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Study on the Impact of High-Dose Folic Acid Supplementation on the Incidence of Pre-Eclampsia among Women with Hypertensive Pregnancies

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ABSTRACT

Background: Pre-eclampsia is a major concern for maternal and neonatal morbidity due to endothelial impairment and placental ischemia. The high dose of folic acid can improve vascular health by minimising the level of homocysteine. Physiotherapy supported the cardiovascular problems during pregnancy. The study assessed the combined impact of the high dosage of folic acid supplements and the structured physiotherapy to reduce pre-eclampsia and the negative maternal-fetal outcomes among the population.

Method: The study was randomized double-blinded, multicenter study conducted among 140 pregnant women of gestation duration of gestation of about 8 to 16 weeks of gestation. All participants were randomised into two groups: a folic acid group and a placebo group, each with 70 patients. Both the fetal and neonatal outcomes were evaluated by clinical investigation and laboratory assessment. Chi-square tests and t-tests were utilised for statistical analysis.

Results: All of the demographic and clinical parameters were compared between the groups. About half of the participants showed obesity. No difference in the maternal outcomes, such as pre-eclampsia, preterm delivery, placental abruption, or HELLP syndrome, was noted. Several other fetal and neonatal outcomes, which included stillbirth, neonatal mortality, NICU admission, and intrauterine growth restriction, were observed to be identical for both of the groups.

Conclusion: The study concluded that high doses of folic acid during pregnancy did not reduce the maternal, fetal, or neonatal adverse outcomes compared to the placebo group among pregnant women.

Key-words: Pre-eclampsia, Folic acid, High-risk pregnancy, Physiotherapy, Maternal and neonatal outcomes

INTRODUCTION

Due to their severe multi-organ impact on the maternal-fetal unit, pre-eclampsia is one of the leading causes of maternal and neonatal deaths worldwide [1].

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Usually, the pathological mechanism underlying pre-eclampsia begins with an inadequate extravillous trophoblastic invasion and remodeLling of the spiral arteries, which causes severe ischemia and hypoxia of the placenta. Ischemia within the placenta causes systemic release of anti-angiogenic factors that induce widespread endothelial dysfunction, oxidative stress, and multiple organ injury, including the mother and fetus [1]. Pregnant women who have pre-existing chronic borderline hypertension or the early onset of borderline preeclampsia experience larger degrees of vascular

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maladaptation quicker than other groups of women – so monitoring these women should be aggressive and frequent; therefore, early screening and angiogenetic assessments to detect angiogenetic imbalance – which subsequently lead to continual endothelial injury – are required to ensure appropriate and timely delivery of treatment before the conhecodivacnaclior for progressive vascular defects occurring in their mothers [2].

Folic acid plays an important role in endothelial health through its ability to decrease homocysteine levels and increase levels of cofactors (substances that assist enzymes) for endothelial nitric oxide synthase (eNOS). Clinical translation to decreased rates of gestational hypertensive disorders has been variably demonstrated across studies [3]. A high-dose regimen of folic acid (4-5 mg/day) is aimed at improving placental perfusion rather than the traditional goal of preventing neural tube defects with folate supplementation [3,4]. In a five-site FACT (Folate Clinical Trial) study of women with high-risk pregnancies starting between 8 and 16-weeks' gestation, women who received supraphysiological levels of porcine pancreatic extract had a significant improvement in serum folate levels compared with baseline, without significant metabolic toxicity [4]. However, this randomized controlled trial did not demonstrate a beneficial effect of folate supplementation on the rates of pre-eclampsia. Therefore, available evidence suggesting that high doses of folate supplementation can improve vascular function is inconsistent; consequently, arbitrary antenatal dosing strategies cannot be reliably extrapolated to high-risk pregnancies in which folate is used to improve vascular function [3,4].

