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Folic acid supplementation and dietary folate intake, and risk of preeclampsia

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Abstract

BACKGROUND/OBJECTIVES—Folic acid supplementation has been suggested to reduce the risk of preeclampsia. However, results from few epidemiologic studies have been inconclusive. We investigated the hypothesis that folic acid supplementation and dietary folate intake before conception and during pregnancy reduce the risk of preeclampsia.

SUBJECTS/METHODS—A birth cohort study was conducted in 2010–2012 at the Gansu Provincial Maternity & Child Care Hospital in Lanzhou, China. A total of 10 041 pregnant women without chronic hypertension or gestational hypertension were enrolled.

RESULTS—Compared with nonusers, folic acid supplement users had a reduced risk of preeclampsia (OR = 0.61, 95% CI: 0.43–0.87). A significant dose–response of duration of use was observed among women who used folic acid supplemention during pregnancy only (*P*-trend = 0.007). The reduced risk associated with folic acid supplement was similar for mild or severe preeclampsia and for early- or late-onset preeclampsia, although the statistical significant associations were only observed for mild (OR = 0.50, 95% CI: 0.30–0.81) and late-onset (OR = 0.60, 95% CI: 0.42–0.86) preeclampsia. The reduced risk associated with dietary folate intake

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during pregnancy was only seen for severe preeclampsia (OR = 0.52, 95% CI: 0.31–0.87, for the highest quartile of dietary folate intake compared with the lowest).

CONCLUSIONS—Our study results suggest that folic acid supplementation and higher dietary folate intake during pregnancy reduce the risk of preeclampsia. Future studies are needed to confirm the associations.

INTRODUCTION

Preeclampsia is a pregnancy-specific syndrome in which gestational onset of hypertension and proteinuria occurs after 20 weeks of gestation.[1] About 2–8% of first-pregnant women are affected, and it is a leading cause of maternal morbidity.[2–4] Impaired placental perfusion is considered the primary cause of preeclampsia, whereas other risk factors remain unclear.[5]

Recent evidence suggested an association between elevated levels of blood circulating homocysteine in women with gestational hypertension and preeclampsia.[6–10] One possibility is that hyperhomocysteinemia might damage the vascular endothelium of the developing placenta, increasing contractile response and production of procoagulants and vasoconstrictors.[1] Folic acid supplements can reduce blood homocysteine levels,[11–13] potentially reducing the risk of preeclampsia. Several epidemiological studies have investigated the association between folic acid supplementation and the risk of preeclampsia; however, results from these studies have been inconsistent. Three studies found that folic acid-containing multivitamins were associated with reduced risk of preeclampsia,[14–16] three studies reported no association with folic acid supplement alone[17,18] and one study observed that dietary folate intake reduced the risk of preeclampsia.[19]

In light of the inconsistent results from limited epidemiologic studies, we analyzed data from a birth cohort study in Lanzhou, China to investigate the association between folic acid supplementation and dietary folate intake and the risk of preeclampsia.

MATERIALS AND METHODS

A birth cohort study was conducted in 2010–2012 at the Gansu Provincial Maternity & Child Care Hospital, the largest maternity and child care hospital in Lanzhou, China.[20] Eligible women were pregnant women who came to the hospital for delivery with gestational age ≥ 20 weeks, had no mental illness and were aged 18 years or older. A total of 14 535 pregnant women came to the hospital for delivery, of whom 176 were judged to be ineligible for the study (13 had mental illness, 39 were aged younger than 18 years and 124 gave birth in <20 gestational weeks). Thus, a total of 14 359 eligible women were contacted. Among those, 3721 women refused to participate and 105 women did not complete in-person interviews, which yielded 10 542 (73.4%) women who completed in-person interviews using a standardized and structured questionnaire after obtaining written consent. The questionnaire collected information on demographic factors, reproductive and medical history, smoking, alcohol and tea consumption, occupational and residential history, physical activity, work environment, supplement intake and diet. Information on birth outcomes and pregnancy complications was abstracted from the medical records. All study

procedures were approved by the Human Investigation Committees at the Gansu Provincial Maternity & Child Care Hospital and Yale University. Eligible women were informed of the study upon arrival at the hospital for delivery.

