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No Association between Maternal Pre-pregnancy Obesity and Risk of Hypospadias or Cryptorchidism in Male Newborns

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Abstract

BACKGROUND—Hypospadias and cryptorchidism, two relatively common male genital anomalies, may be caused by altered maternal hormone levels, blood glucose levels, or nutritional deficiencies. Maternal obesity, which increases risk of diabetes and could influence hormone levels, may therefore be associated with risk of hypospadias and cryptorchidism. The purpose of this study was to assess the association between pre-pregnancy maternal obesity and hypospadias and cryptorchidism.

METHODS—We conducted a case-control study of hypospadias and cryptorchidism in male singleton newborns using Washington State birth records from 1992 to 2008 linked to birth-hospitalization discharge records. Maternal pre-pregnancy body mass index (BMI) was calculated from pre-pregnancy weight and height. Adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs) for hypospadias or cryptorchidism were estimated by fitting multivariable logistic regression models adjusted for year of birth, and maternal age, education, parity, race, and cigarette smoking during pregnancy.

RESULTS—The complete-case analysis included 2,219 hypospadias cases, 2,563 cryptorchidism cases, and 32,734 controls. Maternal obesity (BMI ≥ 30 kg/m²) was not associated with risk of hypospadias or cryptorchidism in male offspring (aOR(95% CI), hypospadias: 1.07(0.95–1.21); cryptorchidism: 0.99(0.89–1.11)), and no trend in risk with increasing maternal BMI was found. There was little indication of risk associated with BMI among any sub-group of mothers examined, including women with pre-existing diabetes or hypertension, women who developed preeclampsia, non-Hispanic white women, first-time mothers, or mothers aged ≥ 30 years.

CONCLUSIONS—The results of this study do not support the hypothesis that pre-pregnancy maternal obesity is a cause of hypospadias or cryptorchidism in male infants.

Keywords

maternal obesity; genital birth defects; hypospadias; cryptorchidism; undescended testicles

INTRODUCTION

The genital defects hypospadias and cryptorchidism are relatively common among male infants, affecting approximately 0.5% and 2–5%, respectively, of boys born in the United

States and Western Europe (Carmichael et al., 2003; Cortes et al., 2008; Paulozzi, 1999; Paulozzi et al., 1997; Thonneau et al.; Virtanen et al., 2007). Affected infants often require corrective medical procedures and are at increased risk of long-term adverse health effects including poor semen quality and testicular cancer (Thorup et al., 2010; Toppari et al., 2010; Virtanen et al., 2007).

Hypospadias and cryptorchidism result from the disruption of developmental processes that are predominantly regulated by androgens (Aschim et al., 2004; Manson and Carr, 2003; Thonneau et al., 2003). Furthermore, the Testicular Dysgenesis Syndrome hypothesis posits that hypospadias, cryptorchidism, testicular cancer, and reduced fecundity share etiology, particularly endocrine disruption (Sharpe, 2003; Skakkebaek, 2003; Skakkebaek et al., 2001).

At least three potential mechanisms may relate maternal obesity to risk of hypospadias and cryptorchidism. Levels of circulating hormones, including androgens, differ between obese and normal-weight women (Blouin et al., 2008; Jansson et al., 2008; Morisset et al., 2008; Pasquali and Gambineri, 2006; Pasquali et al., 2007; Wei et al., 2009). Lower overall diet quality and blood concentrations of micronutrients have also been observed in obese women compared to non-obese women and may relate to risk of birth defects, including hypospadias, although data are inconsistent (Carmichael et al., 2010; Carmichael et al., 2009; Goh et al., 2006; Ormond et al., 2009). Finally, impaired fasting glucose and impaired glucose tolerance before and during pregnancy are associated with obesity (Chu et al., 2007; Siega-Riz and King, 2009), and uncontrolled glucose levels have been associated with birth defects (Carmichael et al., 2010). Based on the reported connections between obesity and these mechanisms that could underlie development of hypospadias and cryptorchidism, we hypothesized that male genital birth defects would be more common in babies born to mothers who were obese before pregnancy relative to babies born to normal-weight mothers.

