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Nutritional factors and hypospadias risks

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SUMMARY

We examined whether hypospadias was associated with several aspects of the diet, including intake of animal products, intake of several nutrients and food groups related to a vegetarian diet and estrogen metabolism, and diet quality. The study included deliveries from 1997 to 2005 that were part of the National Birth Defects Prevention Study. Diet was assessed by food frequency questionnaire during maternal telephone interviews, and two diet quality indices were developed based on existing indices. Analyses included 1,250 cases with second or third degree hypospadias (urethra opened at the penile shaft, scrotum or perineum) and 3,118 male, liveborn, non-malformed controls. All odds ratios (ORs) and 95% confidence intervals (CI) were estimated from logistic regression models that included several potential confounders, including energy intake. Intake of animal products was not associated with hypospadias; e.g., the adjusted OR for any versus no intake of meat was 1.0 (95% CI 0.6, 1.6). Frequency of intake of meat or other animal products was also not associated with hypospadias, nor was intake of iron or several nutrients that are potentially related to estrogen metabolism. Diet quality was also not associated with hypospadias; the ORs for diet quality in the highest versus lowest quartile for the two diet quality indices were 1.0 (95% CI 0.6, 1.6) and 0.9 (95% CI 0.7, 1.1). In conclusion, this large study does not support an association of a vegetarian diet or worse diet quality with hypospadias.

INTRODUCTION

The first study to examine nutritional factors and hypospadias reported an almost fourfold increased risk of hypospadias among vegetarian mothers [1]. This finding has been interpreted as providing potential support for the hypothesis that estrogenic exposures confer increased risk of hypospadias, given that a vegetarian diet is associated with higher intake of phytoestrogens, which may have estrogenic effects. With one exception [2], however, subsequent studies have not confirmed an increased risk of hypospadias with a vegetarian diet or low meat or fish consumption [3–8]. The initial study also reported a two-fold increased risk associated with iron supplements[1], which was confirmed by one study [4] but not by another [9]. Other specific nutrients and food groups may also be associated with estrogen metabolism and estrogen levels; for example, higher intake of cruciferous vegetables, fiber and protein, and lower intake of energy and carbohydrates, may favor increased 2-

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hydroxylated estrogen metabolites, which are less estrogenic than the alternative 16α-hydroxylated metabolites, and vitamin C may be associated with increased estrogen levels [10–14]. The association of these nutrients with hypospadias has not been investigated previously.

A recent study took a more comprehensive approach by examining general diet quality and hypospadias. It characterized dietary patterns based on cluster analysis of foods [9]. The pattern labeled ‘non-health conscious’ was associated with a 50% increased risk of hypospadias, relative to a pattern labeled ‘health conscious.’

The National Birth Defects Prevention Study (NBDPS), a large population-based case-control study that includes hypospadias, provides a unique opportunity to investigate these associations given that it involves an in-depth assessment of dietary and supplement intake. Our objective was to examine the hypotheses that increased hypospadias risks were associated with the mother having low or no intake of animal products, higher iron intake, lower intake of nutrients that favor less estrogenic metabolites, or worse diet quality.

METHODS

The NBDPS is a large population-based, multi-center case-control study of structural congenital malformations. The current analysis includes deliveries with estimated due dates from 1997–2005. The study is an approved activity of the Institutional Review Boards of the participating study centers and the CDC. Detailed study methods have been published[15].

The NBDPS includes second and third degree hypospadias, i.e., the urethra opened on the penile shaft, or at the scrotum or perineum. Medical record information was reviewed by a clinical geneticist at each center who evaluated eligibility. Cases described as chordee alone, mild hypospadias (i.e., first degree, coronal, or glanular), hypospadias not otherwise specified, epispadias, or having ambiguous genitalia without further description were excluded. Cases with recognized single gene disorders or chromosomal abnormalities were excluded. Each case received a final review by one clinical geneticist (RSO) to ensure that all cases met standard eligibility criteria[16] .

