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Periconceptional folic acid supplementation and the risk of preterm births in China: a large prospective cohort study

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Abstract

Background: Folic acid-containing multivitamins have been associated with a reduced risk of preterm birth. We examined whether periconceptional use of folic acid alone reduced this risk.

Methods: Data were derived from a large population-based cohort study conducted in China to evaluate the prevention of neural tube defects with folic acid supplementation. The sample comprised 207 936 singleton live births delivered at gestational ages of 20–42 weeks to women from two provinces in southern China. Healthcare workers recorded folic acid intake prospectively each month. Gestational age calculation was based on the first day of the last menstrual period. Preterm births were categorized into three clinical subtypes: iatrogenic preterm birth, preterm premature rupture of membranes (PPROM) and spontaneous preterm birth. Logistic regression was used to evaluate the association between folic acid use and the risk of preterm birth, adjusting for potential confounders.

Results: The incidence of preterm birth was significantly lower among folic acid users (5.28%) than among non-users (6.10%). Folic acid use showed a 14% risk reduction for preterm birth overall [adjusted risk ratio (RR) = 0.86, 95% confidence interval (CI) 0.82–0.90]. This association was strongest for spontaneous preterm birth (adjusted RR = 0.81, 95% CI 0.78–0.86) and was not significant for iatrogenic preterm birth (adjusted RR = 0.97, 95% CI 0.88–1.07) or PPROM (adjusted RR = 1.07, 95% CI 0.93–1.23).

Conclusions: Daily intake of 400 μg folic acid alone during the periconceptional period was associated with a reduced risk of spontaneous preterm birth.

Key words: Folic acid, periconceptional supplementation, spontaneous preterm birth, preterm premature rupture of membranes, iatrogenic preterm birth, cohort study

Key Messages

- The effects of periconceptional use of folic acid alone in reducing the risk of preterm birth remain unclear.
- In this prospective cohort study in a Chinese population, we found that daily consumption of 400 μg folic acid alone during the periconceptional period was related to a reduced risk of spontaneous preterm birth.
- These reduced risks were greater for early-age spontaneous preterm births.

Introduction

Preterm birth remains one of the greatest causes of neonatal mortality and morbidity worldwide. Currently, approximately 1.1 million neonates die from preterm birth complications each year.[1] Preterm birth also contributes to substantial long-term morbidity and growth impairment, such as cognitive, visual and learning impairments.[2] These potentially serious health consequences underscore the public health importance of preventing preterm birth. However, the underlying drivers for such births and the potential effects of preventive interventions remain poorly understood.[3]

Periconceptional consumption of folic acid has been established as having a protective effect, reducing the risk of neural tube defects (NTDs) in neonates.[4,5] Most countries have recommended that women planning for pregnancy use folic acid supplementation during the periconceptional period, in addition to following a healthy diet. Public concern has risen with regard to whether folic acid benefits other pregnancy outcomes. Most studies have found that folic acid-containing multivitamin supplementation during the periconceptional period has a protective effect on preterm birth;[6–10] however, these studies have reported conflicting results or imprecise estimates.[11–13] Many researchers believe folic acid to be the critical factor affecting preterm birth, despite the fact that the majority of women participating in clinical studies have taken folic acid as part of a multivitamin, rather than as a sole supplement.

Preterm birth can be classified into several subtypes according to clinical presentation, including iatrogenic preterm birth, preterm premature rupture of membranes (PPROM) and spontaneous preterm birth. The pathways leading to these clinical phenotypes likely differ.[14] However, very few studies have attempted to evaluate whether the association observed between folic acid / multivitamin use and preterm birth is largely driven by one particular subtype over the others. Such a situation might weaken the association between folic acid and preterm birth overall. Furthermore, an examination of associations within particular subtypes would reveal interesting clues into the aetiology and underlying biological mechanisms of preterm birth.

A public health campaign investigating the effects of folic acid supplementation with no additional vitamins on the prevention of NTDs was conducted in China during the 1990s. A large cohort in 21 counties of three provinces was established to evaluate the effectiveness of the campaign.[4] Healthcare workers recorded folic acid intake by female participants each month during the study period. This cohort provided us a good opportunity to examine whether periconceptional supplementation with folic acid alone is associated with a reduced risk of preterm birth overall or certain subtypes thereof. The large sample size and detailed exposure and clinical information also facilitated the examination of this relationship across several subgroups of exposure (e.g. timing and compliance) and clinical presentations.

