Folic Acid Supplementation During Early Pregnancy and the Risk of Gestational Hypertension and Preeclampsia

Zhiwen Li, Rongwei Ye, Le Zhang, Hongtian Li, Jianmeng Liu, Aiguo Ren

Abstract—Emerging evidence has suggested that folic acid–containing multivitamins may markedly reduce the risk of gestational hypertension or preeclampsia. We examined whether maternal supplementation with folic acid alone during early pregnancy can prevent the occurrence of gestational hypertension and preeclampsia. The data are from a large population-based cohort study established to evaluate the effectiveness of the campaign to prevent neural tube defects with folic acid supplementation in China. We selected participants who were registered in 2 southern provinces, had exact information on folic acid use, and were not affected by chronic hypertension or diabetes mellitus before 20 weeks gestation. A logistic regression model was used to adjust for the effects of the main potential confounders, including age, body mass index, education, occupation, parity, and multiple births. The study size had 99.9% power (α=0.05) to detect a decrease of 10% over the unexposed rate of 9.4% for gestational hypertension. Among the 193 554 women (47.9% took folic acid, 52.1% did not), the overall incidence of gestational hypertension and preeclampsia was 9.5% and 2.5%, respectively. The incidence of gestational hypertension and preeclampsia was 9.7% and 2.5% for women who took folic acid, and 9.4% and 2.4% for women who did not use it. The adjusted risk ratio associated with folic acid use was 1.08 (95% confidence interval, 1.04–1.11) for gestational hypertension and 1.11 (95% confidence interval, 1.04–1.18) for preeclampsia. Our findings suggest that daily consumption of 400 µg folic acid alone during early pregnancy cannot prevent the occurrence of gestational hypertension and preeclampsia.

Key Words: folic acid supplementation ■ gestational hypertension ■ preeclampsia

Gestational hypertension and preeclampsia are the most common hypertensive disorders of pregnancy. Preeclampsia is among the leading causes of maternal and fetal mortality. Hypertension in pregnancy is also associated with an increased risk for subsequent cardiovascular disease or diabetes mellitus later in life. Although extensive study efforts have been made in past decades, the causes of gestational hypertension remain unclear. Many studies have observed a significant elevation of plasma or serum homocysteine among women with gestational hypertension or preeclampsia during pregnancy or postpartum, suggesting that homocysteine may be an independent risk factor for these disorders. Hyperhomocysteinemia usually can be corrected by supplementation with folic acid. Thus, a major concern has been raised about whether folic acid supplementation can prevent the occurrence of gestational hypertension or preeclampsia. Three studies from the United States and Canada demonstrated that folic acid–containing multivitamins may greatly reduce the risk of gestational hypertension or preeclampsia. However, Ray et al indicated that mandatory folic acid fortification in 1998 did not result in a significant decline in the rate of gestational hypertension and preeclampsia in Canada. Were folic acid supplementation to decrease the risk of gestational hypertension or preeclampsia, it would have important clinical significance in prevention of these disorders. We used the data from a large population-based cohort study to examine whether a woman’s use of folic acid supplements during early pregnancy is associated with a decreased risk of subsequent gestational hypertension and preeclampsia. The original cohort study was established to evaluate the effectiveness of the campaign to prevent neural tube defects (NTDs) with folic acid supplementation (400 µg alone) during the 1990s in China.

Methods

Background and Original Cohort

Beginning in 1993, the Chinese Ministry conducted a public health campaign to prevent NTDs among all women in 21 counties in 2 southern provinces (Zhejiang and Jiangsu) and 1 northern province (Hebei). During this campaign, all women 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. Each month,
local health workers visited each woman to collect information
about the woman’s pill-taking, and filled out a pill-taking form.
To evaluate the effect of folic acid on NTDs, we identified women
who registered with the monitoring system between October 1993
and September 1995, who delivered by December 31, 1996, and
whose fetuses or infants could be confirmed as either having or not
having a NTD, whether liveborn, 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. We have previously reported that the median pill-
taking compliance (the total number of pills taken divided by the
total number of days between starting and stopping pill-taking) was
≥80%, and periconceptional intake of 400 µg folic acid significantly
reduced the risk for NTDs by 79% in the northern population and
by 41% in the southern population.23 The project was approved by
the institutional review boards of the US Centers for Disease Control
and Prevention and Peking University Health Science Center. In the
beginning of 1990s, most rural women in study areas are illiterate,
therefore all women who took pills provided oral informed consent.

