanned, fetal exposure to antihypertensive medications might occur before a woman knows she is pregnant (Han et al., 2005; Magee, 2001). Likewise, the screening and subsequent diagnosis of hypertension might not occur until several weeks into pregnancy, which exposes the fetus to the effects of altered uteroplacental blood flow. In this study, we examined the relationship between antihypertensive medication use during pregnancy, untreated hypertension, and the occurrence of severe hypospadias in the National Birth Defects Prevention Study (NBDPS).

METHODS

Study Design and Population

We analyzed data from the NBDPS, an ongoing, multi-site, population-based, case-control study that investigates genetic and environmental risk factors of 37 major

birth defects (Rasmussen et al., 2003; Yoon et al., 2001). The analysis included cases of severe hypospadias and male control births from eight participating states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, and Texas) with estimated dates of delivery (EDD) from October 1, 1997 through December 31, 2002. Case infants were identified from the population-based birth defects surveillance systems of the participating centers and included stillbirths (greater than 20 weeks gestation) or livebirths diagnosed with severe hypospadias before 1 year of age. Control infants were livebirths without birth defects randomly selected from birth certificates or hospital discharge listings in the same states as the cases. Infants whose mothers did not speak English or Spanish and infants who were adopted or in foster care were excluded. Among eligible infants, participation was 68% among cases and 69% among controls. Each study site has obtained Institutional Review Board approval for the NBDPS.

Clinical Review and Case Classification

Hypospadias cases were reviewed by clinicians to ensure they met the specific case definition and diagnostic criteria for the study. Data abstracted from infants' medical records that were used to confirm a diagnosis of severe hypospadias included clinicians' and nurses' notes, urology consultations, endocrinology consultations, genetic consultations, operative reports, pathology reports, autopsy reports, and radiographic studies. Infants with severe hypospadias (i.e., subcoronal/penile, scrotal, or perineal meatal opening) diagnosed at the time of physical examination, surgery, or autopsy were included in the study. Infants with coronal ("first-degree") hypospadias, a female karyotype (46,XX), true mosaicism (46,XX/46,XY), a known or strongly suspected chromosome abnormality, a diagnosed single gene condition, certain hormonal profile or anatomical features consistent with an intersex condition, or an unconfirmed diagnosis were excluded. Eligible cases of hypospadias were further classified into isolated (hypospadias without other major malformations) and multiple malformation categories (Rasmussen et al., 2003). Statistical analyses were performed on all cases and the subset of isolated cases, the latter being considered a more etiologically homogeneous group of defects than those defects associated with additional anomalies. Because 91.4% of all cases had isolated hypospadias, analyses presented in this report are limited to isolated defects.

Exposure Assessment

The NBDPS collected information on study subjects via a computer-assisted telephone interview. Standard procedures were used for contacting and interviewing mothers of infants within 24 months of the EDD. The interview included questions on the mother's medical and pregnancy history, family demographics, nutrition, and behaviors (Yoon et al., 2001).

Interviewers asked detailed questions about the diagnosis, timing, and treatment of high blood pressure. The computer-assisted telephone interview did not identify types of hypertension (e.g., chronic, preeclampsia). Mothers were asked about use of antihypertensive medication

between 3 months preconception and birth; information included drug name, start and stop dates, and duration and frequency of use. If the mother did not recall the drug name, a list of commonly prescribed antihypertensive medications was read to her. All drug exposures were coded using the Slone Epidemiology Center Drug Dictionary.

Mothers were considered exposed to an antihypertensive medication if they reported a diagnosis of high blood pressure and they reported use of antihypertensive medication at any time from 1 month before pregnancy to birth. Medications were categorized into six classes: antiadrenergic agents, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, diuretics, and direct vasodilators. Antiadrenergic agents were further classified into centrally acting agents, beta blockers, and alpha-beta blockers (drugs with both alpha and beta blocking properties). Individual antiadrenergic agents were categorized as methyldopa, atenolol, and labetalol.

Two windows of exposure were assessed. "Early antihypertensive medication use," defined as medication use between 1 month preconception through pregnancy month 4, was used to capture the period of urethral closure (weeks 8–14 postconception) (Manson and Carr, 2003). Women exposed during this early period included those with treated chronic hypertension. "Late antihypertensive medication use only," defined as medication use between pregnancy month 5 and birth, was used to identify women whose first exposure to an antihypertensive medication occurred after development of hypospadias, and included women who began treatment for exacerbated chronic hypertension, gestational hypertension, or preeclampsia. Women reporting high blood pressure during pregnancy without medication use were classified as having untreated high blood pressure, and women not reporting high blood pressure or medication use were considered unexposed.