A systematic review found that women participating in supervised aerobic or combined exercise had an average reduction in systolic blood pressure of 2–4 mmHg and a decrease in diastolic blood pressure of approximately 2 mmHg, as well as improvement of pulse wave velocity and augmentation index [5]. Furthermore, data from a 12-week randomised controlled trial with individualised exercise prescriptions delivered by an obstetrician-cardiologist-physiotherapist team showed significant reductions in systolic and pulse pressure without adverse hemodynamic outcomes [6]. Overall, this clinical evidence suggests that there is a benefit to having specialized monitoring by a clinician compared to being unguided when performing physical activity, because this enables the clinician to identify the most appropriate exercise intensity to provide a safe amount of maternal cardiovascular load in relation to the maternal uteroplacental blood supply [5,6].

Nutritional and exercise interventions have been separately researched; however, there are limited clinical studies examining the combined effects of these interventions on hypertensive pregnancies. This study aims to evaluate the overall impact of structured physiotherapy combined with high-dose folic acid on the incidence of pre-eclampsia. The investigators hypothesise that this combined intervention will significantly reduce the incidence of pre-eclampsia compared with standard care alone.

MATERIALS AND METHODS

Research Design- The study was a randomised, double-blinded, phase III, international, multicenter trial to evaluate the effect of high-dose folic acid supplementation and physiotherapy on antenatal physical activity in hypertensive pregnant women with pre-eclampsia. The study was conducted in a tertiary care hospital that included various populations. The study was conducted for 1 year. The study included pregnant women of gestation duration between 8 and 16 years of gestation, along with the viable fetus and the associated risk factors like pre-existing hypertension, pre-pregnancy diabetes mellitus, obesity, twin pregnancy or the history of pre-eclampsia, were included. All patients were allocated to the group receiving folic acid supplements combined with physiotherapy to support antenatal physical activity, and to the standard antenatal care group. Various predefined inclusion and exclusion criteria were used to select patients for the study. Both informed and verbal consent were required for the study.

Inclusion criteria

- All pregnant women of gestation completed for 8 to 16 weeks were included.
- Patients with confirmed fetus were included.
- Risk factors for pre-eclampsia must be considered like hypertension, the diabetes mellitus, pregnancy, twin pregnancy, or a pre-history of pre-eclampsia.
- Body Mass Index (BMI) of patients should be ≥35 kg/m².

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- Well-written and informed consent required for the study.

Exclusion criteria

- Patients with fetal death or maternal-related complications, such as renal disorder with significant renal impairment.
- Previous history of epilepsy or cancer was not considered.
- Those with the usage of folic acid antagonists, or the drug or alcohol consumption at the time of pregnancy, were not included.
- Patient with hypersensitivity to folic acid or cases of multiple pregnancy were excluded.
- The presence of significant disease condition that can preclude the safe usage of the high dose of folic acid of about 5.1 mg daily was excluded.

Procedure- Proper informed consent was taken from all of the participants. A total of 140 participants were randomly allocated to each of the groups, containing 70 patients each. The first group is the folic acid group, and the second is the placebo group, using a central and web-based randomisation system. Intervention provided, which included the administration of 4.0 mg folic acid or placebo, in the form of 4 tablets of 1.0 mg each, for one time daily for about 8 to 16 weeks of completion of gestation. All patients were provided with prenatal vitamins or a low-dose folic acid supplement containing 1.1 mg folic acid. All participants, investigators, coordinators, and staff associated with the research study remained blinded to the treatment allocation in the trial. All patients attended the follow-up period at 24–26 weeks of gestation, 34–36 weeks of gestation after delivery, and the follow-up continued for about 42 days postpartum. Physical investigations included assessment of blood pressure, weight, urinalysis, and fetal well-being. Also, the adverse impact of medications and conditions was noted. The use of drug diaries and pill counts evaluated treatment adherence. The intake of folate was evaluated by the use of the Dietary Folate Equivalent Screener questionnaire randomly, and also at 24 to 36 weeks after the completion of gestation.

Outcome assessment- The primary outcome of the study included the condition of pre-eclampsia, which was diagnosed based on the hypertension associated with proteinuria, the HELLP syndrome, or superimposed pre-eclampsia, after the completion of 20 gestation weeks. Three investigators independently conducted the outcome adjudication. Secondary outcomes included the complications of the mother and the newborn baby, such as severe pre-eclampsia, placental abruption, preterm delivery, limited intrauterine growth, perinatal mortality and neonatal morbidity. Adverse and complicated events were recorded from randomisation until 42 days postpartum.