Each center randomly selected approximately 150 liveborn non-malformed controls per study year from birth certificates (AR 2000-current, GA 2001-current, IA, MA, NC, NJ, UT) or birth hospitals (AR 1997–1999, CA, GA 1997–2000, NY, TX) to represent the population from which the cases were derived.

Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, between six weeks and 24 months after the infant’s estimated date of delivery. Interviews were conducted with mothers of 72% of eligible cases (n=1,355) and 67% of controls (n=3,432). Median time from date of delivery to interview was 12.9 months for cases and 8.8 months for controls.

Mothers reported their average intake of foods using a shortened version of the food frequency questionnaire developed by Willett and colleagues for The Nurses Health Study that included 58 food items [17]. Participants reported how often, on average, they consumed food items in the year before they became pregnant. Intake of breakfast cereals, sodas, food supplements and caffeinated tea and coffee were assessed by separate, more detailed questions, which covered intake during the three months before pregnancy. Because few women (mothers of 140 (10%) of cases and 348 (10%) of controls) consumed food supplements (e.g., powdered drink supplements) and nutrient data were not available for many of these products, food supplements were not included in nutrient calculations. The USDA nutrient database (version 19) was the source of nutrient values [18], except for choline, for which USDA version 20 was used because it is more complete [19, 20]. Food groups of interest were derived by summing the frequency of intake of all food items relevant to each particular group.

Women also reported detailed information about intake of vitamin and mineral supplements, including product names and specific start and stop dates. Mothers were asked whether they took any types of multivitamin/mineral supplements, including prenatal formulations, and whether they took single-nutrient supplements containing iron or vitamin C.

We assessed general diet quality based on two diet quality scores that were developed *a priori*. The Mediterranean Diet Score (MDS) is a summary of intake of six positively scored components (legumes, grains, fruits and nuts, vegetables, fish, and the ratio of mono-unsaturated to saturated fatty acid intake) and three negatively scored components (dairy, meat, and sweets) [21, 22]. The Diet Quality Index (DQI) is the summary score of six positively scored components (grains, vegetables, fruits, folate, iron, and calcium) and two negatively scored components (percent of calories from fat, and sweets) [23–26]. We calculated servings per day of each food-based component, ranked each component by quartile based on the distribution among controls, and then summed the components to provide a final value for each index. Further details have been published [27].

Mothers with energy intake <500 or >5,000 kcals and mothers with two or more missing food items (i.e., not queried) from the food frequency questionnaire (54 cases, 105 controls) were excluded from analyses, leaving 1,301 cases and 3,327 male controls available. A total of 1,250 cases and 3,118 controls had complete data on covariates. Logistic regression analyses were conducted to estimate odds ratios (OR) and 95 percent confidence intervals (CI) We examined the association of hypospadias with any versus no intake of meat and any versus no intake of meat or fish as more strict proxies for a vegetarian diet. We also examined intake of meat (including poultry) and fish as quartiles, and also intake of dairy, eggs and iron, as other nutritional factors related to a vegetarian diet. We conducted quartile analyses of cruciferous vegetables, fiber, energy, protein, carbohydrate, and vitamin C, as dietary factors potentially related to estrogen metabolism [10–14]. We also used the quartile approach for analyses of diet quality. Given that supplemental iron and vitamin C are often taken as single-nutrient supplements as well as being contained in multivitamin/mineral preparations, we examined these two sources of these nutrients in combination. For multivitamin/mineral preparations, we used a variable indicating any versus no periconceptional intake of folic acid-containing supplements (largely multivitamin/mineral formulations in this study), during the month before or the first three months of pregnancy. We further categorized intake of iron supplements based on whether they were initiated during the first trimester or later, given that their initiation is common during both time periods.

