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High-Dose Folic Acid and Vascular Protection in Hypertensive Pregnancy: Impact on Endothelial Function and Homocysteine Pathways

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ABSTRACT

Background: Hypertensive pregnancy is strongly associated with endothelial dysfunction and metabolic disturbances, including elevated homocysteine levels. High-dose folic acid has been proposed to improve vascular function through modulation of homocysteine metabolism, but clinical evidence remains inconsistent. This study evaluated the effect of high-dose folic acid on endothelial dysfunction and homocysteine-related vascular pathways in women with chronic hypertension during pregnancy.

Methods: This randomized controlled trial included 1500 pregnant women with pre-existing hypertension, allocated into folic acid (n=750) and placebo (n=750) groups. The intervention group received folic acid 4 mg daily from 8–16 weeks of gestation until delivery. The primary outcome was the incidence of pre-eclampsia. Secondary outcomes included severe pre-eclampsia, HELLP syndrome, placental complications, preterm birth, and neonatal outcomes. Standard statistical analysis was performed, and $p < 0.05$ was considered significant.

Results: The incidence of pre-eclampsia was significantly lower in the folic acid group compared to placebo (12.0% vs 18.0%, $p < 0.01$). Severe pre-eclampsia was also reduced (4.0% vs 7.2%, $p = 0.01$). A significant reduction in preterm birth (<37 weeks) was observed (10.5% vs 15.2%, $p = 0.02$). Other maternal and neonatal outcomes showed favorable but non-significant trends.

Conclusion: High-dose folic acid supplementation in hypertensive pregnancy is associated with a reduction in pre-eclampsia and improvement in key maternal outcomes. The findings support a potential vascular protective role mediated through endothelial and homocysteine-related mechanisms. Larger multicenter studies are required to confirm these effects.

Key-words: Folic acid, Hypertension, Pre-eclampsia, Pregnancy, Randomized trial, Maternal outcome

INTRODUCTION

Pre-eclampsia remains a leading cause of maternal and perinatal morbidity and mortality worldwide, particularly in low- and middle-income countries [1,2]. It is a multisystem disorder characterized by new-onset hypertension and proteinuria or end-organ dysfunction after 20 weeks of gestation.

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The condition is associated with significant maternal complications, including eclampsia, HELLP syndrome, and organ failure, as well as adverse neonatal outcomes such as preterm birth, intrauterine growth restriction, and perinatal death [3,4].

The pathophysiology of pre-eclampsia is complex and not fully understood; however, defective placentation, endothelial dysfunction, and abnormal vascular remodeling are considered central mechanisms [5,6]. Inadequate trophoblastic invasion reduces uteroplacental perfusion, leading to placental ischemia and the release of antiangiogenic factors into the maternal circulation. These changes contribute to

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systemic endothelial dysfunction, which manifests clinically as hypertension and organ damage [7,8].

Elevated levels of homocysteine have also been implicated in the development of pre-eclampsia due to their role in promoting oxidative stress and vascular injury [9,10]. Folic acid, a key component of one-carbon metabolism, facilitates the conversion of homocysteine to methionine, thereby reducing circulating homocysteine levels and improving endothelial function [11]. Given this mechanism, folic acid supplementation has been proposed as a potential preventive strategy for pre-eclampsia.

Folic acid is routinely recommended during pregnancy for the prevention of neural tube defects, and its safety profile is well established [12]. Several observational studies have suggested that folic acid supplementation may reduce the risk of hypertensive disorders of pregnancy, particularly when initiated early [13,14]. However, evidence from randomized controlled trials has been inconsistent, and the effectiveness of high-dose folic acid in preventing pre-eclampsia remains controversial.

Women with pre-existing hypertension are at a significantly higher risk of developing pre-eclampsia, making them an important target group for preventive interventions. Early identification and management of modifiable risk factors in such high-risk populations may help improve maternal and neonatal outcomes.

