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Differences in risk factors for 2nd and 3rd degree hypospadias in the National Birth Defects Prevention Study

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Abstract

Background—Hypospadias is a frequent birth defect with three phenotypic subtypes. With data from the National Birth Defects Prevention Study, a large, multi-state, population-based, case-control study, we compared risk factors for second and third degree hypospadias.

Methods—A wide variety of data on maternal and pregnancy-related risk factors for isolated second and third degree hypospadias was collected via computer-assisted telephone interviews to identify potential etiological differences between the two phenotypes. Logistic regression was used to calculate odds ratios including a random effect by study center.

Results—In total, 1547 second degree cases, 389 third degree cases, and 5183 male controls were included in our study. Third degree cases were more likely to have a non-Hispanic black or Asian/Pacific Islander mother, be delivered preterm, have a low birth weight, be small for gestational age, and be conceived with fertility treatments than second degree cases and controls. Associations with both second and third degree hypospadias were observed for maternal age, family history, parity, plurality, and hypertension during pregnancy. Risk estimates were generally higher for third degree hypospadias except for family history.

Conclusions—Most risk factors were associated with both or neither phenotype. Therefore, it is likely that the underlying mechanism is at least partly similar for both phenotypes. However, some associations were different between 2nd and 3rd degree hypospadias, and went in opposite directions for second and third degree hypospadias for Asian/Pacific Islander mothers. Effect

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estimates for subtypes of hypospadias may be over- or underestimated in studies without stratification by phenotype.

Keywords

hypospadias; risk factors; birth defects; pregnancy

Introduction

Hypospadias is one of the most commonly occurring birth defects, affecting four to six per 1000 male births (Paulozzi, 1999; Paulozzi and others, 1997; Porter and others, 2005). In hypospadias, the urethral opening is displaced to a certain degree, varying from placement just off the tip of the penis to a perineal meatus. Three phenotypic subgroups are identified and classified as first degree hypospadias when the urethral opening is located at the glans or corona, second degree hypospadias when it is located on the shaft of the penis, and third degree hypospadias when the urethra ends in the penoscrotal region, scrotum, or perineum. Patients often undergo surgery in the first two years of life, but may still encounter medical, social, and sexual problems later in life (Mieusset and Soulie, 2005; Schonbucher and others, 2008). Also, the complication rates of surgery are relatively high, especially with the more severe forms of hypospadias (Eassa and others, 2011; Nuininga and others, 2005).

So far, several risk factors for hypospadias have been proposed, including assisted reproductive technology (Brouwers and others, 2007; Brouwers and others, 2010; Carmichael and others, 2007), maternal hypertension during pregnancy (Akre and others, 2008; Caton and others, 2008), thyroid disease (Browne and others, 2009), high maternal age at delivery (Carmichael and others, 2012; Carmichael and others, 2003; Porter and others, 2005), and maternal obesity (Akre and others, 2008; Brouwers and others, 2010). Associations with low birth weight, preterm birth, and primiparity are well established (Porter and others, 2005; van der Zanden and others, 2012). Familial clustering points towards a genetic contribution to the etiology of hypospadias (Carmichael and others, 2012; Harris, 1990; Schnack and others, 2008).

In a study assessing phenotypic differences, Brouwers et al. (2010) found evidence for etiological heterogeneity between the different hypospadias phenotypes. Others found additional associations (van Rooij and others, 2013), but the few studies investigating risk factors for different hypospadias phenotypes were too small to draw firm conclusions. In the present study, data from the National Birth Defects Prevention Study (NBDPS), a large case-control study, were used to investigate etiological heterogeneity of second and third degree hypospadias.

Methods

Study design

Data for this study were collected through the NBDPS, a multi-state, population-based, case-control study funded by the Centers for Disease Control and Prevention (CDC) since 1997. Ten states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York,

North Carolina, Texas and Utah) collected data from mothers of infants with one of 37 birth defects and mothers of live born control infants without major birth defects. A wide range of potential risk factors were assessed using a standardized maternal interview. The NBDPS obtained approval from the institutional review boards for all study sites, and all participants provided informed consent. Participation rates were 65% among the mothers of both eligible cases and controls. Details on study methods have been described elsewhere (Yoon and others, 2001).

