Dieting Behaviors and Risk of Neural Tube Defects

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The authors examined whether maternal dieting behaviors were associated with increased neural tube defect (NTD) risk among offspring, using population-based, case-control data. The analysis included 538 cases and 539 nonmalformed controls delivered from 1989 to 1991 in selected California counties, and exposures were assessed by in-person maternal interview. Among four reported dieting behaviors involving restricted food intake, diets to lose weight (odds ratio = 2.1, 95% confidence interval: 1.1, 4.1), fasting diets (odds ratio = 5.8, 95% confidence interval: 1.7, 20.0), and eating disorders (odds ratio = 1.7, 95% confidence interval: 0.8, 3.6) were associated with increased NTD risk during the first trimester of pregnancy. Risk estimates for these behaviors during the 3 months before conception tended to be closer to 1. The fourth behavior, “other special diets,” was not associated with increased NTD risk during either period. Women also reported whether they took diet pills, laxatives, or diuretics, engaged in binge eating, induced vomiting, or exercised excessively from the first 3 months before conception through the end of pregnancy. Only the intake of diuretics was associated with substantially increased NTD risk (odds ratio = 2.7, 95% confidence interval: 0.7, 10.2). This study suggests that maternal dieting behaviors involving restricted food intake during the first trimester may be associated with increased NTD risk.

Nutrition has been demonstrated to influence neural tube defect (NTD) risk. Best known is the role of folic acid (1, 2). Other nutrition parameters have also been implicated, including various other nutrients (3), poor diet quality (4–6), low maternal weight gain (7), short interpregnancy interval (8), and famine (9, 10), and there are case reports of NTDs among offspring of women who have experienced gastric bypass surgery (11), long-term restrictive diets (12), and weight loss due to dieting during early pregnancy (13). The extent to which these factors explain the burden of NTDs in
the population is unknown, because of a lack of information about the underlying mechanisms of action that cause NTDs. Continued investigation of nutritional exposures related to implicated nutrients will contribute to greater understanding of the nutritional etiologies of NTDs.

This paper examines the association of dieting behaviors with NTD risk, using data from a population-based, case-control study. We hypothesized that compromises in nutritional status that accompany dieting behaviors would be associated with increased risk of having offspring with NTDs.

MATERIALS AND METHODS

Detailed methods for this study have been reported previously (14). In brief, for this study of pregnancies ending between 1989 and 1991, 653 infants/fetuses diagnosed with anencephaly, spina bifida cystica, craniorchischis, or inencephaly were ascertained by reviewing medical records at all hospitals and genetics clinics in selected California counties (15). Controls were randomly selected from area hospitals in proportion to the total population of liveborn infants. Eligible as controls were 644 singleton infants without reportable birth defects (15). Ascertainment was limited to infants/fetuses that were delivered in any California county other than Los Angeles, Ventura, or Riverside, and whose mother gave her residence as California. Interviews were conducted in English (74.2 percent) or Spanish (25.8 percent), primarily in person (95.0 percent), on average 4.9 months for cases and 4.6 months for controls from the actual or estimated date of term delivery. The 100-item Health Habits and History Questionnaire, developed by Block et al., was used to assess usual dietary intake during the 3 months before conception (16). This questionnaire was self-administered, with an interviewer present to answer questions.

After the exclusion of women who spoke only languages other than English or Spanish, there were 624 eligible cases and 612 controls. Interviews were completed for 549 (88.0 percent) case and 540 (88.2 percent) control mothers. We excluded 11 case mothers and one control mother who had a previous NTD-affected pregnancy. Among these subjects, 454 case mothers and 462 control mothers had complete data on dietary intake (14).

Women were asked to report whether they were on “a diet to lose weight,” “a diet that involved any fasting,” or “any other type of special diet”; whether they had “an eating disorder”; and whether they ate “freezer frost, cornstarch, or laundry starch,” “plaster, clay, or dirt,” or “any other items like these” (these latter three behaviors are together referred to as “pica”). They reported the occurrence of each of these behaviors separately for the 3 months before conception and for each of the three trimesters of pregnancy. For “other special diets” and for “eating disorders,” women were asked to describe the behaviors in additional detail. Reports were included if they involved restriction of food intake (e.g., undereating, restriction to only one or two foods, diets intended for weight loss) or other symptoms of true eating disorders (e.g., binge eating, induced vomiting, anorexia). Reports of behaviors, such as irregular eating, overeating, or a healthy pregnancy diet, were considered negative responses. The analysis focused on reports of these behaviors during the first trimester of pregnancy, because this encompasses the relevant time period for neural tube development; analysis of reports of these behaviors during the 3 months before conception were conducted for comparison.