METHODS

Study Design

We conducted a population-based case control study of risk of genital malformations in male newborns from 1992 to 2008, by using Washington State birth records linked to Comprehensive Hospital Abstract Reporting System (CHARS) data. These data include diagnosis and procedure codes from the birth hospitalization for both mother and infant. Infants without hospitalization data available for linkage to Washington State birth records were not included; this excludes approximately 7% of births in Washington State that take place outside of hospitals and do not require hospitalization, and births in a federal facility such as a military hospital (Washington State Department of Health, 2010). Genital anomalies have also been recorded on birth certificates: from 1992–2002, check-boxes for “genital anomalies” and “other urogenital malformation” appeared on the birth record; after 2002, both items were removed and a single check-box for hypospadias was added.

Cryptorchidism and hypospadias cases were identified on the basis of International Classification of Disease, Clinical Modification (ICD-9-CM) diagnostic codes and birth certificate data. Live-born singleton males were eligible to be cases if birth hospitalization records included ICD-9-CM codes denoting cryptorchidism (752.5, 752.51, or 752.52) or hypospadias (752.6x), or if the birth certificate record indicated “malformed genitalia,” “other urogenital anomaly,” or hypospadias. The cryptorchidism and hypospadias case groups were not mutually exclusive.

For each eligible case, five singleton live-born males without index ICD-9-CM codes in the birth hospitalization record and without indication of hypospadias, genital anomaly, or other

urogenital malformation on the birth certificate were randomly selected as eligible controls. Controls were selected from the same year of birth as their corresponding case.

Exclusions

Because ICD-9-CM coding for hypospadias changed from 752.6 to 752.61 in October, 1996, infants initially identified as eligible hypospadias cases but who were diagnosed with ICD-9-CM codes 752.62–752.69 and without 752.61 after 1996 were excluded as hypospadias cases (679 infants). Infants with malformed genitalia (n=182) or “other urogenital anomaly” (n=1,839) indicated on the birth certificate records but without ICD-9-CM for either hypospadias or cryptorchidism indicated in the hospitalization data were excluded. An additional 51 infants born outside a hospital, birthing facility, or other medical clinic; 16 infants for whom the mother’s age was not recorded; and 6 infants with gestational ages less than 20 weeks recorded on birth records were excluded from all analyses. Infants with chromosomal defects, including Down Syndrome, indicated in the hospitalization record (ICD-9-CM code 758) or on the birth certificate were also excluded from all analyses (93 controls; 18 hypospadias cases; 30 cryptorchidism cases; and 4 with both hypospadias and cryptorchidism). Thus, the control group did not include infants with any urogenital defect, recorded on CHARS or on the birth certificate. However, case and control infants may have had other congenital malformations.

Exposure

The primary exposure considered was maternal pre-pregnancy obesity as indicated by body mass index (BMI, weight divided by the square of height (kg/m^2)) (National Institutes of Health, 1998). Pre-pregnancy weight has been recorded on birth certificates in Washington State since 1992. Weight is recorded to the nearest pound and is obtained from the mother’s physician or medical records; whether this information was assessed clinically or resulted from self-report was not indicated. If unavailable from these sources, the mother or another family member may provide pre-pregnancy weight (2003). For births prior to 2003, maternal height was obtained from state driver’s license records linked to maternal information on birth records. Beginning in 2003, maternal height to the nearest inch was collected on birth records in the same manner as pre-pregnancy weight (Washington State Department of Health, 2003). BMI was categorized as underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$), normal weight ($18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$), overweight ($25 \leq \text{BMI} < 30 \text{ kg/m}^2$), or obese ($\text{BMI} \geq 30 \text{ kg/m}^2$). An additional category, morbidly obese ($\text{BMI} > 40 \text{ kg/m}^2$), was added in some analyses as noted. BMI as a continuous variable, included as either a single linear term or linear and quadratic terms, was also examined. For analysis with a single linear BMI term, mothers with BMI less than 18.5 kg/m^2 were excluded.

