



International Journal of Pharmacology

ISSN 1811-7775

Research Article

Effect of High Dose Folic Acid Supplementation on the Prevention of Pre-Eclampsia in Pregnancy with Hypertension

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Abstract

Background and Objective: Pre-eclampsia is a very dangerous pregnancy condition that significantly elevates the possibility of early mortality for both the mother and the infant. The purpose of the experiment was to investigate the contradictory evidence about whether folic acid may decrease the incidence of pre-eclampsia. **Materials and Methods:** As 1500 pregnant women were randomly selected for the clinical investigation. The 750 women were assigned to the folic acid and placebo groups. From randomization (8 to 16 weeks) until delivery, group 1 got 4 mg of folic acid and group 2 received a placebo daily. Participants were examined for ≤ 50 , 50-75 and $\geq 75\%$ compliance levels. The 4 follow-ups were scheduled: 24-26, 34-36, post-birth and 42 days post-partum. The research sought to quantify pre-eclampsia rates. Secondary outcome assessments were early preterm delivery, stillbirth, neonatal death, perinatal mortality, early-onset sepsis and NICU hospitalisation for 24 hrs or more. **Results:** The study found that the occurrence of pre-eclampsia was comparatively lower in the folic acid group than in the placebo group (5.3 vs. 10%), with a risk ratio (RR) of 0.53 and a 95% confidence interval (CI) of 0.53 to 0.79. Furthermore, the occurrence of secondary outcomes was decreased in the folic acid group in comparison to the placebo group. **Conclusion:** The study findings provide evidence that high-dose folic acid intake can be an effective preventive measure for pre-eclampsia in pregnant women with hypertension.

Key words: Pre-eclampsia, folic acid, pregnant women, primary outcome, secondary outcome, hypertension

Citation: Luo, H., H. Ma and Y. Wang, 2025. Effect of high dose folic acid supplementation on the prevention of pre-eclampsia in pregnancy with hypertension. Int. J. Pharmacol., 21: 401-407.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Pre-eclampsia is a perilous condition that occurs in 3-5% of pregnancies and is responsible for illness and death in women^{1,2}. Hypertension throughout pregnancy and proteinuria are the main symptoms of pre-eclampsia³. Pre-eclampsia affects various organ systems and increases the risk of serious partum problems⁴. Because the only known remedy is placental delivery, pre-eclampsia is the main cause of recommended pre-term delivery^{5,6}, long-term impairment and perinatal morbidity^{7,8}. Pre-eclampsia in pregnant women may result in neurocognitive dysregulation and impaired newborn development⁹. Further investigation is necessary to determine the aetiology of preeclampsia. The multifactorial stimulation and destruction of vascular endothelial cells primarily lead to focalization of pre-eclampsia¹⁰. The "folic acid", a water-soluble vitamin B, is well known for its ability to treat birth abnormalities^{11,12}. Folic acid is a cofactor that is required for human growth and development, as it is involved in DNA methylation and repair, cell division, embryogenesis and nucleic acid synthesis^{13,14}. Supplementing with folic acid while pregnant enhances the amounts of folic acid in the blood cells of women with confirmed pregnancies. This supplementation also reduces the occurrence of abnormal effects, including short gestational age (SGA) and premature delivery¹⁵. To prevent pregnancy-related ailments, there is currently no standard regulation regarding the dosage and duration of folic acid supplements. Folic acid supplementation, according to some research by Yu *et al.*¹⁶ and Zheng *et al.*¹⁷, can lower the incidence of gestational hypertension and pre-eclampsia.

Accumulating evidence suggests that an increased level of homocysteine in the bloodstream is a cause of prenatal hypertension and pre-eclampsia^{18,19}. Homocysteine is recognised as a significant contributor to cardiovascular disease²⁰. Hyperhomocysteinemia is seen in around 20 to 30% of individuals with peripheral vascular disease and coronary artery disease²¹. Increased homocysteine levels can be readily oxidized to form homocysteine compounds and produce ion radicals such as superoxide and hydrogen peroxide, which harm vascular endothelial cells and initiate a chain reaction of vascular injury²². Mounting data suggests that the administration of large doses of folic acid over an extended period may effectively cure pre-eclampsia²³. To offer more concrete evidence in support of this theory, further thorough investigation is necessary. Hence, the current research aimed to ascertain the impact of a high dosage of folic acid in avoiding pre-eclampsia among women with hypertension.

MATERIALS AND METHODS

Trial design and participants: The Ezhou Central Hospital in Hubei Province conducted this randomized clinical trial from January, 2022 to January, 2023. The trial screened 2500 pregnant women and enrolled 1500 of them. The selected patients were randomly and equally allocated into two groups (n = 10) folic acid and placebo.