Preeclampsia was defined as having a blood pressure ≥ 140/90 mm Hg (measured twice; 6 h apart) and concurrent proteinuria (two urine specimens containing at least 1+ protein by dipstick test) after 20 weeks of gestation (Table 1). Preeclampsia was further classified as mild preeclampsia, severe preeclampsia, early-onset preeclampsia (EOPE) or late-onset (LOPE).

Information on folic acid supplements was collected for the following four time periods: before conception (12 months before pregnancy), first trimester (1–13 weeks), second trimester (14–27 weeks) and third trimester (>27 weeks). For each time period, duration and frequency of folic acid supplement alone and folic acid-containing multivitamins were ascertained. Folic acid supplement users were defined as those who took folic acid supplement alone or folic acid-containing multivitamins before conception and/or during pregnancy. Nonusers were defined as those who never took folic acid supplement alone or folic acid-containing multivitamins before conception and/or during pregnancy. Dietary information was collected via a semiquantitative food frequency questionnaire. Daily dietary folate intake was estimated from the frequency of consumption and portion size of food items using the Chinese Standard Tables of Food Consumption.[21]

Statistical analysis

After excluding women who gave birth to infants with birth defects and those who had chronic hypertension or gestational hypertension, the final sample size was 10 041. Among those, 365 women were diagnosed with preeclampsia. Distributions of selected characteristics between preeclampsia and normotension were compared using χ^2-tests. Because of the big difference in numbers between the preeclampsia group and the normotension control group, we matched each preeclampsia case to two normotension controls by age (within 1 year) and residence location. Categorization of dietary folate intake into quartiles was based on the distribution of dietary folate intake among controls. Conditional logistic regression models were used to estimate the associations between folic acid supplements and dietary folate intake and the risk of preeclampsia and its subtypes, adjusting for educational level (<college, ≥ college), parity (nulliparous/primiparous), maternal diabetes (yes/no), prepregnancy body mass index (BMI, <18.5, 18.5–23.9, ≥ 24 kg/m^2), weight gain during pregnancy (≤15, 15–18.5, >18.5 kg), family monthly income per capita (<3000, ≥ 3000RMB), maternal employment during pregnancy (yes/no) and previous gestational hypertension (yes/no). Additional adjustment for alcohol consumption, active and passive smoking and physical activity did not result in material changes of the observed associations, and thus they were not included in the final models. Decisions on which covariates to include in the final model were based on a greater than 10% change in the risk estimates for at least one preeclampsia subtype. Additional stratified analyses by maternal age (<30 years, ≥ 30 years), prepregnancy BMI (<18.5 kg/m^2, 18.5-<24.0 kg/m^2, ≥ 24.0 kg/m^2) and parity (primiparous, multiparous) were conducted. All analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Of 10 041 pregnant women, 365 (3.6%) women were diagnosed with preeclampsia (Table 2); among them, 222 cases (60.8%) had severe preeclampsia and 45 cases (12.3%) had early-onset preeclampsia. Compared with women who did not have preeclampsia, women with preeclampsia were more likely to be older, be less educated, have less income, be unemployed during pregnancy, have higher prepregnancy BMI and have weight gain during pregnancy. Women with preeclampsia were also more likely to be multiparous, have a history of gestational hypertension, have maternal diabetes and give multiple births and female birth. Distribution of smoking, alcohol consumption and physical activity were similar between women with and without preeclampsia.

