Original Article

Folic Acid Supplement Use and Increased Risk of Gestational Hypertension

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Abstract—Current results regarding the effect of folic acid (FA) supplement use on gestational hypertension (GH) and preeclampsia are limited and inconsistent. We aimed to investigate whether FA supplement use was associated with GH and preeclampsia. Participants from the Tongji Maternal and Child Health Cohort with information on periconceptional FA supplement use and diagnosis of GH/preeclampsia were included (n=4853). Robust Poisson regression was used to assess the association of FA supplement use and GH and preeclampsia. Among the 4853 participants in this study, 1161 (23.9%) and 161 (3.3%) women were diagnosed with GH and preeclampsia, respectively. The risk ratio of developing GH was higher in women who used ≥800 µg/d FA supplement from prepregnancy through midpregnancy than nonusers (risk ratio, 1.33 [1.08–1.65]). After adjusting for social-demographic, reproductive, lifestyle factors, family history of hypertension, other supplement use, and gestational weight gain, the adverse association remained significant (risk ratio, 1.32 [1.06–1.64]). Restricting the analysis among women with normal weight, without family history of hypertension, and without gestational diabetes mellitus, the positive FA-GH association still existed. We did not find any significant association between FA supplement use and preeclampsia regardless of adjustment. High-dose (≥800 µg/d) FA supplement use from prepregnancy through midpregnancy was associated with increased risk of GH. Attention should be given to avoid the potential risk of GH due to inappropriate FA supplement use in women who are planning or capable of pregnancy. (***Hypertension*. 2020;76:00-00. DOI: 10.1161/HYPERTENSIONAHA.119.14621.)** • **Data Supplement**

Key Words: blood pressure ■ cardiovascular disease ■ folic acid ■ preeclampsia ■ pregnancy

Gestational hypertension (GH) and preeclampsia (PE) are common diseases characterized by hypertensive disorders associated with pregnancy.[1] The global burdens of GH (prevalence ranged from 3.7% to 25.1%) and preeclampsia (prevalence ranged from 2.5% to 12.4%) are heavy.[2,3] GH and preeclampsia are among the leading causes of maternal and neonatal morbidity and mortality, and they are risk factors for type 2 diabetes mellitus, hypertension and cardiovascular diseases (CVD) later in life in both developing and western-industrialized countries.[4] Therefore, understanding the risk factors of GH and preeclampsia is vitally important among pregnant women worldwide.

Folate is a water-soluble vitamin naturally present in dark green leafy vegetables, legumes, and fresh fruits, but lacks stability in food storage and preparation. Folate requirement is dramatically increased during pregnancy to sustain the demand for rapid cell replication, fetal, placental, and maternal tissue growth.[5] Supplements containing folic acid (FA; the synthetic form of folate) are widely recommended for women planning or capable of pregnancy to avoid deficiency. The benefits of FA supplement use among pregnant women on preventing neural tube defects (NTDs),[6] and declining homocysteine (Hcy)[7] have been found by a substantial body of studies. Hyper-Hcy is a valuable risk factor in the occurrence of CVD including GH and preeclampsia.[8]

Recently, there has been an increasing interest in studying the potential effect of FA supplement use on GH and

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preeclampsia. Previous related studies are sparse and have reached inconsistent results. There are a few pieces of literature which recognize the potential adverse effect of FA supplement use on GH and preeclampsia,[2,9,10] whereas the others do not.[11–16] However, these studies have no detailed information on FA doses and duration, failing to find the potential link between dose and the effect. Therefore, for the first time, we aimed to evaluate the association of FA supplement use with GH and preeclampsia with consideration of both doses and duration using data from a prospective cohort in China.

Methods

The authors declare that all supporting data are available within the article and in the Data Supplement.