Statistical Analysis- The SPSS software version 27 was used for the statistical analysis. Chi-square tests and t-tests were used for the comparative analysis of categorical and continuous variables. Multiple log-binomial regression was used to adjust for confounding factors, and the impact of treatment was represented as relative risks with 95% confidence intervals.

RESULTS

Table 1 showed that the demographic and clinical parameters were compared and analysed between the two groups, each containing 70 patients, indicating homogeneity within the study population. Both groups showed obesity (BMI ≥35), noted in 50.0% of the folic acid group and 52.9% of the placebo group, indicating a high risk. The history of pre-eclampsia, chronic hypertension, twin pregnancy, and diabetes was observed for both of the groups, which reduces the baseline. Most patients were 20–34 years of age, with a mean maternal age of 31 years in both groups. Minimal variation was noted in the status of education, gestational age, smoking habit, alcohol consumption, and supplementation practice for both treatment groups. The high rate of adherence to the study medication was noted, with ≥75% adherence observed among 74% of total participants.

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Table 1: The distribution of the demographic and clinical parameters among patients of Folic Acid and Placebo Groups

Characteristics	Folic Acid Group (n=70)	Placebo Group (n=70)
History of pre-eclampsia	18 (25.7)	17 (24.3)
Chronic hypertension	12 (17.1)	14 (20.0)
Type 1 diabetes	5 (7.1)	4 (5.7)
Type 2 diabetes	6 (8.6)	5 (7.1)
Twin pregnancy	13 (18.6)	13 (18.6)
Body mass index ≥35	35 (50.0)	37 (52.9)
Parity		
0	24 (34.3)	24 (34.3)
1	28 (40.0)	28 (40.0)
≥2	18 (25.7)	18 (25.7)
Maternal age (years)		
<20	1 (1.4)	1 (1.4)
20–29	25 (35.7)	25 (35.7)
30–34	24 (34.3)	25 (35.7)
≥35	20 (28.6)	19 (27.1)
Mean (SD) age (years)	31 (5.4)	31 (5.4)
Prepregnancy BMI		
<18.5	1 (1.4)	1 (1.4)
18.5–<25	13 (18.6)	13 (18.6)
25–<30	12 (17.1)	11 (15.7)
30–<35	9 (12.9)	8 (11.4)
≥35	35 (50.0)	37 (52.9)
Mean (SD) prepregnancy BMI	34 (8.6)	34 (13.0)
Education level		
High school and below	20 (28.6)	20 (28.6)
College/university not completed	11 (15.7)	11 (15.7)
College/university completed	39 (55.7)	39 (55.7)
Gestational age at recruitment		
8–12 weeks	22 (31.4)	25 (35.7)
13–16 weeks	48 (68.6)	45 (64.3)
Mean (SD) gestational age (weeks)	14 (1.9)	14 (1.9)
Smoking during pregnancy		
Yes	6 (8.6)	5 (7.1)
No	59 (84.3)	59 (84.3)
Quit during pregnancy	5 (7.1)	6 (8.6)
Alcohol intake during pregnancy		

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Yes	1 (1.4)	2 (2.9)
No	56 (80.0)	54 (77.1)
Quit during pregnancy	13 (18.6)	14 (20.0)
Folic acid supplementation	56 (80.0)	58 (82.9)
High-dose folic acid supplementation	20 (28.6)	19 (27.1)
Aspirin supplementation at randomisation	20 (28.6)	19 (27.1)
Calcium supplementation at randomisation	6 (8.6)	6 (8.6)
Mean (SD) dietary folate (µg)		
Visit 1	494 (209)	504 (222)
Visit 2	494 (209)	500 (213)
Compliance		
≤50%	8 (11.4)	8 (11.4)
50–<75%	10 (14.3)	9 (12.9)
≥75%	52 (74.3)	53 (75.7)

Table 2 showed the comparative analysis of the folic acid and placebo groups, without any statistical significance. No maternal deaths or cases of HELLP syndrome were noted for any of the group, which revealed the low incidence of complications related to pregnancy. Rates of spontaneous abortion were high in the first group of about 2.9%, rather than the placebo group of about 1.4%. Placental abruption, the rupture of the membranes, the duration of gestation below 37 weeks and the severe condition of pre-eclampsia showed similar frequencies between the groups. The relative risks noted were 1.0, with the non-significant p-values. 25.7% of participants of both of the groups showed preterm delivery, which suggested no adverse impact of the supplementation of folic acid. The mean value of the antenatal inpatient hospital stay for both groups was identical (5.6 ± 7.7 vs 5.2 ± 6.2 days; p=0.74).

