

# Hypospadias and Intake of Nutrients Related to One-Carbon Metabolism

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**Purpose:** We examined whether hypospadias is associated with maternal intake of folic acid containing vitamin/mineral supplements or dietary intake of nutrients related to one-carbon metabolism (folate, choline, vitamins B12 and B6, thiamine, riboflavin, methionine and zinc).

**Materials and Methods:** The study included births from October 1997 to December 2003 that were part of the National Birth Defects Prevention Study. Diet was assessed by food frequency questionnaire during maternal telephone interviews. Analyses included 915 cases with second or third degree hypospadias (urethra opened at the penile shaft, scrotum or perineum) and 2,266 male, liveborn, nonmalformed controls. All ORs and 95% CIs were estimated from logistic regression models that included several potential confounders. Nutrient based analyses also included energy intake.

**Results:** Hypospadias risk was not associated with supplement use (adjusted ORs were 1.2, 95% CI 0.9–1.6 for intake beginning in the month before or the first month of pregnancy and 1.1, 95% CI 0.8–1.4 for intake beginning in the second or third month, relative to no intake). Among women who took supplements reduced hypospadias risk was associated with higher dietary intakes of choline, methionine and vitamin B12. The respective ORs (CIs) for the highest vs lowest quartiles were 0.7 (0.5–1.1), 0.6 (0.4–0.9) and 0.7 (0.5–1.0). Among women who did not take supplements increased risk of hypospadias was associated with higher vitamin B12 intake. The OR (CI) for the highest vs lowest quartile was 3.1 (1.1–9.0).

**Conclusions:** This study suggests an association of hypospadias with intake of certain nutrients related to one-carbon metabolism.

**Key Words:** folic acid, hypospadias, maternal nutrition physiology

HYPOSPADIAS is one of the most common structural malformations among male infants, affecting approximately 6 to 8 per 1,000. The condition occurs as a result of abnormal urethral closure at around 8 to 14 weeks of gestation.

The ability of folic acid containing supplements to prevent neural tube defects is well established, and evidence of its preventive effects for other types

of birth defects is growing.<sup>1,2</sup> Folic acid contributes to essential developmental processes that involve one-carbon metabolism, including intracellular methylation, nucleotide biosynthesis and homocysteine metabolism. Therefore, it is likely that multiple mechanisms contribute to its effects. Several other nutrients such as choline, vitamin B12 and methionine also contribute to one-

## Abbreviations and Acronyms

EDD = expected due date

USDA = United States Department of Agriculture

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Study was approved by institutional review boards of participating study centers, and Centers for Disease Control and Prevention.

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carbon metabolism, and evidence that they are associated with birth defects is also accumulating.

Current knowledge regarding the association of nutrient intakes with hypospadias is limited. Two studies from Hungary suggest that hypospadias is less likely among women taking vitamin supplements.<sup>3,4</sup> Other studies have not found an association of hypospadias with intake of supplements.<sup>5–8</sup> A study in England revealed that dietary intake of fruit/vegetable pulses and soy products and vegetarianism were associated with hypospadias, and the authors suggested that differences in micronutrient intakes might be responsible for these findings.<sup>9</sup> These results were not corroborated by other studies investigating dietary factors.<sup>5,6,8</sup> To our knowledge no study has investigated the association of dietary intake of specific micronutrients with hypospadias.

The current analysis attempts to expand our understanding of the association of maternal nutrition with hypospadias risk, using a large, recent data set, with more clearly defined phenotypes and more detailed data on nutrient intakes than previous studies. Specifically given the widespread interest in the preventive effects of folic acid and other related nutrients, the analysis focused on maternal intake of folic acid containing supplements and dietary intake of nutrients involved in one-carbon metabolism (folate, choline, methionine, vitamins B6 and B12, thiamin, riboflavin and zinc). We hypothesized that reduced hypospadias risk would be associated with intake of supplements or higher intake of specific nutrients due to their roles in essential developmental processes that involve one-carbon metabolism.

## METHODS

This study included data on births with estimated due dates from October 1997 to December 2003, which were part of the National Birth Defects Prevention Study, a multistate case-control study of 30 different birth defects. This study was approved by 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 10 states that contributed data to this analysis have been published.<sup>10,11</sup> Briefly, 7 of the 10 states included liveborn, stillborn (fetal deaths at greater than 20 weeks of gestation), and prenatally diagnosed and electively terminated cases (Arkansas, California, Georgia, Iowa, North Carolina, Texas, Utah), 1 state included only liveborn and stillborn cases (Massachusetts), and 2 states included only liveborn cases (New Jersey, New York). Each state randomly selected approximately 100 nonmalformed liveborn controls per study-year from birth certificates (Arkansas 2000 to 2003, Georgia 2001 to 2003, Iowa, Massachusetts, North Carolina, New Jersey, Utah) or from birth hospitals (Arkansas 1997 to 1999, California, Georgia 1997 to 2000, New York, Texas) to represent the population from which the cases were derived. This analysis was 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. Medical record information (including operative reports when available) with anatomical descriptions or diagrams by pediatricians, urologists, geneticists, pathologists or other health care providers was reviewed by a clinical geneticist at each study center, who decided whether to include the case in the National Birth Defects Prevention Study database. Cases described as chordee alone, mild (first degree, coronal or glanular) hypospadias not otherwise specified, epispadias or ambiguous genitalia without further description were excluded from study. Infants with recognized single gene disorders or chromosomal abnormalities were also excluded from study. Each case received a final review by 1 clinical geneticist (RSO) 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 there were only minor anomalies (eg sacral/pilonidal dimple), or as nonisolated if there was at least 1 accompanying major anomaly.<sup>12</sup>

Maternal interviews were conducted using a standardized, computer based questionnaire, primarily by telephone, in English or Spanish, no earlier than 6 weeks after the 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 estimated date of conception, which was derived by subtracting 266 days from the EDD. The EDD was based on maternal self-report. If unknown, EDD was estimated from information in the medical record (less than 2% of subjects).

Women reported their intake of vitamin and mineral supplements during the 12 weeks before conception through the date of delivery. All products were reviewed to assess the folic acid content. Based on when they began taking any folic acid containing supplements, women were assigned to group 1—periconceptional intake (intake began during the month before conception or the first month after conception), group 2—early pregnancy intake (intake began during the second or third month after conception) or group 3—no intake (no intake during the month before conception or the first 3 months after conception). Women were considered exposed based on any vs no intake during the specified period.

To assess dietary intake of nutrients, mothers responded to a version of the Willett food frequency questionnaire, which assessed the frequency of intake of 58 food items during the year before pregnancy.<sup>13</sup> Intake of breakfast cereals, tea, coffee and sodas was assessed by separate, more detailed questions, which covered intake during the 3 months before pregnancy. The USDA Nutrient Database, release 19 was the source of nutrient values.<sup>14</sup> The database is relatively complete for all of the studied nutrients except choline. For choline we recently released databases from the USDA that are more complete, that is we used the USDA Choline Database as our primary source of information and the USDA Nutrient Database, release 20 as a secondary source.<sup>15,16</sup> Dietary folate intake was expressed as dietary folate equivalents,

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