Data Sources and Cohort

All study participants were from the Tongji Maternal and Child Health Cohort, which is a prospective cohort designed to evaluate the impact of maternal nutritional, environmental, and lifestyle exposures on the health status of the pregnant women and the offspring.[17] The cohort was launched in Wuhan, China, in September 2013. Pregnant women were recruited within 16 weeks of gestation at their first prenatal visits and followed up regularly. Until now, the cohort has tracked the health status of the mother-child pair for up to 2 to 4 years. Information on social-demographic status, reproductive factors, family history of diseases, lifestyle factors, dietary intake and supplement use, illnesses, and medical treatments was collected via questionnaire-based interviews at enrollment. Information on lifestyle, dietary intake, and supplement use was obtained in the follow-up visits during midpregnancy and late pregnancy. This study was approved by the ethics committee of Tongji Medical College of Huazhong University of Science and Technology (No. 201302), and written informed consent was obtained from all participants.

Study Population

We included women with detailed information on FA supplement doses and duration. Exclusion criteria are (1) multiple pregnancy; (2) FA supplement use information incomplete, with unclear doses, unclear duration, or varying doses; (3) with diabetes mellitus/hypertension before pregnancy or within 20 weeks of gestation; (4) missing diagnosis of GH/preeclampsia.

Assessment of FA Supplement Use

FA supplement use information was inquired and assessed at enrollment, and then repeated at each follow-up visit during midpregnancy and late pregnancy. Supplement use details, including brand, daily doses, and time to begin and end supplement use were collected. In this study, FA supplement use was defined as taking either FA specific supplement or FA-containing supplement at least 400 µg/d and lasted for at least 4 weeks. Duration was defined and classified as: long duration (continuous FA supplement use from at least 4 weeks prepregnancy and continued for at least 16 weeks through midpregnancy) and short duration (continuous <4 weeks prepregnancy or <16 weeks during pregnancy).[17]

Enrolled pregnant women with reliable FA supplement use information were categorized into 5 groups based on FA supplement use doses and duration: (1) those who never used any FA supplement or used FA with daily dose <400 µg or duration <4 weeks from prepregnancy to midpregnancy (nonusers), (2) those who took FA ≥400 µg but <800 µg daily with short duration, (3) those who took FA ≥400 µg but <800 µg daily with long duration, (4) those who took FA ≥800 µg daily with short duration, and (5) those who took FA ≥800 µg daily with long duration (FA800-L).[17]

Assessment of Dietary Folate

Dietary intake of energy and nutrients was assessed by a validated food frequency questionnaire.[18] Daily dietary folate intake was calculated as the sum of folate in all food items according to Chinese Food Consumption.[19,20] We calculated dietary folate intake among women with food frequency questionnaire within 20 weeks of gestation in this study.

Screening and Diagnosis of GH and Preeclampsia

Blood pressure (BP) was measured at enrollment and each of the follow-up visits by trained medical workers. As recommended by American College of Obstetricians and Gynecologists,[21] it was defined as chronic hypertension if BP elevated at or before 20 weeks of gestation. We used the last BP that was measured within 4 weeks before delivery.[3,21] According to the 2017 American College of Cardiology/American Heart Association guidelines, BP was classified as normal (BP, <120/80 mm Hg), elevated (BP, 120–129/<80 mm Hg), GH stage 1 (130–139/80–89 mm Hg), and GH stage 2 (≥140/90 mm Hg). GH is diagnosed if the BP ≥130/80 mm Hg after 20 weeks of gestation.[22] Preeclampsia is diagnosed among women with GH plus proteinuria (2+ on dipstick or >300 mg/24 h) after 20 weeks of gestation.[23]

Assessment of Covariates

General characteristics of social-demographic status, reproductive factors, family history of diseases, lifestyle, and anthropometric factors were collected at enrollment. Body weight and height were measured at the time of enrollment and repeated in follow-up visits. Body weight before pregnancy was self-reported at enrollment. Gestational age was first calculated by last menstrual period and then confirmed by ultrasound calculation. If the gestational weeks calculated by last menstrual period were >1 week apart from the one calculated by ultrasound, the one calculated by ultrasound was used. Prepregnancy body mass index (BMI) was calculated by dividing self-reported weight before pregnancy in kilograms by the square of height in meters measured at enrollment. Smoking included active (use tobacco before or during pregnancy) and passive smoking (>3×/wk, >30 minutes per time before or during pregnancy). Drinking was defined as those consuming alcohol >3×/wk. Physical activity was defined as >3× per week and lasting for >30 minutes each time. Gestational weight gain was calculated as (body weight at delivery–body weight before pregnancy).