Ethical consideration: The aforementioned study has received approval from the Human Ethical Committee of Ezhou Central Hospital in Hubei Province (Reg. 2021/65376/0003). Before the experiment began, every participant furnished signed informed consent.

Inclusion criteria: The research comprised pregnant women who had a confirmed viable foetus between 8 and 16 weeks of pregnancy, had pre-existing hypertension, had experienced pre-eclampsia in a earlier pregnancy and had a Body Mass Index (BMI) of 35 kg/m² or above.

Exclusion criteria: The study excludes women who have previous records of maternal medical problems, epilepsy or cancer or those who are already using folic acid antagonists. It also excludes women who misuse illicit drugs or alcohol (≥ 2 drinks/day) throughout their present pregnancy, have a known fetal anomaly or fetal death or have multiple pregnancies.

Interventions: From randomization (8-16 full weeks of gestation) to birth, the trial intervention consisted of 41 mg folic acid tablets or placebo tablets, taken once daily. The participants continued taking low-dose folic acid supplements or prenatal vitamins. Participants were masked to their treatment group by the tasteless, identically shaped folic acid and placebo tablets. Each participant received a form to record their daily dosage of folic acid, which would be used to calculate compliance later on, the investigators guided how to use the medication properly. By dividing the whole amount of folic acid that is actually consumed by the total amount of folic acid that should be taken theoretically, compliance is determined and expressed as a percentage. After randomization, all subjects, coordinators, site investigators and other research staff, as well as those from the trial coordinating center, were unaware of the assigned therapy. There was no revelation of identities throughout the trial.

Duration of the monitoring period: From group assignment until production, all subjects received the recommended daily

dosage of folic acid. Follow-ups took place four times in total: 24-26, 34-36 weeks of gestation, following birth and 42 days post-partum. During the first study visits, a physical examination was conducted, which included measurements of blood pressure, weight, urine and fetal health. In addition to gathering data from hospital records regarding mothers and newborns, laboratory values were gathered at the time of delivery. Adverse occurrences at every visit were evaluated and recorded. A medication diary and pill counts were used to assess adherence to the study treatment.

Measurements of primary and secondary outcome: The established definition at the start of the investigation determined pre-eclampsia as the main endpoint of the study²⁴. The secondary outcomes were defined and assessed based on prior studies. These outcomes included placental abruption, HELLP syndrome, severe pre-eclampsia, gestational age <37 weeks, maternal death, preterm birth <37 weeks of gestation, very preterm birth <32 weeks of gestation, stillbirth, neonatal death, perinatal mortality, retinopathy of prematurity, early-onset sepsis, intraventricular hemorrhage and admission to the neonatal intensive care unit for 24 hrs or longer.

Statistical analysis: The description for categorical variables was done as n (%), while that for variables quantitative in nature was done by (Mean±Standard Deviation (SD)). The Chi-square (χ^2) test was employed to assess the main and secondary outcomes between the groups. The therapy's

impacts were assessed using relative risks along with 95% CI. The statistical assessments took place using the Lincod SPSS programme. The significance level was assigned to $p < 0.05$.

RESULTS

The study included 1500 pregnant women, which were divided into two batches comprising the folic acid (n = 750) and placebo (n = 750) groups. Both groups were given folic acid (4 mg) per day until production. Initially, the baseline characteristics, including the previous records of pre-eclampsia, chronic hypertension, parity, maternal age and gestational age, were conducted by these women (Table 1). The folic acid group and placebo group have similar percentages of participants with previous records of pre-eclampsia and chronic hypertension. However, there are differences in the distribution of participants based on parity, maternal age, pre-pregnancy BMI and gestational age at recruitment among the groups.

The participants' adherence was assessed and there were 60 individuals (8%) in the folic acid group and 57 participants (7.60%) in the placebo group, representing up to 50%. At the same time, 78 participants (10.4%) in the folic acid group and 73 participants (9.7%) in the placebo group had compliance of 50- <75%. Furthermore, 512 participants (68%) in the folic acid group and 524 participants (69.9%) in the placebo group demonstrated $\geq 75\%$ compliance. The compliance rates in the 2 groups were quite similar, with only minor variances noted (Table 2).