About half way through the questions regarding the dieting behaviors listed above, women were also asked whether they engaged in several additional behaviors. They were asked to select from the following series of options, which were available on a cue card: “took diet pills,” “took laxatives,” “took diuretics (water pills),” “ate a large amount of food at one time (binge eating),” “induced vomiting (made self vomit),” or “exercised more than 2 hours per day, between 5 and 7 days per week.” The exposure period for these behaviors was broad; women were asked to report whether each of these behaviors occurred at any time from the first 3 months before conception through the end of pregnancy.

Potential covariates included maternal race/ethnicity (non-Hispanic White, US-born Hispanic, foreign-born Hispanic, and other); obesity (prepregnant body mass index of >29.0 kg/m² vs. ≤29.0 kg/m²) (17); periconceptional multivitamin/mineral supplement intake (use began during the 3 months before conception or use began during the first trimester of pregnancy vs. no use during either of these time periods); and dietary intake of folic acid, kilocalories, and protein during the 3 months before conception.

Using logistic regression models, we estimated unadjusted odds ratios for each dieting behavior and NTD risk. We also examined the special diets and eating disorders in combination, as one approach to account for the potential overlap in the reporting of these behaviors. To assess the presence of confounding, we adjusted the risk estimate for each of the dieting behaviors for one covariate at a time; if the risk estimate changed by more than 20 percent, we considered there to be potential confounding by that covariate for that dieting behavior. We also compared risk estimates between the specific strata of each of the covariates to examine the potential for effect modification, but sample sizes in many of the strata were too small to observe any consistent pattern of effect. All analyses were conducted using SAS version 8.2 software (SAS Institute, Cary, North Carolina).

RESULTS

For the four variables reflecting restriction of food intake (i.e., diet to lose weight, fasting diet, other special diet, or eating disorder), 61 cases (11 percent) and 31 controls (6 percent) reported at least one of these behaviors during the first trimester; among these women, six cases and three controls reported two of these behaviors in a variety of combinations. Of these four variables, only that for “other special diets” was not associated with risk for having offspring affected by an NTD during either the first trimester of pregnancy or during the 3 months before conception (table 1). For the first trimester of pregnancy, diets to lose weight, fasting diets, and self-reported eating disorders were all associated with at least a moderately increased risk of having offspring with NTDs. For the 3 months before conception, diets to lose weight were not associated with an
The differences were not explained by the two medical conditions. Among 31 control mothers with dieting behaviors, four (13 percent) had diabetes (all were gestational diabetes) and seven (23 percent) had hypertension; among 63 cases with dieting behaviors, three (5 percent) had diabetes (one was gestational diabetes) and 10 (16 percent) had hypertension.

Any pica behavior during the first trimester of pregnancy was associated with a slightly elevated but imprecise risk (odds ratio = 1.4, 95 percent confidence interval: 0.6, 2.9, based on reports of pica from 16 cases and 12 controls). The risk estimate during the 3 months before conception was closer to one (odds ratio = 0.9, 95 percent confidence interval: 0.3, 2.4, based on reports of pica from seven cases and eight controls).

A total of 109 case mothers (20 percent) and 114 control mothers (21 percent) reported that they took diet pills, laxatives, or diuretics, engaged in binge eating, induced vomiting, or exercised excessively at any time during the 3 months before conception or during pregnancy. Among these 223 mothers, 12 case mothers and 13 control mothers reported two of these behaviors, and one case and one control reported three. Only intake of diuretics was associated with a substantially increased NTD risk (odds ratio = 2.7, 95 percent confidence interval: 0.7, 10.2) (table 2). This association did not appear to be explained by women who reported hypertension during this time period. After excluding women with hypertension, an excess of case infants remained (six cases and one control whose mothers reported diuretic use).

Adjustment of each risk estimate for each potential covariate, one at a time, did not reveal evidence for substantial confounding. There were only a few comparisons for which adjustment resulted in more than a 20 percent change in the

Table 1: Association of self-reported special diets and eating disorders involving restricted food intake with risk of neural tube defects, California, 1989–1991

<table>
<thead>
<tr>
<th>Self-reported special diets and eating disorders</th>
<th>During the first trimester of pregnancy</th>
<th>During the 3 months before pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>No. of controls</td>
</tr>
<tr>
<td>Diet to lose weight†</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Fasting diet‡</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Other special diet§</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Eating disorder¶</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Any special diet or eating disorder#</td>
<td>61</td>
<td>31</td>
</tr>
</tbody>
</table>