Statistical Analysis

Numerical variables were expressed as mean±SD. Categorical variables were expressed as n (%). Maternal characteristics were compared according to FA supplement use status using ANOVA for continuous variables and a χ^2 analysis for categorical data. Robust Poisson regression models with generalized estimating equations estimation were used to investigate the risk ratios (RRs) for GH and preeclampsia using nonusers group as reference. In adjusted models, the adjusted covariates included maternal age, education, work status, monthly income, ethnicity, history of abnormal pregnancy, prepregnancy BMI, smoking, drinking, physical activity, other supplement use, gestational diabetes mellitus (GDM), and gestational weight gain. The association between FA supplement use and GH and preeclampsia stratified by prepregnancy BMI was performed using robust Poisson regression. The effect of FA supplement use on GH and preeclampsia among women without GDM was identified by robust Poisson regression. The statistically significant cutoff of 2-sided *P* value was 0.05. All the data were analyzed with SAS, version 9.4 (SAS Institute, Cary, NC) and Empower stats software (R), version 2.14.9 (X&Y Solutions, Inc, Boston, MA).

Results

Among the 8649 women in Tongji Maternal and Child Health Cohort, 166 were excluded because of multiple pregnancies, 1445 were excluded due to diabetes mellitus/hypertension before pregnancy or within 20 weeks of gestation. Among the 7038 women left, we further excluded 586 (6.8%) who had no information on FA or other supplement use, 256 (3.0%) with unclear doses of FA, 16 (0.2%) with unclear duration of FA

supplement use, and 25 (0.3%) with varying doses of FA supplement use. Among the remaining 6155 women, 870 (14.1%) never used FA or the consumed daily dose was <400 µg, or the duration of supplement use was <4 weeks (nonusers); 2308 (37.5%) used low-dose FA supplement with short duration (FA ≥400 µg but <800 µg daily with short duration); 717 (11.6%) used low-dose FA supplement with long duration (FA ≥400 µg but <800 µg daily with long duration); 1814 (29.5%) used high-dose FA supplement with short duration (FA ≥800 µg daily with short duration); and the rest 446 (7.2%) used high-dose FA supplement with long duration (FA800-L). After the exclusion of an additional 1302 women without reliable information on diagnosis of GH and preeclampsia, a total of 4853 women were included in the final analysis (Figure S1 in the Data Supplement).

As shown in Table 1, the sample sizes for nonusers, FA ≥400 µg but <800 µg daily with short duration, FA ≥400 µg but <800 µg daily with long duration, FA ≥800 µg daily with short duration, and FA800-L were 646, 1772, 573, 1504, and 358, respectively. Table 1 depicts the social-demographic, anthropometric, reproductive, and other relevant characteristics of the participants according to FA supplement use status. There was no significant difference in dietary folate intake among groups. The basic characteristics were similar in participants involved for analysis when compared with those excluded for missing information on FA supplement use and diagnosis of GH/preeclampsia (Table S1).

As shown in Figure S2, among the 4853 participants, 3077 (63.4%) had normal BP (<120/80 mm Hg), 615 (12.7%) had elevated BP (120–129/<80 mm Hg), 976 (20.1%) were found at GH stage 1 (with BP 130–139/80–89 mm Hg), and the rest 185(3.8%) were at GH stage 2 (BP ≥140/90 mm Hg). A total of 1161 (23.9%) were diagnosed with GH, and 161 (3.3%) were diagnosed with preeclampsia.

The risk ratio of GH development was higher in the FA800-L group than in the nonusers group (RR 1.33 [1.08–1.65]). After adjusting for potential covariates, the RR remained significant (RR 1.32 [1.06–1.64]). The RRs were 1.04 (0.88–1.24), 1.13 (0.92–1.39), and 1.04 (0.87–1.24) for FA ≥400 µg but <800 µg daily with short duration, FA ≥400 µg but <800 µg daily with long duration, and FA ≥800 µg daily with short duration group, respectively (Table 2). Our results did not indicate a significant association between FA supplement use and preeclampsia, regardless of adjustment.