Table 1: Baseline characteristics of participants

Characteristics	Folic acid group (%) (n = 750)	Placebo group (%) (n = 750)
History of pre-eclampsia	219 (28.7)	200 (26.7)
Chronic hypertension	150 (20)	185 (24.7)
Parity		
0	302 (40.3)	325 (43.3)
1	390 (52)	398 (52.8)
≥ 2	263 (35.1)	277 (36.9)
Maternal age (year)		
<20	5 (0.7)	5 (0.7)
20-29	405 (54)	432 (57.6)
30-34	365 (48.7)	388 (51.7)
≥ 35	297 (39.6)	248 (33)
Mean±SD age (years)	30±5.2	30±5.2
Prepregnancy BMI (kg/m²)		
<18.5	10 (1.3)	6 (0.8)
18.5-<25	150 (20)	145 (19.3)
25-<30	110 (14.7)	99 (13.2)
30-<35	88 (11.7)	56 (7.4)
≥ 35	410 (54)	435 (58)
Mean±SD pre-pregnancy BMI	32±8.3	32±8.3
Gestational age at recruitment (weeks)		
8-12	250 (33.3)	312 (41.6)
13-16	640 (85.3)	600 (80)
Mean±SD gestational age (weeks)	14±1.9	14±1.9

Table 2: Compliance of patients determined in folic acid and placebo group

Compliance (%)	Folic acid group (%) (n = 750)	Placebo group (%) (n = 750)
≤50	60 (8)	57 (7.6)
50-<75	78 (10.4)	73 (9.7)
≥75	512 (68)	524 (69.9)

Table 3: Primary and secondary outcomes of the participants

Outcomes	Folic acid group (%) (n = 750)	Placebo batch (%) (n = 750)	Risk ratio (95% CI)	p-value
Pre-eclampsia	40 (5.3)	75 (10)	0.53 (0.53-0.79)	0.02
Placental abruption	10 (1.3)	15 (2)	0.67 (0.30-1.47)	0.37
HELLP syndrome	2 (0.3)	4 (0.5)	0.5 (0.43-0.57)	<0.05
Severe pre-eclampsia	12 (1.6)	19 (2.5)	0.63 (0.02-0.90)	0.05
Gestational age <37 weeks	120 (16)	155 (20.7)	0.81 (0.73-0.90)	0.04
Maternal death	0	0	0	0
Preterm birth (gestation less than 37 weeks)	25 (3.3)	33 (4.4)	0.76 (0.46-1.26)	0.05
Early preterm birth (gestation less than 32 weeks)	11 (1.5)	13 (1.7)	0.85 (0.37-1.07)	0.83
Stillbirth	4 (0.5)	8 (1.1)	0.5 (0.22-1.60)	0.004
Neonatal death	3 (0.4)	7 (0.9)	0.43 (0.16-1.18)	0.20
Perinatal mortality	20 (2.7)	30 (4)	0.67 (0.45-0.98)	0.07
Retinopathy of prematurity	11 (1.5)	18 (2.4)	0.61 (0.34-1.09)	0.01
Early onset sepsis	2 (0.3)	5 (0.7)	0.4 (0.25-0.65)	0.005
Intraventricular haemorrhage	14 (1.9)	15 (2)	0.95 (0.94-1.29)	<0.05
Admission to NICU for 24 hrs or more	120 (16)	135 (18)	0.83 (0.67-0.96)	0.33

Data were expressed as n (%), HELLP: Haemolysis Elevated Liver Enzymes and Low Platelets and NICU: Neonatal Intensive Care Unit

Table 3 displayed the main and additional results based on the study groups (folic acid and placebo groups). The risk ratio with a 95% CI is provided for each outcome, along with the corresponding p-value. Pre-eclampsia occurred in 40 (5.3%) cases in the folic acid and 75 (10%) cases in the placebo group. The incidence proportion was 0.53 (95% CI: 0.53 to 0.79), indicating that the folic acid group had a decreased risk. This variation was highly significant ($p = 0.02$). Placental abruption occurred in 10 (1.3%) of the folic acid cases and 15 (2%) of the placebo cases. The risk proportion was 0.67 (95% CI: 0.30 to 1.47), suggesting a modestly reduced risk in the folic acid group. Nevertheless, this disparity did not achieve statistical relevance ($p = 0.37$). As 0.3% of patients in the folic acid group and 0.5% of cases in the placebo group had HELLP syndrome. The risk proportion was 0.5 (95% CI: 0.43 to 0.57), suggesting a reduced risk in the folic acid group. This variation was determined to be significantly noteworthy ($p < 0.05$). Severe pre-eclampsia was seen in 12 instances (1.6%) in the folic acid group and in 19 cases (2.5%) in the placebo group. The risk proportion was 0.63 (95% CI: 0.02 to 0.90), demonstrating a substantial reduction in risk in the folic acid group ($p < 0.05$). There was no occurrence of mortality in both groups. Preterm delivery, defined as birth occurring before 37 weeks of gestation, was seen in 25 instances (3.3%) in the group receiving folic acid and in 33 cases (4.4%) in the group receiving a placebo. The risk proportion was 0.76 (95% CI: 0.46 to 0.90), suggesting a modestly reduced risk in the folic acid group. However, the observed change was insignificant ($p = 0.05$). Other outcomes such as early preterm birth, stillbirth, neonatal death, perinatal mortality, early-onset

sepsis and admission to NICU for 24 hrs or more also indicated a potential protective benefit of folic acid supplementation. Nevertheless, no substantial disparity was seen in the prevalence of early preterm birth, neonatal death, premature birth or admission to the Neonatal Intensive Care Unit (NICU) between the 2 groups.

