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PREVENTION OF NEURAL-TUBE DEFECTS WITH FOLIC ACID IN CHINA

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ABSTRACT

Background Periconceptional use of multivitamins containing folic acid can reduce a woman's risk of having a baby with a neural-tube defect.

Methods As part of a public health campaign conducted from 1993 to 1995 in an area of China with high rates of neural-tube defects (the northern region) and one with low rates (the southern region), we evaluated the outcomes of pregnancy in women who were asked to take a pill containing 400 μg of folic acid alone daily from the time of their premarital examination until the end of their first trimester of pregnancy.

Results Among the fetuses or infants of 130,142 women who took folic acid at any time before or during pregnancy and 117,689 women who had not taken folic acid, we identified 102 and 173, respectively, with neural-tube defects. Among the fetuses or infants of women who registered before their last menstrual period and who did not take any folic acid, the rates of neural-tube defects were 4.8 per 1000 pregnancies of at least 20 weeks' gestation in the northern region and 1.0 per 1000 in the southern region. Among the fetuses or infants of the women with periconceptional use of folic acid, the rates were 1.0 per 1000 in the northern region and 0.6 per 1000 in the southern region. The greatest reduction in risk occurred among the fetuses or infants of a subgroup of women in the northern region with periconceptional use who took folic acid pills more than 80 percent of the time. In the southern region the reduction in risk among the fetuses or infants of women with periconceptional use of folic acid was also significant (reduction in risk, 41 percent; 95 percent confidence interval, 3 to 64 percent).

Conclusions Periconceptional intake of 400 μg of folic acid daily can reduce the risk of neural-tube defects in areas with high rates of these defects and in areas with low rates. (N Engl J Med 1999;341:1485-90.)

A WOMAN'S risk of having a fetus or infant with a neural-tube defect can be reduced by the consumption of a multivitamin containing folic acid during the periconceptional period — before and during the first 28 days after conception. Neural-tube formation is completed during these 28 days, before most women begin taking prenatal vitamins. In 1980, the results of a nonrandomized trial revealed that taking multivitamins during the periconceptional period reduced the risk of having a fetus or infant with a neural-tube defect.[1] Since then, observational studies demonstrated a reduced risk among women who took multivitamin supplements containing folic acid[2,3] and those who had higher dietary intakes of folate[4-6] during early pregnancy.

The efficacy of folic acid in preventing a subsequent occurrence of neural-tube defect among the fetuses or infants of women with a previous affected fetus or infant was first conclusively demonstrated by a Medical Research Council randomized study in the United Kingdom. Women who took 4000 μg of folic acid daily during the periconceptional period in a subsequent pregnancy had a 72 percent reduction in the risk of having an affected fetus or infant.[7] Subsequently, Hungarian researchers showed that multivitamin

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supplements containing 800 μg of folic acid taken periconceptionally reduced the risk of a first occurrence of neural-tube defect.[8] The Public Health Service[9] has recommended that all women who could become pregnant take 400 μg of folic acid daily, and other countries have also adopted this recommendation.[10] We evaluated a public health campaign in China among women preparing for marriage in order to determine the efficacy of a daily dose of 400 μg of folic acid alone in preventing neural-tube defects in two regions of China, one in which the incidence of these defects is high and the other in which it is low.[11]

METHODS

Cohort

The campaign to prevent neural-tube defects was conducted in one northern province of China (Hebei) with relatively high rates of neural-tube defects (5 to 6 per 1000 births) and two southern provinces (Zhejiang and Jiangsu) with lower rates (approximately 1 per 1000 births). All pregnant women and women who were preparing for marriage registered with a pregnancy-monitoring system that serves as the principal record of prenatal care and delivery in all three provinces. We identified women who registered with this monitoring system from October 1993 through September 1995 and who were pregnant at some point between October 1, 1993, and December 31, 1996. The cohort included all women whose fetuses or infants could be confirmed as either having or not having a neural-tube defect. The project was approved by the institutional review boards of the Centers for Disease Control and Prevention and Beijing Medical University, and all women who took pills provided oral informed consent.