Restricting the analysis among women with normal weight, the adverse effects of FA800-L on GH were observed in unadjusted model (RR, 1.34 [1.04–1.73]), model 1 (adjusted for age, education, work status, monthly income, ethnicity, history of abnormal pregnancy, RR, 1.34 [1.04–1.73]), and model 2 (adjusted for prepregnancy BMI, smoking, drinking, family history of diabetes mellitus, family history of hypertension, other supplement use, gestational diabetes mellitus, and gestational weight gain, RR, 1.32 [1.01–1.72]; Table 3). We still did not find significant relationship between FA supplement use and preeclampsia.

We restricted the analysis among women without family history of hypertension, in the unadjusted model, model 1, and model 2, the association between FA800-L and higher GH risk was robust. The RR values were 1.37 (1.07–1.76), 1.38 (1.07–1.78), and 1.36 (1.05–1.76), respectively (Table 4).

A sensitivity analysis was performed among women without GDM; the positive association between FA and GH were consistently shown (Table S2).

Discussion

To the best of our knowledge, this is the first population-based study to explore the association between FA supplement use and the risk of GH and preeclampsia among pregnant women taking into consideration the doses and duration of FA supplement use. The study demonstrated that high-dose FA supplement use (≥800 µg/d) from prepregnancy through midpregnancy was associated with higher risk of GH, but not preeclampsia, compared with nonusers. Social-demographic, reproductive, lifestyle factors, other supplement use, and gestational weight gain do not affect the association of FA supplement use and GH and preeclampsia. Restricting the analysis among women with normal weight, without family history of hypertension and without GDM, the association between FA supplement use and higher GH risk remained robust.

In accordance with the present results, 3 prior studies have demonstrated that FA supplement use was associated with higher risk of hypertensive disorders. A prospective cohort in the Netherlands reported that pregnant women with FA supplement use since prepregnancy had elevated systolic BP and diastolic BP in early, middle, and late pregnancy compared with nonusers.[9] A retrospective cohort in Canada observed an increase in the risk of all forms of GH after fortification (unadjusted prevalence ratio, 1.07 [1.05–1.09]).[10] Similar to our findings, it did not find significant variance in the development of preeclampsia before and after the mandatory FA food fortification in 1998 (before, 3.8% versus after 3.7%). Using the data from a prospective cohort in China (N=193 554), Li et al[2] found women with FA supplement use in early pregnancy was linked with increased odds of GH (odds ratio, 1.08 [1.04–1.11]). Our findings further supported Li et al's[2] idea, demonstrating that the increased risk of GH was only observed in women who used high-dose (≥800 µg/d) FA supplement for long duration (since prepregnancy through midpregnancy). We did not identify any obvious adverse effect in the groups who used FA supplement with lower doses or short duration.

In addition to the studies mentioned above, there were also findings which differed from ours. There were reports demonstrating that FA supplement use had no protective effect on GH and preeclampsia in general women,[11–15] whereas some studies did.[16] There was also study demonstrating beneficial effects of multivitamins containing FA but not FA fortification on GH and preeclampsia.[24] The rather contradictory results in the association of FA and hypertensive disorders, according to various studies, may be ascribed to the differences in sample sizes, doses, timing, and duration of FA supplement use, lifestyle, dietary folate, other supplement use, study population, and so on.[25] Taken together, these results need to be interpreted with caution.