Compared with nonusers, folic acid supplement users had a reduced risk of preeclampsia (OR: 0.61, 95% CI: 0.43, 0.87, Table 3). No dose–response was observed for the duration of supplement use (*P*-trend: 0.55). After stratifying by time periods of using folic acid supplements, significant associations were observed for those who took supplements before conception and during pregnancy (OR: 0.64, 95% CI: 0.42, 0.98) or during pregnancy only (OR: 0.59, 95% CI: 0.41, 0.85). A significant duration of dose–response for folic acid supplement use was observed during pregnancy only (*P*-trend = 0.007). No significant association was observed among women who took supplements before conception only. Although fewer subjects were folic acid-containing multivitamin users compared with folic acid supplement alone users (22 vs 78%), similar inverse associations were observed among women using either type of folic acid supplement (data not shown). No significant associations were observed between dietary folate intake and the risk of preeclampsia (Table 4).

Associations between folate intake and risk of preeclampsia by severity of preeclampsia were presented in Table 5. Compared with nonusers, folic acid supplement users showed similar associations with mild preeclampsia (OR: 0.50, 95% CI: 0.30, 0.81) and severe preeclampsia (OR: 0.69, 95% CI: 0.46, 1.04). In contrast, dietary folate intake during pregnancy was associated with a reduced risk of severe preeclampsia (OR: 0.52, 95% CI: 0.31, 0.87 for the highest quartile compared with the lowest) with significant dose–response (*P*-trend = 0.037), but not mild preeclampsia.

Similar associations were observed for early or late onset of preeclampsia (Table 6), although a statistically significant association was only observed for late onset of preeclampsia (OR: 0.60, 95% CI: 0.42, 0.86 for folic acid supplement users).

We did not observe a joint effect between dietary folate intake and folic acid supplement use (*P* for interaction = 0.08). Maternal age, prepregnancy BMI and parity did not modify the association between folate intake and the risk of preeclampsia (data not shown). Additional sensitivity analysis excluding multiple births did not change the results (data not shown).

DISCUSSION

Our study results support the hypothesis that folic acid supplementation and dietary folate intake during pregnancy are associated with reduced risk of preeclampsia. Our study also suggested that the risk reduction may vary by severity of preeclampsia.

Dietary folate intake reducing preeclampsia risk is biologically plausible.[22] Women with hypertension disorder during pregnancy face a significant elevation of homocysteine.[9,23–26] Folic acid supplementation can reduce circulating homocysteine levels,[27–30] helping to reduce the risk of preeclampsia.[9,14] A two-stage model has been proposed for the development of preeclampsia.[1] The first stage includes abnormal implantation, followed by reduced placental perfusion, which generally occurs during the first and early second trimesters. Then, the maternal syndrome of preeclampsia is followed by systemic endothelial dysfunction at the second stage, which generally occurs during the early third trimester. Folic acid can also prevent and reverse endothelial dysfunction, independent of plasma homocysteine,[31] suggesting that folic acid supplements may have a role in the prevention of preeclampsia at the second stage.

Our study results were consistent with several previous studies,[14–16] but not all.[17,32] Bodnar *et al*.[14] observed that regular use of folic acid-containing multivitamins from before conception to 16 weeks of gestation was associated with a 45% reduced risk of preeclampsia. Hernández-Díaz *et al*.[15] found a 45% reduced risk of gestational hypertension associated with at least 400 μg of folic acid-containing multivitamin intake from 2 months before conception through delivery. Wen *et al*.[16] reported a 63% reduced risk of preeclampsia associated with >100 μg of folic acid-containing multivitamin use during the second trimester. Catov *et al*.[17] reported a 22% reduced risk of preeclampsia associated with multivitamin use but no association with folic acid supplement alone. Recently, Li *et al*.[32] reported an increased risk of preeclampsia (OR: 1.11, 95% CI: 1.04, 1.18) associated with daily consumption of 400 μg of folic acid supplement alone during early pregnancy.