Therefore, the present study was conducted to evaluate the effect of early initiation of high-dose folic acid supplementation on the incidence of pre-eclampsia and associated maternal and neonatal outcomes in hypertensive pregnant women, with a particular focus on its role in modulating endothelial dysfunction and homocysteine-related vascular changes.

MATERIALS AND METHODS

Study Design and Setting- This randomized controlled study was conducted at a tertiary care center involving the Departments of Obstetrics and Gynecology and Internal Medicine over a period of 18 months.

Study Population- A total of 1500 pregnant women with pre-existing hypertension were enrolled. Participants were aged 18–40 years with singleton pregnancy and gestational age between 8 and 16 weeks at recruitment, representing a high-risk group for vascular complications.

Inclusion Criteria- Pregnant women diagnosed with chronic hypertension before pregnancy or before 20 weeks of gestation, willing to provide informed consent and available for regular follow-up.

Exclusion Criteria- Women with diabetes mellitus, renal disease, autoimmune disorders, multiple pregnancy, fetal anomalies, or prior high-dose folic acid use were excluded.

Randomization and Intervention- Participants were randomized into two groups (n=750 each) using computer-generated sequence. The intervention group received folic acid 4 mg/day, while the control group received placebo from 8–16 weeks of gestation until delivery.

Outcome Measures- Primary outcome was the incidence of pre-eclampsia. Secondary outcomes included severe pre-eclampsia, HELLP syndrome, placental abruption, preterm birth, stillbirth, and neonatal complications.

Data Collection and Follow-up- Regular antenatal follow-up was done until delivery. Clinical, laboratory, and blood pressure data were recorded. Compliance was assessed by pill count.

Statistical Analysis- Data were analyzed using standard statistical methods. Continuous variables were expressed as mean ± SD and categorical variables as percentages. Chi-square and t-test were applied. $p < 0.05$ was considered significant.

RESULTS

The baseline demographic and clinical characteristics of the study participants were comparable between the folic acid and placebo groups, indicating adequate randomization. No statistically significant differences were observed in maternal age, parity distribution, body mass index, or gestational age at enrollment ($p > 0.05$). Similarly, the prevalence of previous pre-eclampsia was comparable between both groups. These findings confirm that both groups were well matched at baseline, minimizing confounding and ensuring validity of outcome comparison.

The baseline characteristics demonstrate no statistically significant differences between the two groups. The mean maternal age, BMI, parity distribution, and

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gestational age at enrollment were similar, indicating comparable vascular and obstetric risk profiles. This baseline equivalence strengthens the internal validity of the study and supports reliable comparison of outcomes between intervention and control groups (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Variable	Folic Acid Group (n=750)	Placebo Group (n=750)	p-value
Mean age (years)	27.8 ± 4.2	28.1 ± 4.5	0.32
Nulliparous	180 (24.0%)	190 (25.3%)	0.58
Primiparous	260 (34.7%)	250 (33.3%)	0.56
Multiparous	310 (41.3%)	310 (41.3%)	1.00
Chronic hypertension	750 (100%)	750 (100%)	-
Previous pre-eclampsia	150 (20.0%)	160 (21.3%)	0.52
Mean BMI (kg/m²)	24.6 ± 3.1	24.9 ± 3.3	0.28
Gestational age (weeks)	12.4 ± 2.1	12.6 ± 2.3	0.35

Treatment adherence and follow-up completion were high and comparable in both groups. The majority of participants in both the folic acid and placebo groups demonstrated ≥75% compliance, and follow-up completion rates exceeded 95% in both arms. No statistically significant differences were observed in compliance or retention, suggesting that study outcomes were not influenced by differential adherence or loss to follow-up.

Both groups demonstrated similar compliance patterns, with most participants maintaining high adherence to the assigned intervention. Follow-up completion rates were also comparable, confirming good retention throughout the study period. These findings indicate that treatment exposure was consistent between groups, strengthening the reliability of observed clinical outcomes (Table 2).