In our study, we found the relationship between FA supplement use and GH was still significant among women with normal weight, without family history of hypertension, and without GDM. It had been reported in previous studies that

Table 1. Characteristics of Participants According to FA Supplement use Status (n=4853)

Characteristics	Total (n=4853)	Nonusers (n=646)	FA400-S (n=1772)	FA400-L (n=573)	FA800-S (n=1504)	FA800-L (n=358)
Age at enrollment, y	28.6 ± 3.4	28.1 ± 3.7	28.4 ± 3.5	28.8 ± 2.9	28.8 ± 3.4	29.2 ± 3.1
Prepregnancy BMI, kg/m^2	20.6 ± 2.6	20.7 ± 2.7	20.6 ± 2.6	20.6 ± 2.3	20.7 ± 2.7	20.6 ± 2.5
Prepregnancy BMI, kg/m^2						
<18.5	1008 (20.8)	141 (21.8)	388 (21.9)	111 (19.4)	304 (20.2)	64 (17.9)
18.5–23.9	3334 (68.7)	423 (65.5)	1207 (68.1)	410 (71.6)	1037 (68.9)	257 (71.8)
≥24	511 (105.5)	82 (12.7)	177 (10.0)	52 (9.1)	163 (10.8)	37 (10.3)
Education, y						
<16	740 (15.2)	148 (22.9)	310 (17.5)	70 (12.2)	171 (11.4)	41 (11.5)
≥16	3948 (81.4)	476 (73.7)	1388 (78.3)	489 (85.3)	1288 (85.6)	307 (85.8)
Unclear	165 (3.4)	22 (3.4)	74 (4.2)	14 (2.4)	45 (3.0)	10 (2.8)
Work status						
Employed	4163 (85.8)	533 (82.5)	1497 (84.5)	505 (88.1)	1319 (87.7)	309 (86.3)
Unemployed	487 (10.0)	87 (13.5)	196 (11.1)	42 (7.3)	126 (8.4)	36 (10.1)
Unclear	203 (4.2)	26 (4.0)	79 (4.5)	26 (4.5)	59 (3.9)	13 (3.6)
Monthly income (¥)						
<5000	1951 (40.2)	272 (42.1)	761 (42.9)	235 (41.0)	563 (37.4)	120 (33.5)
≥5000	2786 (57.4)	359 (55.6)	967 (54.6)	320 (55.8)	907 (60.3)	233 (65.1)
Unclear	116 (2.4)	15 (2.3)	44 (2.5)	18 (3.1)	34 (2.3)	5 (1.4)
Ethnicity (Han Chinese)	4726 (97.4)	627 (97.1)	1732 (97.7)	557 (97.2)	1461 (97.1)	349 (97.5)
History of abnormal pregnancy (yes)	1740 (35.9)	230 (35.6)	649 (36.6)	204 (35.6)	522 (34.7)	135 (37.7)
Smoking (yes)	930 (19.2)	145 (22.4)	351 (19.8)	87 (15.2)	291 (19.3)	56 (15.6)
Drinking (yes)	67 (1.4)	13 (2.0)	26 (1.5)	5 (0.9)	21 (1.4)	2 (0.6)
Family history of diabetes mellitus						
Yes	394 (8.1)	41 (6.3)	124 (7.0)	48 (8.4)	133 (8.8)	48 (13.4)
No	4380 (90.3)	594 (92.0)	1613 (91.0)	518 (90.4)	1354 (90.0)	301 (84.1)
Unclear	79 (1.6)	11 (1.7)	35 (2.0)	7 (1.2)	17 (1.1)	9 (2.5)
Family history of hypertension						
Yes	1184 (24.4)	141 (21.8)	436 (24.6)	125 (21.8)	381 (25.3)	101 (28.2)
No	3582 (73.8)	491 (76.0)	1301 (73.4)	440 (76.8)	1103 (73.3)	247 (69.0)
Unclear	87 (1.8)	14 (2.2)	35 (2.0)	8 (1.4)	20 (1.3)	10 (2.8)
Other supplement use (yes)	2759 (56.9)	372 (57.6)	436 (24.6)	127 (22.2)	1476 (98.1)	348 (97.2)
Gestational weight gain (kg)	16.1 ± 4.7	16.0 ± 4.8	16.0 ± 4.6	15.8 ± 4.4	16.2 ± 4.8	16.0 ± 4.6
Dietary folate,* μg/d	392.5 ± 182.9	410.0 ± 225.3	375.5 ± 175.5	425.4 ± 177.1	392.8 ± 170.6	389.8 ± 188.8
GH (yes)	1161 (23.9)	145 (22.4)	408 (23.0)	143 (25.0)	358 (23.8)	107 (29.9)
Preeclampsia (yes)	161 (3.3)	18 (2.8)	57 (3.2)	19 (3.3)	50 (3.3)	17 (4.7)