Different study populations, dosing and time period of use of folic acid supplements may be important. One early study examined the effect of prepregnancy BMI on the association between preconception folic acid supplement use and preeclampsia, and it was found that prepregnancy BMI modified the association.[14] Similarly, a stronger protective effect of folic acid supplement use during pregnancy on preeclampsia risk was shown among women who had a prepregnancy BMI of less than 18.5 kg/m^2. Our hypothesis is that the dose of folic acid supplements may be inadequate to overcome endothelial dysfunction, higher blood pressure and higher inflammation among overweight women.[14]

Only one study conducted in Norway explored the association between diet and risk of preeclampsia,[19] and it was found that greater consumption of vegetables was associated with up to 28% reduced risk of preeclampsia. Our study showed a protective effect from dietary folate intake on the risk of severe preeclampsia but not mild preeclampsia. Another study explored the association with folic acid supplements by severity of preeclampsia but did not observe any difference.[17] It is currently unclear why high dietary folate intake was only

associated with severe preeclampsia. Further studies with larger sample size are needed to assess the association of dietary folate with the risk of mild and severe preeclampsia.

Strengths and limitations should be considered when interpreting the study results. Diagnosis of preeclampsia in our study was based on medical records and was not self-reported, which minimized potential disease misclassification. Detailed information on both folic acid supplements and dietary folate intake were collected, which allowed us to comprehensively examine the associations with both folic acid supplement and dietary folate intake. Although our study had a relatively large sample size, statistical power was limited for stratified analyses. Although many important confounding factors have been adjusted for in the analysis, we cannot rule out the potential for residual confounding. Information on dietary folate and folic acid supplement was collected through in-person interview at delivery, and thus potential recall bias might exist. However, if there was any recall bias, it was likely to be nondifferential and result in an underestimation of the observed association, as the link between folic acid supplementation, dietary folate and preeclampsia risk is unclear. The study was hospital-based, which may limit generalizability. The rate of preeclampsia (3.6%) in our study population was slightly higher than previously reported (2.0–2.5%) studies in China,[32,33] but within the range (2–8%) reported worldwide.[34,35]

Our study suggested that both folic acid supplementation and dietary folate intake during pregnancy are associated with a reduced risk of preeclampsia, and the risk may vary by severity of preeclampsia. Future studies are needed to confirm these associations and to identify women who would have the most benefit from folic acid supplementation.

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Table 1

Definition of preeclampsia and its subtype

	Preeclampsia	Preeclampsia subtypes			
		Mild	Severe	Early onset	Late onset
Systolic blood pressure	≥ 140 mm Hg	140– < 160 mm Hg	≥ 160 mm Hg	≥ 140 mm Hg	≥ 140 mm Hg
Diastolic blood pressure	≥ 90 mm Hg	90– < 110 mm Hg	≥ 110 mm Hg	≥ 90 mm Hg	≥ 90 mm Hg
Proteinuria[a]	≥ 1+	1+	≥ 2+	≥ 1+	≥ 1+
Symptoms of severity[b]	Yes/no	No	Yes	Yes/no	Yes/no
Gestational age of diagnosis	> 20 weeks	> 20 weeks	> 20 weeks	21– < 34 weeks	≥ 34 weeks

[a] Dipstick test in two urine samples.

[b] Including headache, blurred vision, epigastric burning pain, decreased urine output, decreased or absent fetal kick and so on.

Table 2

Distribution of Selected Characteristics of the Study Population (*N* = 10 041), Urban China, 2010–2012