Case classification

Case infants were identified from population-based surveillance systems and reviewed by clinical geneticists to determine study eligibility. Second-degree hypospadias was defined as an infant with the urethral meatus on the shaft (penile), which also included subglanular and subcoronal hypospadias. Third-degree hypospadias was defined as an infant with the urethral meatus in the scrotum or perineum (scrotal, perineal). Cases were excluded if they had a karyotype other than XY, a known or suspected chromosome abnormality, a diagnosed single gene condition, or a hormonal profile or anatomical feature consistent with disorders of sex development. Controls were live born males without major birth defects randomly selected from birth certificates or hospital records in the 10 participating states. Cases and controls had estimated dates of delivery (EDD) between October 1, 1997 and December 31, 2009. Analyses were performed only on cases with isolated hypospadias (90.1% of all cases), since these may be more homogeneous etiologically.

Exposure assessment

Mothers were interviewed between 6 weeks and 24 months after the estimated date of delivery using a computer-assisted telephone interview. On average, case mothers were interviewed 13 months after EDD and control mothers 9 months after EDD. The interviews included detailed questions about exposures between three months before conception and date of delivery (Rasmussen and others, 2003). Several potential risk factors were selected from literature and assessed in the maternal interview: maternal age at EDD, self-defined race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, or other), education (0-12 years or >12 years of schooling), pre-pregnancy body mass index (BMI), and parity (number of previous pregnancies over 20 weeks resulting in a live birth or stillbirth). Family history was defined as hypospadias reported in the infant's first degree relatives or one of the mother's previous pregnancies. Fertility problems were assessed via a gateway question and several follow-up questions to get more details on possible fertility treatments. Subjects with exposure to *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) and clomiphene citrate were only included in the IVF/ICSI category. Maternal smoking, alcohol consumption, cannabis use, and intake of folic acid-containing supplements were examined between one month before conception and the third month of pregnancy. References categories for smoking and cannabis use consisted of mothers who did not report exposure between three months preconception and the end of pregnancy and for alcohol and folic acid-containing supplements until the end of the third month of pregnancy. We analyzed any use of alcohol (yes/no) and binge drinking (defined as 4 or more drinks consumed on one occasion).

Three aspects of maternal health were considered: diabetes mellitus (pre-existing type I or II or gestational diabetes during index pregnancy), chronic and gestational hypertensive disorders, and thyroid disorders. Hypertensive disorders were classified into three groups: untreated hypertension, hypertension with early antihypertensive medication (exposure before the fifth month of pregnancy), or hypertension with late exposure to medication (first exposure between the fifth month of pregnancy and delivery). Mothers who used antihypertensive medication but did not report a hypertensive disorder (n=46) and mothers who reported a diagnosis of hypertension after the index pregnancy (n=20) were excluded from these analyses. Thyroid disorders were identified through reports of thyroid disease or exposure to thyroid medication and reviewed by a clinician blinded to case-control status.

Besides the maternal interview, information about birth weight and gestational age was collected from birth records. Criteria for being small for gestational age (SGA) were adopted from a United States growth reference (Alexander and others, 1996).

Statistical Analysis

Using unconditional logistic regression, crude odds ratios (cORs) with 95% confidence intervals (CIs) were calculated for the above-mentioned variables, comparing second and third degree cases with controls. All potential risk factors were then included in a single logistic model for each phenotype to estimate adjusted odds ratios. A random effect parameter was included to adjust for study center differences. Analyses compared cases to controls stratified by phenotype, using a complete case analysis. Plurality and fertility treatment were combined in one variable to avoid multicollinearity in the model. No ORs were calculated for risk factors with less than three exposed cases. For those factors that showed associations when cases were compared to controls, we estimated odds ratios for 3rd degree versus 2nd degree cases using the same logistic regression method. The results from the binomial models were validated through a multinomial model containing both subtypes and controls. Data analyses were performed using SPSS software version 20.0.

Results

The mothers of 2148 cases with second or third degree hypospadias and 5183 male controls were interviewed. Excluding 212 cases (123 second and 89 third degree) with multiple major anomalies left 1547 second degree and 389 third degree hypospadias cases for analysis.