Nonusers denotes never used any FA supplement or used with daily dose <400 μg or duration <4 wk from prepregnancy to midpregnancy. BMI indicates body mass index; FA, folic acid; FA400-L, FA ≥400 μg but <800 μg daily with long duration; FA400-S, FA ≥400 μg but <800 μg daily with short duration; FA800-L, FA ≥800 μg daily with long duration; FA800-S, FA ≥800 μg daily with short duration; and GH, gestational hypertension.

*The sample sizes for total, nonusers, FA400-S, FA400-L, FA800-S, and FA800-L were 550, 70, 182, 59, 194, and 45, respectively.

prepregnancy BMI may affect the association between FA supplement use and GH,[26] which may be due to the discrepancy in inflammation, oxidative stress, and endothelial dysfunction of the participants.[27] Given FA supplement use was linked with increased GDM risk, we excluded women with GDM. The association between FA supplement use and GH was stable, indicating that the association between FA supplement use and GH was independent of prepregnancy BMI and GDM.

It is interesting that we found a positive association between high-dose FA supplement use and GH, but the precise biological mechanisms remain to be elucidated. There are some possible explanations, as listed below. First, hyper-Hcy

Table 2. RRs and 95% CIs for FA Supplement use Doses, Duration, and GH and Preeclampsia (n=4853)

Categories	GH Case (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Nonusers	145 (22.4)	1.00	1.00
FA400-S	408 (23.0)	1.03 (0.87–1.21)	1.04 (0.88–1.24)
FA400-L	143 (25.0)	1.11 (0.91–1.36)	1.13 (0.92–1.39)
FA800-S	358 (23.8)	1.06 (0.90–1.26)	1.04 (0.87–1.24)
FA800-L	107 (29.9)	1.33 (1.08–1.65)	1.32 (1.06–1.64)
Categories	Preeclampsia Case (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Nonusers	18 (2.8)	1.00	1.00
FA400-S	57 (3.2)	1.15 (0.68–1.95)	1.25 (0.72–2.18)
FA400-L	19 (3.3)	1.19 (0.63–2.25)	1.29 (0.66–2.51)
FA800-S	50 (3.3)	1.19 (0.70–2.03)	1.03 (0.59–1.79)
FA800-L	17 (4.7)	1.70 (0.89–3.27)	1.45 (0.74–2.83)

Adjusted for age, education, work status, monthly income, ethnicity, history of abnormal pregnancy, prepregnancy BMI, smoking, drinking, family history of diabetes mellitus, family history of hypertension, other supplement use, gestational diabetes mellitus, and gestational weight gain. Nonusers denotes never used any FA supplement or used FA with daily dose <400 μg or duration <4 wk from prepregnancy to midpregnancy. BMI indicates body mass index; FA, folic acid; FA400-L, FA ≥400 μg but <800 μg daily with long duration; FA400-S, FA ≥400 μg but <800 μg daily with short duration; FA800-L, FA ≥800 μg daily with long duration; FA800-S, FA ≥800 μg daily with short duration; GH, gestational hypertension; and RR, risk ratio.

Table 3. RRs and 95% CIs for FA Supplement use Doses, Duration and GH and Preeclampsia Among Women With Normal Weight (n=3334)

	Crude RR (95% CI)	Model 1 RR (95% CI)	Model 2 RR (95% CI)
GH			
Nonusers	1.00	1.00	1.00
FA400-S	1.04 (0.85–1.27)	1.05 (0.86–1.29)	1.04 (0.84–1.28)
FA400-L	1.08 (0.84–1.37)	1.09 (0.85–1.39)	1.09 (0.84–1.40)
FA800-S	1.05 (0.85–1.29)	1.05 (0.85–1.29)	1.02 (0.82–1.27)
FA800-L	1.34 (1.04–1.73)	1.34 (1.04–1.73)	1.32 (1.01–1.72)
Preeclampsia			
Nonusers	1.00	1.00	1.00
FA400-S	1.11 (0.59–2.10)	1.10 (0.58–2.10)	1.14 (0.59–2.20)
FA400-L	1.20 (0.56–2.57)	1.19 (0.54–2.59)	1.25 (0.57–2.76)
FA800-S	1.33 (0.70–2.51)	1.28 (0.67–2.45)	1.11 (0.56–2.18)
FA800-L	1.51 (0.68–3.37)	1.48 (0.65–3.35)	1.22 (0.52–2.86)