Exclusions

We excluded female controls, five male controls with missing data for high blood pressure, and 13 male controls whose mothers did not report high blood pressure but reported a drug with antihypertensive properties for another indication.

Statistical Analysis

We used unconditional logistic regression to estimate prevalence ORs and 95% CIs for the associations between antihypertensive medication exposure, untreated hypertension, and the occurrence of severe hypospadias. Risk factors for hypospadias or hypertension previously reported in the literature were selected for evaluation: plurality, maternal age at delivery, education, race/ethnicity, parity, prepregnancy body mass index, pre-existing Type 1 or 2 diabetes, gestational diabetes, fertility treatment or procedure, smoking, oral contraceptive use, and folic acid/multivitamin use. Additionally, ingestion of medications with vasoactive properties (amphetamines, decongestants, bronchodilators, ibuprofen, aspirin, other nonsteroidal anti-inflammatory drugs, and anti-migraine medications) was examined. Covariates for the full multivariable logistic regression models were

selected on the basis of relationships with both exposure and outcome variables in bivariate analyses. Adjusted ORs and CIs were estimated using multivariable models that included terms for those factors that altered the effect estimate generated from the full model by more than 10% when dropped from the model. Final models included study center, maternal age, race/ethnicity, parity, plurality, prepregnancy body mass index, pre-existing diabetes, and gestational diabetes. Models were constructed with exposure terms for "early antihypertensive medication use," "late antihypertensive medication use only," and untreated high blood pressure. Analyses were performed to evaluate the relationship between severe hypospadias and exposures to antihypertensive medications as a group (early and late). When numbers permitted, individual medication classes and medications used during early pregnancy were evaluated. Separate analyses were performed excluding participants with a family history of hypospadias in a first-degree relative, women with pre-existing diabetes, and multiple births. Data management and analysis were performed using SAS software version 9.1 (Cary, NC).

RESULTS

We identified 829 cases of severe hypospadias in the NBDPS among infants with an EDD from October 1, 1997 through December 31, 2002. Of the cases identified, 758 (91.4%) infants had isolated hypospadias. The control group consisted of 2,058 male infants without malformations. Crude analyses comparing controls with isolated cases (Table 1) revealed that cases were more likely to have a family history of hypospadias and were more likely to be a multiple birth, have been born preterm, or have had low birth weight. Mothers of case infants were more likely to be older, to be non-Hispanic, to have higher income and education levels, and to have fewer previous births. They were also more likely to have used folic acid or a multivitamin during early pregnancy or to have pre-existing type 1 or 2 diabetes. Additionally, case mothers and fathers were more likely to have received fertility treatment.

One hundred and forty (18.5%) case mothers and 195 (9.5%) control mothers reported high blood pressure during the study pregnancy, and 28 (3.7%) case mothers and 36 (1.7%) control mothers reported taking antihypertensive medications for the condition at some time between 3 months preconception and birth. Medication users represented 20.0% of case mothers and 18.5% of control mothers who reported high blood pressure during pregnancy. The proportion of mothers exposed to medications increased throughout pregnancy for both cases and controls. Medication use was higher among case mothers than among control mothers at every time period.

Fifteen (2.0%) case mothers and 24 (1.2%) control mothers reported antihypertensive medication use during 1 month preconception through the fourth month of pregnancy (Table 2). The adjusted OR for severe hypospadias was 1.4 (95% CI: 0.7–2.9) in this exposure group relative to those not exposed. Thirteen (1.7%) case mothers and 12 (0.6%) control mothers reported initiating antihypertensive medication treatment after the fourth month of pregnancy (aOR 5.0; 95% CI: 1.9–12.9). In infants of women with untreated high blood pressure, there was

Table 1
Selected Characteristics of Study Participants,
National Birth Defects Prevention Study,
October 1997–December 2002