Characteristics	*Normotension (n = 9,676)*		*Preeclampsia (n = 365)*		P-*value*[a]
	n	%	n	%	
Maternal age (years)					
<25	1536	96.1	62	3.9	<0.0001
25–29	4700	97.3	131	2.7	
≥30	3440	95.2	172	4.8	
Maternal employment					
No	4673	95.6	213	4.4	0.0002
Yes	5003	97.1	152	3.0	
Monthly income per capita (RMB)					
<3000	4847	95.2	242	4.8	<0.0001
≥3000	2911	97.9	84	2.1	
Missing	918	95.9	39	4.1	
Highest education level					
<College	3743	94.6	213	5.4	<0.0001
≥College	5759	97.5	145	2.5	
Missing	174	96.1	7	3.9	
Prepregnancy body mass index [b]					
<18.5	2024	97.9	43	2.1	<0.0001
18.5–23.9	6380	96.6	222	3.4	
≥24.0	963	92.4	79	7.6	
Missing	309	93.6	22	6.4	
Weight gain during pregnancy					
<15 kg	3712	97.6	92	2.4	<0.0001
15–18.5 kg	2230	97.4	59	2.6	
>18.5 kg	3351	94.7	187	5.3	
Missing	383	93.4	27	6.6	
Smoking (passive and active) during pregnancy					
No	7811	96.5	286	3.5	0.26
Yes	1865	95.9	79	4.1	
Alcohol consumption during pregnancy					
No	9655	96.4	384	3.6	0.38
Yes	20	100.00	0	0.00	
Physical activity during pregnancy					
No	1682	96.2	67	3.8	0.63
Yes	7994	96.4	298	3.6	
Parity					
Primiparous	7005	96.7	239	3.3	0.004
Multiparous	2671	95.5	126	4.5	

Characteristics	*Normotension (n = 9,676)*		*Preeclampsia (n = 365)*		P-*value*[a]
	n	%	n	%	
History of gestational hypertension					
No	9634	96.5	345	3.5	<0.0001
Yes	42	67.7	20	32.3	
Maternal diabetes					
No	9591	96.4	357	3.6	0.010
Yes	85	91.4	8	8.6	
Multiple birth					
No	9447	96.9	307	3.2	<0.0001
Yes	229	79.8	58	20.2	
Gender					
Male	5102	96.8	168	3.2	0.010
Female	4546	95.9	197	4.2	
Missing	28	100.0	0	0.0	

[a] Calculated by χ^2-analysis without accounting for missing data.

[b] Weight (kg)/height (m)^2.

Table 3

Associations between folic acid supplement use and the risk of preeclampsia (*N*=1059), Urban China, 2010–2012

Folic acid supplement use	*Controls*	*Preeclampsia*	
		Cases	*OR[a] (95% CI)*
Nonusers	150	115	1
Users	556	238	0.61 (0.43, 0.87)
≤12 weeks	348	147	0.62 (0.43, 0.89)
>12 weeks	208	91	0.60 (0.39, 0.92)
P for trend			0.55
Before conception and during pregnancy	209	97	0.64 (0.42, 0.98)
≤12 weeks	47	22	0.72 (0.38, 1.37)
>12 weeks	162	72	0.61 (0.39, 0.97)
P for trend			0.84
Before conception only	27	14	0.80 (0.36, 1.77)
≤4 weeks	9	4	0.60 (0.16, 2.24)
>4 weeks	18	10	0.93 (0.36, 2.37)
P for trend			1.00
During pregnancy only	320	130	0.59 (0.41, 0.85)
≤8 weeks	147	78	0.76 (0.50, 1.16)
>8 weeks	173	52	0.44 (0.50, 0.69)
P for trend			0.007

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjusted for maternal age, education level, parity, maternal diabetes, prepregnancy BMI, weight gain during pregnancy, family monthly income per capita, multiple birth, maternal employment during pregnancy, history of gestational hypertension and dietary folate intake

Table 4

Associations Between Dietary Folate Intake and Risk of Preeclampsia (*N*=1059), Urban China, 2010–2012

Dietary folate intake (μg/day)	***Controls***	***Preeclampsia***	
		Cases	***OR[a] (95% CI)***
Before conception			
Q1 (<116.0)	176	93	1.00
Q2 (116.0, 152.2)	177	78	0.92 (0.62, 1.39)
Q3 (152.2, 229.9)	177	111	1.22 (0.83, 1.79)
Q4 (≥229.9)	176	71	0.76 (0.50, 1.16)
P for trend			0.50
During pregnancy			
Q1 (<151.6)	176	97	1.00
Q2 (151.6, 194.2)	178	79	0.94 (0.63, 1.42)
Q3 (194.2, 274.4)	176	101	1.11 (0.75, 1.65)
Q4 (≥274.4)	176	76	0.72 (0.47, 1.09)
P for trend			0.24

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjusted for maternal age, education level, parity, maternal diabetes, prepregnancy BMI, weight gain during pregnancy, family monthly income per capita, multiple birth, maternal employment during pregnancy, history of gestational hypertension and folic acid supplementation.