Statistical Analysis

Unconditional logistic regression was used to estimate crude and adjusted odds ratios (aORs) and 95 percent confidence intervals (95% CIs) separately for hypospadias and cryptorchidism.

Based on *a priori* development of causal diagrams to identify confounders, aOR estimates were adjusted for year of birth (1992–1996–1997–2002–2003–2008) and the following maternal characteristics: age (<20y, 20–24y, 25–29y, 30–34y, or ≥ 35 y), race (non-Hispanic White, Hispanic, Asian or Pacific Islander, others), educational attainment (less than high school; completed high school; some college; completed college), number of previous live births (none, 1, 2 or more), and any smoking during pregnancy (yes or no). Maternal pre-pregnancy diabetes, pre-pregnancy hypertension, and preeclampsia were not included as adjustment variables because each is potentially in the causal path between maternal BMI and birth defects. For the same reason, birthweight and gestational age were not considered

as potential confounders. The interaction of dichotomized maternal BMI (≤ 26 kg/m², > 26 kg/m²), maternal age (< 30 , 30–34, ≥ 35 years), and previous births (none, any) was investigated following a previous report (Carmichael et al., 2007). A single variable with 12 levels representing the possible combinations of these variable parameterizations was used as the exposure, with additional adjustment for other potential confounders as in the main analysis. Linear combinations of coefficients from this model were examined for departures from a multiplicative model.

Sensitivity Analyses

Pre-pregnancy BMI was unavailable for approximately 30% of mothers. To explore some possible biases due to missing BMI information, several additional analyses were performed. The completeness of maternal BMI information varied by birth year (1992–1996, 36.1% missing; 1997–2002, 32.1% missing; 2003–2008, 13.7% missing), likely as a result of the changes in recording of height and weight noted above. We therefore repeated the primary analysis separately by birth year (1992–1996–1997–2002–2003–2008). In separate analyses, pre-pregnancy weight, categorized into quintiles or as a continuous variable, was used in place of BMI. Finally, we repeated analyses only for non-Hispanic whites, among whom BMI information was more complete.

In addition, we applied multiple imputation separately to the hypospadias and cryptorchidism analyses. Twenty sets of values of the natural logarithm of BMI were predicted using multivariate normal imputation from the potential confounders listed above and a dichotomous variable indicating case status, including only mother-infant pairs with complete confounder information. From these results imputed BMI was calculated and used in multivariable logistic regression models including the same adjustment variables as the complete-case analysis, following standard multiple imputation analysis techniques to combine aOR point estimates and standard errors (Lee and Carlin, 2010; Rubin, 1987; Schafer, 1997).

To examine the sensitivity of our results to other potential sources of bias, several restricted analyses were performed. The complete-case analysis was repeated separately after restriction to each of the following: birthweight 2500 – 4200 g; gestational age 37–42 weeks; mothers without pre-pregnancy hypertension; mothers without pre-pregnancy diabetes; mothers who did not develop preeclampsia; and mothers without diabetes, hypertension, or preeclampsia.

We repeated the complete-case primary analysis after restriction of controls to infants with no congenital defects of any kind and restriction of cases to those infants with only the index defect and no others (“isolated cases”). In addition, the complete-case analysis was repeated restricting hypospadias cases to those born after 1996 with additional diagnosis of congenital chordee indicated in the birth hospitalization record (ICD-9-CM 752.63; N=137); and, separately, to hypospadias cases indicated on both the specific birth certificate checkbox and the birth hospitalization record (2003–2008 only; N=258).

The sensitivity of the results to non-differential misclassification was examined using a published statistical simulation tool implemented in Microsoft Excel 2003 (Fox et al., 2005; Lash, 2009). In summary, this tool back-calculates the “true” odds ratio after randomly selecting values of sensitivity and specificity for both exposure and disease, from ranges provided by the user. The software repeated this calculation 5,000 times to generate a “simulation interval” that includes 95% of all back-calculated “true” ORs, accounting for misclassification and random error. To prevent computer memory overrun the number of controls was reduced to 1,000 with obese mothers and 3,068 with normal-BMI mothers. Only normal-BMI and obese mothers were included in a dichotomized exposure

classification, ignoring other women for the purposes of sensitivity analysis, and we did not include stratification on any potential confounders in the simulations. For both disease and exposure, the sensitivity and specificity of classification varied from 60–80% and 85–100%, respectively.

