ORIGINAL ARTICLE

Effectiveness of Vitamin E Supplementation in Preventing Pre-Eclampsia Among High-Risk Pregnant Women: A Quasi-Experimental Study

Naila Shoukat*, Khansa Iqbal, Humera Noreen, Maliha Sadaf, Sabeen Ashraf, Saliha Afzal

ABSTRACT

Objective: To evaluate the effectiveness of Vitamin E supplementation in preventing preeclampsia among high-risk pregnant women.

Study Design: Quasi-experimental study.

Place and Duration of Study: This study was conducted at the Department of Gynecology and Obstetrics, Holy Family Hospital, Rawalpindi, Pakistan, from 1st March 2025 to 30th June 2025.

Methods: A total of 320 pregnant women between 12 and 16 weeks of gestation, identified as high risk for preeclampsia, were enrolled through non-probability consecutive sampling. Participants were divided equally into two groups: one received Vitamin E supplementation (tocopheryl acetate), and the other received a placebo; both groups continued until delivery. Blood pressure and proteinuria were monitored throughout pregnancy. The primary outcome was the incidence of preeclampsia, diagnosed as new-onset hypertension and significant proteinuria after 20 weeks of gestation. Data were analyzed using SPSS version 26.0, with a Chi-Square test applied to assess associations between variables and preeclampsia incidence.

Results: The mean maternal age was 33.28 ± 6.35 years. Preeclampsia developed in 65 women (20.3%) overall. Vitamin E supplementation significantly reduced the incidence of preeclampsia (12.5% vs. 28.1% within respective groups; 6.3% vs. 14.1% of the total sample), with the logistic regression model confirming it as a significant predictor (*P* = .001). The analysis revealed a negative coefficient (B = -1.008) and an odds ratio of 0.365, indicating that the intervention group was 63.5% less likely to develop the condition.

Conclusion: Vitamin E supplementation in early pregnancy may reduce the risk of preeclampsia among high-risk women, offering a potential preventive strategy in resource-limited healthcare settings.

Keywords: *Antioxidants, Body Mass Index, Dietary Supplements, Gestational Age, Pre-Eclampsia, Pregnancy, Vitamin E.*

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Introduction

Hypertensive disorders of pregnancy, especially preeclampsia, remain major contributors to poor maternal and neonatal outcomes, with disease mechanisms linked to placental oxidative stress and endothelial dysfunction.[1,2] Current management focuses on monitoring and timely delivery, as no curative treatment exists.[3,4] Preventive strategies such as antioxidant therapy, particularly Vitamin E, are being studied to restore vascular balance and reduce risk, especially in resource-limited settings.[5,6] Vitamin E, particularly alpha-tocopherol, exerts its protective effect through neutralization of free radicals, inhibition of lipid peroxidation, and preservation of endothelial cell membrane integrity. By scavenging reactive oxygen species generated during placental ischemia-reperfusion injury, Vitamin E may attenuate the oxidative cascade implicated in the pathogenesis of preeclampsia,

Department of Obstetrics and Gynecology
Holy Family Hospital
Rawalpindi Medical University, Rawalpindi, Pakistan

Correspondence:
Dr. Naila Shoukat
Department of Obstetrics and Gynecology
Holy Family Hospital
Rawalpindi Medical University, Rawalpindi, Pakistan
E-mail: nailashoukat530@gmail.com

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thereby protecting placental vasculature and maintaining normal blood pressure regulation.[7,8]

Evidence from clinical trials investigating antioxidants in pregnancy has yielded mixed outcomes. In a randomized controlled trial, Aminuddin NA et al. demonstrated a reduction in preeclampsia incidence among women receiving the tocotrienol-rich fraction (TRF), a form of Vitamin E, with an incidence of 0.7% in the intervention group versus 4.1% in the placebo group.[5] Mahdy ZA et al. reported no statistically significant difference in the incidence of pregnancy-induced hypertension (PIH) between the TRF group (2.6%) and the placebo group (7.4%), despite a lower numerical incidence in the supplemented group.[9] Shi H et al. found that women with lower Vitamin E concentrations during the first trimester had a higher risk of developing preeclampsia, based on a cohort of over 73,000 pregnancies.[10]

