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Neural Tube Defects among Mexican Americans Living on the US-Mexico Border: Effects of Folic Acid and Dietary Folate

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Populations of Mexican descent have high occurrences of neural tube defects (NTDs). A recent study suggested that folic acid supplements may not protect these populations from NTDs. In a case-control study, the authors investigated the role of folic acid and dietary folate intake in NTD risk among Mexican Americans living along the Texas-Mexico border. From January 1995 to February 1999, 148 Mexican-American women with NTD-affected pregnancies and 158 women with normal live births were interviewed in person about use of vitamin supplements and dietary intakes during a 6-month periconceptional period (from 3 months before conception to 3 months after conception). Daily preconceptional consumption of vitamin supplements containing folic acid was 2.5% in control women and 2.0% in case women (odds ratio = 0.77; 95% confidence interval (CI): 0.19, 3.22). With adjustment for maternal age, education, obesity, and previous stillbirth or miscarriage, the risk estimate was essentially null (odds ratio = 1.12; 95% CI: 0.22, 5.78). Combined folic acid intake from diet and supplements showed only a modest risk reduction for intakes of ≥1.0 mg per day (adjusted odds ratio = 0.73; 95% CI: 0.31, 1.72). The fact that the primary folic acid exposure was in the form of dietary polyglutamates rather than the more easily absorbed supplemental monoglutamates may explain an apparent decreased effect in this population. *Am J Epidemiol* 2000;152:1017–23.

case-control studies; diet; folic acid; Mexican Americans; neural tube defects; pregnancy; vitamins

Evidence strongly suggests that a substantial portion of neural tube defects (NTDs), malformations of the developing brain and spinal cord, are due to a folate deficiency and can be prevented. Observational studies and clinical trials carried out in a variety of populations have shown that women who consume 0.4 mg of folic acid daily reduce their risk of an NTD by 50–100 percent (1–4). Contradicting this evidence are the results of a recent case-control study from California which showed no risk reduction among Hispanics using folic acid-containing multivitamins (5). Because a 40 percent risk reduction was observed among non-Hispanic Whites, the study investigators concluded that folic acid supplements may not protect populations of Mexican descent—populations with high occurrences of NTDs (5, 6).

Mexican Americans have NTD risks 50–200 percent higher (9–16 per 10,000 live births) than those of non-Hispanic Whites (6 per 10,000) and African Americans (5 per 10,000) (6–8). NTDs are particularly common among populations living on the Texas-Mexico border, where 95 percent of the births are to women of Mexican descent. In 1990, Cameron County, a Texas county on the US-Mexico border, recorded the highest US NTD prevalence since the 1970s (29 per 10,000) (Texas Department of Health, unpublished report, 1992). Investigation of this cluster and subsequent prevalence studies confirmed that NTDs are endemic to the entire Texas-Mexico border population (8; Texas Department of Health, unpublished reports, 1992, 1995).

It is not clear why NTD risk among Mexican Americans would not be amenable to folic acid supplementation. The NTD risk pattern of migrant Mexicans would seem to implicate an environmental cause, such as a folate-deficient diet, rather than an underlying genetic defect. Mexican women migrating to the United States have NTD risks (14–16 per 10,000 live births) that are intermediate between those of women living in Mexico (36 per 10,000) and US-born Mexican-American women (7–10 per 10,000) (6, 8, 9). In turn, US-born Mexican Americans have slightly higher risks than non-Hispanic White women. The progressive shift in risk toward the lower risk among US non-Hispanic Whites suggests a shift toward more folate-rich diets. However, other observations contradict this idea. While it might be expected that Mexican Americans have diets low in folate, Mexican-American women of childbearing age consume more dietary folate than other North American women (10–12), although they use multivitamins less often (13, 14).

Except for the study by Shaw et al. (5), who studied a population that was essentially of Mexican descent, all US

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Abbreviations: CI, confidence interval; NTD(s), neural tube defect(s).