Subjects for Current Study
We selected the participants who were registered in 2 southern prov-
inces (Jiangsu Province and Zhejiang Province). These 2 neighboring
provinces had detailed records about hypertensive disorders of preg-
nancy in their pregnancy monitoring system. We excluded women
who stopped taking folic acid before the index pregnancy or whose
dates of pill-taking could not be exactly confirmed. We also excluded
those who were affected by chronic hypertension or diabetes mellitus
before 20 weeks gestation, and those whose gestational hypertension
diagnosis was unknown.

Diagnosis of Gestational Hypertension and
Preeclampsia
Appropriate cuff bladder size was determined at each visit based on
arm circumference. Blood pressure was measured in the right arm
with a mercury sphygmomanometer and was observed on 2 or more
consecutive occasions with an interval of ≥6 hours. Gestational
hypertension was defined as an absolute blood pressure ≥140/90
mm Hg after 20 weeks of gestation, or as a blood pressure increment
of ≥30/15 mm Hg after 20 weeks of gestation as compared with the
first trimester.24 Preeclampsia (including eclampsia) was defined as a
blood pressure of ≥140/90 mm Hg or a blood pressure increment of
30/15 mm Hg after 20 weeks of gestation, with concurrent proteinuria
(a single random urine specimen containing at least 1+ protein by
dipstick test) after 20 weeks of gestation.

Statistical Analysis
We compared mean age and body mass index, and distributions of
parity, ethnic origin, education, occupation, and multiple births
between the groups of women who had or had not taken folic acid.
We calculated the incidences of gestational hypertension and pre-
eeclampsia, according to use of folic acid, differences in compliance
with folic acid use, and other characteristics. We estimated risk ratios
by dividing the incidence of gestational hypertension and preeclampsia
among women who had taken folic acid by the incidence among
women who had not. A logistic regression model was used to adjust
for the main potential confounders, including age (continuous), body
mass index (continuous), education, occupation, parity, and multiple
births. Considering the different heritability, clinical manifestations,
and prognosis of early- and late-onset gestational hypertension and
preeclampsia,15,25 we classified gestational hypertension into 2 types:
early onset (onset at <28th week of gestation) and late onset (onset at
≥28th week of gestation), and then compared the distribution of the
2 types of outcome according to the use of folic acid. All data were
analyzed using SPSS 11.5 (SPSS, Inc, Chicago, IL).

Results
Among the 215,871 women who enrolled in the selected coun-
ties of the 2 provinces, we excluded 17,107 (7.9%) women
who stopped pill-taking before the index pregnancy, and 159 (0.07%)
women for whom the dates of pill-taking could not be exactly confirmed.
We further excluded 3856 (1.9%) women who were affected by hypertension or diabetes mel-
litus before 20 weeks gestation, and 1195 (0.6%) women
whose diagnosis of hypertensive disorders of pregnancy was unknown.
The final analysis included 193,554 women, of whom 92,731 (47.9%)
had taken folic acid during early pregnancy
and 100,823 (52.1%) had not (Figure). Table 1 shows the selected characteristics of the participants according to use
of folic acid. More than 99% of the women were of Han eth-
nicity. Women who took folic acid were on average 1.3 years
younger and 0.5 kg/m² less in body mass index than those who
did not take it. Women who took folic acid supplements were
more likely to be primiparous, to be factory workers, and to
have higher levels of education.