Many descriptive characteristics differed among the three groups (table 1). Mean birth weight, gestational age, and SGA were statistically significantly different among all three groups (unpaired t-test, $p<0.001$), with the highest proportion of low or very low birth weight, preterm delivery, and SGA infants among third degree cases. Time to interview, study center, and year of EDD varied between both phenotypes and controls, as well.

Many risk factors were associated with one or both of the hypospadias subtypes in the crude analyses (table 2) and were included in table 3. After adjustment for confounding, the adjusted odds ratios (aORs) for 5 of the 15 potential risk factors were statistically significantly different between second and third degree hypospadias (table 3). Family

history of hypospadias, increasing maternal age, and primiparity were associated with both phenotypes. The OR for family history was higher for second than third degree hypospadias, although the OR for 2nd vs 3rd degree hypospadias was not statistically significant. The associations for maternal age and primiparity were stronger for third than second degree hypospadias. Decreased odds ratios were observed for second degree hypospadias for all racial/ethnic categories except for non-Hispanic black mothers when compared to non-Hispanic white mothers, whereas for third degree hypospadias, elevated ORs were observed for non-Hispanic black and Asian/Pacific Islander mothers. Early exposure to antihypertensive medication was not associated with hypospadias, but exposure to medication later in pregnancy and untreated hypertension were associated with both phenotypes. These associations were stronger for third than second degree hypospadias. The association with thyroxin exposure was of borderline statistical significance in second degree hypospadias only. The associations for plurality and fertility treatments remained elevated when combined into a 6-level variable in the multivariable analysis. Compared to singleton infants conceived without assistance, increased aORs were observed for multiples conceived without fertility treatment for both second and third degree hypospadias. IVF/ICSI was associated with both hypospadias phenotypes, whereas treatment with clomiphene citrate prior to conception was only associated with third degree hypospadias, regardless of plurality. Results from a multinomial model with both subtypes and controls did not differ substantially from the results obtained through the binomial models described above.

Discussion

Most risk factors evaluated were either associated with both second and third degree hypospadias or with neither phenotype, indicating that the underlying mechanism is partly similar for second and third degree hypospadias. Effect estimates were generally larger for third degree hypospadias than for second degree hypospadias, except for a family history of hypospadias which seemed to occur more often among second degree hypospadias.

The odds ratios for a family history of hypospadias were by far the strongest effect estimates observed in our study, with odds ratios of 25.9 (95% CI 13.1-51.3) for second degree hypospadias and 16.4 (95% CI 6.2-43.5) for third degree hypospadias. Most other studies, that also included first degree hypospadias cases, similarly showed lower risks for family history in third degree cases when compared to less severe subtypes (Brouwers and others, 2010; Fredell and others, 2002; van Rooij and others, 2013), but one U.S. study did not (Bauer and others, 1979).

Associations between non-Hispanic white race/ethnicity and isolated hypospadias have been reported by several researchers (Carmichael and others, 2003; Porter and others, 2005; van der Zanden and others, 2012). For third degree hypospadias, however, the risk for non-Hispanic white mothers was similar to that for Hispanic mothers and those with other race/ethnicities, whereas elevated odds ratios were observed for non-Hispanic black and Asian/Pacific Islander mothers. To our knowledge, the latter associations have not been observed before, but suggest that several race/ethnicities have different risks for certain phenotypes of hypospadias.

A link between hypospadias and placental insufficiency was first published by Stoll et al. (1990), showing an association between hypospadias and low placental weight. Others found that hypospadias was more likely to occur in the smallest of monozygotic twins (Fredell and others, 1998) and that SGA newborns with hypospadias had a high rate of early onset intrauterine growth retardation due to placental insufficiency (Yinon and others, 2010). Placental human chorionic gonadotropin (hCG) stimulates fetal testicular steroidogenesis before the fetus' own production is started, and placental insufficiency may result in a failure to transfer hCG to the fetus in early pregnancy (Brouwers and others, 2007; Fredell and others, 1998). Therefore, placental insufficiency could result in both hypospadias and early onset intrauterine growth retardation. Our findings that boys with hypospadias were more likely to have a low birth weight or to be SGA support this. Since these associations seemed to be stronger for third degree than second degree cases, the role of placental insufficiency may be more prominent in the etiology of the third degree hypospadias phenotype.