Covariate	Controls	Isolated
	(n = 2,058)	hypospadias (n = 758)
	n (%)	n (%)
Plurality		
Singleton	1,991 (96.9)	690 (91.3)
Multiple	63 (3.1)	66 (8.7)
Age at delivery		
<20 years	249 (12.1)	47 (6.2)
20–34 years	1,521 (73.9)	554 (73.1)
≥35 years	288 (14.0)	157 (20.7)
Parity		
0 births	812 (39.6)	399 (52.8)
1 birth	728 (35.5)	239 (31.6)
≥2 births	513 (25.0)	118 (15.6)
Race/ethnicity		
Non-Hispanic White	1,231 (60.1)	540 (71.7)
Non-Hispanic Black	237 (11.5)	100 (13.3)
Hispanic	467 (22.7)	72 (9.6)
Other	118 (5.7)	41 (5.4)
Education		
<12 years	348 (17.1)	69 (9.2)
12 years	520 (25.5)	142 (18.8)
13–15 years	547 (26.9)	194 (25.7)
≥16 years	621 (30.5)	349 (46.3)
Prepregnancy body mass index (kg/m ³)		
Underweight (<18.5)	130 (6.6)	40 (5.4)
Normal (18.5–<25)	1,133 (57.4)	416 (56.0)
Overweight (25–<30)	446 (22.6)	176 (23.7)
Obese (≥30)	265 (13.4)	111 (14.9)
Folic acid/multivitamin use*		
Yes	1,748 (85.1)	690 (91.3)
No	305 (14.9)	66 (8.7)
Pre-existing diabetes		
Yes	13 (0.6)	9 (1.2)
No	2,045 (99.4)	749 (98.8)
Gestational diabetes		
Yes	117 (5.7)	46 (6.1)
No	1,941 (94.3)	712 (93.9)
Oral contraceptive use [†]		
Yes	282 (13.7)	83 (11.0)
No	1,772 (86.3)	672 (89.0)
Fertility treatment [†]		
Any		
Yes	82 (4.0)	81 (10.7)
No	1,970 (96.0)	676 (89.3)
Preterm birth (<37 weeks)		
Yes	180 (8.7)	195 (25.8)
No	1,878 (91.3)	561 (74.2)
Low birthweight (<2,500 g)		
Yes	119 (5.8)	193 (25.7)
No	1,927 (94.2)	558 (74.3)
Smoking*		
Yes	414 (20.3)	139 (18.4)
No	1,630 (79.7)	616 (81.6)
Family history of hypospadias		
Yes	3 (0.1)	39 (5.1)
No	2,055 (99.9)	719 (94.9)

*Any time 1 month preconception through month 3 postconception.

[†]Any time between 3 months preconception and birth.

approximately a doubling of risk for hypospadias (aOR 2.1; 95% CI: 1.6–2.9). Risks were not appreciably different after excluding case infants with a family history of hypospadias in a first-degree relative, cases that were multiple births, and case mothers with pre-existing diabetes.

Subclasses of antiadrenergic agents (e.g., centrally acting antiadrenergic agents, alpha-beta blockers, beta blockers) were the most commonly reported drugs used by case mothers during 1 month preconception through pregnancy month 4 (Table 3). Subclasses of antiadrenergic agents (e.g., centrally acting antiadrenergic agents, beta blockers), calcium channel blockers, and ACE inhibitors were the drugs most commonly reported by control mothers during the preconception period and the first trimester. The centrally acting antiadrenergic agent methyl dopa was the most common treatment choice, and women were more likely to continue preconception treatment, begin initial treatment, or change treatment from other drug classes to methyl dopa during early pregnancy. Evaluating risks related to specific classes or individual medications during early pregnancy was difficult because of the number of women changing treatments, taking more than one drug class, or taking a combination drug. The adjusted OR for hypospadias in infants of women reporting exposures only to antiadrenergic agents at any time between 1 month preconception and the fourth month of pregnancy was 1.6 (95% CI: 0.6–4.2).

Because our study focus was on maternal hypertension and its treatment, we made an *a priori* decision to exclude study subjects whose mothers reported drugs with antihypertensive properties but did not report high blood pressure. Thirteen control infants met this exclusion criterion, while no case infants were affected. The medications reported were beta blockers, calcium channel blockers, and diuretics, which have other indications for use. To examine the impact of the exclusion on the associations between early and late medication use and the risk of severe hypospadias, we reanalyzed the data without this exclusion. The adjusted OR for severe hypospadias was 1.2 (95% CI: 0.6–2.4) and 2.9 (95% CI: 1.2–7.0) for early and late medication use, respectively.