Of these 193,554 women, 18,474 women were diagnosed
with gestational hypertension and 4756 with preeclampsia.
The incidence rate of gestational hypertension and pre-
eeclampsia was 9.5% and 2.5%, respectively. The incidence rate of gestational hypertension and preeclampsia was
9.7% and 2.5% for women who took folic acid, and 9.4% and
2.4% for women who did not take it. Compared with women
with no folic acid use, the risk ratios of gestational hypertension and preeclampsia for those with folic acid
use during the first trimester were 1.03 (95% confidence
interval, 1.00–1.06) and 1.06 (95% confidence interval,
1.00–1.12). Older age, greater body mass index, nonfarmer occupation, lower education, multiple births, and being primi-
parous were associated with elevated risk of gestational hypertension or preeclampsia (Table 2). After adjustment
for the effects of these major confounding factors, the risk ratios for gestational hypertension and preeclampsia with

![Flowchart of participants.](http://hyper.ahajournals.org/ Downloaded from)
regard to folic acid use were 1.08 (95% confidence interval, 1.04–1.11) and 1.11 (95% confidence interval, 1.04–1.18), respectively. We did not find decreased risk ratios with increasing compliance with folic acid use; on the contrary, we found an increasing trend of risk with increasing compliance with folic acid use (Table 3). We compared the distribution of the early- and late-onset cases according to the use of folic acid and found that the percentages of early-onset cases of gestational hypertension and preeclampsia were similar between women who did and did not take folic acid (4.5% versus 4.4%, \( P = 0.81 \) for gestational hypertension; and 2.2% versus 2.3%, \( P = 0.89 \) for preeclampsia). Exclusion of major external birth defects from the analysis did not change our results.

### Discussion

In this large population-based cohort study that included 193,554 pregnant women, we did not find a decrease in the risks of gestational hypertension or preeclampsia among women who took folic acid supplements in the first trimester of pregnancy, as compared with those who did not. We also did not find a significant difference in the distribution of early- or late-onset cases of gestational hypertension and preeclampsia among women with and without folic acid use. Our study size had 99.9% power (\( \alpha = 0.05 \)) to detect a decrease of 10% over the unexposed rate of 9.4% for gestational hypertension, and 94.2% power to detect a decrease of 10% over the unexposed rate of 2.4% for preeclampsia.

Three previous cohort studies from the United States and Canada reported an association between supplementation of multivitamins containing folic acid and reduced risk of hypertensive disorders of pregnancy (Table 4).19–21 All these investigators consider that folic acid may be an important component of the effect, although they realized that other vitamins or minerals may also play some role in the preventive effect. However, based on a large longitudinal study in Canada, Rey et al22 failed to observe any significant decline in the risk of preeclampsia and all hypertensive disorders of pregnancy, after the introduction of the mandatory Canadian folic acid food fortification program in January 1998 (Table 4). The discrepancy of these study results may be a result of various factors, including the timing of the intervention, the dose of folic acid, the other components in the supplements, and the population.

Our findings are supported by many other observational studies reporting that maternal plasma or serum folate concentrations were not significantly decreased among women with gestational hypertension or preeclampsia.2–9,14,26,27 In addition, 2 prospective cohort studies did not observe a lower risk of hypertensive disorders of pregnancy with a greater intake of folate during the first trimester or between 13 and 21 weeks gestation.28,29

The interest in folic acid for the prevention of cardiovascular disease stems from its critical role in lowering plasma homocysteine, which was found to be associated with a higher risk of cardiovascular disease in epidemiological studies.30 Many studies in past decades showed that women with gestational hypertension or preeclampsia had a significant elevation of homocysteine postpartum, in the third trimester, in the second trimester, or even in early pregnancy.5–10 Taking into consideration this emerging evidence, in combination with other data implicating hyperhomocysteinemia as an independent risk factor for vascular disease, some researchers hypothesized that hyperhomocysteinemia might be an independent risk factor for gestational hypertension.8,12 However, recent trials have failed to demonstrate a benefit of lowering homocysteine for cardiovascular disease.31,32 Steegers-Theunissen et al33 believed that, in most cases, hyperhomocysteinemia may be a consequence rather than a cause of hypertensive disorders of pregnancy. Folic acid supplementation can effectively reduce homocysteine.15–18 Thus,

### Table 1. Characteristics of Women Who Enrolled in the Pregnancy Monitoring System According to Their Folic Acid Use, China, 1993 to 1996