The rationale of the current study is to assess the effectiveness of Vitamin E supplementation in preventing preeclampsia among high-risk pregnant women in Pakistan, where hypertensive disorders remain a major contributor to maternal morbidity and mortality. This investigation aims to generate locally relevant evidence by addressing oxidative stress, a key factor in the disease process, and evaluating the practicality of integrating antioxidant supplementation into maternal care in resource-limited settings. The findings may support the use of Vitamin E as a cost-effective preventive strategy to reduce hypertensive complications during pregnancy and improve maternal health outcomes.

Methods

This quasi-experimental study was conducted at the Department of Gynecology and Obstetrics, Holy Family Hospital, Rawalpindi, Pakistan, from 1st March 2025 to 30th June 2025, following approval from the Institutional Ethics Committee vide letter no: 618/IREF/RMU/2024, dated 15th February 2024. The sample size was determined using the WHO sample size calculator, based on estimated preeclampsia incidence rates of 0.7% in the Vitamin E group and 4.1% in the placebo group, with a 5% level of significance and 80% statistical power.[5] The calculated sample size was 317. For ease of allocation, 320 participants were enrolled and divided into two equal groups of 160 each.

Participants were selected through non-probability consecutive sampling. Eligible women were between 20 and 40 years of age, with a confirmed gestational age of 12 to 16 weeks on ultrasound and categorized as high risk for preeclampsia. Risk factors included obesity (BMI >30 kg/m²), previous preeclampsia, placental abruption, gestational history of gestational hypertension, gestational diabetes mellitus, multifetal pregnancy, or a first-degree family history of hypertension. Women with chronic hypertension, those on antihypertensive medication, known allergy to Vitamin E, chronic liver disease, or lipid malabsorption disorders were excluded.

After obtaining written informed consent, baseline demographic and clinical data were recorded, including maternal age, gestational age, parity, family history of hypertension, and anthropometric measurements used to calculate BMI. Blood pressure readings were documented at the booking visit between 12 and 16 weeks of gestation. Participants were assigned to two groups under the supervision of the attending consultant. Group A Received Vitamin E supplementation in the form of tocopheryl acetate capsules (400 IU/day), while Group B received an identical-looking placebo capsule containing an inert substance (micro-crystalline cellulose). Supplementation commenced between 12 and 16 weeks of gestation and continued until delivery. Participants were monitored throughout pregnancy for preeclampsia, defined as new-onset hypertension (systolic ≥140 mmHg or diastolic ≥90 mmHg) and significant proteinuria (≥300 mg/day) after 20 weeks' gestation in women without prior hypertension or proteinuria. Blood pressure was measured at each antenatal visit using a sphygmomanometer and the auscultatory method, with the baseline reading taken during the first visit. Proteinuria was assessed using dipstick analysis of midstream urine samples, with results interpreted by the duty resident. A dipstick reading of +1 or greater was considered significant. The primary outcome of the study was the incidence of preeclampsia during the antenatal period.

Data were analyzed using SPSS version 26.0, presenting numerical data as means ± SD and categorical data as frequencies and percentages. The Pearson Chi-Square test was used to assess

associations between categorical variables and preeclampsia, with $P \leq 0.05$ considered significant. Stratified analysis further evaluated the effect of Vitamin E supplementation across various maternal and obstetric risk factors.

Results

The study enrolled 320 pregnant women. The mean maternal age was 33.28 ± 6.35 years, with a range of 23 to 44 years. A total of 128 women (40.0%) were aged between 18 and 30 years, while 192 women (60.0%) were between 31 and 45 years. Gestational age at presentation ranged from 10 to 20 weeks, with 154 participants (48.1%) presenting between 10 and 15 weeks and 166 participants (51.9%) presenting between 16 and 20 weeks. Regarding body mass index (BMI), 122 women (38.1%) had a normal BMI, 185 (57.8%) were overweight, and 13 (4.1%) were obese. Regarding parity, 180 participants (56.3%) were multiparous, while 140 (43.8%) were primiparous. A previous history of preeclampsia was reported in 10 women (3.1%), and 23 women (7.2%) had a history of placental abruption. Sixty participants (18.8%) had a history of gestational diabetes mellitus. A family history of hypertension in a first-degree relative was present in 21 women (6.6%), while 9 women (2.8%) reported a history of multifetal gestation.