Premarital Examination

In China, all couples planning to marry undergo a premarital examination, which includes a physical examination and laboratory tests. Beginning in October 1993, all women who completed this examination were asked to purchase pills containing 400 μg of folic acid and to take one of these pills every day through the end of the first trimester of pregnancy. Each bottle contained 31 pills, and the women were asked to take one bottle of pills each month. Village health workers recorded the dates that the women started and stopped taking folic acid. At the end of each month, the workers recorded how many pills remained in each bottle and the dates of all menstrual periods. For each woman, we computed compliance as the percentage of folic acid pills that were taken as compared with the number that could have been taken.

Use of Folic Acid Pills

We divided the women who took folic acid pills according to the pattern of use on the basis of the dates they started and stopped taking folic acid. We defined women with periconceptional use as those who started taking folic acid pills before their last menstrual period before conception and who stopped at the end of the first trimester. We defined women with late use as those who started taking folic acid pills during the first trimester but sometime after their last menstrual period. We defined women with early discontinuation of folic acid as those who started and stopped taking the pills before their last menstrual period before conception. Women with missing dates were considered unclassifiable and were not assigned to any group. To determine the optimal effect of folic acid supplementation, we identified a subgroup of women who took more than 80 percent of the assigned pills. Women who either did not agree to take the pills at the time of registration or who were already in their second trimester of pregnancy at registration and never had the opportunity to start taking folic acid pills periconceptionally were considered not to have taken folic acid.

TABLE 1. OUTCOMES AMONG WOMEN WHO REGISTERED IN THE PREGNANCY-MONITORING SYSTEM IN ONE NORTHERN AND TWO SOUTHERN PROVINCES IN CHINA BETWEEN OCTOBER 1, 1993, AND SEPTEMBER 30, 1995.

OUTCOME	NORTHERN REGION (N=37,425)	SOUTHERN REGION (N=248,111)
	no. of women (%)	
No pregnancy	1,281 (3)*	6,968 (3)*
Infertile	980	5,984
Other reasons†	301	984
Pregnancy	36,144 (97)*	241,143 (97)*
Lost to follow-up	1,761 (5)	9,037 (4)
Withdrew from study	940 (3)	1,804 (0.7)
Moved or gave birth outside study area	821 (2)	7,233 (3)
Neural-tube–defect status of fetus or infant unknown	2,423 (7)	16,235 (7)
Delivery after December 31, 1996	1,149 (3)	9,074 (4)
Spontaneous abortion	851 (2)	4,317 (2)
Induced abortion	406 (1)	2,704 (1)
Ectopic pregnancy or hydatidiform mole	17 (0.05)	140 (0.06)
Neural-tube–defect status of fetus or infant known	31,960 (88)	215,871 (90)
Live birth	31,456 (87)	213,880 (89)
Stillbirth	206 (0.6)	423 (0.2)
Fetal death	295 (0.8)	1,562 (0.6)
Termination of pregnancy after prenatal diagnosis of birth defect	3 (0.008)	6 (0.002)

*The value in parentheses is the percentage of all women in the group who registered with the system. All other values in parentheses are the percentages of all women who became pregnant.

†Other reasons were the death of either partner, divorce, and use of contraception.

Neural-Tube Defects

We identified infants with neural-tube defects through a birth-defects surveillance system. This system, which was established in January 1993, collects detailed data about infants and fetuses with external structural birth defects. Live-born infants with birth defects were included in the surveillance system if they had a gestational age of at least 20 weeks and had a birth defect that was diagnosed by 6 weeks of age.[12] We requested photographs of every infant born with a suspected birth defect and of all stillborn infants, whether or not a structural abnormality was recognized. We also collected information on all pregnancies, even those with gestations of less than 20 weeks that were electively terminated after the prenatal diagnosis of any birth defect. Three pediatricians, who were unaware of the women's pill-taking status, independently reviewed the reports and photographs and assigned diagnostic codes, and a clinical geneticist validated the diagnoses. The definition of neural-tube defect included anencephaly, spina bifida, iniencephaly, craniorachischisis, and encephalocele, but not isolated hydrocephalus.