Data cleaning, logistic regression, and multiple imputation were completed with Stata/SE versions 10 and 11 (StatCorp LP, College Station, TX).

Ethical Conduct of Research

The Internal Review Board for Protection of Human Subjects at the University of Washington, Seattle, and the Washington State Department of Health approved this research.

RESULTS

The study included for analysis 3,268 male singleton infants diagnosed with hypospadias, 3,946 diagnosed with of cryptorchidism, and 48,874 controls randomly selected from all singleton male infants without any genital defect. Of these, maternal pre-pregnancy BMI data were missing for 909 hypospadias cases (27.8%), 1,187 cryptorchidism cases (30.1%), and 13,606 controls (27.8%). Therefore, analyses included 2,359 hypospadias cases and 2,759 cryptorchidism cases, including 36 infants with both conditions, in addition to 35,268 controls with complete maternal BMI information (Table 1).

Compared to mothers of controls, a larger proportion of mothers of boys with hypospadias were over 35 years of age, non-Hispanic White, and college-educated (Table 1). In contrast, mothers of infants with cryptorchidism were very similar to mothers of controls. Infants with either anomaly were more often the mother's first child than were control infants.

Infants born to underweight, overweight or obese mothers were not at higher risk of hypospadias or cryptorchidism relative to infants born to normal-BMI mothers (Table 2). No association was observed when maternal BMI was included as a linear continuous variable in the statistical model (Table 2); and addition of a quadratic BMI term did not change results (not shown). Crude odds ratio estimates and estimates adjusted for year of birth and maternal age, race, parity, education, and smoking during pregnancy differed only slightly, suggesting minimal confounding by these maternal characteristics (Table 2). When obese mothers were divided into obese ($30 < \text{BMI} < 40 \text{ kg/m}^2$) and morbidly obese ($\text{BMI} \geq 40 \text{ kg/m}^2$) categories, risk estimates did not differ substantially between the two categories and were similar to estimates with a single obese category (aOR (95%CI) comparing morbidly obese to normal BMI, hypospadias: 1.15 (0.89–1.48); cryptorchidism: 1.04 (0.82–1.33)). Results of analysis substituting quintiles of maternal pre-pregnancy weight, in the place of BMI, yielded similar results; aOR (95%CI) comparing the uppermost quintile of pre-pregnancy weight ($>79.1 \text{ kg}$) to the second-lowest quintile ($54.5 - 61.0 \text{ kg}$) were 1.13 (1.00–1.28) for hypospadias and 1.02 (0.91–1.15) for cryptorchidism. Pre-pregnancy weight as a continuous variable was also not associated with risk of either malformation.

No important differences in the association of BMI, dichotomized at 26 kg/m^2 , with either malformation were observed between strata formed by maternal age and parity. For hypospadias, the strongest association with maternal BMI over 26 kg/m^2 compared to those below 26 kg/m^2 was observed among nulliparous mothers over age 35 (125 cases total; aOR (95%CI): 1.37 (0.93–2.02)). Similar analysis of cryptorchidism consistently showed very weak associations among all strata combining maternal age and parity (not shown).

Pre-existing maternal diabetes, chronic hypertension, or preeclampsia were more common among mothers of infants with hypospadias or cryptorchidism (Table 1). Analysis of the association between maternal BMI and hypospadias and cryptorchidism restricted to women without each of these conditions, or without any of them, yielded results similar to the primary analysis among all participants (not shown). Results of restricted analysis including only infants born after 37 – 42 weeks gestation, or weighing 2.5 – 4.0 kg at birth, also did not differ substantially (not shown).