There were no statistically significant differences in baseline characteristics between the Vitamin E and placebo groups. During the study period, preeclampsia was diagnosed in 65 women (20.3%), whereas 255 women (79.7%) did not develop the condition. A significant association was found between Vitamin E supplementation and the incidence of preeclampsia, with fewer cases observed in the Vitamin E group (20 women, representing 12.5% of that group and 6.3% of the total sample) compared to the placebo group (45 women, representing 28.1% of that group and 14.1% of the total sample) ($\chi^2 = 12.066$, $P = 0.001$) (Figure 1).

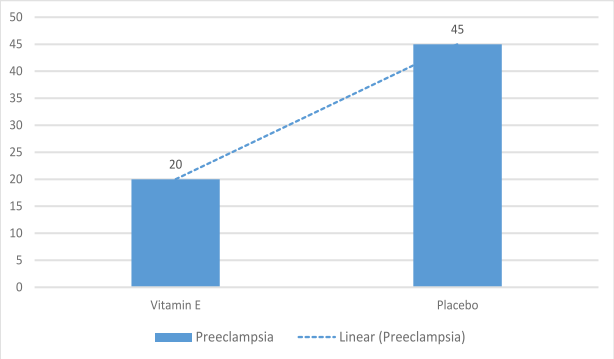

Fig.1: Incidence of Preeclampsia by Intervention Group (Vitamin E vs. Placebo)

The mean gestational age at the time of preeclampsia diagnosis was slightly higher in the Vitamin E group (30.7 ± 3.31 weeks) than in the Placebo group (29.6 ± 2.36 weeks). However, this difference was not statistically significant ($P = 0.194$). Stratified analysis demonstrated that the reduction in preeclampsia incidence associated with Vitamin E supplementation was consistent across maternal age groups, gestational age at presentation, parity, BMI categories, and obstetric risk factors, as detailed in Table 1 and Table 2.

Table 1: Maternal demographic risk factors and incidence of preeclampsia in vitamin E vs. placebo groups

Parameters		Preeclampsia	Placebo (N, %)	Vitamin E (N, %)	χ^2	*P*-value
Age groups	18-30 years	No	(45, 35.16%)	(58,45.31%)	6.451	0.011
		Yes	(18, 14.06%)	(7, 5.47%)		
	31-45 years	No	(70, 36.46%)	(82, 42.71%)	5.827	0.016
		Yes	(27, 14.06%)	(13, 6.77%)		
Gestational age at presentation	10-15 weeks	No	(54, 35.06%)	(71, 46.10%)	10.046	0.002
		Yes	(22, 14.29%)	(7, 4.55%)		
	16-20 weeks	No	(61, 36.75%)	(69, 41.57%)	3.246	0.072
		Yes	(23, 13.86%)	(13, 7.83%)		
Parity	Multiparous	No	(66, 36.67%)	(77, 42.78%)	5.392	0.020
		Yes	(25, 13.89%)	(12, 6.67%)		
	Primiparous	No	(49, 35.00%)	(63, 45.00%)	6.866	0.009
		Yes	(20, 14.29%)	(8, 5.71%)		

Table 2: Medical and obstetric history risk factors for preeclampsia in Vitamin E vs. placebo groups