For analyses of any versus no intake of meat or fish and of vitamin/mineral supplements, we began with unadjusted analyses. Initial analyses of other dietary factors were adjusted for energy intake. We then adjusted all analyses for the following covariates, which were selected *a priori* based on potential associations with hypospadias and/or nutritional status: maternal race/ethnicity, education, age, number of previous live births, body mass index, periconceptional intake of folic acid-containing supplements, and study site. Odds ratios tended to be closer to one after adjustment, so we have presented only the adjusted estimates.

RESULTS

Mothers of cases tended to be more likely to be non-Hispanic white, have higher education, be older and nulliparous, and take folic acid-containing supplements, relative to control mothers (Table 1).

Only 1.8% of case and 1.5% of control mothers reported no intake of any meat, with an odds ratio of 1.0 (Table 2). A vegetarian diet defined as no meat or fish intake was even more rare; the odds ratio was less than one but imprecise. No case mother and one control mother reported zero intake of meats, fish, dairy and eggs (a proxy for veganism). Quartile-based analyses of nutrients, food groups and diet quality produced odds ratios that were close to one, with one exception (Table 3). Highest-quartile protein intake was associated with reduced risk (adjusted OR 0.6, 95% CI 0.5, 0.9), and the p-value for a test for trend across the quartiles was <0.001.

Relative to women who did not take vitamin C or folic acid-containing supplements, women who took either of these types of supplements were at increased risk of having offspring with hypospadias in unadjusted analyses (data not shown). However, after adjustment, odds ratios no longer suggested increased risk (Table 4). The same pattern of no association was observed for iron supplements.

DISCUSSION

These analyses focused on investigating several hypotheses, based on findings from previous studies: that a maternal diet low in meat or animal products would be associated with increased risk of hypospadias, that higher intake of iron would be associated with increased risk, that lower intake of nutrients that favor less estrogenic estrogen metabolites would be associated with increased risk, and that better general diet quality would be protective. Our results do not support these hypotheses.

With one exception [2], the finding of increased risk of hypospadias among vegetarian mothers reported by North and Golding [1] has not been confirmed [3–8]. A variety of study designs and approaches to case ascertainment, with various strengths and weaknesses, have been used and may contribute to inconsistent findings. For example, in some studies participation among controls has been low (<50%) and the time since delivery long (several years) [4, 6], which raises questions regarding validity. Approaches to dietary assessment also varied. Our study was advantaged by its detailed dietary assessment. We did not explicitly ask whether mothers were vegetarians, although it is likely that a vegetarian diet would have been captured. Akre et al. [2] reported a 4.6-fold increased risk (95% CI 1.6, 13.0) of hypospadias among babies born to vegetarian mothers. However, the point estimate had low precision and the potential for bias as the analysis was based on grouping/pooling of subjects from three studies that had different study designs. It is also possible that something unique about the dietary patterns of vegetarians in the two positive studies is driving the increased risk. In general, previous studies have been based on limited dietary assessments, usually including only a few questions about vegetarian diets and consumption of animal products. This makes it difficult to rule out alternative explanations, such as higher or lower intake of certain nutrients among vegetarians. Pierik et al. quantified intake of lignans (a phytoestrogen) and soy protein (high in isoflavones, a class of phytoestrogens) using a short food frequency questionnaire, given that phytoestrogens have estrogenic properties and their consumption may be higher in vegetarians [3]. In that study, these items were not associated with hypospadias, but the study included only 56 cases. We recommend that future studies examine not just strict vegetarianism but also whether the frequency of intake of animal products is associated with risk (given how rare a strict vegetarian diet is in certain populations) and whether results can be explained by higher or lower intake of particular nutrients among vegetarians.

In our study, iron intake from foods or supplements was not associated with hypospadias. As noted above, North and Golding reported increased hypospadias associated with intake of iron supplements (OR 1.8, 95% CI 0.9, 3.6) [1]. This finding was repeated by Brouwers et al. (OR 2.1, 95% CI 0.9, 5.2)[4] but not by de Kort et al. (OR 0.8, 95% CI 0.4, 1.6) [9]. Again, explanations for inconsistencies are uncertain but could include variations in and limitations of study designs. One limitation common to all studies, including ours, is lack of information on dose of supplemental iron.

