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Maternal Progestin Intake and Risk of Hypospadias

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Background: Previous studies have suggested that maternal intake of progestins during early pregnancy may be associated with an increased risk of hypospadias. Progesterone and its derivatives are commonly prescribed during early pregnancy, for example, in cases of luteal phase dysfunction and in conjunction with ovulation stimulation drugs.

Objective: To examine whether risk of hypospadias was associated with periconceptional progestin intake.

Design and Setting: The National Birth Defects Prevention Study, a population-based, multistate, case-control study including deliveries that had estimated due dates from October, 1997 to December, 2000.

Participants: Participation in the study was 71% among case mothers and 68% among control mothers. This analysis included 502 subjects diagnosed with second- or third-degree hypospadias (ie, the urethra opened at the penile shaft, scrotum, or perineum) and 1286 male, live-born, nonmalformed control subjects.

Results: Forty-two case mothers (8.4%) and 31 control mothers (2.4%) reported any pregnancy-related progestin intake from 4 weeks before through 14 weeks after conception, resulting in an odds ratio of 3.7 (95% confidence interval [CI], 2.3-6.0). Analyses stratified by several potential covariates also suggested elevated risks. For example, among the 10 cases and 13 controls who did not report any fertility-related procedures or treatments other than progestins, the odds ratio was 2.2 (95% CI, 1.0-5.0). Progestin intake for the purpose of contraception was not associated with increased risk.

Conclusion: This study found that pregnancy-related intake of progestins was associated with increased hypospadias risk.

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HYPOSPADIAS, A CONGENITAL malformation in which the urethral opening is on the ventral side of the penis, occurs as a result of abnormal urethral closure at around 8 to 14 weeks after conception. A variety of mechanisms involving exposures to endocrine disruptors and genetic impairment have been proposed to cause hypospadias,[1,2] but their actual contribution to its etiology remains elusive. It has also been suggested that maternal exposure to progestins (ie, natural progesterone and synthetic progesterone, and testosterone derivatives that produce biologic effects similar to those of progesterone) during early pregnancy may increase hypospadias risk by interfering with the production or action of fetal androgens, which are critical to normal closure of the urethra.[3] Progesterone and its derivatives are commonly prescribed during early pregnancy, for example, in cases of luteal phase dysfunction and in conjunction with ovulation stimulation drugs.

The first studies to suggest an increased risk of hypospadias associated with maternal progestin intake were case series.[4-6] Mixed results emerged from prospective[7-14] and retrospective[15-23] studies. A few studies reported a 2- to 3-fold increased risk,[9,17,20,22] but most studies reported risks closer to 1. Effective November, 2000, the US Food and Drug Administration no longer required that progestational drugs (which include natural progesterone and all synthetic progestins, other than progestin-containing products for contraception) carry a warning regarding genital defects.[24] In its place, it recommended that the drugs be labeled on an individual basis.

Although results of previous studies have been mixed, it is difficult to compare them because of temporal differences in the indications for progestin use and in the chemical structures and endocrine properties of progestins that were used. It is also difficult to apply previous results to current exposures. Only 2 previous studies included pregnancies that occurred less than 20 years ago.[22,23] Since then, the indications and types of progestins prescribed have changed substantially. The administration of 3 to 5 days of progestin to induce withdrawal menstruation, as a form of pregnancy testing, was previously one of the most common indications for progestin use; this no longer

occurs owing to the widespread availability of pregnancy tests. In recent years, newly developed, natural progesterone products have provided an alternative to synthetic progestins during early pregnancy (ie, micronized progesterone in pill or gel form), and the progestins currently included in contraceptives are at lower doses and are less androgenic than those used previously.[25]

Using recently collected data from a large, multistate, population-based, case-control study, we examined whether risk of severe hypospadias was associated with periconceptional progestin intake.

