

## Preplanned Studies

# Periconceptional Folic Acid Use and Its Effects on Neural Tube Defects — Five Counties, Shanxi Province, China, 2010–2016

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## Summary

### What is already known about this topic?

Robust evidence indicates that supplementing with folic acid periconceptionally may decrease the risk of neural tube defects (NTDs) in fetuses.

### What is added by this report?

Over half of the mothers in both the NTD case group and the control group utilized folic acid supplements during the periconceptional period, showing no notable variations between the two groups. However, there was a significantly higher percentage of mothers with NTD cases who exhibited poor compliance in folic acid use compared to control mothers. A significantly lowered compliance with folic acid intake was observed among women facing unintended pregnancies and those with lower education levels.

### What are the implications for public health practice?

Universal education regarding folic acid action for women of childbearing age should be strengthened to improve compliance with folic acid supplementation in the periconceptional period and further reduce the prevalence of NTDs.

Neural tube defects (NTDs) are profound congenital malformations of the brain and spinal cord that occur in fetuses in early pregnancy. Empirical evidence suggests that the periconceptional use of folic acid considerably reduces the risk of developing NTDs (1–2). In 2009, China's National Health Commission, formerly the Ministry of Health (MOH), rolled out a nationwide program aimed at promoting folic acid supplementation among women planning for pregnancy. The program aimed to motivate 70% of women to commence folic acid supplementation at least three months before conception (3–4). However, studies have indicated suboptimal adherence levels (below 40%), significantly short of the MOH's target (5–6), though the degree of adherence noticeably improved with higher maternal educational levels (6). This study investigates the use of folic acid, its

protective effect against NTDs, and the significant features influencing adherence to the supplementation protocol in five counties within China's Shanxi Province following the rollout of the national supplementation program. These research findings indicate that more than half of the women in the case and control groups used folic acid during the periconceptional period. Nevertheless, cases of NTDs were significantly more prevalent among women who demonstrated poor adherence. Additionally, non-compliance was notably higher among women with unintended pregnancies and with lower educational levels. In order to reduce the prevalence of birth defects, particularly NTDs, there is a need to strengthen education regarding folic acid supplementation for childbearing-aged women with the aim of improving adherence during the periconceptional period.

A population-based, case-control study of major external birth defects, conducted between 2010 and 2016, identified 213 cases of NTDs and selected 442 normal controls in five counties of Shanxi Province (including Pingding, Xiyang, Shouyang, Taigu, and Zezhou). The population-based birth defect surveillance system had previously indicated these locations to have immensely high NTD prevalence before 2009. Each case was matched with a healthy newborn of the same sex and from the same county, having the closest conception date to the case's.

Trained health professionals collected data through structured interviews from participants within 10 days of delivery or pregnancy termination due to identified birth defects. The gathered information encompassed demographics, gravidity history, lifestyle behaviors, and folic acid intake practices.

From the initial group, 113 subjects (14.7%) were excluded due to incomplete folic acid intake data, resulting in a final sample size of 655 subjects. Compliance with folic acid supplementation was defined as consuming no less than a 60-day supply, beginning over a month prior to the last menstrual period (LMP) and extending to less than a month

post-LMP. Non-compliance was defined as consuming less than a 60-day supply or starting supplementation after one month post-LMP.

This study was granted approval by the Institutional Review Board of Peking University (IRB00001052–16061) and written informed consent was procured from all participants.

In order to assess the relationship between folic acid intake and the risk of NTDs, a logistic regression analysis was conducted. Unadjusted odds ratios (*ORs*) were calculated, including 95% confidence intervals (*CI*s). This was followed by the computation of adjusted odds ratios (*aORs*) that also included 95% *CI*s, after accounting for potential confounding variables. These variables consisted of maternal age, pre-pregnancy body mass index (BMI), history of pregnancies affected by birth defects, incidences of fever or flu in early pregnancy, and exposure to secondhand smoke. The statistical analysis was conducted using SPSS software (version 24.0; SPSS Inc., Armonk, NY, USA).

A total of 213 cases of NTD and 442 control subjects were included in this analysis. The NTD cases comprised of 74 anencephaly cases, 115 spina bifida cases, and 24 encephalocele cases. Other malformations, such as orofacial clefts or gastroschisis, were present in 16 (7.5%) of the NTD cases. Mothers of NTD cases showed a lower level of education, an elevated rate of exposure to passive smoking, a more frequent history of pregnancies affected by birth defects, a higher prevalence of fever or flu contractions, and a higher rate of unintended pregnancies as compared to mothers of control subjects. Moreover, they were more likely to be 30 years or older and have a pre-pregnancy BMI of at least 25 kg/m<sup>2</sup> (Table 1).