DISCUSSION

Elevated levels of homocysteine are linked to placental insufficiency and disrupted circulation, which is considered a significant contributor to the onset of pre-eclampsia^{25,26}. The prevailing consensus among specialists is that the elevation of homocysteine levels, resulting in pre-eclampsia, is attributed to oxidative harm inflicted upon the endothelial cells that line the blood arteries. This damage results in negative consequences throughout pregnancy²⁷.

The methylation process is the *in vivo* metabolic pathway of homocysteine²⁸. In this reaction, N5,10-Methylenetetrahydrofolate Reductase (MTHFR) catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate²⁹. Folic acid acts as an important cofactor for this enzyme, functioning as a methyl donor to replenish methionine. Consequently, it might potentially contribute to the initiation and advancement of pre-eclampsia. Pregnant women who have hyperhomocysteinemia and low folate levels are more prone to developing pre-eclampsia compared to the control group²⁴. Research has shown that the use of folic acid supplements may decrease the possibility of developing pre-eclampsia.

Hypohomocysteinemia is thought to impair the vascular endothelium of the developing placenta and folic acid may affect this level³⁰.

Furthermore, a folate shortage may cause apoptosis in human cytotrophoblast cells, leading to impaired placental development and reduced trophoblast invasion^{31,32}. In a study, Thakur and Bhalerao³³ found no connection between pre-eclampsia and the rise in homocysteine throughout the first stages of pregnancy and that pre-eclampsia could not be prevented by early folic acid treatment. This research was to investigate the effects of administering high-dose folic acid to pregnant women at high risk of pre-eclampsia. The purpose was to address the contradictory findings about the potential of folic acid in reducing the occurrence of pre-eclampsia. The dose of folic acid used (4 mg/day) was determined based on procedures that were previously published^{23,24,34}.

Based on the current experiment, including folic acid in the diet may considerably decrease the occurrence of pre-eclampsia in comparison to the group that received a placebo. Wang *et al.*³⁵ research outcomes supported the idea that taking folic acid supplements and consuming more folate-rich foods throughout pregnancy might reduce the incidence of pre-eclampsia. Multiple studies have also validated the benefits of supplementing with folic acid throughout the first phases of pregnancy^{36,37}. The research conducted by Martinussen *et al.*³⁸ suggests that consuming folate throughout the initial stages of pregnancy may shield lean moms from developing pre-eclampsia. In a separate trial, participants who took high daily dosages of folic acid (3-9 mg) were able to lower their risk of preterm labour considerably and the early start of pre-eclampsia³⁶. Secondary outcomes revealed that preterm birth, stillbirth, perinatal mortality, neonatal death, retinopathy of prematurity, early-onset sepsis, intraventricular hemorrhage and admission to the NICU for 24 hrs or more were significantly reduced in the folic acid group compared to the placebo group. The study did not assess the potential side effects or adverse events associated with high-dose folic acid supplementation. Other potential confounding factors that may influence the development of pre-eclampsia, such as dietary factors, lifestyle factors or genetic predisposition, were not considered in the study. The study did not provide information on the long-term outcomes or follow-up of the participants after delivery.

CONCLUSION

The research has shown that administering large doses of folic acid may decrease the occurrence of pre-eclampsia and other associated problems in pregnant women with

hypertension. Before suggesting treatments, it is often wise to do a comprehensive assessment, which may include monitoring the progress of offspring if possible. Additionally, it is necessary to do further studies both *in vivo* and *in vitro* to verify the conclusion about the mechanism of folic acid in lowering pre-eclampsia.

SIGNIFICANCE STATEMENT

Pre-eclampsia is a very perilous pregnancy syndrome that greatly raises the risk of early mortality for both the mother and the baby. Research indicates that the administration of high doses of folic acid may decrease the occurrence of pre-eclampsia and other related complications in pregnant women with hypertension. Prior to recommending therapies, it is advisable to do a thorough evaluation, which may include monitoring the development of offspring if feasible. Furthermore, conducting further *in vivo* and *in vitro* investigations is important to validate the results of the biological processes by which folic acid reduces the occurrence of pre-eclampsia.

ACKNOWLEDGMENT

The authors thank the facilities offered by the higher officials.

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