There is concern that estrogenic exposures (i.e., exposures associated with higher levels of estrogen or higher estrogen receptor activity) may increase risk of hypospadias, since estrogens induce hypospadias experimentally [28]. For example, exposures that favor 2-hydroxylation of estrogen are considered less estrogenic than exposures that favor 16α-hydroxylated metabolites, given that the former are weakly estrogenic, and the latter are highly estrogenic. Our hypothesis was that several nutrients that may result in increased 2-hydroxylated estrogen metabolites (low energy intake, high protein intake, low carbohydrate intake, high cruciferous vegetable intake, and high fiber intake) would be associated with reduced risk of hypospadias among offspring [10–14]. In contrast, high vitamin C intake was hypothesized to result in increased estrogen levels; vitamin C competes with estrogens for sulphate conjugation during first-pass metabolism, thus resulting in reduced clearance of estrogen via the hepatic drug-oxidizing system [29–31]. Our results did not support these hypotheses, with the exception of our finding that protein intake in the highest versus lowest quartile was associated with lower risk (OR 0.6, 95% CI 0.5–0.9). To our knowledge, these hypotheses have not been investigated previously for hypospadias.

Diet quality was not associated with hypospadias in our study. In contrast, de Kort et al. reported that a dietary pattern referred to as ‘health conscious’ was protective [9]. That study used data-driven cluster analysis to derive dietary patterns, whereas our diet quality measures were defined *a priori*. However, the general qualities of the diets had similarities, such as higher consumption of fruit and vegetables, fish, legumes, and unsaturated fats. Study design differences could contribute to differences in findings. For example, the de Kort et al. study was based on ‘current’ diet, which was reported two to six years after delivery; the food frequency questionnaire was shorter (28 items); and control participation was only 33%. Two small studies conducted in Italy reported that hypospadias was not associated with frequent intake of dairy products, legumes, fruits or vegetables [5, 8].

A notable difference between our study and previous studies is that our study excludes mild, or glanular hypospadias (i.e., the meatus is distal to the coronal sulcus). Not all studies reported the proportion of glanular cases in their case groups, but it is likely to be substantial, given that most hypospadias cases are glanular [4]. Akre et al. stated that their results did not differ by severity, among subjects for which this information was available, but results were not presented [2]. Existing evidence tends to point toward similarity of etiology, regardless of severity. Descriptive risk factors such as age, parity and race-ethnicity tend to be similar by severity [32, 33], and urethral closure involves a continuous process of ventral fusion in the proximal to distal direction, with the urethral plate extending to the tip of the penis [34, 35].

Our study is strengthened by its relatively large size, detailed dietary intake data, and adjustment for several covariates. Potential limitations include measurement error and recall and selection bias. In order to minimize errors in recalling exposures, we did not interview mothers more than two years after delivery. Although the food frequency questionnaire we used was not internally validated, validation studies indicate that it provides reasonable estimates of usual dietary intake in the distant past [36]. We do not expect recall bias to be a major problem (either based on case status itself or the longer median time to interview among cases), given that dietary assessment involved multiple questions, but we cannot rule it out. We expect the generalizability of our findings is likely to be good, given the population-based study design, active case ascertainment, and the racial-ethnic, geographic and socioeconomic diversity of the study population. We examined several potential confounders, but certainly residual confounding remains a possibility. We also acknowledge that a vegetarian diet was rare in our study, which limits our ability to detect differences.

In conclusion, we did not confirm previous findings regarding associations of hypospadias with a vegetarian diet, iron intake or diet quality. Several studies have addressed vegetarian diets and iron intake, with the majority finding no association. Our study is the second to address diet quality and the first to examine several nutrients that may be associated with estrogen metabolism. Comparison of results across studies is challenging due to differences in study design, especially with regard to dietary assessment. We recommend that future studies try to incorporate more in-depth dietary assessment, so that the complexities of nutrition can be more rigorously investigated. It remains possible that the studied nutritional factors are associated with hypospadias in certain study populations, but based on previous observations in conjunction with ours, the associations are likely to be modest.