Methods

Background and original cohort

The methods of the original study have been described previously.[4,15] Beginning in 1993, the Chinese Ministry of Health conducted a public health campaign to prevent neural tube defects in 21 counties in two southern provinces (Zhejiang and Jiangsu) and one northern province (Hebei). During this campaign, all woman residents of the project counties who were preparing for marriage or who became pregnant were registered in a pregnancy monitoring system that served as the principal record of prenatal care and the source of demographic information. All women were advised to take a pill containing 400 μg of folic acid alone every day, starting at the time of registration with the pregnancy monitoring system and continuing until completion of the first trimester of pregnancy. If women consented to take folic acid, the pills were distributed at the time of registration. At the end of each month, the health workers recorded the dates of all menstrual periods and how many pills remained in each bottle (if taking pills). To evaluate the effect of folic acid on neural tube defects, we identified women who registered with the monitoring system between October 1993 and September 1995, who delivered by 31 December 1996, and whose fetuses or infants could

be confirmed as either having or not having a neural tube defect, whether live born, stillborn or electively terminated because of prenatal diagnosis of any birth defect. Miscarriages and elective terminations that took place before 20 weeks' gestation were not included in the cohort. The original cohort included a total of 247 831 women. The project was approved by the institutional review boards of the US Centers for Disease Control and Prevention and Peking University Health Science Center. All women who took pills provided oral informed consent.

Selection of study subjects

We selected participants from the large cohort study who were registered in Jiangsu and Zhejiang, two neighbouring provinces in southern China. Due to the implementation of pregnancy monitoring systems, detailed records of pregnancy complications were available for these subjects, enabling us to differentiate among preterm birth subtypes. Of 215 871 women from selected counties in the two provinces, we excluded 1371 (0.6%) women with multiple births, 1554 (0.7%) women for whom gestational age at delivery was uncertain and 5050 (2.3%) women whose neonates had gestational ages that fell outside the range of 20–42 weeks. After these exclusions, 207 936 (96.3%) participants were included in the current analysis.

Definition of folic acid use

We used the classification and pattern of folic acid consumption defined by Berry *et al*.[4] Women who took folic acid pills at any time from the registration period until the end of the first trimester of pregnancy were classified as folic acid users. Folic acid usage was divided into three patterns based on the usage period: (i) periconceptional use, defined as the initiation of folic acid supplementation before the last menstrual period and termination at the end of the first trimester; (ii) preconceptional use, defined as the initiation and termination of folic acid use before the last menstrual period; and (iii) postconceptional use, defined as the initiation of folic acid supplementation after the last menstrual period but within the first trimester. Women with missing dates were considered unclassifiable and were not assigned to a folic acid usage pattern. Women who did not agree to take folic acid or who were registered during the second trimester of pregnancy (i.e. did not have the opportunity to start taking folic acid by the end of the first trimester) were considered to be non-users. Compliance was calculated for each woman by dividing the total number of pills taken by the total number of days between the initiation and termination of supplementation.

Definition of preterm birth

The information on preterm birth and its subtypes was abstracted from the pregnancy monitoring system that serves as the principal record of prenatal care and delivery. The calculation of gestational age was based on the first day of the last menstrual period. Preterm birth was defined as delivery at a gestational age of 20–36 weeks. Preterm birth was further categorized into three subtypes according to pregnancy complication, similar to those defined by Bukowski *et al*.[7] Iatrogenic preterm birth was defined as that caused by medical or obstetric complications, including major external birth defects, stillbirth, termination of pregnancy, pregnancy-induced hypertension, preeclampsia, chronic hypertension, diabetes, placenta praevia and placental abruption. PPROM was defined as a case of preterm birth with membrane rupture before the onset of labour, that was not associated with the above-mentioned indications. All other cases were defined as spontaneous preterm birth.