In total, 51.6% (110/213) of mothers in the case group reported folic acid intake during the periconceptional period, a proportion slightly less than that of the control group, where 58.8% (260/442) reported intake. No significant differentiation was found between the two groups in terms of folic acid usage. However, a significant difference was observed concerning compliance, with the proportion of good compliance being significantly lower in the NTD case mothers (13.1%) compared to the control mothers (27.6%). After adjusting for factors such as maternal age, pre-pregnancy BMI, occurrences of fever or flu in early pregnancy, exposure to passive smoking during the periconceptional period, and history of birth defect-implicated pregnancies, the *aOR* for good compliance was calculated to be 0.517 (95% *CI*:

0.300–0.891) (Table 2).

Table 3 illustrates that there is a significant association between unintended pregnancy, lower education levels (defined as junior high school or less), and decreased compliance rate (all *P*<0.05). This association remains significant even after adjusting for potential confounding variables.

## DISCUSSION

Over half of expectant women in Chinese regions with a high prevalence of NTDs reported taking folic acid supplements during the periconceptional period; no significant disparities in NTDs emerged between the case and control groups. After the implementation of a national folic acid supplementation program in 2009, periconceptional intake in these areas displayed an increasing trend, albeit remaining significantly lower than that in Beijing, which is at 97.2% (6). Considering that neural tube closure transpires within the first month of pregnancy, early supplementation during the periconceptional period and regular usage are crucial in preventing NTDs. Table 2 demonstrates that robust protective effects were observed whether women commenced folic acid intake more than 1 month prior to LMP, or from 1 month before to 1 month after LMP. The United States Preventive Services Task Force (USPSTF) advocates that women planning or capable of pregnancy should begin taking folic acid 1 month before conception and continue until 3 months post-conception, consuming at least 24 capsules monthly; in Western countries, 42.2% of women adhere to this recommendation (7). One study found a significantly lower prevalence of NTDs among women who used folic acid-containing multivitamins during the initial 6 weeks of pregnancy, compared to those who never used such supplements (prevalence ratio 0.27; 95% *CI*: 0.12–0.59) (8). In this study, merely 13.1% of mothers in the NTD case group demonstrated satisfactory compliance with supplementation, the figure lower than the control group (27.6%, *P*<0.05). However, applying the USPSTF standard, the fraction of sufficient compliance in the NTD group declined further to 6.6% (14/213). These findings unequivocally indicate that, despite this study's definition of satisfactory compliance being less strict, there was still a significant protective effect on NTDs (*aOR*: 0.517, 95% *CI*: 0.300–0.891).

TABLE 1. Demographic and lifestyle attributes of mothers of NTD cases and controls in five counties of Shanxi Province, China, 2010–2016.

Characteristics of mothers	NTD cases (n=213)*		Controls (n=442)*		P
	N	%	N	%	
Age (years)					0.031
<25	77	36.8	211	48.3	
25–29	74	35.4	140	32.0	
30–34	39	18.7	60	13.7	
≥35	19	9.1	26	6.0	
Prepregnancy BMI (kg/m <sup>2</sup> )					<0.001
<18.5	20	9.8	40	9.2	
18.5–24.9	115	56.7	311	71.3	
≥25	68	33.5	85	19.5	
Occupation					0.221
Farmer	146	73.0	287	68.2	
Others	54	27.0	134	31.8	
Education					<0.001
Junior high school or lower	160	75.5	256	58.2	
Senior high school	33	15.6	101	22.9	
College or higher	19	8.9	83	18.9	
Parity					0.675
Primiparas	123	60.0	271	61.7	
Multiparas	82	40.0	168	38.3	
History of birth defect-affected pregnancy					0.010
Yes	9	4.3	5	1.1	
No	201	95.7	430	98.9	
Fever or flu in early pregnancy					<0.001
Yes	76	38.8	67	16.5	
No	120	61.2	339	83.5	
Passive smoking exposure					<0.001
Yes	124	60.5	135	31.1	
No	81	39.5	299	68.9	
Unintended pregnancy					<0.001
No	116	55.5	304	71.7	
Yes	93	44.5	120	28.3	

Abbreviation: NTDs=neural tube defects; BMI=body mass index.

\* The total number may not be the sum of the values due to missing information for some subjects.

Our research identified notable disparities in folic acid adherence among women experiencing unintended pregnancies, which underscored by significantly lower compliance rates. After controlling for potential confounders, the association persisted (*aOR*: 2.753, 95% *CI*: 1.687–4.494). Unintended pregnancies proved prevalent, constituting 22.1% to 35.1% of all cases (9–10). Interestingly, mothers of NTD cases had higher rates of unintended pregnancies

at 44.5%, exceeding the frequency seen in the broader population. Prior research discovered that 61% of women initiated supplementation upon realizing their pregnancy status (10), rendering adherence to recommended folic acid supplementation impossible for women with unexpected pregnancies. The study further revealed that the impact of education on compliance was modest, particularly among those women with lower education levels. Therefore, it is

TABLE 2. Associations between periconceptional folic acid supplementation and fetal NTDs in five counties of Shanxi Province, China, 2010–2016.