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studies of folic acid and NTD risk have been carried out among non-Hispanic White women. Outside of the United States, a small, nonrandomized recurrence prevention study showed a strong protective effect among Cuban women (15), and a hospital-based case-control study in Spain reported a 30 percent risk reduction for postconception folic acid use (16). These populations, however, may be distinctly different from Mexican Americans in terms of Amerindian genetic admixture and NTD-related risk factors, such as diabetes and obesity (17, 18). Because of the contradictory evidence from the California case-control occurrence study (5, 6), we wanted to evaluate the folic acid issue in a comparable high risk Mexican-American population. Using a population-based case-control design, we investigated the role of folic acid supplements and dietary folate in the NTD risk of Mexican Americans living along the Texas-Mexico border.

MATERIALS AND METHODS

Study subjects

Data for this study came from the Texas Department of Health's Neural Tube Defect Project. This project studies the occurrence of NTDs in the 14 Texas counties along the US-Mexico border. It includes multisource active surveillance, a folic acid intervention, and a case-control study. Surveillance involves prospective case-finding through the 21 hospitals, 39 birthing centers, four genetics clinics, 74 ultrasound centers, four licensed abortion centers, and approximately 150 midwives in the region. In this study, cases were defined as infants or fetuses who had anencephaly (including craniorachischisis and iniencephaly), spina bifida, or encephalocele identified at birth or prenatally between January 1995 and February 1999. Cases included diagnoses made among liveborns, stillborns, and fetuses at all gestational ages, and included abortions, whether induced or spontaneous.

We identified control women from residents of the study area who had normal births during the same time period. Within 17 hospital or hospital/birthing center strata, control women were randomly selected annually in proportion to the estimated number of live births. If the selected control woman was not a resident of the area or had an infant with an apparent or prenatally diagnosed congenital anomaly, we used the mother of the next sequential normal live birth as a control. A control woman was not replaced if she refused to participate.

Subjects were approached about study enrollment either prenatally or in the hospital at the time of delivery or pregnancy termination. Interviews were scheduled approximately 1 month postpartum. Before the interview, written informed consent was obtained in the subject's preferred language. The protocol, consent forms, and questionnaire were approved by the Texas Department of Health institutional review board for the protection of human subjects.

Case and control women were interviewed at home in Spanish or English, using a standard instrument modeled after the Centers for Disease Control and Prevention's 1993 mother questionnaire for birth defects risk factor surveillance. The complete instrument assessed maternal health history; reproductive history; family demographic data and medical history; use of medications, nutritional supplements, herbal preparations, tobacco, alcohol, illegal drugs, and inhalants; and environmental and occupational exposures. Women were paid $20 for the 2-hour interview. The date of conception for each woman was determined from the gestational age recorded in the medical record. To help each respondent remember exposures and events, the interviewer used a personalized calendar focusing on the 3 months before and after conception.

Folic acid supplements

To measure the use of folic acid supplements, we asked women whether they had taken prenatal vitamins, multivitamins, or single-ingredient folic acid tablets during the periconceptional period (from 3 months before conception to 3 months after conception). Women were asked about the brand name(s) of the vitamin supplements used and were asked to show the bottles to the interviewer if they still had them. For each month during the 6-month period, interviewers recorded whether women had used each type of folic acid supplement (prenatal vitamins, regular multivitamins, or folic acid tablets), the number of pills taken daily or weekly, and the number of days or weeks in which vitamins were taken.

For analysis, we focused on the use of folic acid-containing vitamins during the 3 months before conception, since reported use of vitamins during this time period is thought to most closely reflect true intake during neural tube closure (~1 month postconception). We chose this exposure definition because it was the same as the one used in the California study of Mexican Americans (5) and was less likely to introduce misclassification errors. Data showed that nearly all women who reported initiation of vitamin use during the first month postconception were recalling prenatal vitamin use. Moreover, a reanalysis showed that when the exposure window was extended or restricted to the first month postconception, overall results were unchanged.