DISCUSSION

In our large case-control study of birth defects, the risk of severe hypospadias in infants of women reporting antihypertensive medication treatment in early pregnancy was approximately 40% higher than in infants of women without high blood pressure and with no medication use. The CI included the null value. The upper 95% confidence bound was below 3.0, suggesting that if there is any risk, it is likely to be modest. Clinicians were most likely to prescribe a pregnant woman methyl dopa, a centrally acting agent, which is in line with the current guidelines for treatment in pregnant women published by the National High Blood Pressure Education Program (NHBPEP, 2004). Although our data for specific drugs were sparse, we saw no suggestion of a large risk associated with use of any of the specific drugs reported by study subjects. These findings are consistent with other studies that have failed to demonstrate increased risks in

Table 2
OR for the Association between Early Antihypertensive Medication Use, Late Antihypertensive Medication Use Only, Untreated High Blood Pressure, and the Risk of Severe Hypospadias, National Birth Defects Prevention Study, October 1997–December 2002

High blood pressure treatment	Controls No. (%)	Cases No. (%)	OR (95% CI)	Controls No. (%)	Cases No. (%)	aOR* (95% CI)
Early antihypertensive medication use [†]	24 (1.2)	15 (2.0)	1.9 (1.0–3.6)	24 (1.2)	15 (2.0)	1.4 (0.7–2.9)
Late antihypertensive medication use only [‡]	12 (0.6)	13 (1.7)	3.3 (1.5–7.2)	12 (0.6)	12 (1.6)	5.0 (1.9–12.9)
Untreated high blood pressure [§]	159 (7.7)	112 (14.8)	2.1 (1.6–2.7)	155 (7.9)	106 (14.4)	2.1 (1.6–2.9)
Unexposed	1,863 (90.5)	618 (81.5)	Reference	1,774 (0.9)	602 (81.9)	Reference

*Adjustment factors; study center, age, race/ethnicity, parity, plurality, prepregnancy body mass index, pre-existing diabetes, and gestational diabetes.

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

[‡]Any time after the fourth month of pregnancy to birth.

[§]High blood pressure without medication use.

^{||}No high blood pressure or medication use.

infants of women exposed to antihypertensive medications as a group (Heinonen et al., 1977) or to calcium channel blockers specifically (Sorensen et al., 2001). On the other hand, some epidemiologic studies have suggested an increased risk of severe hypospadias in infants of women exposed to beta blockers (Briggs et al., 2003; Czeizel, 1989). The Hungarian Case Control Study found a nonsignificantly higher proportion of hypospadias cases among infants whose mothers were exposed to propranolol (0.25%) compared with controls (0.12%) (Czeizel, 1989), and an excess of hypospadias cases was observed in infants of women with first trimester exposures to atenolol (four observed vs. zero expected) in the Michigan Medicaid Surveillance Study, an unpublished study reported by Briggs et al. (2003).

Women treated with antihypertensive medications after the fourth month of pregnancy had a risk of severe hypospadias five times greater than that of women without high blood pressure or medication use. Because the medication treatment occurred beyond the period of urethral tube closure, these findings, if valid, would suggest that factors associated with late-treated hypertension are also associated with severe hypospadias. While specific forms of hypertension were not identified, other data suggest that the large majority of women who are first treated for hypertension after the fourth month of pregnancy are likely to have gestational hypertension or preeclampsia (Afifi and Churchill, 2003; Magee, 2001). An association of hypospadias with late-treated hypertension is consistent with results from a Swedish birth and surgical record linkage study (aOR 2.1; 95% CI: 1.4–3.1) and a Danish Hospital Discharge Registry and Birth Registry linkage study (aOR 2.4; 95% CI: 1.4–4.1), which both found increased risks of hypospadias in infants of women with preeclampsia (Akre et al., 1999; Sorensen et al., 2005). The stronger relationship observed in our study of treated hypertension may reflect more severe hypertension. Alternatively, the adjusted estimate in our study may be imprecise due to the small number of exposed subjects. The approximate doubling of risk among infants of women with untreated high blood pressure in our study more closely approximates the associations with preeclampsia reported in the literature (Akre et al., 1999; Sorensen et al., 2005), because in our study,

the untreated high blood pressure group may have included a mix of women with untreated preeclampsia, gestational hypertension, and chronic hypertension. Other studies, however, have failed to show a relationship between hypertension and the risk of severe hypospadias (Aschim et al., 2004; Heinonen et al., 1977; Husain et al., 2002).