Maternal hypertension is also associated with placental insufficiency and was found to be a risk factor for hypospadias in several studies (Akre and others, 2008; Brouwers and others, 2010; Caton and others, 2008; van der Zanden and others, 2012; van Rooij and others, 2013). An earlier NBDPS study that did not include a stratification by phenotype found that late exposure to antihypertensive medication was related to hypospadias and suggested that these cases could represent mothers with hypertension caused by severe placental insufficiency (Caton and others, 2008). In our analysis, which included approximately 3000 additional controls and over 1000 additional hypospadias cases, both phenotypes were associated with late use of antihypertensive medication and with untreated hypertension. The fact that treatment started late in pregnancy might indicate that these mothers received treatment for gestational hypertension or (pre)eclampsia, which have been linked to placental insufficiency (Mayhew and others, 2004). The aOR for late treatment was higher for third than for second degree hypospadias, which is a new finding, supporting a more prominent role for placental insufficiency in the most severe phenotype.

Our findings that primiparity and multiple gestations were associated with hypospadias in both phenotypes, with the highest odds ratios observed for third degree hypospadias, confirms earlier findings (van Rooij and others, 2013). We also found some evidence for associations between fertility treatments and hypospadias. The largest odds ratio was seen for multiples with third degree hypospadias born after use of clomiphene citrate. These results confirm the findings by Meijer et al (2006), but differ from earlier NBDPS findings based on a smaller amount of data (Reefhuis and others, 2011). It was not possible to evaluate whether these findings were due to the treatment itself or to the underlying subfertility, since women were not asked about time-to-pregnancy or a possible subfertility diagnosis.

Because consistent case finding and classification is difficult for first degree hypospadias, this phenotype is not included in the NBDPS. Patients with a subglanular and subcoronal meatus were classified as second degree hypospadias, whereas some other studies classify these phenotypes as first degree hypospadias, which limits comparability. Although the risk factors for first and second degree hypospadias were similar in a previous study (van Rooij

and others, 2013), the results may not be generalizable to all phenotypes. In addition, rates of hypospadias varied considerably between study sites, indicating possible differences in case finding. We tried to adjust for this by including a random effect for study center in our multivariable model. Sub-analyses excluding centers with the lowest hypospadias prevalence rates showed no appreciable change in effect estimates. There is a possibility of some remaining ascertainment bias by race or fertility treatment, but we expect this to be minimal, and at least partially addressed by the random effect. Mothers were provided with pregnancy calendars before the interview to improve recall of timing of exposures, but due to the self-reported nature of our exposure data, recall bias cannot be ruled out. Due to the relatively large number of exposures studied, we cannot exclude the possibility that some of our findings are due to chance.

The large, population-based, multistate design of the NBDPS is one of the key strengths of this study. Strict case ascertainment and classification protocols ensured consistent classification of subtypes. The large amount of exposure data allowed us to study rare exposures and to adjust for many possible confounders in one multivariable model, while keeping sufficient statistical power. Information on timing of exposure was available, which created the opportunity to study exposures in early pregnancy. However, we could not assess the effects of exposure on the last stages of urethral closure which take place in the fourth month of pregnancy, as most of the data were collected by trimester after the third month of pregnancy.

Conclusions

The fact that most risk factors identified were associated with both phenotypes indicates that the embryological process is at least partly similar. Many effect estimates, however, were larger for third degree hypospadias than for second degree hypospadias, while our findings regarding race/ethnicity and fertility treatment also showed some differences between the two phenotypes. Since mild hypospadias is more common than severe forms, studies without stratification by phenotype may over- or underestimate the effects of exposures or the role of genetics in the more severe subtypes. Identifying etiological differences between hypospadias phenotypes could bring us closer to understanding the disease mechanisms and developing preventive strategies.