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Any Use (n=92731)*</th>
<th>No Use (n=100823)*</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at pregnancy, y (mean [SD])</td>
<td>24.21 (2.47)</td>
<td>25.54 (3.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m² (mean [SD])</td>
<td>20.37 (2.29)</td>
<td>20.89 (2.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primiparous</td>
<td>85098</td>
<td>72996</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple births</td>
<td>554</td>
<td>679</td>
<td>0.030</td>
</tr>
<tr>
<td>Han ethnic group</td>
<td>92116</td>
<td>99841</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or higher</td>
<td>10435</td>
<td>10183</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Junior high school</td>
<td>58622</td>
<td>55407</td>
<td>55.0</td>
</tr>
<tr>
<td>Primary school or lower</td>
<td>23417</td>
<td>34785</td>
<td>34.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>257</td>
<td>448</td>
<td>0.4</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmer</td>
<td>49532</td>
<td>66457</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Factory worker</td>
<td>29930</td>
<td>21715</td>
<td>21.5</td>
</tr>
<tr>
<td>Other</td>
<td>13136</td>
<td>12344</td>
<td>12.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>133</td>
<td>307</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Values for some characteristics may not be equal to the total numbers of 2 groups because of missing values.

Table 1. Characteristics of Women Who Enrolled in the Pregnancy Monitoring System According to Their Folic Acid Use, China, 1993 to 1996

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Hypertension

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theoretically, if elevated homocysteine is a cause of gestational hypertension or preeclampsia, folic acid supplementation during early pregnancy may significantly reduce the risk of these outcomes or may change the distribution of the early-onset cases. However, our large cohort study results did not find a protective effect of folic acid supplementation on gestational hypertension or preeclampsia, and, thus, supports the hypothesis that elevated blood homocysteine during pregnancy may be a consequence or a concomitance rather than a cause of gestational hypertension.14

The overall incidences of gestational hypertension and preeclampsia are consistent with those from other investigations in the Chinese general population. The gestational hypertension incidence (9.5%) in our population is similar to that reported in a Chinese national survey on gestational hypertension in 1988 (9.4%).23 The incidence of preeclampsia (2.5%) is similar to the preeclampsia incidence of 2.03% in a Taiwanese study covering 206,551 deliveries from 1993 to 1997.33 The incidences of gestational hypertension and preeclampsia in our study are also similar to those reported from a retrospective cohort study in the United States by Hernández-Díaz (9.7% for gestational hypertension, 2.2% for preeclampsia).39

The significant association between folic acid supplementation and increased risk of gestational hypertension and preeclampsia in our study was unexpected. This small difference may have little clinical significance, and the statistical significance of this association is probably a result of the large numbers of women in our study. This result

Table 2. Incidence and Crude RR of Gestational Hypertension and Preeclampsia According to Use of Folic Acid Supplement in First Trimester and Other Women’s Characteristics, China, 1993 to 1996