Statistical Analysis

We compared the numbers of women who took folic acid pills and those who did not in each region (northern and southern) according to the time of registration in relation to their last menstrual period, age, level of education, occupation, total number of previous pregnancies, and body-mass index. For each region, we calculated the rate of neural-tube defects (the number of cases

TABLE 2. CHARACTERISTICS OF THE WOMEN FOR WHOM THE STATUS OF THE FETUS OR INFANT WITH RESPECT TO A NEURAL-TUBE DEFECT WAS KNOWN, ACCORDING TO REGION AND THE USE OF FOLIC ACID PILLS.*

CHARACTERISTIC	NORTHERN REGION (N=31,960)		SOUTHERN REGION (N=215,871)	
	ANY USE OF FOLIC ACID PILLS (N=18,591)	NO USE OF FOLIC ACID PILLS (N=13,369)	ANY USE OF FOLIC ACID PILLS (N=111,551)	NO USE OF FOLIC ACID PILLS (N=104,320)
Age — yr	24±2	26±4	24±2	26±4
Registration before last menstrual period — no. of women (%)	18,083 (97)	3,318 (25)	103,594 (93)	28,265 (27)
No. of previous pregnancies — no. of women (%)				
0	17,353 (93)	7,632 (57)	56,437 (51)	43,642 (42)
1	732 (4)	3,366 (25)	34,692 (31)	28,395 (27)
≥2	106 (0.6)	995 (7)	18,571 (17)	28,140 (27)
Unknown	400 (2)	1,376 (10)	1,851 (2)	4,143 (4)
Body-mass index†	21.4±2.1	21.8±2.0	20.4±2.3	20.9±2.5
Han ethnic group — no. of women (%)	17,837 (96)	12,601 (94)	109,064 (98)	100,412 (96)
Level of education — no. of women (%)				
High school or college	1,660 (9)	957 (7)	12,639 (11)	10,232 (10)
Junior high school	13,925 (75)	10,035 (75)	68,939 (62)	55,690 (53)
Elementary school or none	2,390 (13)	1,706 (13)	27,886 (25)	35,017 (34)
Unknown	616 (3)	671 (5)	2,087 (2)	3,381 (3)
Occupation — no. of women (%)				
Farmer	15,766 (85)	11,684 (87)	58,391 (52)	66,878 (64)
Factory worker	1,085 (6)	414 (3)	35,459 (32)	21,818 (21)
Other	1,178 (6)	608 (5)	15,784 (14)	12,393 (12)
Unknown	562 (3)	663 (5)	1,917 (2)	3,231 (3)

*Plus–minus values are means ±SD. Because of rounding, percentages may not total 100.

†Body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.

per 1000 pregnancies of at least 20 weeks' gestation) according to the use of folic acid. We estimated risk ratios by dividing the risk of neural-tube defects among the fetuses or infants of all women who took folic acid pills by the risk among the fetuses or infants of those who did not take folic acid. We also estimated risk ratios by dividing the risk among the fetuses or infants of women with a periconceptional pattern of use of folic acid by the risk among the fetuses or infants of those with no intake who registered before their last menstrual period. For all risk ratios we used SAS statistical software[13] to calculate 95 percent confidence intervals according to the Mantel–Haenszel test.

RESULTS

Characteristics of the Pregnant Women

Among the 285,536 women who registered with health authorities from October 1993 through September 1995, 277,287 (97 percent) were pregnant at some point between October 1, 1993, and December 31, 1996 (Table 1). After the exclusion of pregnant women who were lost to follow-up or those for whom the status of the fetus or infant with respect to a neural-tube defect was unknown, there were 247,831 pregnant women, 31,960 in the northern region and 215,871 in the southern region (88 percent and 90 percent of all pregnant women, respectively) for whom the neural-tube–defect status of their fetus or infant was known. In both regions, the women who took folic acid pills were approximately two years younger than those who did not, were more likely to have registered before their last menstrual period, and were more likely to be pregnant for the first time (Table 2). In both regions the two groups were similar with respect to all other characteristics.