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Table 1

Descriptive characteristics of isolated hypospadias cases and male controls, National Birth Defects Prevention Study, 1997- 2009

Characteristic	Male controls (n=5183)	2nd degree hypospadias (n=1547)	3rd degree hypospadias (n=389)
Birth weight			
Mean (in grams)	3403	3161	2391
Very low (<1500g)	43 (0.8%)	73 (4.8%)	85 (22.4%)
Low (1500-2499g)	248 (4.9%)	192 (12.6%)	104 (27.4%)
Normal (2500-3999g)	4184 (82.0%)	1099 (72.4%)	177 (46.6%)
Macrosomic (≥4000g)	628 (12.3%)	154 (10.1%)	14 (3.7%)
Gestational age			
Mean (in weeks)	38.6	38.0	35.9
Very preterm (<32 weeks)	77 (1.5%)	71 (4.6%)	62 (16.0%)
Preterm (32-36 weeks)	414 (8.0%)	221 (14.3%)	111 (28.7%)
Term (37-45 weeks)	4692 (90.5%)	1255 (81.1%)	214 (55.3%)
Small for gestational age			
Yes	347 (7.0%)	211 (14.8%)	134 (41.5%)
No	4610 (93.0%)	1213 (85.2%)	189 (58.5%)
Time from due date to interview			
Mean (in months)	9.1	14.0	12.7
center			
Arkansas	638 (12.3%)	210 (13.6%)	48 (12.3%)
California	591 (11.4%)	53 (3.4%)	38 (9.8%)
Georgia	544 (10.5%)	198 (12.8%)	43 (11.1%)
Iowa	574 (11.1%)	128 (8.3%)	24 (6.2%)
Massachusetts	619 (11.9%)	316 (20.4%)	86 (22.1%)
New Jersey	260 (5.0%)	238 (15.4%)	48 (12.3%)
New York	449 (8.7%)	87 (5.6%)	33 (8.5%)
North Carolina	429 (8.3%)	144 (9.3%)	43 (11.1%)
Texas	652 (12.6%)	17 (1.1%)	14 (3.6%)
Utah	427 (8.2%)	156 (10.1%)	12 (3.1%)
Year of estimated date of delivery			
1997-2000	1302 (25.1%)	362 (23.4%)	103 (26.5%)
2001-2003	1248 (24.1%)	330 (21.3%)	84 (21.6%)
2004-2006	1346 (26.0%)	403 (26.1%)	109 (28.1%)
2007-2009	1287 (24.8%)	452 (29.2%)	92 (23.7%)
Chordee			
Yes	*a*	749 (48.4%)	262 (67.4%)
No	*a*	798 (51.6%)	127 (32.6%)

[a]Data on presence of chordee in controls was not available

Table 2

Crude Odds Ratios for Associations between Selected Exposures and the Risk of Hypospadias Stratified by Subtype, National Birth Defects Prevention Study, 1997- 2009

Variable	Male Controls (n=5183)	2nd degree hypospadias (n=1547)	cOR (95% CI) for 2nd degree vs controls	3rd degree hypospadias (n=389)	cOR (95% CI) for 3rd degree vs controls
Maternal age (mean [SD])	27.6 (6.1)	29.3 (6.1)	1.05 (1.04-1.06)	29.3 (6.0)	1.05 (1.03-1.06)
Maternal race/ethnicity					
Non-Hispanic white	2976	1183	1 (ref)	235	1 (ref)
Non-Hispanic black	569	177	0.8 (0.7-0.9)	60	1.3 (1.0-1.8)
Hispanic	1242	101	0.2 (0.2-0.3)	50	0.5 (0.4-0.7)
Asian/Pacific Islander	146	34	0.6 (0.4-0.9)	27	2.3 (1.5-3.6)
Other	242	51	0.5 (0.4-0.7)	16	0.8 (0.5-1.4)
Maternal education					
0-12 years	2119	401	1 (ref)	113	1 (ref)
>12 years	2934	1115	2.0 (1.8-2.3)	267	1.7 (1.4-2.1)
Maternal pre-pregnancy BMI					
Non-obese (<30.0 kg/m^2)	4076	1248	1 (ref)	303	1 (ref)
Obese (≥30.0 kg/m^2)	864	271	1.0 (0.9-1.2)	73	1.1 (0.9-1.5)
Family history of hypospadias[a]					
Yes	10	85	30.1 (15.6-58.1)	11	15.1 (6.4-35.7)
No	5173	1462	1 (ref)	378	1 (ref)
Parity					
0	2048	774	1.5 (1.4-1.7)	238	2.5 (2.0-3.1)
≥1	3121	767	1 (ref)	147	1 (ref)
Plurality					
Singletons	5022	1448	1 (ref)	333	1 (ref)
Multiples	149	95	2.2 (1.7-2.9)	56	5.7 (4.1-7.9)
Any fertility issues					
Yes	237	157	2.4 (1.9-2.9)	65	4.2 (3.1-5.7)
No	4922	1384	1 (ref)	320	1 (ref)
Fertility treatment[b]					