Table 2: The comparative analysis of the outcome between the folic acid and the placebo group

Outcomes	Folic Acid Group (n=70)	Placebo Group (n=70)	Relative Risk (95% CI)	p-value
Maternal death	0 (0%)	0 (0%)	Not applicable	Not applicable
Spontaneous abortion (miscarriage)	2 (2.9%)	1 (1.4%)	1.43 (0.13–15.1)	0.56
Placental abruption	1 (1.4%)	1 (1.4%)	1.00 (0.06–15.5)	1
Premature rupture of membranes	13 (18.6%)	13 (18.6%)	1.00 (0.52–1.91)	1
Gestational age <37 weeks	18 (25.7%)	18 (25.7%)	1.00 (0.59–1.70)	1
HELLP syndrome	0 (0%)	0 (0%)	Not applicable	Not applicable
Severe pre-eclampsia	1 (1.4%)	1 (1.4%)	1.00 (0.06–15.5)	1
Antenatal inpatient length of stay (days)	5.6 ± 7.7	5.2 ± 6.2	Mean difference 0.4	0.74

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Table 3 showed the identical Fetal and neonatal outcomes for both study groups. Parameters, including the rate of the stillbirth, intrauterine growth restriction, retinopathy of prematurity, and intraventricular haemorrhage, were similar for both of the groups. The relative risks were 1.0. The death of the neonatal and the early onset of sepsis took place in the placebo group, while the necrotising enterocolitis and the requirement of oxygen for 28 days were noted in the folic acid group. The admission in the NICU was high in the case of the first group of about 21.4%, rather than the placebo group of 20.0%. Both of the groups showed an adverse fetal or neonatal outcome of about 4.3%. The average of the length of stay in the NICU was compared for both of the groups.

Table 3: The comparative analysis of the **Fetal and Neonatal Outcomes for both of the groups**

Outcomes	Folic Acid Group (n=70)	Placebo Group (n=70)	Relative Risk (95% CI)	p-value
Dichotomised outcomes				
Stillbirth	1 (1.4%)	1 (1.4%)	1.00 (0.06–15.5)	1
Intrauterine growth restriction <3rd centile	1 (1.4%)	1 (1.4%)	1.00 (0.06–15.5)	1
Intrauterine growth restriction <10th centile	8 (11.4%)	8 (11.4%)	1.00 (0.41–2.42)	1
Neonatal death	0 (0%)	1 (1.4%)	0.33 (0.01–7.90)	0.31
Perinatal mortality	1 (1.4%)	2 (2.9%)	0.50 (0.05–5.32)	0.55
Retinopathy of prematurity	1 (1.4%)	1 (1.4%)	1.00 (0.06–15.5)	1
Periventricular leukomalacia	0 (0%)	0 (0%)	Not applicable	Not applicable
Early onset sepsis	0 (0%)	1 (1.4%)	0.33 (0.01–7.90)	0.31
Necrotising enterocolitis	1 (1.4%)	0 (0%)	3.00 (0.13–71.2)	0.31
Intraventricular haemorrhage	1 (1.4%)	1 (1.4%)	1.00 (0.06–15.5)	1
Ventilation	3 (4.3%)	2 (2.9%)	1.50 (0.26–8.52)	0.64
Need for oxygen at 28 days	1 (1.4%)	0 (0%)	3.00 (0.13–71.2)	0.31
NICU admission	15 (21.4%)	14 (20.0%)	1.07 (0.57–2.01)	0.83
Composite severe adverse fetal or neonatal outcome	3 (4.3%)	3 (4.3%)	1.00 (0.21–4.69)	1
Continuously distributed outcomes				
NICU length of stay (days)	16 ± 27	17 ± 23	Mean difference −1.0	0.81