* The reference for each comparison is women who did not report the particular behavior; analyses included a total of 538 cases and 539 controls; three cases were excluded from analyses of “eating disorder” and “any special diet or eating disorder” because of missing data.
† A total of 11 controls and 22 cases reported diets to lose weight during both time periods.
‡ A total of one control and five cases reported fasting diets during both time periods.
§ Includes only reports of other special diets that involved restriction of food intake; three controls and two cases reported other special diets during both time periods.
¶ Includes only reports of eating disorders that involved restriction of food intake; three controls and six cases reported an eating disorder during both time periods.
# A total of 18 controls and 30 cases reported any special diet or eating disorder during both time periods.
TABLE 2. Association of self-reported dieting behaviors with neural tube defect risk, California, 1989–1991*

<table>
<thead>
<tr>
<th>Behavior</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Unadjusted odds ratio†</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Took diet pills</td>
<td>14</td>
<td>11</td>
<td>1.3</td>
<td>0.6, 2.2</td>
</tr>
<tr>
<td>Took diuretics</td>
<td>8</td>
<td>3</td>
<td>2.7</td>
<td>0.7, 10.2</td>
</tr>
<tr>
<td>Took laxatives</td>
<td>34</td>
<td>36</td>
<td>0.9</td>
<td>0.6, 1.5</td>
</tr>
<tr>
<td>Binge eating</td>
<td>36</td>
<td>44</td>
<td>0.8</td>
<td>0.5, 1.3</td>
</tr>
<tr>
<td>Induced vomiting</td>
<td>10</td>
<td>13</td>
<td>0.8</td>
<td>0.3, 1.8</td>
</tr>
<tr>
<td>Excessive exercise</td>
<td>21</td>
<td>22</td>
<td>1.0</td>
<td>0.5, 1.8</td>
</tr>
</tbody>
</table>

* Behaviors were reported for any time during the 3 months before pregnancy or during pregnancy.
† The reference for each comparison is women who did not report the particular behavior; analyses included 538 cases and 539 controls.

risk estimate, and adjustment did not substantially change the pattern of results that was observed overall or for any single dieting behavior (data are available from the author upon request). Exclusion of mothers reporting diabetes from the analyses did not substantially alter any of the risk estimates (in total, 29 case mothers reported diabetes, 29 of which had gestational diabetes, and 36 control mothers reported diabetes, 32 of which had gestational diabetes).

DIscussIoN

Several self-reported dieting behaviors that involved food restriction during the first trimester of pregnancy were associated with increased risk of delivering offspring affected by NTDs. Self-reports of these behaviors during the 3 months before conception tended not to be associated with NTD risk. Diuretic intake was also associated with increased NTD risk, but the exposure window for this behavior was broad (any time during the 3 months before conception or throughout pregnancy).

We are aware of one previous report of an association between periconceptional dieting behaviors and NTD risk (18). Preliminary analyses from that population-based, case-control study suggested that periconceptional use of diuretics, laxatives, and “pep” pills was associated with increased NTD risks, but reports of dieting or eating little food for a day or more were not associated with increased risk.

The dieting behaviors investigated here may be associated with NTD risk because of their impacts on the intake, absorption, and metabolism of micronutrients, including but not necessarily limited to folic acid. It has also been proposed that ketosis, which may accompany restricted food intake, may contribute to NTD risk (13, 19), given the findings of increased NTD risk during times of famine (10), among diabetic women (20), in a case series of women who reported weight loss during the first month of pregnancy (15), and among users of valproic acid (a known cause of NTDs), which has a structure similar to the short chain fatty acids produced during ketosis (13, 19). It is unknown whether any of these mechanisms contributed to our results.

Our finding that dieting behaviors were more likely to be associated with NTD risk during the first trimester than during the 3 months before pregnancy suggests that the potentially harmful effects of dieting on fetal structural development may be more acute than long term. However, differential reporting by case mothers and control mothers remains a possible alternative explanation, as does random variation.

It is also possible that our observed NTD risks are due to residual confounding. Although we adjusted results for potential confounding by known risk factors for NTDs, including folic acid intake from supplements and from foods, obesity, and race/ethnicity, another unknown factor related to these dieting behaviors may be the explanation for elevated risks. The relatively small number of exposed subjects for many of the dieting behaviors also limited our ability to assess the presence of confounding or effect modification. Diabetes and hypertension did not appear to explain our results, but measurement of these conditions was limited to self-report. Information about the duration, frequency, and intensity of the dieting behaviors was not available. In addition, for some of the measures (e.g., diuretics), the timing of the behaviors was not specific to the periconceptional period.

There is extensive evidence that a variety of nutritional exposures are associated with the occurrence of NTDs. Continued inquiry into the potential impact of various nutritional exposures on NTD risk should move us closer to understanding the mechanisms by which nutrients, including folic acid, prevent NTDs.

ACKNOWLEDGMENTS

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