Neural-Tube Defects

We identified 275 women who had a fetus or infant with a neural-tube defect: 112 in the northern region and 163 in the southern region. In both regions female fetuses or infants were more likely to be affected than male fetuses or infants (ratio of males to females, 1:1.6 in the northern region and 1:1.3 in the southern region). In the northern region, 47 percent of the neural-tube defects consisted of spina bifida, with anencephaly (20 percent) and craniorachischisis (21 percent) together accounting for 41 percent. In the southern region, 33 percent of the neural-tube defects consisted of spina bifida, with anencephaly (35 percent) and craniorachischisis (13 percent) accounting for 48 percent.

TABLE 3. RATES OF NEURAL-TUBE DEFECTS ACCORDING TO THE PATTERN OF USE OF FOLIC ACID PILLS.

PATTERN OF USE*	PREGNANT WOMEN†	MEAN COMPLIANCE	NEURAL-TUBE DEFECTS	
			NO.	RATE/1000 PREGNANCIES OF ≥20 WK GESTATION
	no. (%)	%		
Northern region				
Periconceptional use	13,012 (70)	81	13	1.0
Late use	3,681 (20)	75	6	1.6
Early discontinuation	1,838 (10)	68	6	3.3
Total	18,531 (100)	78	25	1.3
Southern region				
Periconceptional use	58,638 (53)	87	34	0.6
Late use	35,647 (32)	74	25	0.7
Early discontinuation	17,107 (15)	78	18	1.1
Total	111,392 (100)	81	77	0.7

*We defined women with periconceptional use as those who started taking folic acid pills before their last menstrual period before conception and who stopped at the end of the first trimester. We defined women with late use as those who started taking folic acid pills during the first trimester but sometime after their last menstrual period. We defined women with early discontinuation of folic acid pills as those who started and stopped taking folic acid pills before their last menstrual period before conception.

†The analysis excludes 60 women in the northern region and 159 in the southern region whose fetuses or infants did not have neural-tube defects for whom the pattern of use of folic acid pills could not be classified.

Use of Folic Acid Pills

The most common pattern of use was periconceptional use of folic acid pills in both the northern region (70 percent) and the southern region (53 percent) (Table 3). The rate of neural-tube defects was higher in the northern region than in the southern region, and within each region, it was lowest among the fetuses or infants of the women with periconceptional use of folic acid pills.

Among the women who did not take any folic acid, the rates of neural-tube defects among fetuses or infants were 6.5 per 1000 pregnancies of at least 20 weeks' gestation in the northern region and 0.8 per 1000 pregnancies of at least 20 weeks' gestation in the southern region (Table 4). Among the fetuses or infants of the women with any folic acid use, the respective rates were 1.3 and 0.7 per 1000 pregnancies of at least 20 weeks' gestation.

The reduction in the risk of neural-tube defects among the fetuses or infants of the women who took folic acid (as compared with the fetuses or infants of women who did not take folic acid) was greater in the northern region (79 percent) than in the southern region (16 percent). In the northern region, the reduction in risk among the fetuses or infants of women with periconceptional use of folic acid was the same as that in the entire folic acid group (79 percent); in the southern region, however, the reduction in risk in this subgroup (41 percent) was larger than that for the group as a whole.

Among the fetuses or infants of women with periconceptional use who took folic acid more than 80 percent of the time, the reduction in risk was 85 percent in the northern region and 40 percent in the southern region. The rates of neural-tube defects were similar in these two subgroups (0.7 and 0.6 per 1000 pregnancies of at least 20 weeks' gestation, respectively) (Table 4). In the northern region, the risk of neural-tube defects in this subgroup was half that among fetuses or infants of the women who were compliant with the periconceptional use of folic acid no more than 80 percent of the time.