Dietary folate

We measured dietary folate intake with a 98-item food frequency questionnaire developed for the study population. To develop the instrument, we conducted 100 24-hour dietary recalls among new enrollees in the federal Women, Infants, and Children (WIC) nutrition program in Cameron, El Paso, Hidalgo, and Webb counties. These enrollees, poor Mexican-American women of childbearing age, typified the high risk border population. In these women, the most important source of folate was refried beans, which accounted for 16 percent of folate consumption, followed by orange juice (11 percent), other bean preparations (12 percent), and whole milk (4 percent). The final instrument was a four-page, 98-item questionnaire in Spanish and English that took 10–15 minutes to administer and that followed the general questionnaire interview. For each food item, women estimated their usual frequency of intake (average number

of times per month, week, or day) over the 6-month periconceptional period. Average daily folate intake from the diet during the 3 months before and after conception was computed with a food frequency software program (Food Frequency Data Entry and Analysis Program, University of Texas Health Science Center). Exposure categories for dietary folate intake were based on quartiles derived from the distribution of controls.

We estimated each woman's combined exposure to supplemental folic acid and dietary folate by adding the average daily dose of folic acid to the average daily dietary folate intake. For all women who had taken vitamins at any time during the months before conception, average daily folic acid intake was estimated from the type of supplement used (prenatal vitamin or multivitamin), the frequency of use, and the duration of use. Prenatal vitamins were assumed to contain 1 mg of folic acid; multivitamins or single folic acid tablets were assumed to contain 0.4 mg. If the number of pills taken per day or the duration of use was unknown, the dosage was assumed to be zero. Categories for combined exposure reflected recommended daily folic acid levels for women of childbearing age (0.4 mg) and the common dosage of multivitamins (0.4 mg) and prenatal vitamins (1 mg).

Analysis

Relative risks of NTDs associated with use of folic acid-containing vitamins and levels of dietary folate were based on odds ratios and 95 percent confidence intervals computed using Stata software (19). Odds ratio estimates were adjusted for potentially confounding variables with the use of logistic regression. Potentially confounding variables were identified from a review of all previous NTD case-control studies (2, 4, 5, 20, 21). These variables included maternal age at conception, education, annual family income, preconceptional cigarette smoking and alcohol use, gravidity, previous stillbirth or miscarriage, prenatal care during the first trimester, country of birth, diabetes history, and obesity. Preconceptional cigarette smoking and alcohol use were defined as any use during the 3 months before conception. In accordance with the Institute of Medicine (22), obesity was defined as having a body mass index (weight (kg)/height $(m)^2$) greater than 29. Diabetes history was based on the question, "Were you ever told by a doctor or other health care provider that you had diabetes or high blood sugar?" This would have included insulin-dependent and non-insulin-dependent diabetes mellitus as well as gestational diabetes. Only maternal age, education, obesity, and previous stillbirth or miscarriage proved to be important risk factors or confounders in preliminary analysis; these were later included in the adjustment of estimates.

RESULTS

Interviews were completed for 154 (72 percent) case women and 165 (53 percent) control women. Information was not obtained for the 8 percent of case women and 21 percent of control women who refused to be interviewed, the 6 percent of case women and 13 percent of control women who had moved out of the study area, and the 14 percent of case women and 14 percent of control women who were missed at the time of their delivery. Analysis was restricted to the 148 case women and 158 control women who identified themselves as Mexican-American. Of the NTD case infants/fetuses, 44 percent ($n = 65$) had anencephaly; 45 percent ($n = 67$) had spina bifida; and 11 percent ($n = 16$) had encephalocele. Of the affected pregnancies, 71 resulted in live births, 26 in stillbirths, three in spontaneous abortion, and 48 (32 percent) in elective termination. At birth or termination, 22 percent of the case fetuses/infants were of less than 20 weeks' gestation and 36 percent were of greater than 35 weeks' gestation.

Table 1 shows the demographic characteristics of case and control women. Reflecting the population characteristics of the Texas-Mexico border region, nearly half of case and control women lived on annual incomes of $10,000 or less, and only half of all study women had completed 12 years of education. Case and control women were equally divided into those born in the United States and those born in Mexico. Substantial proportions of both case (29 percent) and control (24 percent) women had not had prenatal care during the first trimester.