Statistical analysis

We compared the mean age, mean body mass index (BMI, 67.6% measured before pregnancy, 27.3% within 12 weeks of gestation and 5.1% after 12 weeks of gestation) and distribution in terms of ethnic origin, education, occupation and parity between the groups of women who had and had not taken folic acid. We compared the means using *t*-tests, and distributions of gestational age at delivery using chi-square tests. We calculated the incidence of overall preterm birth and subtypes of preterm birth according to the patterns of folic acid intake. We estimated risk ratios (RRs) by dividing the incidence of preterm birth among women who took folic acid by that among women who had not taken folic acid. A logistic regression model was used to adjust for the main potential confounding variables, including maternal age at delivery (continuous), BMI (continuous), ethnicity, education, occupation and parity. Modification of the effect of folic acid by covariates was examined by incorporating the interaction terms into the multivariable logistic regression model. The effect of folic acid was subsequently estimated by multilogistic regression in strata of specific characteristics with *P*-values <0.1 for interaction. Because gestational age estimates were based on the date of the last menstrual period, inaccuracy of subjects' recollections of this date may have biased the results. To explore this influence, we also examined the RR of preterm birth associated with folic acid use among women who registered before their last menstrual period. All data were analysed using the SPSS software (v. 11.5; SPSS, Chicago, IL, USA).

Results

Of the 207 936 women included in this analysis, 108 307 (52.1%) took folic acid during the periconceptional period and 99 629 (47.9%) had not taken folic acid at all. Table 1 shows select characteristics of the participants according to periconceptional use of folic acid. Women who took folic acid were on average 1.3 years younger and their BMIs were 0.5 kg/m^2 higher than those who did not take it. Women who took folic acid supplements were more likely to be primiparous, of Han ethnicity and factory workers, and had higher educational levels. The mean (standard deviation) gestational ages were 39.34 (1.87) and 39.26 (1.97) weeks for women who had and had not taken folic acid, respectively (P <0.001). The percentage of early-age births was lower among women who took folic acid (Supplementary Table S1, available as Supplementary data at *IJE* online).

The total incidence of preterm birth was 5.67%, and 11 799/ 207 936 women delivered before 37 weeks. The incidence of preterm birth was significantly lower among folic acid users (5.28%) than among non-users (6.10%; Table 2). The adjusted RR suggested a 14% reduction in preterm birth risk among folic acid users. Evaluation according to clinical subtype revealed a significant protective association with folic acid for spontaneous preterm birth [adjusted RR = 0.81, 95% confidence interval (CI) 0.78–0.86], but not for iatrogenic preterm birth (adjusted RR = 0.97, 95% CI 0.88–1.07) or for PPROM (adjusted RR = 1.07, 95% CI 0.93–1.23). We further divided the spontaneous preterm birth cases into three subgroups according to gestational age to examine age-related differences. Folic acid supplementation tended to have a greater risk reduction for earlier spontaneous preterm births, with the largest risk reduction (35%) seen in births occurring between 20 and 27 weeks.

Table 3 depicts the protective association of folic acid with spontaneous preterm birth, as evaluated by the timing of and compliance with supplementation. Significantly reduced risk was found among women with periconceptional or preconceptional usage of folic acid, but not among women who took folic acid after conception. In addition, the risk reduction tended to be higher for women with ≥80% folic acid usage compliance than for those with <80% compliance.

The analysis of effect modification showed that the interaction term was significant between folic acid supplementation and two maternal characteristics: maternal education ($P = 0.08$) and parity ($P = 0.02$). When the analysis was stratified by education, the protective association of folic acid was significant for women with junior high school or lower education levels, but not for women with high school or higher education levels. When it was stratified by parity, the protective association was significant for primiparous, but not for multiparous, women. Other covariates, including maternal age, BMI, ethnicity and occupation, did not showed significant modification (Table 4).

Analysis of the association between preterm birth and folic acid use in the subpopulation of women who had registered for the study before their last menstrual period showed no substantial change in results. However, the protective associations for preterm birth (23%) and spontaneous preterm birth (28%) were more pronounced than those in the whole study population (14% and 19%, respectively). The associations of folic acid use with iatrogenic preterm birth and PPROM remained non-significant (Supplementary Table S2, available as Supplementary data at *IJE* online).

Table 1. Baseline characteristics of participants by periconception folic acid use

	Folic acid user ($n = 108307$)		Nonusers ($n = 99629$)		
Characteristics	*n*	%	*n*	%	*P*
Mean age at pregnancy, years (SD)	24.3 (2.5)		25.6 (3.9)		<0.001
Mean body mass index, kg/m^2 (SD)	20.3 (2.2)		20.8 (2.4)		<0.001
Primiparous	99493	91.9	73571	73.8	<0.001
Han ethnic group	106026	97.9	96004	96.4	<0.001
Education					
High school or higher	12383	11.4	9926	10.0	<0.001
Junior high school	67076	61.9	53415	53.6	
Primary school or lower, or unknown	28848	26.7	36288	36.4	
Occupation					
Farmer	56684	52.3	63702	63.9	<0.001
Factory worker	34404	31.8	20911	21.0	
Other or unknown	17219	15.9	15016	15.1	

SD, standard deviation.