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Table 1

Descriptive characteristics of mothers of 1,250 infants with hypospadias and 3,118 male control infants, National Birth Defects Prevention Study, 1997–2005.

	Percent of cases [a] (n)	**Percent of controls [a] (n)**
Maternal race-ethnicity		
Non-Hispanic White	73 (909)	62 (1,941)
Non-Hispanic Black	12 (152)	12 (364)
Hispanic	8 (105)	20 (609)
Other	7 (84)	7 (204)
Maternal education		
< High school	8 (98)	15 (454)
High school	19 (235)	25 (786)
> High school	73 (917)	60 (1,878)
Maternal age		
< 25 years	23 (284)	33 (1,029)
25–34 years	56 (698)	53 (1,643)
35+ years	21 (268)	14 (446)
Number of previous live births		
0	55 (685)	41 (1,272)
1	30 (371)	34 (1,050)
2 or more	16 (194)	26 (796)
Maternal Pre-pregnancy BMI (kg/m^2)		
Underweight BMI (<18.5)	5 (61)	6 (189)
Normal weight (18.5 – <25.0)	54 (678)	56 (1,736)
Overweight (25 – <30.0)	2 (295)	23 (702)
Obese (>= 30.0)	17 (216)	16 (491)
Folic acid-containing supplement intake[b]		
Yes	94 (1,169)	88 (2,749)
No	6 (81)	12 (369)
Study center		
Arizona	12 (148)	13 (399)
California	5 (67)	12 (380)
Iowa	5 (65)	12 (360)
Massachusetts	23 (283)	14 (423)
New Jersey	22 (281)	8 (237)
New York	6 (78)	9 (290)
Texas	2 (28)	11 (347)
Centers for Disease Control, Atlanta, Georgia	15 (182)	11 (348)
North Carolina	5 (67)	6 (176)
Utah	4 (51)	5 (158)

[a]Numbers may not add to 100% due to rounding.

[b]During the month before or the first three months of pregnancy.

Table 2

Odds ratios for hypospadias and any versus no intake of meat or fish.

	Percent of Cases (n)	**Percent of Controls (n)**	**Covariate-Adjusted OR [95% CI][a]**
Meat			
None	1.8 (22)	1.5 (46)	1.0 [0.6, 1.6]
Any	98.2 (1228)	98.5 (3072)	Reference
Meat or fish			
None	0.8 (10)	1.1 (33)	0.6 [0.3, 1.2]
Any	99.2 (1240)	98.9 (3085)	Reference

[a]Adjusted for maternal race-ethnicity, education, age, parity, body mass index, folic acidcontaining supplement intake, study center, and energy intake (kcal).

Table 3

Odds ratios for hypospadias with dietary intake of food groups and nutrients that may be related to a vegetarian diet or estrogen metabolism, and with diet quality indices, among mothers of 1,250 infants with hypospadias and 3,118 male control infants.

Nutritional factor and quartile ranges[†]	Covariate-Adjusted OR (95% CI) [a]
Nutrients related to a vegetarian diet	
Meat (servings/day)	
<0.8	Reference
≥0.8 – <1.1	1.0 (0.8, 1.3)
≥1.1 – <1.6	1.1 (0.9, 1.4)
≥1.6	1.0 (0.8, 1.3)
Fish (servings/day) [b]	
0	Reference
>0 – <0.07	0.9 (0.7, 1.1)
≥0.07 – <0.14	1.0 (0.8, 1.2)
≥0.14	0.8 (0.7, 1.0)
Dairy (servings/day)	
<1.1	Reference
≥1.1 – <1.6	0.9 (0.7, 1.1)
≥1.6 – <2.6	0.8 (0.7, 1.0)
≥2.6	0.8 (0.6, 1.0)
Eggs (servings/day)	
<0.1	Reference
≥0.1 – <0.3	1.1 (0.9, 1.3)
≥0.3 – <0.4	0.8 (0.7, 1.0)
≥0.4	0.9 (0.8, 1.1)
Iron (mg/day)	
<8.5	Reference
≥8.5 – <12.4	1.0 (0.8, 1.2)
≥12.4 – <17.8	1.0 (0.8, 1.2)
≥17.8	0.9 (0.7, 1.1)
Nutrients associated with estrogen metabolism	
Cruciferous vegetables (servings/day) [b]	
0	Reference
≥0 – <0.14	1.0 (0.8, 1.2)
≥0.14 – <0.29	0.9 (0.7, 1.1)
≥0.29	1.0 (0.8, 1.2)
Fiber (g/day)	
<10.6	Reference
≥10.6 – <15.2	1.0 (0.9, 1.3)