METHODS

STUDY DESIGN

This study includes data on deliveries that had estimated due dates from October, 1997 to December, 2000 and were part of the National Birth Defects Prevention Study, a multistate, case-control study of 30 different birth defects. This study is an approved activity of the institutional review boards of the participating study centers and the Centers for Disease Control and Prevention. Detailed study methods and descriptions of the surveillance systems in the 8 states that contributed data to this analysis have been published.[26] In brief, 5 of the 8 states included live-born, stillborn (fetal deaths at greater than 20 weeks gestation), and prenatally diagnosed and electively terminated cases (Arkansas, California, Georgia, Iowa, Texas), 1 state included only live-born and stillborn cases (Massachusetts), and 2 states included only live-born cases (New Jersey, New York). Each state randomly selected approximately 100 nonmalformed, live-born controls per study year from birth certificates (Iowa, Massachusetts, New Jersey) or from birth hospitals (Arkansas, California, Georgia, New York, Texas), to represent the population from which the cases were derived. This analysis is restricted to male controls. Case information obtained from multiple hospital reports and medical records was entered into a standardized database.

This study included only second- and third-degree hypospadias, ie, the urethra opened at the penile shaft, scrotum, or perineum; 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 at each study center by a clinical geneticist who decided about inclusion or exclusion in the National Birth Defects Prevention Study database. Cases described as chordee alone, mild (ie, first degree, coronal, or glandular), hypospadias not otherwise specified, epispadias, or having ambiguous genitalia without further description were excluded. Infants with recognizable single-gene disorders or chromosomal abnormalities were excluded. Each case received a final review by a clinical geneticist (R.S.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 minor anomalies (eg, sacral/pilonidal dimple), or as nonisolated if there was at least 1 accompanying major anomaly.[27]

Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, no earlier than 6 weeks after the infant's estimated date of delivery, and no later than 24 months after the estimated due date. Exposures to a variety of factors were assessed, relative to the woman's estimated date of conception, which was derived by subtracting 266 days from the woman's expected due date. The expected due date was based on the mother's self-report; if unknown, expected due date was estimated from information in the medical record (less than 2% of subjects).

STUDY VARIABLES

Exposures to progestins were reported in response to 5 different questions during the maternal interview: (1) Did you take any medications to help you become pregnant? (2) After you became pregnant, did you take any medications to prevent pregnancy complications or pregnancy loss? (3) Did you take any medications, remedies, or treatments that we have not already talked about? (This question was asked after a series of questions about a variety of medications, without any information regarding indication.) (4) Did you use any birth control pills or morning after pills? and (5) Did you use any other method of contraception? Responses to the first 3 questions were reported with start and stop dates; dates were transformed to correspond to 4 weeks before conception and weeks 1 to 4, 5 to 8, and 9 to 14 after conception, which encompasses the embryonic timing of the development of hypospadias. For the last 2 questions regarding contraceptives, mothers were asked to report exposures by month, including the month before pregnancy and each of the first 3 months of pregnancy, without any reference to exact dates. Dose and frequency of intake were not reported. Route of administration was recorded for some but not all responses. Each reported medication was categorized based on chemical composition and/or route of administration.

Progestin exposures associated with improving fertility or preventing pregnancy complications or loss were examined separately from progestin exposures associated with contraception because of differences in indication, formulations, and timing of exposures. Progestin exposures reported as part of question 3, mentioned earlier, without reference to indication were grouped with the pregnancy-related progestins because of the types of medications that were reported. Contraceptives were further categorized as containing (1) combinations of progestins and estrogens, (2) progestins only, or (3) having unknown contents.

ANALYSIS

First, we examined the bivariate association of intake of any pregnancy-related progestin with risk of hypospadias, from 4 weeks before through 14 weeks after conception. We then conducted separate analyses by timing, duration, and indication of exposure. We examined risk estimates stratified by the following factors to assess potential effect modification or confounding: (1) maternal education (<high school graduation, high school graduation, 1-3 years of college, ≥4 or more years of college); (2) maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other); (3) maternal age (<25, 25-34, ≥35 years at the time of conception); (4) number of previous live births (0, 1, ≥2); (5) number of previous miscarriages (0, 1, ≥2); (6) maternal subfertility treatments and procedures; and (7) study site. The subfertility variable was based on any positive response to 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? or (3) Did you have any other procedures to help you become pregnant?