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Gestational Hypertension</th>
<th>Preeclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Incidence (%)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>986</td>
<td>6.5</td>
</tr>
<tr>
<td>20–25</td>
<td>111391</td>
<td>9.3</td>
</tr>
<tr>
<td>25–30</td>
<td>56515</td>
<td>9.6</td>
</tr>
<tr>
<td>≥30</td>
<td>24662</td>
<td>10.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>28366</td>
<td>8.4</td>
</tr>
<tr>
<td>18.5–23.9</td>
<td>122859</td>
<td>9.3</td>
</tr>
<tr>
<td>24–27.9</td>
<td>11186</td>
<td>12.4</td>
</tr>
<tr>
<td>≥28</td>
<td>1019</td>
<td>19.0</td>
</tr>
<tr>
<td>Education</td>
<td></td>
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<tr>
<td>High school or higher</td>
<td>20618</td>
<td>9.2</td>
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<tr>
<td>Junior high school</td>
<td>114029</td>
<td>9.5</td>
</tr>
<tr>
<td>Primary school or lower</td>
<td>58202</td>
<td>9.7</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmer</td>
<td>115989</td>
<td>9.3</td>
</tr>
<tr>
<td>Factory worker</td>
<td>51645</td>
<td>9.9</td>
</tr>
<tr>
<td>Other</td>
<td>25480</td>
<td>10.2</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiparous</td>
<td>35460</td>
<td>8.4</td>
</tr>
<tr>
<td>Primiparous</td>
<td>158094</td>
<td>9.8</td>
</tr>
<tr>
<td>No. of fetuses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>189715</td>
<td>9.4</td>
</tr>
<tr>
<td>Multiple</td>
<td>1233</td>
<td>38.0</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Han</td>
<td>191957</td>
<td>9.5</td>
</tr>
<tr>
<td>Other</td>
<td>1597</td>
<td>9.9</td>
</tr>
<tr>
<td>Folic acid use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>100823</td>
<td>9.4</td>
</tr>
<tr>
<td>Use</td>
<td>92731</td>
<td>9.7</td>
</tr>
<tr>
<td>&lt;70% compliance</td>
<td>16222</td>
<td>9.6</td>
</tr>
<tr>
<td>70% to &lt;90% compliance</td>
<td>43590</td>
<td>9.6</td>
</tr>
<tr>
<td>≥90% compliance</td>
<td>32919</td>
<td>9.8</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and RR, risk ratios.
might also be a result of a limitation of our study. Folic acid use was not randomized, and the women who took folic acid may have differed systematically from those who did not in some factors that could influence the frequency of gestational hypertension. Although we have adjusted for some known important confounders, some undetected confounding may still exist. We did not collect information on maternal smoking. However, smoking is uncommon among women in China. Results of the 1996 national smoking prevalence survey in China indicated that the smoking prevalence among women aged 20 to 29 years was <2%.34 Another limitation is the population selection. In the original study cohort, 2 southern provinces and 1 northern province were included because of the differences in levels of dietary folate between the 2 regions. Northern women of childbearing age had significantly lower blood folate levels than those in the south.35 Our previous study showed that the preventive effect of folic acid on NTDs was larger in the northern province than in the southern provinces.23 The preventive effect in current cohort (48%) was similar to that reported in original cohort for the southern population (41%). The variation of dietary folate nutrition may be equally important as to whether folic acid supplementation has any impact on preeclampsia. However, the current analysis included only 2 southern provinces because clinical information about hypertensive disorders of pregnancy is not completely recorded in the northern province. Thus, we could not observe the effect in the northern Chinese population, who are relatively deficient in folic acid and may gain benefit.

Our study has several strengths. The study was population-based, with nearly complete ascertainment of gestational hypertension and preeclampsia among large numbers of women whose pregnancies lasted at least 20 weeks. Folic acid use was prospectively recorded in each month before the outcome was known, thus minimizing the potential for recall bias. Nearly all women (>99.0%) in the study population were of Han ethnicity; therefore, their genetic background is

### Table 3. The Association of Folic Acid Use With Gestational Hypertension and Preeclampsia in Multivariate Logistic Regression, China, 1993 to 1996

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Gestational Hypertension</th>
<th>Preeclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted RR 95% CI</td>
<td>Adjusted RR 95% CI</td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>1.04 (1.03, 1.05)</td>
<td>1.06 (1.04, 1.07)</td>
</tr>
<tr>
<td>Body mass index (continuous)</td>
<td>1.05 (1.05, 1.06)</td>
<td>1.07 (1.06, 1.08)</td>
</tr>
<tr>
<td>Factory worker</td>
<td>1.10 (1.05, 1.14)</td>
<td>1.04 (0.97, 1.13)</td>
</tr>
<tr>
<td>Other occupation</td>
<td>1.14 (1.08, 1.20)</td>
<td>1.12 (1.01, 1.24)</td>
</tr>
<tr>
<td>Junior high school</td>
<td>1.11 (1.05, 1.18)</td>
<td>1.18 (1.05, 1.33)</td>
</tr>
<tr>
<td>Primary school or lower</td>
<td>1.11 (1.04, 1.19)</td>
<td>1.30 (1.15, 1.48)</td>
</tr>
<tr>
<td>Multiple births</td>
<td>6.19 (5.44, 7.03)</td>
<td>10.00 (8.52, 11.73)</td>
</tr>
<tr>
<td>Primiparous</td>
<td>1.47 (1.39, 1.57)</td>
<td>1.79 (1.59, 2.01)</td>
</tr>
<tr>
<td>Folic acid use</td>
<td>1.08 (1.04, 1.11)</td>
<td>1.11 (1.04, 1.18)</td>
</tr>
<tr>
<td>&lt;70% compliance</td>
<td>1.07 (1.01, 1.14)</td>
<td>1.04 (0.93, 1.17)</td>
</tr>
<tr>
<td>70% to &lt;90%</td>
<td>1.07 (1.02, 1.11)</td>
<td>1.06 (0.98, 1.15)</td>
</tr>
<tr>
<td>≥90% compliance</td>
<td>1.09 (1.04, 1.14)</td>
<td>1.21 (1.11, 1.31)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and RR, risk ratios.