As table 2 illustrates, the consumption of folic acid-containing vitamins, primarily multivitamins, before conception was extremely low among both case and control women. Approximately half of case and control women had started taking vitamins after conception—most often prenatal vitamins prescribed well after the time of neural tube

TABLE 1. Demographic characteristics of Mexican-American case women with neural tube defect-affected pregnancies and control women in 14 Texas-Mexico border counties, 1995–1999

	Case women ($n = 148$)		Control women ($n = 158$)	
	No.	%	No.	%
Maternal age (years)				
<20	38	25.7	40	25.3
20–24	53	35.8	47	29.7
25–29	34	23.0	42	26.6
≥30	23	15.5	29	18.4
Education (years)				
<7	31	20.9	21	13.3
7–11	43	29.1	57	36.1
≥12	74	50.0	80	50.6
Annual income*				
≤$10,000	69	47.6	64	41.0
$11,000–$15,000	26	17.9	28	17.9
$16,000–$25,000	26	17.9	33	21.2
>$25,000	24	16.6	31	19.9
Country of origin				
Mexico	74	50.0	79	50.0
United States	74	50.0	79	50.0

* Three case women and two control women were missing information on income.

TABLE 2. Periconceptional vitamin use* among Mexican-American case women with neural tube defect-affected pregnancies and control women in 14 Texas-Mexico border counties, 1995–1999

Periconceptional vitamin use	Case women (n = 148)		Control women (n = 158)	
	No.	%	No.	%
None (6-month interval)	66	44.6	68	43.0
Preconception (≤3 months before)				
Any reported use	8	5.4	5	3.2
Daily use in every month	3	2.0	4	2.5
Postconception (≤3 months after)	74	50.0	85	53.8

* Maternal use of multivitamins, prenatal vitamins, or single-ingredient folic acid tablets from 3 months before conception to 3 months after conception.

closure, in the second or third month of pregnancy. Considerable proportions of case and control women (>40 percent) did not consume folic acid-containing vitamins at all during the periconceptional period. There were only three case women and four control women who reported daily use of folic acid-containing vitamins throughout the entire preconception period. Compared with nonuse, the odds ratio associated with daily consumption of vitamins during the preconception period was 0.77 (95 percent confidence interval (CI): 0.19, 3.22); adjustment for maternal age, education, obesity, and previous stillbirth or miscarriage eliminated any measurable reduction in risk (odds ratio = 1.12; 95 percent CI: 0.22, 5.78).

Deviating from linearity, odds ratios for quartiles of average daily dietary folate intake during the periconceptional period showed a reduced risk only for the third quartile of intake when compared with the lowest quartile (table 3). Combining the estimated daily folate intake from diet with the estimated daily dose from vitamins showed modest risk reductions of 17 percent and 39 percent for daily intakes of 0.4–0.99 mg and ≥1.0 mg, respectively. However, these risk reduction estimates were further diminished when data were adjusted for maternal age, education, obesity, and previous stillbirth or miscarriage (table 4). All estimates had 95 percent confidence intervals that overlapped with the null.

DISCUSSION

The fact that so few Mexican-American women in this study consumed multivitamins during the critical time period severely limited what could be determined about supplemental folic acid and NTD risk in this study population. In this population with low folic acid exposure, we found no apparent benefit of using multivitamins (adjusted odds ratio = 1.12; 95 percent CI: 0.22, 5.78). This minimal and seemingly ineffectual exposure to supplemental folic acid made dietary folate much more consequential in this population. However, risk estimates for dietary folate levels lacked statistical precision and did not conform to a linear relation. Combining the estimated folic acid intakes from supplements and from dietary sources did not reveal any strong effects. There was only a 27 percent risk reduction

TABLE 3. Effect of average daily dietary folate intake on risk of neural tube defects among Mexican-American women in 14 Texas-Mexico border counties, 1995–1999*

Dietary folate intake (mg/day)	No. of case women	No. of control women	Odds ratio	95% confidence interval	Adjusted† odds ratio	95% confidence interval
0.128–0.413	41	37	1.00‡		1.00‡	
0.414–0.597	39	38	0.93	0.49, 1.74	1.06	0.54, 2.06
0.598–0.761	21	38	0.50	0.25, 1.00	0.53	0.25, 1.09
0.762–2.103	31	37	0.76	0.39, 1.45	0.97	0.49, 1.91

* Thirteen women who took folic acid-containing vitamins preconception, six additional women without food frequency data, and five additional women without an obesity value were excluded.
† Adjusted for maternal age, education, obesity, and previous stillbirth or miscarriage.
‡ Referent.