Nutritional factor and quartile ranges[†]	Covariate-Adjusted OR (95% CI) [a]
≥15.2 – <22.6	1.0 (0.8, 1.2)
≥22.6	1.0 (0.7, 1.3)
Energy (kcal/day)	
<1114.9	Reference
≥1114.9 – <1444.1	0.9 (0.8, 1.1)
≥1444.1 – <1916.7	1.0 (0.8, 1.2)
≥1916.7	0.9 (0.7, 1.1)
Protein (g/day)	
<50.2	Reference
≥50.2 – <65.1	0.9 (0.7, 1.0)
≥65.1 – <84.5	0.8 (0.7, 1.1)
≥84.5	0.6 (0.5, 0.9)
Carbohydrate (g/day)	
<148.0	Reference
≥148.0 – <200.3	1.1 (0.9, 1.3)
≥200.3 – <281.3	1.1 (0.9, 1.4)
≥281.3	1.1 (0.7, 1.6)
Vitamin C (mg/day)	
<59.6	Reference
≥59.6 – <102.1	1.0 (0.9, 1.3)
≥102.1 – <154.4	0.9 (0.7, 1.1)
≥154.4	1.0 (0.8, 1.3)
Diet Quality Indices	
Mediterranean Diet Score	
2–10	Reference
11–12	0.9 (0.7, 1.1)
13–15	1.1 (0.9, 1.3)
16–25	0.9 (0.7, 1.1)
Diet Quality Index	
0–8	Reference
9–12	1.2 (1.0,1.5)
13–16	0.9 (0.8,1.2)
17–24	1.0 (0.8,1.2)

[a]Adjusted for maternal race-ethnicity, education, age, parity, body mass index, intake of folic acid-containing supplements, study site, and energy intake (kcal).

[b]For these variables, more than 25% of mothers reported no intake or intake less than once per month, so the remaining three comparison groups were divided into tertiles, based on the distribution among the remaining controls.

Table 4

Odds ratios for hypospadias with intake of vitamin C and iron supplements, stratified by intake of folic acid-containing supplements.

		No. Cases / Controls	**Covariate-Adjusted OR (95% CI)** [a]
Vitamin C single supplements [b]	Folic-acid containing supplements [b]		
No	No	78 / 361	Reference
Yes	No	3 / 8	1.4 (0.3, 5.7)
No	Yes	1119 / 2592	1.3 (1.0, 1.7)
Yes	Yes	48 / 151	1.0 (0.6, 1.5)
Iron single supplements [c]	Folic-acid containing supplements [b]		
No	No	65 / 259	Reference
Yes	No	16 / 106	0.7 (0.4, 1.3)
No	Yes	924 / 2012	1.2 (0.9, 1.6)
Yes	Yes	242 / 730	0.9 (0.6, 1.2)

[a] Adjusted for maternal race-ethnicity, education, age, parity, body mass index, study site, and energy intake (kcal).

[b] During the month before or the first three months of pregnancy; folic acid-containing supplements consisted primarily of prenatal and multivitamin/mineral formulations.

[c] Any intake during pregnancy.