For contraceptives, we examined bivariate risks associated with any intake during the month before pregnancy or the first 3 months of pregnancy, intake during each month separately, and intake by medication content.

To estimate risks, maximum likelihood estimates of the odds ratios (OR) and their corresponding 95% confidence intervals (CI) were calculated from logistic regression models using SAS 9.1 statistical software (SAS Institute, Cary, NC).[28,29] We also

Table 1. Descriptive Characteristics of Mothers of Case and Control Subjects

	Cases, % (n = 502)	Controls, % (n = 1286)
Maternal education		
<High school	11	16
High school	19	27
1-3 y of college	27	28
≥4 y of college	43	27
Unknown	1	1
Maternal race/ethnicity		
Non-Hispanic white	71	62
Non-Hispanic black	14	11
Hispanic	10	22
Other	4	4
Unknown	1	1
Maternal age, y		
<25	25	34
25-34	54	52
≥35	21	14
Unknown	0	0
Previous live births		
0	59	39
1	27	34
≥2	14	26
Unknown	<1	<1
Previous miscarriages		
0	73	77
1	18	18
≥2	8	4
Unknown	<1	<1
Maternal subfertility treatments and procedures		
None	87	95
Any	13	4
Unknown	<1	<1
Infant birth weight		
<2500 g	26	6
≥2500 g	72	87
Unknown	2	7
Study site		
Arkansas	12	11
California	5	14
Georgia	18	12
Iowa	2	13
Massachusetts	16	14
New Jersey	36	12
New York	8	11
Texas	4	13

Table 2. Association Between Hypospadias Risk and Intake of Progestins, by Timing and Duration of Exposure*

	Cases (n = 500)	Controls (n = 1284)	OR (95% CI)
4 wks before conception			
None	458	1253	†
Any exposure	25	13	5.3 (2.7-10.4)
1-13 d	12	6	5.5 (2.0-14.7)
14-27 d	7	2	9.6 (2.0-46.2)
28 d	6	5	3.3 (1.0-10.8)
1-4 wks after conception			
None	458	1253	†
Any exposure	38	24	4.3 (2.6-7.3)
1-13 d	5	6	2.3 (0.7-7.5)
14-27 d	12	6	5.5 (2.0-14.7)
28 d	21	12	4.8 (2.3-9.8)
5-8 wks after conception			
None	458	1253	†
Any exposure	36	28	3.5 (2.1-5.8)
1-13 d	6	2	8.2 (1.7-40.8)
14-27 d	3	7	1.2 (0.3-4.6)
28 d	27	19	3.9 (2.1-7.1)
9-14 wks after conception			
None	458	1253	†
Any exposure	30	22	3.7 (2.1-6.5)
1-13 d	6	4	4.1 (1.2-14.6)
14-27 d	9	5	4.9 (1.6-14.8)
≥28 d	15	13	3.2 (1.5-6.7)
Total duration of exposure			
None	458	1253	†
Exposed during all 4 time periods	18	9	5.5 (2.4-12.3)
Exposed during all 3 time periods during pregnancy	9	10	2.5 (1.0-6.1)
Other patterns of exposure	15	12	3.4 (1.6-7.4)
Any exposure	42	31	3.7 (2.3-6.0)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Includes intake to help become pregnant, to prevent pregnancy complications or pregnancy loss, or unstated indication.
†Reference includes women with no intake of progestins during the 4 weeks before to 14 weeks after conception.

examined risk estimates separately for: (1) cases with birth weight less than 2500 g vs 2500 g or more because it is possible that cases of normal and low birth weight may be etiologically distinct[30,31]; (2) cases that were isolated; (3) cases from singleton births; (4) and cases with no first degree family history of hypospadias (ie, the father or any brothers).