TABLE 4. Effect of average daily folate intake from vitamin supplements and diet on risk of neural tube defects among Mexican-American women in 14 Texas-Mexico border counties, 1995–1999*

Folate intake (mg/day)	No. of case women	No. of control women	Odds ratio	95% confidence interval	Adjusted† odds ratio	95% confidence interval
<0.400	37	34	1.00‡		1.00‡	
0.400–0.999	89	99	0.83	0.48, 1.43	0.96	0.54, 1.71
≥1.000	14	21	0.61	0.27, 1.39	0.73	0.31, 1.72

* Seven women without food frequency data and five women without obesity values were excluded.
† Adjusted for maternal age, education, obesity, and previous stillbirth or miscarriage.
‡ Referent.

(the estimate overlapped with the null) for intakes of ≥1.0 mg per day, after adjustment for covariates.

The present findings are consonant with those of a California study (5) showing no effect of folic acid-containing vitamins and only modest dietary folate effects among Hispanics. Among Hispanics using vitamins preconceptionally, Shaw et al. (5) estimated the same null odds ratio as did this study. For combined folate consumption between 0.4 mg and 1.0 mg, Shaw et al.'s unadjusted estimate was 0.8 (95 percent CI: 0.3, 1.9). More convincing risk reductions were observed among California Hispanics with combined intakes above 1.0 mg (odds ratio = 0.6; 95 percent CI: 0.2, 2.0). These risk reductions contrasted sharply with the much greater reductions seen among non-Hispanic White women at the same levels (5). This ethnic difference in effective dosage might have been due to the contrasting intake ratios of dietary folate to supplemental folic acid between the two groups. It is likely that Hispanic women obtained most of their combined intake from dietary folates in the polyglutamated form, in which only about 50 percent of the folate is bioavailable (23). Non-Hispanic White women would have received a greater proportion of their combined intake as folic acid in a monoglutamated form, which is almost 100 percent bioavailable.

Despite strong evidence that supplemental folic acid and dietary folate reduce the risk of NTDs in a variety of populations worldwide, this Texas-Mexico study and the California study (5) appear to suggest that folate has a reduced effect in Mexican-American populations. However, this reduced effect can easily be explained by the rare use of periconceptional vitamins in this population. At best, exposure to supplemental folic acid was only 5 percent among women in this study, and exposure may have been equally low among Hispanics in the California study. Calculating from Shaw et al.'s (24) published data on Mexico-born women (who comprised most of the 385 study subjects of Mexican descent), vitamin use was also only 5–6 percent. The modest or weak effect of folate among Mexican Americans suggests that levels are insufficient for achieving the reductions seen in other populations, or insufficient for overcoming other underlying risk factors. The economically disadvantaged and medically underserved Mexican-American population on the Texas-Mexico border is unique; it is characterized by a distinct gene admixture and a traditional yet atypical dietary pattern, and is afflicted with many NTD-related risk factors. If the high NTD risk in this population is not explained by a folic acid deficiency, this leaves open the possibility of an influence of many individual susceptibility factors. Logically, these host susceptibility factors center on a genetic or acquired variability in the intake, uptake, or metabolism of folic acid or the interference of environmental toxicants, to which this population may be heavily exposed. These contaminants may include pesticides from farm working or fumonisin, a naturally occurring mycotoxin in corn which has recently been shown to affect cellular folate uptake (25, 26). Alternatively, Mexican Americans may simply require higher intakes of folate to prevent NTDs, given recent reports of much higher frequencies of specific folate pathway gene polymorphisms in this population (27; Robert Barber, University of Nebraska Medical Center, unpublished manuscript).