Restriction of the control group to infants without a diagnosis of any congenital defects (ICD-9-CM 740.0 – 759.9) excluded 1,271 infants. Restriction of case groups to infants without defects other than hypospadias or cryptorchidism excluded 350 and 288 infants, respectively. Among this restricted set of infants, the aORs comparing obese to normal-weight mothers for hypospadias (aOR (95% CI), 1.02 (0.89–1.16)) or cryptorchidism (aOR (95% CI), 0.97 (0.86–1.09)) were not substantially different compared to the results in Table 2.

Approximately 30% of birth records for infants eligible for inclusion in this study were missing maternal BMI information. From 2003 to 2008, maternal height was recorded directly on the birth certificate, and the proportion of birth records missing maternal BMI dropped to 14%, but results of analyses restricted to this range of birth years did not differ substantially from the main analysis results (aOR (95% CI) comparing obese to normal-weight women, restricted to 2003–2008, hypospadias: 1.02 (0.86–1.21); cryptorchidism: 0.88 (0.75–1.04)).

The estimated ORs for hypospadias or cryptorchidism in each of the multiple imputation analyses also showed little difference from the complete-case analysis. Multiple imputation resulted in the inclusion of an additional 714 hypospadias cases, 934 cryptorchidism cases, and 10,906 controls. Including imputed data, the estimated aORs (95% CI) comparing obese to normal-weight women were 1.09 (0.98–1.22) and 0.97 (0.87–1.09) for hypospadias and cryptorchidism, respectively, similar to the result of the complete-case analysis.

DISCUSSION

Overall, we observed little or no evidence of association between pre-pregnancy maternal body mass index and risk of hypospadias or cryptorchidism, two of the most common genital defects in male infants.

Our study has important strengths. It is population-based, with the vast majority of births in Washington State over 17 years eligible to be included. To our knowledge, our study includes the largest number of cases of studies to date of the relationship between maternal BMI and these defects in the United States. One previous study, conducted in Sweden (Blomberg and Kallen, 2010), included nearly 3,000 hypospadias cases but did not examine cryptorchidism.

We relied on height and weight information routinely collected as part of the Washington State birth registration system. According to the protocol for completing birth records, maternal pre-pregnancy weight and, after 2002, height, were obtained from medical records. It is not known whether the information in the medical record is self-reported or clinically assessed, but in either case, weight information in the medical record was obtained prior to birth and therefore was not influenced by malformations in the infant. We also used simulations to examine the impact of misclassification of maternal BMI and found that this is an unlikely explanation for our results. For maternal height prior to 2003, information from Washington State driver's license records was linked to birth records. Women may have misrepresented their heights, provided by self-report at the time of driver's license

issue, but misclassification of height information is unlikely to be differential with respect to the case status of a woman's child. The minimization of potential differential misclassification of pre-pregnancy maternal BMI is a strength of our methodological approach.

Approximately 30% of cases and controls eligible for our study were missing either height or weight information, precluding calculation of BMI for these individuals. We observed that BMI information was more likely to be missing for Hispanic and African-American mothers, and among mothers with lower educational attainment. Because these groups could have differing risk of congenital defects, the direction of bias introduced by missing BMI cannot easily be predicted. However, the proportions of infants with missing maternal BMI information in each case group and among controls were nearly identical (29%, 31%, and 30% for hypospadias, cryptorchidism, and controls, respectively). Furthermore, we investigated the impact of missing BMI by using restricted analyses and multiple imputation. Neither approach suggested that the complete-case analysis we undertook is substantially biased due to incomplete BMI data on some mothers.