Parameters		Preeclampsia	Placebo (N, %)	Vitamin E (N, %)	χ^2	*P*-value
History of pre-eclampsia	No	No	(110, 35.48%)	(137, 44.19%)	12.860	<0.0001
		Yes	(44, 14.19%)	(19, 6.13%)		
	Yes	No	(5, 50.00%)	(3, 30.00%)	0.104	0.747
		Yes	(1, 10.00%)	(1, 10.00%)		
Placental abruption	No	No	(107, 36.03%)	(130, 43.77%)	11.829	0.001
		Yes	(42, 14.14%)	(18, 6.06%)		
	Yes	No	(8, 34.78%)	(10, 43.48%)	0.379	0.538
		Yes	(3, 13.04%)	(2, 8.70%)		
History of gestational diabetes mellitus	No	No	(94, 36.15%)	(115, 44.23%)	9.174	0.002
		Yes	(35, 13.46%)	(16, 6.15%)		
	Yes	No	(21, 35.00%)	(25, 41.67%)	2.856	0.091
		Yes	(10, 16.67%)	(4, 6.67%)		
Family of HTN in 1st relative	No	No	(105, 35.12%)	(133, 44.48%)	11.886	0.001
		Yes	(42, 14.05%)	(19, 6.35%)		
	Yes	No	(10, 47.62%)	(7, 33.33%)	0.359	0.549
		Yes	(3, 14.29%)	(1, 4.76%)		
History of multifetal gestation	No	No	(112, 36.01%)	(138, 44.37%)	11.348	0.001
		Yes	(42, 13.50%)	(19, 6.11%)		
	Yes	No	(3, 33.33%)	(2, 22.22%)	0.225	0.635
		Yes	(3, 33.33%)	(1, 11.11%)		

Table 3: Binary logistic regression results for preeclampsia risk

Variable	B	S.E.	Wald	df	*P* value	OR (Exp(B))	95% C.I. for OR
Vitamin E Group	-1.008	0.297	11.530	1	.001	0.365	[0.204, 0.653]
Constant	2.954	0.509	33.618	1	<.001	19.174	-

The binary logistic regression model was statistically significant, indicating that Vitamin E treatment is a meaningful predictor of preeclampsia risk, as detailed in Table 3. The negative coefficient B = (-1.008) and an Odds Ratio (OR) of 0.365 suggest that the intervention group had significantly lower odds of developing preeclampsia compared to the control group. Individuals receiving Vitamin E were approximately 63.5% less likely to experience preeclampsia, a statistically significant result (*P* = 0.001).

Discussion

Hypertensive disorders of pregnancy remain a major cause of maternal and neonatal morbidity and mortality, with preeclampsia being the most severe form. Its pathogenesis is primarily linked to abnormal placentation, oxidative stress, systemic inflammation, and endothelial dysfunction, all of which contribute to the disease's clinical manifestations.[1,11,12] Current management strategies rely on antihypertensive therapy, close monitoring, and timely delivery, as no intervention has been shown to reverse the underlying disease process.[3,4] This therapeutic gap has led to increasing interest in preventive approaches, particularly those targeting oxidative imbalance. Among potential interventions, Vitamin E has attracted attention for its strong antioxidant properties and role in vascular

protection. Placental ischemia-reperfusion injury during early gestation generates excessive reactive oxygen species (ROS), which promote lipid peroxidation, endothelial dysfunction, systemic inflammation, and maternal hypertension.[2,7,8] Vitamin E, as a lipid-soluble antioxidant, interrupts lipid peroxidation, stabilizes cellular membranes, and helps maintain vascular reactivity. By neutralizing free radicals and enhancing nitric oxide bioavailability, it may restore endothelial function and reduce vascular resistance. Experimental studies confirm that supplementation reduces oxidative stress markers and improves arterial relaxation, supporting the biological plausibility of its role in preventing preeclampsia. Timing appears to be a critical factor: antioxidant therapy introduced early in pregnancy, during placental development and vascular remodeling, may prevent pathological changes, whereas late supplementation may have limited benefit. Despite promising evidence, outcomes have varied across different populations. In low- and middle-income countries, where dietary deficiencies and limited nutritional monitoring are more common, supplementation is more likely to confer measurable benefits, consistent with our findings. Conversely, in populations with adequate baseline intake, the marginal impact may be small, and in certain contexts, elevated serum Vitamin E concentrations have even been associated with increased risk, as observed in a Chinese cohort where higher circulating levels correlated with higher odds of preeclampsia.[13] These inconsistencies may reflect differences in genetic background, comorbid conditions such as obesity and diabetes, and population-specific dietary patterns, all of which influence antioxidant metabolism and efficacy. Therefore, while Vitamin E supplementation appears biologically and clinically plausible as a preventive strategy, especially in nutritionally vulnerable populations, universal application is unlikely to be appropriate. Tailored approaches that consider regional nutritional status and maternal risk profiles may optimize benefits while minimizing potential harms.