RESULTS

Participation in the study was 71% among case mothers and 68% among control mothers. Interviews were available for mothers of 502 subjects with hypospadias (2 were stillborn) and 1286 male control subjects. Among these subjects, the median time between the date of delivery and the interview was 12.9 months among case mothers and 7.3 months among control mothers. A majority of both case and control mothers had greater than a high school education, were non-Hispanic white, and were 25- to 34-years-old at the time of conception (**Table 1**). Case mothers were more likely than control mothers to be nulliparous and to deliver low-birth-weight infants.

Forty-two case mothers (8.4%) and 31 control mothers (2.4%) reported any pregnancy-related progestin intake during the 4 weeks before or 14 weeks after conception. Case mothers were 3.7 times more likely to be exposed than control mothers (95% CI, 2.3-6.0). Odds ratios for any use during more specific time periods ranged from 3.5 to 5.3 (**Table 2**). Odds ratios did not vary consistently based on number of days exposed during each time period or total duration of exposure, but data were relatively sparse for some of these comparisons (Table 2).

Most exposures were reported as progesterone not otherwise specified, and most were reported in response to the question about prevention of pregnancy complications or loss (**Table 3**). Odds ratios by indication were similar to the overall OR of 3.7; OR was 3.9 (95% CI, 2.2-6.9) for those taking it for pregnancy complications and

Table 3. Types of Progestins Reported by Case and Control Mothers*

	No. of Cases	Indication			No. of Controls	Indication		
		Pregnancy Complications	Become Pregnant	Unknown		Pregnancy Complications	Become Pregnant	Unknown
Gel or cream	8	6	2	0	2	2	0	0
Vaginal suppository	2	1	0	1	3	0	1	2
Prometrium	1	1	0	0	1	1	0	0
Medroxyprogesterone acetate	2	0	2	1	1	0	1	0
Progesterone NOS	30	21	8	2	26	17	7	2
Total subjects	42	29	12	4	31	20	9	4

Abbreviation: NOS, not otherwise specified.
*The table represents a total of 42 exposed cases and 31 controls; row and column totals do not sum because 1 case reported progesterone not otherwise specified for 2 indications, 1 case reported medroxyprogesterone acetate for 2 indications, 1 case reported 2 medications, and 2 controls reported 2 medications.

3.9 (95% CI, 1.6-9.7) for those taking it to help get pregnant. Exclusion of women who took estrogen (3 case and 1 control mothers) or steroids (2 case and 4 control mothers) for pregnancy-related reasons, and women who took contraceptive medications (34 case and 113 control mothers) during the month before pregnancy through the third month of pregnancy resulted in an OR of 3.3 (95% CI, 2.0-5.4). Excluding subjects with hypospadias who were nonisolated (n=41) or low birth weight (n=128), and exclusion of all subjects who were non-singletons (n=45 cases and 47 controls) or had a family history of hypospadias (n=23 cases and 1 control) did not substantially alter the observed results (data not shown).

Odds ratios for any vs no exposure to pregnancy-related progestins during the 4 weeks before or 14 weeks after conception were examined within the strata of each potential covariate. Although some of the stratum-specific ORs were relatively imprecise, most suggested at least a 2-fold increased risk of hypospadias among women who took progestins (**Table 4**). Among the cases and controls whose mothers did not report any additional subfertility procedures or treatments, risk remained elevated (OR, 2.2), suggesting that underlying fertility treatments did not explain the elevated risk associated with progestin intake. The low risk among women with 1 previous miscarriage (OR, 1.3) was not expected, but the observation that risks were substantially elevated among women with no miscarriages (OR, 5.3) and women with 2 or more miscarriages (OR, 2.7) suggests that the association observed between hypospadias risk and progestin intake is not explained by an underlying indication of repeated previous miscarriages. Potential variability in the association by study site could not be fully evaluated because the number of subjects who were exposed to progestins was limited in most sites.