TABLE 4. RATES AND RISKS OF NEURAL-TUBE DEFECTS ACCORDING TO THE USE OF FOLIC ACID PILLS.*

USE OF FOLIC ACID PILLS	NORTHERN REGION (N=31,960)				SOUTHERN REGION (N=215,871)			
	NO. OF PREGNANT WOMEN	RATE OF NEURAL-TUBE DEFECTS/1000 PREGNANCIES OF ≥20 WK GESTATION (NO.)	RISK RATIO (95% CI)	REDUCTION IN RISK (95% CI)	NO. OF PREGNANT WOMEN	RATE OF NEURAL-TUBE DEFECTS/1000 PREGNANCIES OF ≥20 WK GESTATION (NO.)	RISK RATIO (95% CI)	REDUCTION IN RISK (95% CI)
				%				%
None†	13,369	6.5 (87)	1.0	0	104,320	0.8 (86)	1.0	0
Any	18,591	1.3 (25)	0.21 (0.13 to 0.32)	79 (68 to 87)	111,551	0.7 (77)	0.84 (0.61 to 1.14)	16 (−14 to 39)
None; registration before last menstrual period†	3,318	4.8 (16)	1.0	0	28,265	1.0 (28)	1.0	0
Periconceptional use	13,012	1.0 (13)	0.21 (0.10 to 0.43)	79 (57 to 90)	58,638	0.6 (34)	0.59 (0.36 to 0.97)	41 (3 to 64)
≤80% compliance	4,898	1.4 (7)	0.30 (0.12 to 0.70)	70 (30 to 88)	11,643	0.5 (6)	0.52 (0.20 to 1.19)	48 (−19 to 80)
>80% compliance	8,114	0.7 (6)	0.15 (0.06 to 0.38)	85 (62 to 94)	46,995	0.6 (28)	0.60 (0.36 to 1.02)	40 (−2 to 64)

*CI denotes confidence interval.

†This group was the reference group.

DISCUSSION

We found that daily ingestion of 400 μg of folic acid alone during the periconceptional period reduced a woman's risk of having a fetus or infant with a neural-tube defect. This reduction occurred in an area of China in which the frequency of neural-tube defects is high and one in which it is low, and the magnitude of the reduction varied, depending on the base-line rate of neural-tube defects.

The strengths of our evaluation were that it was population-based, with nearly complete ascertainment of outcomes among large numbers of women whose pregnancies lasted at least 20 weeks, and that we prospectively documented the timing of the use of folic acid pills during the period of gestation within which neural-tube closure occurs, before the outcome of the pregnancy was known. Other strengths were the use of the system of prospective surveillance for birth defects, which was established before our evaluation began and identifies all affected fetuses and infants, and the establishment of diagnoses on the basis of photographs taken at birth and reviews of reports by several clinicians.

In this evaluation, women were not randomly selected to take or not to take folic acid pills. Therefore, the women who took them may have differed systematically from those who did not in factors that influence the frequency of neural-tube defects.[14] Differences between the two groups in the numbers of women in whose fetuses birth defects were diagnosed prenatally and the rates of termination of pregnancies involving fetuses with neural-tube defects could result in differences in the rates of neural-tube defects, but prenatal diagnosis of birth defects is uncommon in all areas of China, and our surveillance system was designed to identify all affected fetuses. As compared with the women who took folic acid, those who did not were slightly older and were more likely to have been pregnant before. Stratification according to age and the number of previous pregnancies, however, did not change our results, nor did taking into account a woman's socioeconomic status (i.e., education and occupation).

In the southern region, the rates of neural-tube defects were lower among the fetuses or infants of women who took folic acid periconceptionally than among those of women who registered before their last menstrual period and who did not take any folic acid. Furthermore, in the northern region, higher rates of compliance (more than 80 percent) among the women who took folic acid periconceptionally were associated with a greater reduction in the frequency of neural-tube defects in their fetuses and infants, as compared with the women with lower rates of compliance. The fact that the ingestion of 400 μg of folic acid alone per day resulted in a reduction in risk similar to that reported in earlier studies,[2-6,8] which evaluated the effect of folic acid in combination with multivitamins, suggests that most of the reduction in risk in the earlier studies was due to folic acid. However, our findings do not preclude the possibility that other vitamins or minerals may have an additional protective effect.