Although the data from this study and the California study are consistent with the supposition that usual doses of supplemental folic acid may have a reduced effect in Mexican Americans, the evidence gathered is inconclusive because of several methodological problems. First, as noted above, the extremely low intake of preconceptional folic acid supplements among Mexican Americans makes it difficult to study this exposure. Given the study size and the 3 percent prevalence of vitamin use among unaffected women, the power to detect a 50 percent reduction in risk was dismally low (14 percent). At such low levels of exposure to folic acid-containing vitamins, the study would require 10 times the existing number of cases and controls (~1,500) to adequately gauge an effect from folic acid ($\alpha = 0.05$, $\beta = 0.80$). Second, the relative homogeneity of dietary exposures in this population would also decrease the probability of identifying this component cause of NTDs (28). Third, several sources of bias further weakened the ability to measure the effects of folate in this population. Use of the food frequency instrument probably produces overestimates of folate consumed (29, 30), perhaps more so in minority populations with low levels of education (31, 32). An overestimate of true folate intake among Mexican-American women would have made effects appear weaker than they were. Additionally, the food frequency questionnaire referenced a single 6-month period, from 3 months before conception to 3 months after conception, not distinguishing the postconception time from the preconception time. Because many women adhere to a healthier diet during pregnancy, women may have selectively recalled these healthier foods (e.g., folate-rich foods), consumed after the neural tube closed (~1 month postconception), rather than their more relevant preconception intake. If case and control women misclassified their exposures to the same extent, estimated odds ratios would have been biased toward the null.

Another problem is the differential recall period between case and control women, produced by not matching case and control infants/fetuses for gestational age. Given the earlier termination of NTD-affected pregnancies, at the time of interview control women were recalling exposures further in the past than case women. Although the case-control difference in recall time was only about 1 month, the shorter recall time for case women may have caused them to remember exposures somewhat more accurately than control women. Combined with the possibility that women with affected pregnancies would recall exposures more carefully, this differential exposure misclassification also would have attenuated observed protective folate effects.

A final concern is the differing participation rates between case and control women (72 and 53 percent, respectively). If selection bias produced the weak or null folate effect observed in this study, then control women with higher socioeconomic status (better diets or more vitamin use) must have refused participation more often. Although no information was available on the characteristics of nonparticipants, we used vital statistics data to compare the demographic profile of participating control women with that of the source population from which they were drawn. In terms of demographic characteristics, control women were virtually identi-

cal to all border Hispanic women who gave birth during the study years (age <20 years: 25 percent vs. 24 percent; ≥12 years of education: 51 percent vs. 50 percent; maternal birth in the United States: 50 percent vs. 50 percent). It therefore seems unlikely that controls misrepresented the border population in exposure-related characteristics.

Possibly, the most important finding from this study was the very low preconceptional use of folic acid-containing vitamins among Mexican-American women. Only two out of 100 women in the study consumed multivitamins daily, a practice that could provide some protection against NTDs. This low level of use of folic acid-containing vitamins can be contrasted with that in a national March of Dimes survey, where one third of the women reportedly took multivitamins daily (33). Without supplemental sources of folic acid, this Mexican-American population must depend on foods that are naturally rich in folate (e.g., legumes, orange juice, and green vegetables) or foods fortified with folic acid (cereal and bread). Beginning in 1998, the federal Food and Drug Administration required US food manufacturers to fortify grain products with up to 0.140 mg of folic acid per 100 grams of weight (34). Although food fortification is expected to have widespread impact on the US prevalence of NTDs (35), it is difficult to predict whether food fortification alone will raise folate levels enough to reduce NTDs along the US-Mexico border.

Since 1991, we have sought to explain and eliminate the causes of the high NTD prevalence in the predominantly Hispanic population along the US-Mexico border. The investigation of the now-famous 1991 anencephaly cluster in Brownsville, Texas failed to pinpoint any particular risk factor that might have caused the unusual occurrence (Texas Department of Health, unpublished report, 1992). Continuing surveillance of multiple case-ascertainment sources shows that the prevalence of NTDs along the border remains high (8). The present study of supplemental folic acid and dietary folate is integral to the ongoing inquiry into a wide range of maternal and paternal risk factors, including environmental contaminants, occupational exposures, infectious agents, and genetic factors. However, we must conclude that the question of whether folic acid reduces NTD risk in Mexican Americans to the extent observed in other populations needs additional testing in a larger population more highly exposed to folic acid. Although the public is often more concerned about possible environmental toxicants, folic acid supplementation and food fortification remain the best prospects for reducing NTD risk.

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