Thirty-four case mothers and 113 control mothers reported intake of hormonal contraceptive medications during the month before pregnancy or during the first 3 months of pregnancy. Case mothers were 0.8 times as likely to be exposed than control mothers (95% CI, 0.5-1.1). Odds ratios by month and by type of contraceptive also did not suggest an increased risk of hypospadias among the exposed subjects (data not shown). Exclusion of women who took pregnancy-related progestins, estrogens or steroids during the 4 weeks before through 14 weeks after conception did not substantially alter the results (data not shown).

COMMENT

This study observed an increased risk of second- and third-degree hypospadias among infants delivered to women who took progestins during early pregnancy to help them become pregnant or to prevent pregnancy complications or loss. The crude OR suggested a 3.7-fold increased risk. Odds ratios stratified by various maternal characteristics, including other fertility treatments, tended to suggest at least a 2-fold increase in risk. Progestin intake for the purpose of contraception was not associated with increased risk of hypospadias.

In addition to their questionable relevance to current exposures, previous studies of the potential association between hypospadias and progestin intake have had various methodologic limitations, eg, analysis of all exposures as a single entity regardless of indication; type of progestin, timing, or duration of exposure; small sample sizes; potentially differential ascertainment of outcomes between cases and controls; and inability to examine potential covariates. One of the most recent studies, which included deliveries that occurred from 1986 to 1989, is also probably one of the most comparable to the current study, given its case-control design and inclusion of several potential covariates.[22] The study, which derived its subjects from birth defects registries from several different countries, included 24 case mothers and 9 control mothers who reported progestin intake 6 to 14 weeks after conception. The OR for progestin intake was 2.3 (95% CI, 1.2-4.4), and adjustment for maternal age, smoking, infertility, early pregnancy bleeding, and previous fetal deaths did not substantially alter the results. About two thirds of the exposures were to natural progesterone and the indication for progestin use for most women was pregnancy bleeding. The findings of the current study are consistent with that of Kallen et al,[22] which included primarily mild cases. Our study is further strengthened by its consistent method of case ascertainment, review, and inclusion of other fertility treatments and demographic factors.

Although the current study offers a more detailed analysis than most previous studies, data regarding several aspects of progestin intake were limited. For example, information was not available regarding dose or route of administration for most responses, and the type of proges-

Table 4. Stratum-Specific Odds Ratios for Hypospadias Risk and Maternal Intake of Progestins*

Stratification Variables	No. of Cases Reporting Any Progestin Intake (Total Cases)	No. of Controls Reporting Any Progestin Intake (Total Controls)	Stratum-Specific OR (95% CI)
Maternal education			
<High school	0 (53)	0 (211)	†
High school	2 (95)	1 (350)	†
Some college	11 (135)	8 (356)	3.9 (1.5-9.8
College degree	29 (214)	22 (352)	2.4 (1.3-4.2)
Maternal race/ethnicity			
Non-Hispanic white	36 (354)	28 (793)	3.1 (1.9-5.2)
Non-Hispanic black	2 (69)	3 (145)	1.4 (0.2-8.7)
Hispanic	2 (50)	0 (278)	†
Other	2 (20)	0 (53)	†
Age, y			
<25	1 (124)	0 (437)	†
25-34	21 (270)	20 (666)	2.7 (1.5-5.1)
≥35	20 (106)	11 (181)	3.6 (1.6-7.8)
Previous live births			
0	33 (295)	21 (506)	2.9 (1.6-5.1)
1	7 (133)	6 (441)	4.0 (1.3-12.2)
≥2	2 (71)	4 (333)	2.4 (0.4-13.3)
Previous miscarriages			
0	24 (368)	13 (993)	5.3 (2.6-10.4)
1	5 (90)	10 (233)	1.3 (0.4-4.0)
≥2	13 (41)	8 (54)	2.7 (1.0-7.2)
Subfertility treatments and procedures			
Any	32 (61)	18 (53)	2.1 (1.0-4.6)
None	10 (438)	13 (1228)	2.2 (1.0-5.0)
Study site			
Arkansas	0 (59)	2 (142)	†
California	0 (24)	0 (178)	†
Georgia	9 (90)	6 (155)	2.8 (0.9-8.0)
Iowa	1 (12)	1 (170)	†
Massachusetts	9 (78)	12 (177)	1.8 (0.7-4.5)
New Jersey	20 (177)	5 (148)	3.6 (1.3-10.0)
New York	2 (42)	4 (141)	1.7 (0.3-9.7)
Texas	1 (18)	1 (173)	†

Abbreviations: CI, confidence interval; OR, odds ratio.