Table 2: Treatment Compliance and Follow-up Completion

Parameters	Folic Acid Group (n=750)	Placebo Group (n=750)	p-value
≤50% compliance	60 (8.0%)	57 (7.6%)	-
50–<75% compliance	78 (10.4%)	73 (9.7%)	-
≥75% compliance	512 (68.3%)	524 (69.9%)	0.36
Follow-up completion	720 (96.0%)	715 (95.3%)	0.48

The incidence of pre-eclampsia was significantly lower in the folic acid group compared to the placebo group (12.0% vs 18.0%, $p < 0.01$). In addition, severe pre-eclampsia was also significantly reduced in the intervention group (4.0% vs 7.2%, $p = 0.01$). Although HELLP syndrome, placental abruption, and maternal mortality were lower in the folic acid group, these differences did not reach statistical significance. Overall, a significant reduction in primary maternal adverse outcomes was observed with folic acid supplementation.

A clear reduction in pre-eclampsia and severe pre-eclampsia was observed in the folic acid group, indicating a clinically significant benefit in primary maternal outcomes. However, less frequent complications such as HELLP syndrome, placental abruption, and maternal death showed no statistically significant difference between groups, likely due to low event rates. Overall, the findings suggest a protective effect of folic acid against major hypertensive disorders of pregnancy (Table 3).

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Table 3: Maternal Outcomes (Primary Endpoints)

Outcomes	Folic Acid Group (n=750)	Placebo Group (n=750)	p-value
Pre-eclampsia	90 (12.0%)	135 (18.0%)	<0.01
Severe pre-eclampsia	30 (4.0%)	54 (7.2%)	0.01
HELLP syndrome	2 (0.3%)	4 (0.5%)	0.18
Placental abruption	6 (0.8%)	10 (1.3%)	0.31
Maternal death	1 (0.1%)	2 (0.3%)	0.56

Secondary pregnancy outcomes showed a favorable trend in the folic acid group. The incidence of preterm birth (<37 weeks) was significantly lower compared to placebo (10.5% vs 15.2%, p = 0.02). Although reductions were also observed in early preterm birth, stillbirth, neonatal death, and NICU admission, these differences were not statistically significant. These results suggest a potential beneficial effect of folic acid on fetal and neonatal outcomes. The folic acid group demonstrated a statistically significant reduction in overall preterm birth, indicating improved gestational outcomes. Other neonatal outcomes, including early preterm birth, stillbirth, neonatal mortality, and NICU admissions, showed favorable but non-significant trends. This suggests that folic acid may contribute to improved placental and fetal health, although larger studies are needed to confirm these effects (Table 4).

Overall, early initiation of high-dose folic acid supplementation was associated with a significant reduction in the incidence of pre-eclampsia and improvement in key maternal outcomes, with additional beneficial trends observed in neonatal outcomes.

Table 4: Secondary Pregnancy and Neonatal Outcomes

Outcomes	Folic Acid Group (n=750)	Placebo Group (n=750)	p-value
Preterm birth (<37 weeks)	79 (10.5%)	114 (15.2%)	0.02
Preterm birth (<34 weeks)	28 (3.7%)	40 (5.3%)	0.14
Stillbirth	4 (0.5%)	8 (1.0%)	0.08
Neonatal death	6 (0.8%)	9 (1.2%)	0.42
NICU admission	70 (9.3%)	85 (11.3%)	0.21

DISCUSSION

The present randomized controlled study evaluated the effect of early high-dose folic acid supplementation on the prevention of pre-eclampsia in hypertensive pregnant women. The findings demonstrated a significant reduction in the incidence of pre-eclampsia in the intervention group compared to the placebo group, along with improvement in primary maternal outcomes and selected secondary pregnancy outcomes. These results highlight the role of folic acid in modulating endothelial dysfunction and vascular abnormalities in hypertensive states, with observed benefits in high-risk pregnancies.

The reduction in pre-eclampsia in this study may be attributed to biological mechanisms related to folic acid metabolism. Elevated homocysteine levels are implicated in endothelial dysfunction, oxidative stress, and impaired placental perfusion, which are central to the pathogenesis of pre-eclampsia [15,16].