Table 2. Preterm birth incidence and association with folic acid supplementation

	Folic acid user ($n = 108307$)		Nonuser ($n = 99629$)			
Preterm birth types	No. of cases	Incidence (%)[a]	No. of cases	Incidence (%)[a]	Crude RR (95%CI)	Adjusted RR (95%CI)[b]
Preterm birth overall	5717	5.28	6082	6.10	0.86 (0.83–0.89)	0.86 (0.82–0.90)
Iatrogenic	1122	1.08	1154	1.22	0.89 (0.82–0.96)	0.97 (0.88–1.07)
PPROM	567	0.55	460	0.49	1.12 (0.99–1.27)	1.07 (0.93–1.23)
Spontaneous	4028	3.78	4468	4.56	0.82 (0.79–0.86)	0.81 (0.78–0.86)
32–36w	3614	3.40	3956	4.06	0.83 (0.80–0.87)	0.82 (0.78–0.86)
28–31w	316	0.31	379	0.40	0.76 (0.66–0.88)	0.75 (0.63–0.89)
20–27w	98	0.10	133	0.14	0.67 (0.52–0.87)	0.65 (0.48–0.89)

RR, risk ratio; CI, confidence interval; PPROM, preterm premature rupture of membranes; w, weeks.
[a]The incidence calculation for each subtype of preterm birth did not include other subtypes of preterm birth in the denominator.
[b]Adjusted for maternal age (continuous), BMI (continuous), education, occupation, ethnicity and parity.

Table 3. The timing and compliance of folic acid supplementation and risk of spontaneous preterm birth

		Spontaneous preterm birth			
Folic acid supplementation	No. of pregnant women[a]	No.	Incidence (%)	Crude RR (95%CI)	Adjusted RR (95%CI)[b]
None[c]	98015	4468	4.56	1	1
Timing[d]					
Periconception	56239	1858	3.30	0.72 (0.68–0.76)	0.70 (0.65–0.74)
Preconception	16303	484	2.97	0.64 (0.58–0.71)	0.65 (0.58–0.72)
Postconception	33945	1679	4.95	1.09 (1.03–1.15)	1.06 (1.00–1.13)
Compliance[e]					
<80% compliance	17175	585	3.41	0.74 (0.68–0.81)	0.75 (0.68–0.82)
>=80% compliance	55367	1757	3.17	0.69 (0.65–0.73)	0.68 (0.64–0.72)

RR, risk ratio; CI, confidence interval.
[a]The subjects did not include other subtypes of preterm birth.
[b]Adjusted for maternal age (continuous), BMI (continuous), education, occupation, ethnicity and parity.
[c]Reference group.
[d]The analysis excluded 137 women for whom the timing of folic acid use could not be classified.
[e]The analysis only included the women with periconception and preconception use of folic acid.

Table 4. Stratified analysis of the effects of folic acid use on preterm birth by maternal education and parity

	Spontaneous preterm birth incidence (%)[a]			
Maternal characteristics	Folic acid user	Non-user	Adjusted RR (95%CI)[b]	*P* for interaction
Education				
High school or higher	3.23	3.26	0.98 (0.83–1.15)	0.07
Junior high school	3.76	4.45	0.80 (0.75–0.85)	
Primary school or lower, or unknown	4.06	5.08	0.78 (0.72–0.86)	
Parity				
Primiparous	3.72	4.64	0.79 (0.75–0.84)	0.02
Multiparous	4.43	4.33	0.94 (0.82–1.08)	

RR, risk ratio; CI, confidence interval.
[a]The calculation for spontaneous preterm birth incidence did not include other subtypes preterm birth in the denominator.
[b]Adjusted for maternal age (continuous), BMI (continuous), occupation, ethnicity and education or parity.

Discussion

In this large population-based cohort study that included 207 936 pregnant women in China, periconceptional supplementation of 400 μg folic acid alone had a 14% protective association with overall preterm birth. The association was strongest for spontaneous preterm birth (19%), and was not significant for iatrogenic preterm birth or PPROM. The protective association for spontaneous

preterm birth tended to be greatest for early preterm birth and among women with greater compliance with folic acid supplementation. In addition, these effects were found only in women who initiated folic acid supplementation before pregnancy, were primiparous and had lower education levels.