Model 1 adjusted for age, education, work status, monthly income, ethnicity, and history of abnormal pregnancy. Model 2 adjusted for smoking, drinking, family history of diabetes mellitus, family history of hypertension, other supplement use, gestational diabetes mellitus, and gestational weight gain based on model 1. Nonusers denotes never used any FA supplement or used FA with daily dose <400 μg or duration <4 wk from prepregnancy to midpregnancy. FA indicates folic acid; FA400-L, FA ≥400 μg but <800 μg daily with long duration; FA400-S, FA ≥400 μg but <800 μg daily with short duration; FA800-L, FA ≥800 μg daily with long duration; FA800-S, FA ≥800 μg daily with short duration; GH, gestational hypertension; and RR, risk ratio.

may be a consequence instead of a cause of GH.[28] According to some studies, FA plays an important role in reducing Hcy of which the high level may be a risk factor of CVD.[7,8] However, results from high-quality randomized clinical trials did not find a benefit of lowering Hcy for the development of CVD.[29,30] Second, FA supplement use may be correlated with increased red cell blood mass, which was identified to be correlated with elevated BP and hematocrit levels.[31] Third, interactions between gene and nutrient may also be involved. FA supplement use may affect placental implantation and vascular remodeling by influencing the process of DNA and protein synthesis and antioxidant defenses.[32] Lastly, there exist explanations from the aspects of the imbalance between FA and vitamin B12[33] and the role of unmetabolized FA in the circulation[34] due to high-dose FA supplement use. More researches on these topics need to be undertaken before the association between FA and GH can be clearly understood.

FA supplement use had been globally recommended for women planning or capable of pregnancy to prevent NTDs.[6] Previous studies indicated that FA supplement use of 400 μg/d for 8 weeks or 800 μg/d for 4 weeks was effective to decrease the incidence of NTDs.[35] Higher doses did not have additional protective effect against NTDs, although might be related to higher risk of other adverse outcomes.[17,36] These studies suggested that high-dose FA supplement use for long period may be unnecessary for women and should be avoided. It is unclear whether our results can be generalized to other populations since genetic polymorphism of folate-related enzymes, dietary folate intake, FA fortification policies, and FA supplement use recommendations may vary by race/ethnicity.[6]

Our study has several strengths that worth mentioning. First, the participants came from a large cohort with high follow-up rate and high-quality questionnaires. Detailed information of supplement use, including doses and duration, was collected at enrollment and in the follow-up visits by trained researchers, and the final analysis only included the participants who had reliable information on FA supplement use. Second, a nationwide project named Supplementing Folic Acid to Prevent NTD has been implemented in China for many years instead of the mandatory FA food fortification programs in other countries. Therefore, FA supplement was the only source of synthetic FA in our study population. Lastly, dietary folate intake was also calculated, and no difference was found among participants in different FA groups. Other covariates, such as prepregnancy BMI, gestational weight gain, and other supplement use, were also taken into consideration, allowing for relevant adjustments.

Inevitably, our study has limitations. First, the FA exposure was measured according to self-reported FA supplement use rather than plasma folate measurement. Hence, there exists a risk of misclassification. However, great efforts were made to ensure reliable FA supplement use information was collected timely by trained medical workers with meticulous follow-up. Moreover, self-reported FA from supplements had been found to be correlated with plasma folate and was considered a reliable measurement of folate exposure.[7] Second, under the circumstances of wider maternal nutrition, a single micronutrient such as FA may not be the only answer to the puzzle

Table 4. RRs and 95% CIs for FA Supplement use Doses, Duration, GH and Preeclampsia Among Women Without Family History of Hypertension (n=3582)