These results regarding hypospadias are consistent with one early study (Polednak and Janerich, 1983), but stand in contrast to those reported from several more recent studies in which there was increased risk of hypospadias among infants born to obese mothers compared with normal-weight mothers (Akre et al., 2008; Blomberg and Kallen, 2010; Carmichael et al., 2007; Waller et al., 2007). Two of these reports arose from the same study sample that ascertained cases from birth defects registries in 8 different US states and controls from separate hospital records, and relied on maternal self-report of pre-pregnancy weight up to 24 months after delivery (Carmichael et al., 2007; Waller et al., 2007; Yoon et al., 2001). Carmichael *et al.* (2007) also suggested that the association between maternal BMI and risk of hypospadias varied depending on maternal age and the number of previous births, and was strongest among older, first-time mothers. In our study we observed at most a small difference in risk of hypospadias and cryptorchidism among these groups, and our aOR estimates were accompanied by wide confidence intervals, suggesting that any difference may reflect a chance finding. A larger study based upon Swedish birth records, hospital data, and birth defects registry data produced results similar to those of Carmichael *et al.* (2007), in which boys born to obese mothers had a statistically significant ~30% higher odds of hypospadias (Blomberg and Kallen, 2010; Carmichael et al., 2007; Waller et al., 2007). A smaller study, combining Swedish and Danish cases recruited from clinical and administrative sources and which also relied on self-reported pre-pregnancy weight, estimated an odds ratio of 2.6 for hypospadias, comparing obese to normal-BMI mothers (Akre et al., 2008). All of these studies excluded infants with congenital defects from the control group, in contrast to our approach. However, when we did exclude infants with other defects from our control group and restricted analysis to isolated cases, our results were not changed.

Risk of cryptorchidism persisting for one year after birth has also been associated with high maternal BMI in a case-control study (Depue, 1984) and prospective cohort study (Berkowitz et al., 1995). However, these reports contrast with the results of a recent prospective study in Denmark and Finland in which cryptorchidism was assessed at 3 months of age (Damgaard et al., 2008), and with the results of an earlier clinic-based case-control study that included only infants with cryptorchidism at age 1 year or later (McBride et al., 1991), which both reported no association. Our results indicate no relationship between maternal BMI and cryptorchidism assessed at birth or shortly thereafter. Thus, considerable uncertainty remains about whether maternal obesity is associated with risk of cryptorchidism, and may result in part from differences in case definition and ascertainment.

Non-differential misclassification of maternal BMI or diagnosis of genital defects in our study could have attenuated our estimates of association. To assess this possibility, we simulated the combination of non-differential misclassification of exposure and disease (Fox et al., 2005; Lash, 2009). A study in California found that less than 10% of hypospadias cases reported in hospital discharge records are false positives, but did not quantify false positive cryptorchidism cases (Hexter et al., 1990). The sensitivity of hospital discharge records in detecting hypospadias and cryptorchidism may be as low as ~70% and 65%, respectively (Calle and Khoury, 1991). Using these values as a plausible range, and the values for the sensitivity and specificity of maternal BMI, the results of our simulations estimated a corrected aOR for hypospadias and 95% simulation interval of 1.15 (0.97–1.36), comparing obese mothers to normal-BMI mothers. Thus the results of our study are not likely to be fully accounted for by non-differential misclassification of maternal BMI, infant case status, or both.

A reliance on hospital-discharge diagnosis codes to determine case and control status among infants limited our ability to determine the severity of hypospadias or cryptorchidism. Because surgical correction of these defects is typically an outpatient procedure and therefore is not reflected in the hospitalization data, we could not use evidence of such treatment to refine or confirm the diagnoses. Three degrees of severity are usually recognized for hypospadias depending on the location of the urethral meatus; with a more proximal location considered more severe (Baskin et al., 2001; Brouwers et al., 2010; Madhok et al., 2009). According to previous reports, 60–80% of hypospadias cases are distal, with a glanular or coronal meatus, and less than 10% are the most severe, characterized by the meatus on or below the scrotum (Baskin and Ebbers, 2006; Baskin et al., 2001; Carlson et al., 2009; Madhok et al., 2009). Thus we expect that the majority of the cases included in our analysis were glanular or coronal and relatively mild, in contrast to some earlier studies that focused on more severe hypospadias (Carmichael et al., 2007; Waller et al., 2007).