### Table 4. Summary of Previous Studies of Folic Acid Use and Hypertensive Disorders of Pregnancy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Site, Year</th>
<th>Sample Size</th>
<th>Folic Acid Use</th>
<th>Disorder Studied</th>
<th>Adjusted RR/OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hernández-Díaz et al19</td>
<td>Retrospective cohort study</td>
<td>United States, 1993–2000</td>
<td>2100</td>
<td>Multivitamins containing at least 0.4 mg of folic acid from 2 mo before conception through the entire pregnancy</td>
<td>Gestational hypertension</td>
<td>0.55 (0.39–0.79)</td>
</tr>
<tr>
<td>Bodnar et al20</td>
<td>Prospective cohort study</td>
<td>United States, 1997–2001</td>
<td>1835</td>
<td>Multivitamins containing folic acid (dose not shown) from before conception to &lt;16 wk gestation</td>
<td>Preeclampsia</td>
<td>0.55 (0.32–0.95)</td>
</tr>
<tr>
<td>Wen et al21</td>
<td>Prospective cohort study</td>
<td>Canada, 2002–2005</td>
<td>2951</td>
<td>Multivitamins containing 1.0 mg or higher folic acid during 12–20 wk gestation</td>
<td>Preeclampsia</td>
<td>0.37 (0.18–0.75)</td>
</tr>
<tr>
<td>Ray et al22</td>
<td>Retrospective population-based longitudinal study</td>
<td>Canada, 1990–2000</td>
<td>1001441</td>
<td>Food fortification between 0.1 to 0.2 mg of additional folic acid per day</td>
<td>Hypertensive disorders of pregnancy</td>
<td>1.09 (1.07–1.11)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio; and RR, risk ratios.
homogeneous. 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. 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.

**Perspectives**

The results from this large folic acid intervention study among Chinese women suggest that daily consumption of 400 μg folic acid alone during early pregnancy may not prevent the occurrence of gestational hypertension and pre-eclampsia, although the dose was sufficiently high to result in a major reduction of NTDs in this population. However, the findings could not exclude a potential preventive effect of folic acid on gestational hypertension or pre-eclampsia during other pregnancy periods, or an effect of multivitamins containing folic acid.

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**Disclosures**

None.

**References**


**Novelty and Significance**

**What Is New?**
- Although emerging evidence has suggested that folic acid–containing multivitamins may reduce the occurrence of gestational hypertension or preeclampsia, there is a lack of population studies examining the effect of folic acid alone on these hypertensive disorders of pregnancy.
- The large sample size facilitates the examination of this relationship across several subgroups.

**What Is Relevant?**
- The study examines whether supplementation with folic acid during early pregnancy is associated with a decreased risk of gestational hypertension or preeclampsia.
- The study findings may contribute important data for the development and modification of relevant public health policies about the prevention of hypertensive disorders of pregnancy.

**Summary**
Daily consumption of 400 μg folic acid alone during early pregnancy may not prevent the occurrence of gestational hypertension or preeclampsia among the southern Chinese population.
Folic Acid Supplementation During Early Pregnancy and the Risk of Gestational Hypertension and Preeclampsia
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