Our study demonstrated a significant reduction in the incidence of preeclampsia among women who received Vitamin E supplementation. The incidence in the intervention group was 6.3%, compared with 14.1% in the placebo group (P = 0.001). This protective effect was consistent across age groups, parity categories, and baseline maternal risk factors, suggesting a broad benefit irrespective of demographic variation. These findings support the biological plausibility that Vitamin E can modulate oxidative stress pathways during early gestation, thereby reducing the likelihood of clinical disease manifestation.

The results of this study align with earlier research investigating the association between Vitamin E and the risk of preeclampsia. Aminuddin NA et al. reported that antenatal supplementation with tocotrienol-rich fraction (TRF) significantly lowered the incidence of preeclampsia. In their trial, only 0.7% of women in the intervention arm developed preeclampsia compared with 4.1% in the placebo arm.[5] These findings, much like ours, suggest that Vitamin E may alter the trajectory of disease development when administered during the early stages of placental growth.

Duan S et al. examined serum Vitamin E levels in a large retrospective cohort and found that Vitamin E deficiency independently increased the risk of preeclampsia, with an odds ratio of 2.206.[14] They also reported that lower Vitamin E concentrations were correlated with more severe presentations, further strengthening the association between antioxidant deficiency and disease severity.[14] Similarly, Shi H et al. investigated over 73,000 pregnancies and concluded that women with lower first-trimester Vitamin E levels were significantly more likely to develop preeclampsia. These large-scale studies provide strong epidemiological evidence supporting the hypothesis that antioxidant capacity influences disease risk.[10]

Other interventional studies have produced consistent results. Cardoso and Surve demonstrated that combined supplementation with Vitamin C and E reduced the incidence of both preeclampsia (7% vs. 13%) and severe preeclampsia (2% vs. 7%).[15] In Nigeria, Nnamdi C et al. compared women with preeclampsia against normotensive pregnant women and found significantly lower levels of Vitamin E and C among affected individuals (0.29 ± 0.07 mg/dl vs. 0.64 ± 0.16 mg/dl).[16] These findings reflect a direct biochemical link between antioxidant depletion and the pathogenesis of preeclampsia.

A meta-analysis by Alves P et al., incorporating 32 studies and more than 22,000 participants, reported a modest but statistically significant reduction in preeclampsia incidence with antioxidant supplementation (RR 0.86; 95% CI: 0.75–0.99).[17] This review also noted improvements in intrauterine growth restriction among treatment studies, suggesting that the benefits of antioxidant therapy may extend beyond maternal outcomes. Taken together, the body of evidence from randomized trials, observational studies, and meta-analyses supports a protective role for Vitamin E, although variability in effect sizes and significance persists across different populations and study designs.

Despite consistent trends, not all studies have demonstrated clear benefits. Mahdy ZA et al. investigated the use of tocotrienol-rich fraction in 299 women and observed a lower incidence of pregnancy-induced hypertension in the treatment group (2.6%) compared with the placebo group (7.4%). The difference did not achieve statistical significance (P = 0.058), though the trend was favorable.[9] Their findings suggest that sample size, population characteristics, or variations in supplementation regimen may influence outcomes.

Hemeda MS et al. examined high-risk primigravidas with abnormal uterine artery Doppler readings. Although supplementation with Vitamin C and E led to improved biochemical markers of oxidative stress, no significant reduction in preeclampsia incidence was observed (8% vs. 24%, P = 0.123).[18] These results suggest that antioxidant therapy may alter intermediate pathways but does not consistently translate into reduced clinical events, particularly in high-risk women with established vascular abnormalities.