Nonetheless, we identified 101 hypospadias cases also diagnosed with congenital chordee, a second defect associated with more severe hypospadias (Baskin and Ebbers, 2006; Baskin et al., 2001), and repeated our primary complete-case analysis. Results were largely unchanged, although the precision of the aOR estimates was greatly reduced. We also conducted a separate analysis restricted to hypospadias cases identified on both the birth certificate and hospital records, on the assumption that defects recorded in both places may be more readily apparent and hence, more severe. No noteworthy change in the aOR estimates resulted given the small size of these subgroups. Nonetheless, to the extent that disease of differing severity has different etiology, misclassification of case status by severity could bias our results.

For cryptorchidism there is an accepted distinction between cases that resolve spontaneously in the months following birth, and more serious cases that ultimately require surgical correction. Overall, 2–5% of male infants are born with cryptorchidism, but the prevalence at birth is as high as 20–30% among infants less than 2500 g at birth (Berkowitz et al., 1993; Boisen et al., 2004; Cortes et al., 2008). About 50% of cryptorchidism cases resolve within 3 months of birth, irrespective of birthweight (Berkowitz et al., 1993; Boisen et al., 2004; Cortes et al., 2008). We performed two additional analyses, restricted to full-term (37–42 weeks) and to full-term normal-weight infants (37–42 weeks and 2.5–4.0 kg), and the results did not change. However, because we lacked follow-up information on the severity of cryptorchidism or follow-up data on infants in our study sample, we were unable to identify cryptorchidism cases that later resolved through spontaneous descent. Thus, although we observed no association between high maternal BMI and cryptorchidism, such an association may be limited to the 25–50% of cases whose cryptorchidism does not

spontaneously resolve. Given the large number of cases included in our study, however, such an association could not be strong or we would likely have observed some evidence of it in our analyses.

In summary, we observed no relation between maternal BMI and the male genital anomalies hypospadias and cryptorchidism. Although non-differential misclassification may be present in our study sample, simulations indicate that it would need to be extreme to account for our results if the true association between maternal obesity and hypospadias and cryptorchidism is consistent with previous studies (Akre et al., 2008; Berkowitz et al., 1995; Blomberg and Kallen, 2010; Carmichael et al., 2007). Missing BMI information is also unlikely to explain our observations, based on the results of analysis restricted to years with the most complete data, and the results of analysis employing multiple imputation to predict missing maternal BMI values. Therefore, the results of this study are most consistent with the conclusion that pre-pregnancy maternal obesity is not associated with risk of either hypospadias or cryptorchidism in male offspring.

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Table 1

Characteristics of mothers with complete body mass index (BMI) information, control infants, and infants with hypospadias or cryptorchidism, selected for study from Washington State registered births, 1992–2008

	Controls		Hypospadias		Cryptorchidism	
	N	%	N	%	N	%
Birth Year	35268		2359		2759	
1992–1996	8893	25.2	649	27.5	711	25.8
1997–2002	14128	40.1	676	28.7	901	32.7
2003–2008	12247	34.7	1034	43.8	1147	41.6
Mother's Age						
Less than 20	3450	9.8	184	7.8	293	10.6
20–24	8589	24.4	542	23.0	680	24.6
25–29	10057	28.5	660	28.0	732	26.5
30–34	8462	24.0	580	24.6	673	24.4
35+	4710	13.4	393	16.7	381	13.8
Previous Live Births						
0	14668	41.6	1097	46.5	1324	48.0
1	11548	32.7	738	31.3	789	28.6
2+	8857	25.1	514	21.8	624	22.6
Missing	195	0.6	10	0.4	22	0.8
Mother's Education						
Less than High School	5784	16.4	274	11.6	498	18.1
High School Graduate	9743	27.6	633	26.8	751	27.2
Some College	9334	26.5	683	29.0	700	25.4
College Graduate	8788	24.9	682	28.9	686	24.9
Missing	1619	4.6	87	3.7	124	4.5
Mother's Race/Ethnicity						
White	26594	75.4	1984	84.1	2013	73.0
Hispanic	3399	9.6	100	4.2	271	9.8
Asian/Pacific Islander	2645	7.5	113	4.8	228	8.3
Other	1890	5.4	109	4.6	192	7.0