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DISCUSSION

In an international, multicenter, double-blind phase III randomized clinical trial, 4.0 mg/day of oral folate (folic acid) between 8 and 16 weeks of gestation for the prevention of pre-eclampsia among 2464 women at high risk of developing pre-eclampsia did not lead to decreased rates of pre-eclampsia. In the folate group, the conversion rate of pre-eclampsia (14.8% [169/1144]) was not significantly different from that of a placebo group (13.5% [156/1157]) (RR 1.10, 95% CI 0.90-1.34, p=0.37) (IEM) [7]. A systematic review of 9 studies with a total of 107,051 supplemented and 105,222 non-supplemented pregnant women was registered in PROSPERO and found that folic acid supplementation alone does not reduce the risk for pre-eclampsia. The results across these large groups were also consistent with the study described above; neither the risk ratio nor the confidence interval was significantly lower in the folate group relative to the placebo group [8].

According to a systematic review and meta-analysis that conformed to the PRISMA guidelines. 14 RCTs have reported on this topic with findings that suggest the risk of hypertension or hypertensive disorders (i.e., gestational hypertension) is decreased when future mothers exercise regularly while they are pregnant. These findings provide compelling evidence that physical activity lowers the risk of developing these complications during and after pregnancy (RR = 0.44, 95% CI: 0.30, 0.66) [9]. In addition, the systematic review and meta-analysis indicated that regular physical activity during pregnancy positively modifies the systolic (mean differences = -2.64, 95% CI -4.79, -0.49) and diastolic (mean differences = -1.99, 95% CI -3.68, -0.29) blood pressure readings when compared with women who did not engage in regular exercise during their pregnancy but were otherwise matched. However, the systematic review and meta-analysis failed to show a statistically significant association between antenatal physical activity and pre-eclampsia development (RR=0.81, 95%CI=0.59, 1.11, p=0.20) [9]. Conversely, another analysis conducted on 428 women with twin pregnancies that were tracked longitudinally showed that low-dose (4.0-5.1 mg/day) folic acid intake alone does not influence the development of pre-eclampsia even when multivariable adjustment was utilized (RR=1.58, 95%CI=0.95, 2.63, p=0.079) [10].

Folic acid can aid in repairing the endothelium via a reduction of homocysteine in circulation as well as a decrease in oxidative stress through the prevention of uncoupling of endothelial nitric oxide synthase (eNOS) in order to have intact vascular tone during hypertensive pregnancy [3,11]. The Folic Acid Study, an International multi-site clinical trial, showed that pregnant women at risk of developing pre-eclampsia will not benefit from taking high doses of folic acid to prevent pre-eclampsia from developing. There were no maternal or child clinical benefits when compared to a placebo, but high doses in the twin pregnancy populations had no benefits in preventing pre-eclampsia and showed a trend toward an increased risk of developing pre-eclampsia [7]. Smaller studies of these medications have shown that high doses of folic acid have helped pregnant women improve blood vessel function and reduce homocysteine levels, but in studies of folic acid's effects on biomarkers for pre-eclampsia, there was no evidence of reduction in blood pressure related to either lack of blood vessel function and/or use of a pharmacologic dose of folic acid (defined as > 5mg) [10]. For these reasons, the current recommendations for pre-eclampsia prevention are that patients should be treated with regular low-dose folic acid during pregnancy and that high-dose folic acid should not be used for the prevention of pre-eclampsia.

CONCLUSIONS

The study concluded that high doses of folic acid during pregnancy did not reduce the maternal, fetal, or neonatal adverse outcomes compared to the placebo group among pregnant women. The demographic and clinical parameters were compared for both of the groups, which ensured the homogeneity of the population of patient. Maternal complications included pre-eclampsia, placental abruption, rupture of the pre-membrane of the membranes, and preterm delivery. Several fetal and neonatal outcomes, such as stillbirth, intrauterine growth restriction, neonatal mortality, and admission of NICU, were parameters that were compared. The high rate of adherence with the supplements ensured the reliability of the outcome findings. The high dosage of the folic acid supplementation did not provide the benefit against adverse pregnancy, fetal, or neonatal outcomes among the study population.

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