	Crude RR (95% CI)	Model 1 RR (95% CI)	Model 2 RR (95% CI)
GH			
Nonusers	1.00	1.00	1.00
FA400-S	1.03 (0.85–1.25)	1.04 (0.86–1.26)	1.06 (0.86–1.29)
FA400-L	1.04 (0.82–1.32)	1.06 (0.83–1.34)	1.07 (0.84–1.37)
FA800-S	1.02 (0.84–1.25)	1.02 (0.84–1.25)	0.99 (0.81–1.22)
FA800-L	1.37 (1.07–1.76)	1.38 (1.07–1.78)	1.36 (1.05–1.76)
Preeclampsia			
Nonusers	1.00	1.00	1.00
FA400-S	1.19 (0.64–2.20)	1.19 (0.64–2.22)	1.26 (0.66–2.42)
FA400-L	0.95 (0.43–2.09)	0.97 (0.43–2.21)	1.02 (0.44–2.33)
FA800-S	1.20 (0.64–2.25)	1.21 (0.64–2.29)	1.11 (0.57–2.15)
FA800-L	1.68 (0.77–3.70)	1.71 (0.77–3.81)	1.52 (0.67–3.47)

Model 1 adjusted for age, education, work status, monthly income, ethnicity, history of abnormal pregnancy, and prepregnancy BMI. Model 2 adjusted for smoking, drinking, family history of diabetes mellitus, other supplement use, gestational diabetes mellitus, and gestational weight gain based on model 1. Nonusers denotes never used any FA supplement or used FA with daily dose <400 µg or duration <4 wk from prepregnancy to midpregnancy. BMI indicates body mass index; FA, folic acid; FA400-L, FA ≥400 µg but <800 µg daily with long duration; FA400-S, FA ≥400 µg but <800 µg daily with short duration; FA800-L, FA ≥800 µg daily with long duration; FA800-S, FA ≥800 µg daily with short duration; GH, gestational hypertension; and RR, risk ratio.

of CVD disease. The effects of FA and other micronutrients were hard to separate if they were consumed together though we adjusted for other supplement use. Other limitations, including the lack of information on autoimmune disorders, genetic polymorphisms of folic metabolism, the concentration of serum folate, and Hcy, which might involve in the FA-GH association, exist.

In conclusion, our study is the first one, to our knowledge, demonstrating that FA supplement use ≥800 µg/d from prepregnancy through midpregnancy was associated with higher risk of GH compared with nonusers. Given the efficiency of FA supplement use with a daily dose of 400 µg, our findings suggest that high-dose FA supplement use for long duration should be avoided for general women planning or capable of pregnancy, which might provide important public health implications in preventing GH. In the future, more prospective cohort studies and mechanism researches are needed.

Perspectives

For general women planning or capable of pregnancy, high-dose FA supplement use for long duration should be avoided, which might have important public health implications in the prevention of GH. More prospective cohort studies and biological mechanism researches are needed to further investigate the underlying association between FA supplement use and higher GH risk.

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Disclosures

None.

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Novelty and Significance

What Is New?

- To our knowledge, this is the first study aiming to evaluate the association of folic acid (FA) supplement use with gestational hypertension (GH) and preeclampsia with consideration of both doses and duration.

What Is Relevant?

- The study demonstrated that high-dose FA supplement use (≥800 µg/d) from prepregnancy through midpregnancy was associated with higher risk of GH, but not preeclampsia, compared with nonusers. Social-demographic, reproductive, lifestyle factors, other supplement use, and gestational weight gain do not affect the association of FA supplement use and GH and preeclampsia. Restricting the analysis among women with normal weight, without family history of hypertension, and without gestational diabetes mellitus, the association between FA supplement use and higher GH risk remained robust.

Summary

This study found that high-dose (≥800 µg/d) FA supplement use from prepregnancy through midpregnancy was associated with increased GH risk among women who are planning or capable of pregnancy. Given the recommendation of FA supplement use is 400 µg/day, our findings suggest that high-dose FA supplement use for long duration should be avoided for general women planning or capable of pregnancy.