Factors	Case [n (%)]	Control [n (%)]	Crude OR (95% CI)	Adjusted OR* (95% CI)
Folic acid supplementation				
No	103 (48.4)	182 (41.2)	1	1
Yes	110 (51.6)	260 (58.8)	1.338 (0.963–1.858)	1.023 (0.686–1.526)
When folic acid supplementation began <sup>†</sup>				
>1 month before LMP	20 (18.2)	70 (26.9)	0.418 (0.233–0.750)	0.458 (0.236–0.890)
From 1 month before to 1 month after LMP	21 (19.1)	89 (34.2)	0.345 (0.196–0.608)	0.322 (0.170–0.612)
>1 month after LMP	69 (62.7)	101 (38.9)	1	1
The total number of days taken folic acid supplementation <sup>†</sup>				
<60 days	47 (42.7)	71 (27.3)	1	1
≥60 days	63 (57.3)	189 (72.7)	0.501 (0.314–0.798)	0.497 (0.291–0.851)
Compliance with folic acid intake				
No folic acid intake	103 (48.4)	182 (41.2)	1	1
Poor	82 (38.5)	138 (31.2)	1.050 (0.729–0.252)	1.189 (0.771–1.834)
Good	28 (13.1)	122 (27.6)	0.406 (0.252–0.653)	0.517 (0.300–0.891)

Abbreviation: NTDs=neural tube defects; OR=odds ratio; CI=confidence interval; LMP=last menstrual period.

\* Adjusted for variables such as maternal age, body mass index during pregnancy, history of pregnancies affected by birth defects, occurrence of fever or flu in early pregnancy, and exposure to passive smoking.

<sup>†</sup> Pertains to pregnant women who had consumed folic acid.

TABLE 3. Factors influencing compliance with folic acid intake in five counties of Shanxi Province, China, 2010–2016.

Factors	Compliance with folic acid intake <sup>§</sup>		Crude OR (95% CI)	Adjusted OR <sup>†</sup> (95% CI)
	Good [n (%)]	Poor or no intake [n (%)]		
Unintended pregnancy*				
No	120 (81.6)	300 (61.7)	1	1
Yes	27 (18.4)	186 (38.3)	2.756 (1.747–4.347)	2.753 (1.687–4.494)
Education*				
Junior high school or lower	68 (45.3)	348 (69.3)	4.204 (2.631–6.717)	2.632 (1.382–5.013)
Senior high school	36 (24.0)	98 (19.5)	2.236 (1.295–3.860)	1.733 (0.933–3.219)
College or higher	46 (30.7)	56 (11.2)	1	1

Abbreviation: OR=odds ratio; CI=confidence interval.

\* Values may not sum to the total due to missing data from some subjects;

<sup>†</sup> Adjusted for factors including maternal age, body mass index during pregnancy, occupational status, historical incidence of birth defects, and parity;

<sup>§</sup> Folic acid intake is categorized as good (coded as 0) or poor/no intake (coded as 1).

vital to amplify educational efforts promoting periconceptional supplementation of folic acid among women of childbearing age in the regions investigated.

This study possesses notable strengths. It utilizes a population-based birth-defect surveillance system distinguished by a high prevalence of NTDs and an impressive participation rate. Both cases and controls were culled from congruent regions, and the implemented evaluation of compliance with folic acid intake enabled an exhaustive analysis of how varied inception times and usage durations affect NTD risk. To our understanding, this stands as the inaugural

study to concurrently investigate the status of folic acid use and its prophylactic effect on NTDs in these Chinese regions renowned for their high NTD prevalence, subsequent to the enforcement of the nationwide folic acid supplement program.

The present study was not without limitations. Folic acid intake, as reported by participating women during their postpartum period, presents the potential for recall bias, thus potentially influencing the study outcomes. Other significant factors that could likely affect compliance, such as awareness and intricate knowledge about folic acid, were not explored, thereby

limiting our ability to examine their impacts on adherence rates. It would be beneficial for forthcoming research to amalgamate data on folic acid intake with information on plasma folate concentrations, coupled with other important factors likely to affect folic acid use like understanding and disposition towards supplementation.

This study found that high adherence to folic acid supplementation was linked to a reduced risk of NTDs. However, the rate of adherence was markedly low among mothers with NTD-affected pregnancies, at just 13.1%, despite a nationwide folic acid supplementation program. Consequently, there is a clear need to intensify universal education on the benefits of folic acid for women of childbearing age. This will potentially enhance adherence to folic acid supplementation during the periconceptional period, and subsequently, decrease the occurrence rate of NTDs.

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