The difference in the rates of neural-tube defects between the northern region and the southern region was well documented by the comprehensive birth-defects surveillance system, which we established in January 1993. Because the use of folic acid pills began in October 1993, July 1994 was the first month in which full-term infants who had been exposed in utero to folic acid could have been born. This meant that there was an 18-month period when surveillance was conducted but there was no exposure, or only limited exposure, to folic acid among infants born between January 1993 and June 1994; during this period the base-line rate was 5.5 per 1000 births in the northern region and 1.0 per 1000 births in the southern region. During the period when the effects of folic acid should have been evident (July 1994 to December 1996), rates in the population as a whole (which included our study cohort) were 3.3 per 1000 births in the northern region and 0.8 per 1000 births in the southern region.

The difference in the base-line rates of neural-tube defects in the northern region and the southern region (which have similar, ethnically homogeneous populations) suggests that factors other than ethnic background may have a role in a woman's risk of having a fetus or infant with a neural-tube defect. Neither previously discussed potential risk factors (such as those shown in Table 2) nor differences in the rates of prenatal diagnosis of birth defects explain this regional difference. However, as a whole, the southern region (which is adjacent to Shanghai) is one of the wealthiest regions in China and has a more temperate climate with a longer growing season than the northern region. Whether these factors explain the regional difference in the rates of neural-tube defects is unclear. We were not able to collect information on the diets of the women or to determine whether there was a difference in diet between the northern region and the southern region. However, the fact that women with periconceptional ingestion of folic acid pills who were highly compliant in both the northern region and the southern region had similarly low rates of affected fetuses or infants suggests that the differences in background rates could be due in part to differences in dietary folic acid intake.

Neural-tube defects are a worldwide problem, affecting an estimated 300,000 or more fetuses or infants each year.[15] Our results demonstrate that the ingestion of 400 μg of folic acid alone per day during the periconceptional period prevents neural-tube defects in areas of both high and low frequency. The higher rates in the northern region of China and the magnitude of the reduction there suggest that daily

doses of folic acid of less than 4000 μg — the dose recommended by the Public Health Service for women with a previously affected fetus or infant[16] — may be effective in reducing risk in subsequent pregnancies, as others have also suggested.[17,18] The preventive effect in the southern region of China, in which the base-line rate is similar to that in the United States and elsewhere,[14] suggests that the daily ingestion of 400 μg of folic acid alone during the periconceptional period may help reduce the rate of the first occurrence of neural-tube defects in many parts of the world.