Variable	Male Controls (n=5183)	2nd degree hypospadias (n=1547)	cOR (95% CI) for 2nd degree vs controls	3rd degree hypospadias (n=389)	cOR (95% CI) for 3rd degree vs controls
Clomiphene citrate only	89	49	2.0 (1.4-2.8)	23	4.0 (2.5-6.4)
IVF/ICSI	47	52	3.9 (2.6-5.9)	20	6.5 (3.8-11.2)
Plurality and fertility treatment					
Singleton without treatment	4809	1335	1 (ref)	298	1 (ref)
Singleton with IVF/ICSI	24	24	3.6 (2.0-6.4)	6	4.0 (1.6-9.9)
Singleton with clomiphene citrate only	78	43	2.0 (1.4-2.9)	16	3.3 (1.9-5.7)
Multiples without treatment	103	46	1.6 (1.1-2.3)	22	3.4 (2.1-5.5)
Multiples with IVF/ICSI	23	28	4.4 (2.5-7.6)	14	9.8 (5.0-19.3)
Multiples with clomiphene citrate only	11	6	2.0 (0.7-5.3)	7	10.3 (4.0-26.7)
Use of oral contraceptives after conception[c]					
Yes	171	48	0.9 (0.7-1.3)	12	0.9 (0.5-1.7)
No	4924	1474	1 (ref)	371	1 (ref)
Maternal alcohol use[d]					
Yes	1875	661	1.3 (1.2-1.5)	150	1.1 (0.9-1.4)
No	3167	846	1 (ref)	228	1 (ref)
Binge drinking (≥4 drinks per occasion)[d]					
Yes	639	189	1.1 (0.9-1.3)	35	0.8 (0.5-1.1)
No	3167	846	1 (ref)	228	1 (ref)
Maternal smoking[e]					
Yes	949	266	0.9 (0.8-1.1)	58	0.8 (0.6-1.1)
No	4069	1228	1 (ref)	316	1 (ref)
Maternal cannabis use[e]					
Yes	210	42	0.7 (0.5-0.9)	10	0.6 (0.3-1.2)
No	4891	1482	1 (ref)	372	1 (ref)
Folic acid supplement use[d]					
Any use	4330	1391	1.8 (1.5-2.2)	346	1.7 (1.2-2.4)
No use	837	150	1 (ref)	39	1 (ref)
Maternal diabetes mellitus					
Pre-existing type I or II	29	18	2.1 (1.2-3.8)	1	*f*
Gestational	232	86	1.3 (1.0-1.6)	19	1.1 (0.7-1.7)

Variable	Male Controls (n=5183)	2nd degree hypospadias (n=1547)	cOR (95% CI) for 2nd degree vs controls	3rd degree hypospadias (n=389)	cOR (95% CI) for 3rd degree vs controls
No	4768	1409	1 (ref)	363	1 (ref)
Maternal hypertension					
Untreated hypertension	584	251	1.6 (1.3-1.8)	74	2.0 (1.5-2.6)
Early treatment	67	29	1.6 (1.0-2.4)	10	2.4 (1.2-4.6)
Late treatment	30	19	2.3 (1.3-4.1)	14	7.4 (3.9-14.0)
No hypertension	4432	1222	1 (ref)	281	1 (ref)
Maternal thyroid disorder					
Any	118	62	1.8 (1.3-2.5)	9	1.0 (0.5-2.0)
Thyroxine exposed	87	52	2.0 (1.4-2.9)	9	1.4 (0.7-2.8)
No	5065	1485	1 (ref)	380	1 (ref)

[a] Family history of hypospadias in the father, a sibling or in one of the mother's previous pregnancies

[b] Reference category was no reported fertility issues

[c] Exposure measured any time in the first three months post-conception

[d] Exposure and reference category measured between one month preconception and three months post-conception

[e] Exposures were measured between one month preconception and three months post-conception. Reference category is no exposure between three months preconception and the end of pregnancy