Given that the development of hypospadias is complete before late-onset high blood pressure and its treatment occur, there are three possible explanations for our findings related to antihypertensive medication exposures initiated after the fourth month of pregnancy: (1) hypospadias and late-treated hypertension share the same risk factors; (2) hypospadias and late-treated hypertension share a common mechanism; and (3) hypospadias causes late-treated hypertension. In preeclampsia, failure in the transformation of the spiral arteries during placen-

Table 3
Early Antihypertensive Medication Class Use,
National Birth Defects Prevention Study,
October 1997–December 2002

Medication class	Any use*	
	Controls (n = 2,058)	Cases (n = 758)
Antiadrenergic agent	17 (0.8)	13 (1.7)
Centrally acting antiadrenergic agent	11 (0.5)	6 (0.8)
Methyldopa	10 (0.5)	6 (0.8)
Alpha-beta blocker	1 (<0.1)	5 (0.7)
Beta blocker	6 (0.3)	5 (0.7)
Atenolol	4 (0.2)	2 (0.3)
Other beta blocker	1 (<0.1)	3 (0.4)
Calcium channel blocker	5 (0.2)	2 (0.3)
ACE inhibitor	5 (0.2)	1 (0.1)
Angiotensin II receptor blocker	0 (0.0)	0 (0.0)
Diuretic	2 (0.1)	4 (0.5)
Direct vasodilator	0 (0.0)	0 (0.0)

*Any time 1 month preconception through month 4 postconception.

tation is postulated as the mechanism for decreased placental perfusion (Kliman, 2000; Mayhew et al., 2004), and it has been suggested that this disturbance in early pregnancy, though not yet manifest as clinical hypertension, causes hypospadias (Akre et al., 1999; Moller and Weidner, 1999). Assuming that medication is most often used to treat more severe hypertension and the differences in the adjusted estimates are real, our findings of the highest risk in late medication users and a moderate risk in the untreated hypertension group suggest that the risk of severe hypospadias might be highest in infants of women with the most severe placental insufficiency. Thus, severe hypospadias and late-treated hypertension might share a common mechanism of placental insufficiency.

Our study had a number of strengths. We used a large, multicenter, population-based, birth defects study that included a standardized protocol for maternal interviews performed between 6 weeks and 24 months after the EDD. Strict definitions and clinical review of cases allowed for a consistent case ascertainment. The large study allowed analyses of a rare exposure. The study collected a wide array of data on potential confounders, and information on timing of medication use was available to evaluate exposures during the critical window of urethral tube closure.

Potential limitations in our study were inaccuracies in the retrospective ascertainment of medication exposures, confounding by indication, and misclassification of hypertension. Recall bias and reporting inaccuracy were minimized by a questionnaire design that identified medication use by indication (Kallen, 2005; Mitchell et al., 1986; Mitchell, 2000; Rockenbauer et al., 2001; Ward, 2001; Werler et al., 1989). Because recall error tends to be lower for prescription medications used for chronic conditions than for those used for a shorter period of time, this potential bias was likely minimized in women reporting medications for the treatment of chronic hypertension in early pregnancy (Rockenbauer et al., 2001). Our *a priori* decision to exclude study subjects whose mothers reported drugs with antihypertensive properties but did not report high blood pressure disproportionately affected the control group. These women reported drugs with other indications for use, and they may not have had high blood pressure. Alternatively, there may have been differential recall of short-term medication use in these women. When these subjects were included in the analysis, the adjusted ORs were reduced. However, the association with late treatment remained elevated. Particularly with respect to late pregnancy, it is important to note that we did not have information on the nature of hypertension reported by study subjects, leaving us to assume, with some basis, that the large majority were cases of gestational hypertension and preeclampsia. Finally, as in any observational study of medication use, it is difficult to disentangle the effects of hypertension from the effects of the medications used in its treatment (Kallen, 2005; Mitchell, 2000; Ward, 2001).

In conclusion, the findings presented here suggest that hypertension treated with medications in early pregnancy is not strongly associated with severe hypospadias, whereas treatment that begins in late pregnancy is associated with the urogenital malformation. Because hypospadias occurs early in pregnancy, we speculate that the cause of this defect may be related to uteroplacental per-

fusion problems that precede recognition and/or treatment of gestational hypertension and preeclampsia.

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