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APPENDIX

The following persons participated in the China–U.S. Collaborative Project for Neural Tube Defect Prevention: **Ministry of Health** — Qin Xinhua, Shi Malin, Gu Shiguang, Shi Jiefang, Shi Anli, Liu Junli, Mu Yingying, Xu Lanfang, Li Zhongze; **Beijing Medical University** — Wang Debing, Ji Jingde, Lin Zhibin, Peng Ruicong, Yan Renying, He Guanqing (deceased), Qian Yuping (deceased), Liu Shijie, Li Tianlin, Li Kemin, Zhang Chao, Zhang Yansheng (deceased), Guan Yubei, Ye Rongwei, Liu Xiangdong, Xiong Zhaoxia, Gao Weixian, Zhang Qiaoyi, Tang Yi, Huhe Muren, Chen Yahua, Dai Guangsheng, Wang Long, Zhao Xiuqin, Zhang Li, Li Ting, Zhang Zefeng, Yang Wenhong, Lu Hongyu, Dao Jingjing, Qiu Yongtian, Shen Yanhui, Wang Mei, Wang Yuequn, Hu Yousheng, Hu Lin, Chen Hong, Chen Gang, Yuan Hongbo, Wang Zhonghong, Xu Xiaohui, Yin Zaidong, Zhu Huiping, Gu Zhihui, Gao Zhiping, Su Guanghui, Xiao Lan, Chen Xin, Chen Xing, Shen Liyang, He Lihua, Xiao Jun, Pei Lijun, Ji Chengye, Zheng Junchi, Zhao Rubing, Zhang Qing, Li Haojie, Wang Lina, Wang Yu, Liu Jianmeng, Gao Wanzhen, Liu Mingzhu, Liu Yan, Wang Jizhe, Li Nan, Liu Yanshu, Gu Haiqin, Li Kewei, Li Yong, Hu Yuanhua, Bao Yueqin, Li Wanzhen, Ma Yuwen, Wang Linhong, Wang Taimei, Zhao Gengli, Chen Lijun, Lin Qing, Zhang Wei, Sun Shanggong, Qu Chuanyan, Zhao Fenglin, Bai Zhi, Li Ying, Lu Qinghao, Wang Puyu, Wang Qiaoqiao, Liu Yanfei, Li Fengning; **Hebei Province** — Wang Youhui, Yang Qian, Duan Li, Wang Liren, Li Hongying, Zhao Yan, Chen Xunzhao, Feng Guoan, Zhang Mingqing, Fan Fusheng, Ran Dewang, Shi Congyi, Sun Aiying, Sun Chenyan, Tian Wenrui, Liang Guowen, Zhao Yurong, Liu Tianen, Liu Weihe, Wang Wenxiu, Jia Limin, Jing Rui, Tian Junfeng, Zhang Xueqin, Tian Gengzhi, Li Changlin, Xin Cuizhi, Hu Wei, Ma Jie; *Mancheng County:* Lu Wenzhan, Yao Xiuzhi, Liu Zhixin (deceased), Zhang Shufen; *Shijiazhuang City:* Zhang Chenglu, Li Jefen, Xie Lianyun; *Yuanshi County:* He Huandai, Hu Xiaomei, Jia Wenfang; *Fengrun County:* Du Bing, Yue Chunxiang, Hou Guangwang; *Laoting County:* Yin Shufen, Zhao Surong, Cai Yunzong, Wang Xianglin; *Langfang City:* Zhu Liwen; *Xianghe County:* Shi Wenzhi, Du Weiyan, Yao Xiaoyun; **Shanxi Province** — Wang Zhifang, Li Ruiyu, Yang Yushu, Sun Shizhang, Hao Shengfang, Pan Yuying, Gao Fengju, Sheng Shucai, Li Shuangting, Jia Li; *Fenyang County:* Zhang Guozhong; *Taiyuan Nancheng:* Liu Yuee; **Zhejiang Province** — Zhuang Bingjin, Zhou Kun, Fan Baling, Kang Mingdao, Zhou Aizhen, Zhang Guohua, Shen Jiaxian, Shen Rongde, Zhang Menghua, Jin Shifang, Chen Xingya; *Jiaxing City:* Mu Huiyuan, Yang Dongping, Jiang Yanying, Tong Qiaoling, Chen Hua; *Jiashan County:* Jiang Lianfu, Chen Yuyuan, Xie Quanying; *Jiaxing County:* Chen Meiying, Chen Duofei, Qian Yingming; *Haiyan County:* Ling Jingeng, Ba Disheng, Pan Yujuan, Fei Minjuan; *Pinghu City:* Feng Meixian, Zhang Taihua, Wu Limin; *Tongxiang City:* Xu Yifen, Chen Minqiang, Chen Hao; *Haining City:* Yao Shuiyin, Gao Yuelin, Sun Xiamei; *Ningbo City:* Ling Guolian, Zhu Yuanqing, Zhou Minggao (deceased), Chen Yanyu; *Cixi City:* Chen Jiguang, Shi Boyao, Wang Qiaohua; *Fenghua City:* Liu Rongjiao, Xia Pinguo, Wang Haiming; *Yin County:* He Changhui, Yu Cuilin, Jin Lingui; *Ninghai County:* Zhu Shuidi, Yang Xianming, Wang Jiamei; *Zhoushan City:* Wang Shihe, Yang Erchang, Zhou Qingxin; **Jiangsu Province** — Chen Ping, Chen Hao, Wang Zhuping, Zhou Dayan, Zhou Mingqi, He Shuxiang, Chen Xiaohui, Yang Jianxiong, Fu Caiqin, Pu Shaotang, Zhang Yingzhong, Zhu Xingyuan, Zhou Yonglan, Zhang Menglan, Zhao Nengxiu, Wang Xuelin, Pan Zhongyue, Xu Chongjia, Xu Haifeng, Zhang Ying, Zheng Yinlin, Chen Zhong, Jiang Zhongliang, Tang Yaogen, Wu Xuansheng, Zhao Gongtai, Jiang Jiongyuan; *Suzhou City:* Zhu Yongxin, Jiang Meifang; *Kunshan City:* Shao Peiyuan; *Taicang City:* Chen Huifang, Zhou Caiping, Zhang Menglan; *Wujiang City:* Tang Jianfang; *Wu County:* Yang Xiaoling; *Wuxi City:* Zhang Huaixi, Chen Yafen, Zhu Wenyu; *Xishan City:* Shen Quanzhen; *Jiangyin City:* Xu Jiafu.