	Controls		Hypospadias		Cryptorchidism	
	N	%	N	%	N	%
Missing	740	2.1	53	2.2	55	2.0
Mother Smoked During Pregnancy						
No	30181	85.6	2015	85.4	2300	83.4
Yes	4723	13.4	324	13.7	423	15.3
Missing	364	1.0	20	0.8	36	1.3
Gestational Age (weeks)						
Less than 37 weeks	2055	5.8	269	11.4	271	9.8
37–42 weeks	32762	92.9	2068	87.7	2450	88.8
42+ weeks	37	0.1	1	0.0	1	0.0
Missing	414	1.2	21	0.9	37	1.3
Birth Weight (g)						
Less than 2500	1140	3.2	215	9.1	219	7.9
2500–3999	28526	80.9	1845	78.2	2212	80.2
≥4000	5538	15.7	288	12.2	319	11.6
Missing	64	0.2	11	0.5	9	0.3
Maternal Diabetes						
No diabetes	33287	94.4	2206	93.5	2554	93
Pre-existing diabetes	138	0.4	14	0.6	17	1
Gestational diabetes	1397	4.0	95	4.0	126	5
Missing	446	1.3	44	1.9	62	2
Chronic Hypertension						
No	34472	97.7	2281	96.7	2660	96.4
Yes	350	1.0	34	1.4	37	1.3
Missing	446	1.3	44	1.9	62	2.2
Preeclampsia						
No	32970	93.5	2127	90.2	2509	90.9
Yes	1852	5.3	188	8.0	188	6.8
Missing	446	1.3	44	1.9	62	2.2
BMI category (kg/m ²)						
Underweight (< 18.5)	1421	4.0	97	4.1	130	4.7

	Controls		Hypospadias		Cryptorchidism	
	N	%	N	%	N	%
Normal (18.5–24.9)	19367	54.9	1266	53.7	1484	53.8
Overweight (25–29.9)	8168	23.2	545	23.1	651	23.6
Obese (30+)	6312	17.9	451	19.1	494	17.9

Table 2

Crude (OR) and adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) of association between maternal pre-pregnancy body mass index (BMI) category and hypospadias or cryptorchidism among Washington State male singleton infants, 1992–2008

	Controls		Hypospadias				Cryptorchidism							
	N*	N**	N*	OR*	(95% CI)	N**	aOR**	(95% CI)	N*	OR*	(95% CI)	N**	aOR**	(95% CI)
BMI Category[†]														
Underweight	1421	1283	97	1.04	(0.84–1.29)	83	1.06	(0.84–1.33)	130	1.20	(0.99–1.44)	116	1.14	(0.93–1.39)
Normal	19367	17895	1266	Ref.		1193	Ref.		1484	Ref.		1382	Ref.	
Overweight	8168	7600	545	1.02	(0.92–1.13)	518	1.04	(0.93–1.16)	651	1.04	(0.95–1.15)	606	1.03	(0.93–1.14)
Obese	6312	5956	451	1.09	(0.98–1.22)	425	1.07	(0.95–1.21)	494	1.02	(0.92–1.14)	459	0.99	(0.89–1.11)
per 5 kg/m ^{2††}				1.03	(0.99–1.07)		1.03	(0.99–1.07)		1.01	(0.98–1.05)		1.01	(0.97–1.05)

* includes infants with complete maternal body mass index data but incomplete maternal education, previous births, race, or smoking information; unadjusted (crude) OR and 95% CI.

** includes infants with complete maternal BMI and adjustment variables; OR and 95% CI adjusted for mother's age, mother's education, previous number of live births, mother's race, year of birth, and maternal smoking during pregnancy.

[†] BMI categories: underweight (<18.5 kg/m²); normal (18.5 – 24.9 kg/m²); overweight (25.0 – 29.9 kg/m²); obese (≥ 30 kg/m²)

^{††} BMI modeled as a single linear continuous variable, excluding mothers with BMI<18.5 kg/m²