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Original Article

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

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ABSTRACT

Background: "Pre-eclampsia" is one of the most dangerous pregnancy complications, increasing the risk of both the mother and the baby dying prematurely. Because there have been conflicting findings on whether folic acid can reduce the incidence of pre-eclampsia, we conducted a randomized clinical trial of high-dose folic acid administration to pregnant women at a high risk of pre-eclampsia. **Materials and Methods:** The study was a randomized clinical trial involving 1500 pregnant women. These women were randomly assigned into the Folic acid group (*n*=750) and Placebo group (*n*=750). From randomization (gestation period of 8 to 16 complete weeks) to birth, group 1 received 4mg of folic acid and group 2 received placebo per day. Participants were also analyzed for compliance over ≤50%, 50-<75% and ≥75%. Four follow-ups were scheduled at 24-26, 34-36 gestational weeks, after birth and 42 days post-partum. The primary outcome measure was the incidence of pre-eclampsia. In contrast, secondary outcome measures included early pre-term birth, stillbirth, neonatal death, perinatal mortality, early-onset sepsis and admission to NICU for 24 hr or more. **Results:** The present investigation showed that the incidence of pre-eclampsia was significantly lower in the folic acid group compared to placebo group (5.3% vs 10%) with a Risk Ratio (RR) of 0.53 95% Confidence Interval (CI): 0.53 to 0.79. Similarly, the incidence of secondary outcomes was also reduced in the folic acid group compared to the placebo group. **Conclusion:** The results of the study lend support to the idea that pregnant women with "hypertension" should take high-dose folic acid supplements as a prophylactic measure against pre-eclampsia.

Keywords: Pre-eclampsia, Folic acid, Pregnant women, Primary outcome, Secondary outcome, Hypertension.

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INTRODUCTION

"Pre-eclampsia" is a dangerous pregnancy ailment that affects 3-5% of pregnancies and is the cause of morbidity and mortality in women.[1,2] Hypertension throughout pregnancy and proteinuria are the main symptoms of pre-eclampsia.[3] Pre-eclampsia affects various organ systems and increases the risk of serious partum problems.[4] Because the only known remedy is placental delivery, pre-eclampsia is the leading 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 development.[9] The aetiology of preeclampsia is yet unknown and has to be investigated further. The multifactorial stimulation and destruction of vascular endothelial cells primarily lead to the focalization of pre-eclampsia.[10]

"Folic acid", a water-soluble vitamin B, is well known for treating birth abnormalities.[11,12] Folic acid is a cofactor required for human growth and development, as it is involved in DNA methylation and repair, cell division, embryogenesis and nucleic acid synthesis.[13,14] Prenatal folic acid supplementation enhances plasma and erythrocyte folic acid levels in women with confirmed pregnancy. It decreases the incidence of abnormal outcomes such as Small Gestational Age (SGA) and premature delivery.[15] 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,[16,17] can lower the incidence of gestational hypertension and preeclampsia.

Accumulating evidence suggests that an increased level of homocysteine in the blood is a cause of prenatal hypertension and pre-eclampsia.[18,19] Homocysteine is one of the risk factors known

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for cardiovascular disease,[20] and hyperhomocysteinemia is found in between 20 to 30% of patients suffering from peripheral vascular disease and coronary artery disease.[21] 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 injury.[22] There is increasing evidence that high-dose or usage of folic acid for a longer period could successfully treat pre-eclampsia.[23] A further thorough investigation is necessary to offer more concrete evidence supporting this theory. Therefore, the present study was designed to determine the effect of high-dose folic acid supplementation in preventing pre-eclampsia in pregnant women with hypertension.

MATERIALS AND METHODS

Trial design and participants

This randomized clinical trial was conducted at the data in the text are taken from public databases. for three years. 2500 pregnant women were screened, and 1500 were enrolled in the trial. Patients were randomly and equally allocated into two groups: folic acid (n = 750) and placebo (n = 750).

Inclusion criteria

Pregnant women with a proven viable fetus between 8- and 16-weeks gestation, pre-existing hypertension, pre-eclampsia from a prior pregnancy, and a Body Mass Index (BMI) of ≥35 kg/m^2 were included in the study.

Exclusion criteria

The study excludes women who have a history of maternal medical complications, epilepsy, cancer, or current use of folic acid antagonists. It also excludes women who misuse illicit drugs or alcohol (≥2 drinks/day) during their current 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 four 1 mg folic acid 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 and 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, and the investigators guided how to use the medication properly. Compliance is determined and expressed as a percentage by dividing the total amount of folic acid consumed by the total amount that should be taken theoretically. After randomization, all subjects, coordinators, site investigators, and other research staff and members of the trial coordinating centre were blinded to treatment allocation. No unmasking occurred during the trial.