REFERENCES

1. Smithells RW, Sheppard S, Schorah CJ, et al. Possible prevention of neural-tube defects by periconceptional vitamin supplementation. Lancet 1980;1:339-40.
2. Mulinare J, Cordero JF, Erickson JD, Berry RJ. Periconceptional use of multivitamins and the occurrence of neural tube defects. JAMA 1988;260:3141-5.
3. Milunsky A, Jick H, Jick SS, et al. Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. JAMA 1989;262:2847-52.
4. Bower C, Stanley FJ. Dietary folate as a risk factor for neural-tube defects: evidence from a case-control study in Western Australia. Med J Aust 1989;150:613-9.
5. Werler MM, Shapiro S, Mitchell AA. Periconceptional folic acid exposure and risk of occurrent neural tube defects. JAMA 1993;269:1257-61.
6. Shaw GM, Schaffer D, Velie EM, Morland K, Harris JA. Periconceptional vitamin use, dietary folate, and the occurrence of neural tube defects in California. Epidemiology 1995;6:219-26.
7. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991;338:131-7.
8. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med 1992;327:1832-5.
9. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR Morb Mortal Wkly Rep 1992;41(RR-14):1-7.
10. Cornel MC, Erickson JD. Comparison of national policies on periconceptional use of folic acid to prevent spina bifida and anencephaly (SBA). Teratology 1997;55:134-7.
11. Xiao KZ, Zhang ZY, Su YM, et al. Central nervous system congenital malformations, especially neural tube defects in 29 provinces, metropolitan cities and autonomous regions of China: Chinese Birth Defects Monitoring Program. Int J Epidemiol 1990;19:978-82.
12. Moore CA, Li S, Li Z, et al. Elevated rates of severe neural tube defects in a high-prevalence area in northern China. Am J Med Genet 1997;73:113-8.
13. SAS/STAT software: changes and enhancements through release 6.12. Cary, N.C.: SAS Institute, 1997.
14. Olney R, Mulinare J. Epidemiology of neural tube defects. Ment Retard Dev Disabil Res Rev 1998;4:241-6.
15. Murray CJL, Lopez AD, eds. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Vol. 1 of Global burden of disease and injury series. Cambridge, Mass.: Harvard School of Public Health, 1996.
16. Use of folic acid for prevention of spina bifida and other neural tube defects — 1983–1991. MMWR Morb Mortal Wkly Rep 1991;40:513-6.
17. Smithells RW, Nevin NC, Seller MJ, et al. Further experience of vitamin supplementation for prevention of neural tube defect recurrences. Lancet 1983;1:1027-31.
18. Kirke PN, Daly LE, Elwood JH. A randomized trial of low dose folic acid to prevent neural tube defects. Arch Dis Child 1992;67:1442-6.

CORRECTION

Prevention of Neural-Tube Defects with Folic Acid in China

Prevention of Neural-Tube Defects with Folic Acid in China . On page 1485, the sentence that begins on line 14 of the Results paragraph of the Abstract should have read, ``The greatest reduction in risk occurred among the fetuses or infants of a subgroup of women in the northern region with periconceptional use who took folic acid pills more than 80 percent of the time (reduction in risk, 85 percent as compared with the fetuses or infants of women who registered before their last menstrual period and who took no folic acid; 95 percent confidence interval, 62 to 94 percent).´´ We regret the error.