Table 5

Associations between folate intake and risk of preeclampsia by severity of preeclampsia (*N*=1059), Urban China, 2010–2012

Folate intake	***Controls***	***Mild preeclampsia (n = 137)***		***Severe preeclampsia (n = 216)***	
		Cases	***OR[a] (95% CI)***	***Cases***	***OR[a] (95% CI)***
Folic acid supplements					
Nonusers	150	43	1	72	1
Users	556	94	0.50 (0.30, 0.81)	144	0.69 (0.46, 1.04)
Dietary folate intake (μg/day)					
Before conception					
Q1 (<116.0)	176	27	1	66	1
Q2 (116.0, 152.2)	177	31	1.19 (0.65, 2.17)	47	0.86 (0.53, 1.40)
Q3 (152.2, 229.9)	177	47	1.85 (1.05, 3.26)	64	0.98 (0.62, 1.56)
Q4 (≥229.9)	176	32	1.13 (0.61, 2.07)	39	0.63 (0.39, 1.05)
P for trend			0.38		0.15
During pregnancy					
Q1 (<151.6)	176	27	1	70	1
Q2 (151.6, 194.2)	178	32	1.30 (0.71, 2.39)	47	0.85 (0.52, 1.38)
Q3 (194.2, 274.4)	176	41	1.71 (0.95, 3.08)	60	0.98 (0.62, 1.57)
Q4 (≥274.4)	176	37	1.25 (0.69, 2.27)	39	0.52 (0.31, 0.87)
P for trend			0.36		0.037

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjusted for maternal age, education level, maternal diabetes, prepregnancy BMI, weight gain during pregnancy, family monthly income per capita, multiple birth, maternal employment during pregnancy, parity, history of gestational hypertension and dietary folate intake or folic acid supplements.

Table 6

Associations between folate intake and risk of preeclampsia by onset of preeclampsia (*N*=1059), Urban China, 2010–2012

Folate intake	*Controls*	*Early onset (n = 45)*		*Late onset (n = 308)*	
		Cases	*OR[a] (95% CI)*	*Cases*	*OR[a] (95% CI)*
Folic acid supplements					
Nonusers	150	15	1	100	1
Users	556	30	0.76 (0.35, 1.63)	208	0.60 (0.42, 0.86)
Dietary folate intake (μg/day)					
Before pregnancy					
Q1 (<116.0)	176	14	1	79	1
Q2 (116.0, 152.2)	177	15	1.13 (0.48, 2.61)	63	0.88 (0.57, 1.37)
Q3 (152.2, 229.9)	177	8	0.69 (0.26, 1.83)	103	1.33 (0.89, 2.00)
Q4 (≥229.9)	176	8	0.53 (0.19, 1.47)	64	0.80 (0.51, 1.24)
P for trend			0.15		0.79
During pregnancy					
Q1 (<151.6)	176	13	1	84	1
Q2 (151.6, 194.2)	178	12	1.30 (0.52, 3.25)	67	0.92 (0.60, 1.41)
Q3 (194.2, 274.4)	176	13	1.35 (0.55, 3.32)	88	1.12 (0.74, 1.70)
Q4 (≥274.4)	176	7	0.58 (0.20, 1.71)	69	0.73 (0.47, 1.12)
P for trend			0.44		0.30

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjusted for maternal age, education level, parity, maternal diabetes, weight gain during pregnancy, family monthly income per capita, multiple birth, maternal employment during pregnancy, history of gestational hypertension, and dietary folate intake or folic acid supplements.