*Includes intake to help become pregnant, to prevent pregnancy complications or pregnancy loss, or unstated indication. Odds ratios compare any vs no intake reported during the 4 weeks before to 14 weeks after conception.

†Odds ratios were not estimated for strata with fewer than 5 exposed subjects.

tin and indication were not specified in detail. Data on maternal and paternal fertility were also limited; information on treatments and procedures was available, but more general indicators such as time to conception were not available. Even though this study included more exposed cases and controls than most previous studies, the sparsity of data within many strata of the potential covariates precluded the use of a more complex multivariate modeling approach. Thus, we cannot be certain that observed results did not arise from intricate confounding relationships. The applicability of our findings to mild cases of hypospadias is unknown. The generalizability of this study's findings beyond the study population is also uncertain but likely to be better than what has been achieved by many previous studies, given its use of recently collected, population-based data, active case ascertainment from multiple sources, random selection of nonmalformed controls from the birth population, comprehensive tracing and contact procedures that helped optimize participation, and the racial/ethnic, geographic, and socioeconomic diversity of the study population. Although data to evaluate the variability in numbers of cases contributed by each state were unavailable, some possible contributing factors include differences in the size of the sampling frame and differences in the availability of confirmatory clinical information. Data to compare progestin exposure among participants and nonparticipants were not available, but we have no evidence to suggest that exposure would have differentially influenced participation among cases and controls and thus contributed to selection bias. As with most retrospective studies, we were unable to evaluate potential recall bias. Median time to interview was longer for cases than controls, likely due to the delayed availability of confirmatory clinical information for the cases, but we do not know whether time to interview would substantially bias recall of the exposures of interest. The finding that intake of progestins for contraception was not related to hypospadias risk lowers the possibility that recall bias was responsible for our results regarding pregnancy-related progestin intake. Furthermore, the prevalence of assisted reproductive techniques among the controls in our data (0.9%) was comparable to estimates from other data sources.[32,33]

In addition to their progestational properties, progestins may have varying androgenic or estrogenic prop-

erties. As such, they may interfere with sex hormone binding and subsequent developmental programming in the embryo. Progesterone also acts as a precursor to testosterone, and it may inhibit the conversion of testosterone to the more biologically active dihydrotestosterone.[34] It is unknown which of these mechanisms may contribute to the observed association between hypospadias risk and maternal intake of progesterone or its synthetic derivatives.

Hypospadias is a relatively common major malformation among male infants, with most estimates ranging from 3 to 4 cases per 1000 total live births.[35-37] This study was restricted to second- and third-degree cases, which account for approximately 20% to 30% of all cases.[37] Most previous studies have included primarily mild cases, including the study by Kallen et al,[22] described earlier, which had similar findings to those observed here. Recent evidence supports a theory of the entire urethra being formed by dorsal growth and fusion of the urethral folds, in contrast to previously proposed differences in the formation of the distal and proximal urethra.[30,38-40] Assuming mild cases have a similar association with progestins as we observed for severe cases, ie, a 2- to 4-fold increased risk, the attributable fraction would be 2% to 7% among all cases in the study population. The prevalence of progestin use among the control mothers was 2.4%. Other current, population-based estimates of progestin use were unavailable, but exposure is likely to be increasing, given the increasing number of women seeking fertility treatments.[41]

The effectiveness of progestin use as a component of other fertility treatments or to prevent pregnancy complications is not well-supported by existing studies.[42-46] The current study suggests that the risk-benefit ratio of using progesterone and its derivatives to treat fertility problems or pregnancy complications should be considered.

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