[f] No OR was calculated for variables with <3 exposed cases

Table 3

Adjusted Odds Ratios for Associations between Selected Exposures and the Risk of Hypospadias Stratified by Subtype, National Birth Defects Prevention Study, 1997-2009[a]

Variable	aOR (95% CI) for 2nd degree vs controls	aOR (95% CI) for 3rd degree vs controls	aOR (95% CI) for 3rd degree vs 2nd degree[b]
Maternal age (per year)	1.03 (1.02-1.05)	1.07 (1.04-1.09)	1.03 (1.0-1.05)
Maternal race/ethnicity			
Non-Hispanic white	1 (ref)	1 (ref)	1 (ref)
Non-Hispanic black	0.9 (0.8-1.2)	1.7 (1.2-2.4)	1.5 (1.0-2.2)
Hispanic	0.3 (0.2-0.3)	0.7 (0.5-1.1)	2.3 (1.5-3.7)
Asian/Pacific Islander	0.5 (0.3-0.8)	2.3 (1.4-3.7)	4.3 (2.3-7.7)
Other	0.6 (0.4-0.8)	1.2 (0.7-2.2)	2.0 (1.0-3.8)
Maternal education >12 years	1.2 (1.0-1.4)	1.0 (0.7-1.4)	0.9 (0.6-1.2)
Pre-pregnancy BMI ≥30 kg/m^2	1.0 (0.8-1.2)	1.1 (0.8-1.5)	
Family history of hypospadias[c]	25.9 (13.1-51.3)	16.4 (6.2-43.5)	0.6 (0.3-1.2)
Parity			
0	1.7 (1.5-1.9)	2.8 (2.2-3.7)	1.6 (1.2-2.1)
≥1	1 (ref)	1 (ref)	1 (ref)
Use of oral contraceptives after conception[d]	1.0 (0.7-1.5)	1.2 (0.6-2.3)	
Maternal alcohol use[e]	1.1 (0.9-1.2)	1.0 (0.8-1.3)	
Maternal smoking[f]	0.9 (0.7-1.1)	0.9 (0.7-1.3)	
Maternal cannabis use[f]	0.7 (0.5-1.1)	0.9 (0.5-1.8)	
Folic acid supplement use[e]	1.2 (1.0-1.5)	1.1 (0.7-1.6)	
Gestational diabetes mellitus	1.2 (0.9-1.7)	0.7 (0.4-1.3)	
Maternal hypertension			
Untreated hypertension	1.5 (1.2-1.8)	2.2 (1.6-3.0)	1.3 (1.0-1.9)
Early treatment	1.2 (0.8-2.2)	1.5 (0.6-3.5)	1.4 (0.6-3.6)
Late treatment	2.1 (1.0-4.5)	9.0 (4.3-19.1)	3.9 (1.7-9.0)
Maternal exposure to thyroxine	1.5 (1.0-2.2)	1.2 (0.6-2.7)	0.9 (0.4-1.9)
Plurality and fertility treatment			
Singleton without treatment	1 (ref)	1 (ref)	1 (ref)
Singleton with IVF/ICSI	1.8 (0.9-3.7)	2.4 (0.9-6.2)	1.1 (0.4-3.0)
Singleton with clomiphene citrate only	1.2 (0.8-1.8)	2.5 (1.4-4.5)	2.0 (1.1-3.7)
Multiples without treatment	1.5 (1.0-2.3)	3.1 (1.8-5.5)	1.9 (1.0-3.4)
Multiples with IVF/ICSI	1.9 (1.0-3.4)	5.2 (2.5-11.0)	2.2 (1.1-4.7)
Multiples with clomiphene citrate only	1.0 (0.3-3.1)	7.5 (2.6-22.1)	5.6 (1.7-17.9)

[a] Analyses were restricted to cases and controls with valid answers for all variables (1293 second degree cases, 324 third degree cases and 4300 controls). A full model approach was used to adjust for potential confounding.

[b] Only included if there was an association observed for 2nd or 3rd degree hypospadias when compared to controls

[c] Family history of hypospadias in the father, a sibling or one of the mother's previous pregnancies

[d] Exposure measured any time in the first three months post-conception

[e] Exposure and reference category measured between one month preconception and three months post-conception

Exposures were measured between one month preconception and three months post-conception. Reference category is no exposure between three months preconception and the end of pregnancy