Duration of follow-up

From the time of group assignment until production, all subjects received the recommended daily dosage of folic acid. Follow-ups occurred four times: 24-26 weeks, 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 collected at delivery time. 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

Pre-eclampsia was the primary outcome, defined according to the recognised definition when the research began.[24] Secondary outcomes were defined and measured using previous research,[25] and the items were listed as placental abruption, HELLP syndrome, severe pre-eclampsia, gestational age <37 weeks, maternal death, pre-term birth (<37 weeks gestation), early pre-term birth (<32 weeks' gestation), stillbirth, neonatal death, perinatal mortality, retinopathy of prematurity, early-onset sepsis, intraventricular hemorrhage and admission to NICU for 24 hr or more.

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 primary and secondary outcomes between the groups were compared using the chi-square ($\chi 2$) test. Treatment effects were expressed as relative risk with 95% confidence intervals. P values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS software.

RESULTS

The study included 1,500 pregnant women bisected into two batches comprising the folic acid (n = 750) and the placebo (n = 750) batch. Both the groups were supplemented with 4 mg of folic acid per day until production. Initially, the baseline characteristics, including the history 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 a history 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 between the two groups.

Evaluation of the participants' compliance showed that 60 participants (8%) in the folic acid batch and 57 participants (7.60%) in the placebo batch complied with up to 50%. At the same time, 78 participants (10.4%) in the folic acid group and

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 (yrs)		
<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/m^2)		
<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)

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 ≥75% compliance. The compliance rates in the two groups were quite similar, with only minor variances noted (Table 2).

The primary and secondary outcomes according to the study group (folic acid and placebo group) are shown in Table 3. The risk ratio with a 95% CI is provided for each outcome, along with the corresponding p-value. The Pre-eclampsia occurred in 40 (5.3%) cases in the folic acid and 75 (10%) in the placebo group. The risk ratio was 0.53 (95% CI: 0.53 to 0.79), indicating that the folic acid group had a decreased risk, and the difference was statistically significant (p=0.02). Placental abruption occurred in 10 (1.3%) folic acid cases and 15 (2%) placebo cases. The risk ratio was 0.67 (95% CI: 0.30 to 1.47), indicating a slightly lower risk in the folic acid group, although the difference was not statistically significant (p=0.37). HELLP syndrome occurred in 2 (0.3%) cases in the folic acid group and 4 (0.5%) cases in the placebo group. The risk ratio was 0.5 (95% CI: 0.43 to 0.57), suggesting a lower risk in the folic acid group and the difference was found statistically significant (p<0.05). Severe pre-eclampsia occurred in 12 (1.6%) cases in the folic acid group and 19 (2.5%) cases in the placebo group. The risk ratio was 0.63 (95% CI: 0.02 to 0.90), indicating a significantly lower risk in the folic acid group (p<0.05). There were no cases of maternal death in either group. Pre-term birth (less than 37 weeks' gestation) occurred in 25 (3.3%) cases in the folic acid group and 33 (4.4%) cases in the placebo group. The risk ratio was 0.76 (95% CI: 0.46 to 0.05), indicating a slightly lower risk in the folic acid group, but the difference was not statistically significant (p=0.05). Other outcomes such as early pre-term birth, stillbirth, neonatal death, perinatal mortality, early-onset sepsis, and admission to NICU for 24 hr or more also showed that the folic acid supplementation may have a protective effect. However, there was no significant difference observed in the occurrence of early pre-term birth, neonatal death, perinatal mortality and admission to the NICU between the two groups.

DISCUSSION

A rise in homocysteine concentration causes placental insufficiency and circulatory disparity, which is theoretically a significant basis for the onset of pre-eclampsia.[26] Many researchers trust that this rise in levels of homocysteine that leads to pre-eclampsia is caused by peroxidative damage to vascular endothelial cells, which results in various unfavourable pregnancy outcomes.[27]

The methylation process is the *in vivo* metabolic pathway of homocysteine.[28] In this reaction, N5,10-Methylenetetrahydrofolate Reductase (MTHFR) catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate.[29] Folic acid is a cofactor for this enzyme and acts as a methyl donor to regenerate methionine. It may thus play a role in the onset and progression of pre-eclampsia. According to one study,[30] pregnant women with hyperhomocysteinemia and low folate status are more likely than the control group to develop pre-eclampsia. Folic acid supplementation has been demonstrated to lower the risk of pre-eclampsia. Hypohomocysteinemia is thought to impair the

Table 3: Primary and secondary outcomes of the participants.