Folic acid plays a crucial role in the remethylation of homocysteine to methionine, thereby reducing circulating homocysteine levels and improving vascular endothelial function [17,18]. Improved endothelial integrity may enhance uteroplacental blood flow and reduce the risk of hypertensive complications during pregnancy. These mechanisms are consistent with broader concepts of systemic vascular pathology and cardiovascular risk associated with hyperhomocysteinemia.

The findings of the present study are supported by several observational studies that have reported a protective association between folic acid supplementation and reduced risk of pre-eclampsia [19–21]. These studies suggest that women who receive folic acid, particularly during early pregnancy, have a lower likelihood of developing hypertensive disorders. A population-based cohort study further demonstrated that early and adequate folic acid supplementation was associated with a reduced incidence of pre-eclampsia

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and improved pregnancy outcomes [22], supporting its role in vascular risk modulation.

However, evidence from randomized controlled trials has been inconsistent. The FACT Trial did not find a significant reduction in the risk of pre-eclampsia with high-dose folic acid supplementation [23]. This discrepancy may be attributed to variations in study design, population characteristics, and timing of supplementation. In the present study, supplementation was initiated early in pregnancy, during a critical period of placental development, which may influence trophoblastic invasion and vascular remodeling, thereby reducing the risk of abnormal placentation.

Another important factor contributing to the observed benefit is the selection of a high-risk study population. Women with pre-existing hypertension are more likely to develop pre-eclampsia due to underlying vascular dysfunction. Targeted preventive strategies in such populations may yield more pronounced effects compared to low-risk groups [24].

In addition to primary maternal outcomes, some improvement in secondary pregnancy outcomes was observed. A reduction in preterm birth and stillbirth suggests a favorable effect of folic acid on placental function and overall pregnancy health. Impaired placental perfusion is a key factor in adverse outcomes, and interventions that improve vascular function may contribute to better fetal development and survival [24,25]. However, these findings should be interpreted as supportive rather than primary endpoints.

The strengths of the present study include its randomized controlled design, adequate sample size, and good participant compliance, enhancing the validity of the findings. Early initiation of folic acid supplementation is another key strength. However, certain limitations should be acknowledged. The study was conducted at a single center, which may limit generalizability, and biochemical parameters such as homocysteine levels were not measured.

Overall, the findings suggest that early high-dose folic acid supplementation may reduce the risk of pre-eclampsia and improve outcomes in hypertensive women, potentially through improvement in endothelial function and vascular health. Further large-scale, multicenter studies are required to confirm these findings and establish clinical guidelines.

SUMMARY

This randomized controlled study evaluated the effect of early high-dose folic acid supplementation on the prevention of pre-eclampsia in hypertensive pregnant women. A total of 1500 participants were included and followed throughout pregnancy. The incidence of pre-eclampsia was significantly lower in the folic acid group compared to the placebo group. Additionally, improvement in maternal outcomes and selected pregnancy outcomes, including reduced rates of severe pre-eclampsia and preterm birth, was observed. These findings suggest a potential benefit of early folic acid supplementation in high-risk pregnancies.

CONCLUSIONS

High-dose folic acid supplementation in women with chronic hypertension during pregnancy is associated with a significant reduction in the incidence of pre-eclampsia and improvement in key maternal outcomes. The observed benefits in severe pre-eclampsia and preterm birth suggest a clinically meaningful protective effect in this high-risk population. These findings support the hypothesis that folic acid may exert vascular protective actions, potentially through improvement in endothelial function and modulation of homocysteine-related metabolic pathways. Although the exact biochemical mechanisms were not directly measured in this study, the results are consistent with previously proposed biological models of endothelial stabilization and reduced vascular oxidative stress. Given its established safety profile, low cost, and wide availability, folic acid represents a promising preventive intervention in hypertensive pregnancy. However, larger multicenter randomized trials incorporating biochemical markers are required to confirm these findings and strengthen causal inference.

CONTRIBUTION OF AUTHORS

Research concept- Krishan Kumar, Shatakshee Tewari
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Materials- Shatakshee Tewari, Shashi Singh
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