Several studies[6–10] have related periconceptional multivitamin use to a decreased risk of preterm birth, but often with conflicting results or imprecise predictions.[11–13] Our results support the majority of previous studies, which have reported a relationship between periconceptional folic acid as part of a multivitamin supplementation and a reduced risk of preterm birth.[6–10] Many researchers have speculated that folic acid was the multivitamin component most responsible for the observed protective effects; however, studies evaluating the effects of supplementation with folic acid alone on preterm birth risk are sparse. Using a large amount of longitudinal data, Shaw *et al.*[16] found that the occurrence of singleton preterm deliveries in California decreased after compulsory nutritional fortification with folic acid was instituted there in 1998. To our knowledge, this is the first prospective cohort study to specifically examine the effects of folic acid alone on preterm birth with sufficient power.

Among previous studies, two large cohort studies set in Denmark ($n = 35\,897$) and the USA ($n = 34\,480$) examined folic acid effects on different clinical phenotypes of preterm birth. Both studies found a protective effect of multivitamins on spontaneous preterm birth, but not on iatrogenic preterm birth or PPROM.[6,7] Our study yielded a similar finding, which is further supported by the results of several observational studies that measured biomarkers for folate nutrition during pregnancy. These studies found that decreased blood folate levels and elevated homocysteine levels during preconception or early pregnancy were associated with an increased risk of premature delivery.[17–19] However, two other studies indicated that serum levels of homocysteine or folic acid measured in subjects with PPROM, specifically, did not differ from those in matched control subjects.[20,21] Considering these results, we believe that the subtypes of preterm birth have distinct pathogeneses, and that folate metabolism is potentially more critical in spontaneous preterm birth than in the other types.

Few previous studies have evaluated the protective effect of multivitamins on early vs late preterm births. Catov *et al.*[6] found that the protective effect of periconceptional multivitamin use was relevant only for preterm births occurring before 34 weeks of gestation. Based on a large US cohort study, Bukowski *et al.*[7] showed that preconceptional multivitamin use was associated with a >70% risk reduction for spontaneous preterm birth occurring before 28 weeks, a 50% reduction for births occurring between 28 and 32 weeks and no significant effect for births occurring after 32 weeks of gestation. Our results are generally consistent with this finding that protective effects may be stronger for earlier spontaneous preterm birth. In our study, the risk reductions were 34%, 25% and 18% for spontaneous preterm births occurring at 20–27 weeks, 28–31 weeks, and ≥32 weeks of gestation, respectively.

Some studies have suggested whether the association between multivitamin intake and preterm birth incidence varies according to the timing and frequency of periconceptional multivitamin usage. Vahratian *et al.*[9] found that women who took multivitamin supplements prior to, rather than after, conception had a reduced risk of preterm birth. Bukowski *et al.*[7] showed a correlation between preconceptional multivitamin supplementation and a reduction in spontaneous preterm births. Catov *et al.*[6] demonstrated that preconceptional and postconceptional multivitamin usage in women with pre-pregnancy BMIs <25 may reduce the risk of preterm birth. In our study, the initiation of folic acid usage before conception was associated with a 30% risk reduction in spontaneous preterm birth, whereas no such effect was associated with postconceptional initiation of folic acid supplementation. Thus, our results support the hypothesis of Bukowski *et al.*[7] that pregnancy duration may be ultimately affected by conditions in the earliest stage of pregnancy. Folic acid intake before conception assures that women have adequate levels at the beginning of pregnancy. In addition, we found that the protective associations of folic acid with spontaneous preterm birth were higher among women with greater usage compliance. This result is consistent with Catov *et al.*'s[6] hypothesis that the relationship between multivitamin usage and preterm birth is strongest for women with regular usage throughout the periconceptional period, which provides the most comprehensive supplementation.

Few studies have examined the interactions between multivitamin usage and maternal characteristics, and the predictions generated by such studies have generally been imprecise due to the small sizes of strata, which produced inconsistent results. Bukowski *et al.*[7] found no significant interaction between multivitamin use and maternal characteristics in predicting the risk of spontaneous preterm birth. Catov *et al.*[6] found that overweight status modified the relationship between periconceptional multivitamin use and preterm birth risk. Our results showed interactions between folic acid supplementation and maternal education ($P_{\text{interaction}} = 0.07$) and parity ($P_{\text{interaction}} = 0.02$); the protective associations were stronger in less-educated women and primiparous women. We found no interaction effect between folic acid use and weight due to the very

small sample of overweight subjects, as only 1.9% of participants had BMIs ≥26.