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

Data were expressed as n (%). HELLP=Haemolysis, Elevated liver enzymes, Low platelets. NICU=Neonatal Intensive Care Unit.

vascular endothelium of the developing placenta, and folic acid may affect this level.[31]

Furthermore, a folate shortage may cause apoptosis in human cytotrophoblast cells, affecting placental development and trophoblast invasion.[32,33] In one study, Fernández *et al.*[34] found no correlation between pre-eclampsia and the rise in homocysteine during the early stages of pregnancy, and that pre-eclampsia could not be prevented by early folic acid treatment. In our study, we conducted a randomized clinical trial of high-dose folic acid administration in pregnant women at high risk of pre-eclampsia because there has been conflicting evidence about whether folic acid can reduce the incidence of pre-eclampsia. The high folic acid dosage (4 mg/day) was derived from previously published methods.[30,35,36]

According to the present trial, folic acid supplementation can considerably lower the incidence of pre-eclampsia compared to the placebo group. The findings of Wang *et al.'s* study,[37] which showed that folic acid supplementation and increased dietary folate intake during pregnancy lower the incidence of pre-eclampsia, corroborated this finding. Numerous studies have also confirmed the advantages of folic acid supplementation in the early stages of pregnancy.[38,39] The research conducted by Martinussen *et al.*[40] 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 pre-term labour considerably and the early start of pre-eclampsia.[36] Among the secondary outcomes, we found that pre-term birth, stillbirth, perinatal mortality, neonatal death, retinopathy of prematurity, early-onset sepsis, intraventricular hemorrhage and admission to NICU for 24 hr or more were remarkably lowered in the folic acid group compared to the placebo group.

CONCLUSION

According to the study, pregnant women with hypertension who take large dosages of folic acid supplements had a decreased risk of developing pre-eclampsia and other related issues. Nonetheless, it is usually wise to conduct a comprehensive evaluation, including offspring follow-up when available, before proposing medications. More *in vivo* and *in vitro* studies on the folic acid mechanism in lowering pre-eclampsia are needed to confirm the results.

LIMITATIONS

The study did not assess the potential side effects or adverse events associated with high-dose folic acid supplementation. The study did not consider other potential confounding factors that may influence the development of pre-eclampsia, such as dietary factors, lifestyle factors, or genetic predisposition. The study did not provide information on the long-term outcomes or follow-up of the participants after delivery.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

BMI: Body Mass Index; **RR:** Risk ratio; **CI:** Confidence interval; **SGA:** Small gestational age; **HELLP:** Haemolysis, Elevated liver enzymes, Low platelets; **NICU:** Neonatal Intensive Care Unit; **MTHFR:** N5,10-methylenetetrahydrofolate reductase; **SD:** Standard Deviation.

AUTHOR CONTRIBUTIONS

Hongxia Luo contributed to the study's conception and design. Material preparation and data collection were performed by Honglian Ma, Youxin Wang and Hongxia Luo. Data analysis was performed by Honglian Ma, Youxin Wang. The first draft of the manuscript was written by Hongxia Luo, Honglian Ma and all authors commented on previous versions. Finally, all authors read and approved the final manuscript.

ETHICAL APPROVAL

All the patients gave their approval to the author during their treatments. The study made use of the patients' data while protecting their anonymity. The Declaration of Helsinki (World Medical Association) was followed when conducting the study.

CONSENT TO PARTICIPATE

All patients (or parents/guardians) gave written informed consent to participate in the study.

SUMMARY

Pre-eclampsia is a dangerous pregnancy ailment that affects 3-5% of pregnancies and is the cause of morbidity and mortality in women. There is increasing evidence that high-dose or usage of folic acid for a more extended period could successfully treat pre-eclampsia. To offer more concrete evidence supporting this theory, a further thorough investigation is necessary. Therefore, the present study was designed to determine the effect of high-dose folic acid in preventing pre-eclampsia in women with hypertension. This study was a randomized clinical trial involving 1500 pregnant women, with 750 in the folic acid group and 750 in the placebo group. Participants in the folic acid group received four 1 mg folic acid tablets daily from 8 to 16 weeks of gestation until birth. The primary outcome measure was the incidence of pre-eclampsia, and the secondary outcome measures included early pre-term birth, stillbirth, neonatal death, perinatal mortality, early-onset sepsis, and admission to NICU for 24 hr or more. The incidence of pre-eclampsia was significantly lower in the folic acid group compared to the placebo group (5.3% vs 10%) with a Risk Ratio (RR) of 0.53. The study findings support the use of high-dose folic acid supplementation as a preventive strategy for pre-eclampsia in pregnant women with hypertension.

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