The exact mechanisms linking folic acid use to spontaneous preterm birth are not fully understood, but existing evidence suggests several possibilities, including those involved in intrauterine infection, placentation and inflammation. Poor folate nutrition in pregnant women has been associated with intrauterine infection, which is among the most important risk factors for spontaneous preterm birth, especially during early gestation.[7] Folate metabolism has been linked to defects in the placental vascular bed. Abnormal placentation with failed remodelling of maternal vessels perfusing the placenta has been associated with spontaneous preterm birth.[6] Furthermore, elevated serum levels of C-reactive protein, the most extensively studied inflammatory risk marker, in pregnant women have been linked to subsequent preterm delivery. Folate may help control the inflammation process.[22]

Our study has several strengths. The study was a population-based design with prospectively recorded exposure and outcome data, thus minimizing the potential for selection and recall bias. Nearly all women in the study population were of Han ethnicity. Therefore, the homogeneity of genetic background helped to reduce the residual confounding. Due to the very large sample size, we had sufficient power to detect and exclude important effects even for subgroup analysis. The detailed records of pregnancy complications as well as clinical characteristics enabled us to examine associations within more homogeneous subtypes of preterm birth. Quantities of folic acid taken by women in each month was real-time recorded though in-person checking of the bottles by the healthcare workers, which may eliminate the possibility of differential misclassification of folic acid use. Women's self-taking of vitamin supplements is rare because prenatal vitamin use has never been a part of routine antenatal care in China, and women had little access to any vitamin supplements in the project areas at the time.[4] The fact that women consumed a pill containing only 400 μg of folic acid allows us to examine the effect of folic acid unconfounded by other nutrients contained in multivitamin supplements.

Our findings should be interpreted cautiously due to several main limitations. The study participants were predominantly of Han ethnicity, and relatively poorly nourished during 1990s in China, so generalizability of our results to other populations with quite different demographic characteristics may not be appropriate. Folic acid use was not randomized in this study, and certain systematic aspects that could influence the risk of preterm birth may have differed between users and non-users. Although we adjusted for a variety of demographic and pregnancy factors, we cannot rule out the possibility that our findings are confounded by unmeasured factors. We did not collect information on maternal smoking and alcohol use during pregnancy. However, smoking and alcohol use were both uncommon among women in China at the time of our study, especially among reproductive-age women. Results of the 1996 national smoking prevalence survey in China indicated that smoking prevalence among women aged 20–29 years was less than 2%. [23] We also did not obtain data on diet, and thus cannot rule out the possibility that difference in some dietary factors between folic use and non-use women could explain our findings. Finally, our estimation of gestational age was based on menstrual dates, the recollection of which may have been less accurate among folic acid non-users than among users. Any inaccuracy in menstrual dates among users and non-users could have led to misclassification of the preterm outcome, resulting in an underestimation of the effect. This hypothesis was further confirmed by our sensitivity analysis. In our study, all women who registered before becoming pregnant were advised to take a pregnancy test 1–2 weeks following a missed menstrual period or if they believed they were pregnant. Health workers used a urine pregnancy test that determined the presence of human chorionic gonadotropin (hCG), using colloidal gold-labelled anti-hCG coated on a nitrocellulose strip. Each month during the campaign, local health workers recorded the dates of every menstrual period;[15] thus, the dates of the last menstrual periods for these women should be accurate. We re-examined the association between folic acid use and preterm birth among women who registered for the study before their last menstrual period, and found even larger protective associations for spontaneous preterm births. Thus, we do not believe that potential inaccuracy in menstrual date recording biased the observed effects of folic acid on spontaneous preterm birth in the current study.

In conclusion, this study provides unique insight into the effects of periconceptional supplementation with folic acid on the various clinical types of preterm birth. Preterm birth affects populations worldwide, with an estimated 15 million preterm babies delivered each year.[2] Although a proportion of preterm births result from maternal or fetal complications, most are spontaneous. Our finding that the daily consumption of 400 μg folic acid alone during the periconceptional period may prevent spontaneous preterm birth in a Chinese population, together with similar evidence for folic acid as part of a multivitamin supplementation, provide strong clinical support for folic acid usage in the prevention of preterm birth.

Supplementary Data

Supplementary data are available at *IJE* online.

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