Christiansen CH et al. performed a meta-analysis of 33,356 women across six trials. They found that only two randomized controlled trials demonstrated significant benefit, while pooled analyses of observational studies showed no clear association (RR 0.85; 95% CI: 0.69–1.03).[19] The heterogeneity of study designs, supplementation protocols, and population characteristics complicates interpretation and suggests that results may not be generalizable across populations.

More strikingly, Liu Y et al. reported paradoxical findings in a matched case-control study of pregnant Chinese women.[13] While dietary Vitamin A intake appeared protective, higher serum Vitamin E concentrations were associated with an increased risk of preeclampsia (OR 11.97; 95% CI: 4.01–35.77).[13] Interestingly, no correlation was observed between dietary Vitamin E intake and disease risk, suggesting that serum levels may reflect complex metabolic or genetic factors not directly influenced by supplementation.

Yang W et al., in a retrospective cohort from China, found no significant difference in serum Vitamin E levels between preeclamptic and normotensive women, although Vitamins A, C, and B12 were significantly lower in affected pregnancies.[20] These results suggest that the antioxidant profile influencing preeclampsia risk may vary by region, with Vitamin E playing a smaller role in some populations than in others. These inconsistencies suggest that Vitamin E supplementation is not universally effective and that its impact may be context dependent. Factors such as population baseline nutritional status, genetic polymorphisms in antioxidant metabolism, dietary habits, and supplementation protocols may all modify its effectiveness.

Our findings carry significant clinical implications. The reduction in preeclampsia incidence observed with Vitamin E supplementation suggests a feasible, low-cost intervention that could be integrated into antenatal care protocols. This is particularly relevant in healthcare systems with limited access to advanced monitoring or therapeutic interventions. For clinical practice, early initiation of supplementation appears essential. The critical period for placental vascular remodeling occurs in the first trimester, and intervention at this stage may prevent the development of irreversible pathophysiological changes. In our cohort, supplementation during 10–20 weeks of gestation demonstrated a significant protective effect, supporting the rationale for early administration. While supplementation alone cannot replace established preventive and monitoring strategies, it may serve as an adjunct to routine antenatal care. When combined with blood pressure monitoring, risk stratification, and timely referral, antioxidant therapy may help reduce the burden of preeclampsia-related complications.

Several limitations are acknowledged. First, adherence to supplementation was self-reported, introducing potential recall and compliance bias. Objective measures, such as pill counts or serum Vitamin E concentrations, were not used. Second, confounding variables such as dietary intake of antioxidants, physical activity, socioeconomic factors, and environmental exposures were not systematically controlled, though they may independently influence preeclampsia risk. The study was limited to maternal outcomes, specifically the incidence of preeclampsia. Important secondary outcomes such as rates of preterm delivery, intrauterine growth restriction, neonatal morbidity, and long-term maternal cardiovascular health were not assessed. These outcomes are crucial for determining the overall clinical relevance of antioxidant therapy. The study was conducted in a single population, and the findings may not be generalizable to populations with different genetic backgrounds, dietary habits, or healthcare systems. This study lacked formal blinding; participants and investigators were aware of group allocations, which may have introduced performance and detection bias. Future studies should adopt double-blind, placebo-controlled designs to strengthen causal inference.

Future research should focus on large, multicenter randomized controlled trials with standardized dosing regimens and rigorous adherence monitoring. Stratification by baseline Vitamin E levels is necessary to identify women most likely to benefit. Combined supplementation with other antioxidants or micronutrients, such as Vitamin C, Vitamin A, or B12, may provide synergistic benefits and should be systematically evaluated. Long-term follow-up of both mothers and offspring will be required to determine whether supplementation reduces the risk of maternal cardiovascular disease or adverse developmental outcomes in children. Since preeclampsia has been linked to increased cardiovascular morbidity in later life, interventions that lower its incidence may have enduring benefits. Exploring genetic and metabolic factors influencing Vitamin E absorption, transport, and utilization may also provide insights into population-level variability in responses. Such work could enable the development of precision supplementation strategies tailored to individual or regional needs.

Conclusion

Vitamin E supplementation significantly reduced the risk of preeclampsia compared with placebo and was a statistically significant predictor of improved maternal outcomes. The intervention group demonstrated substantially lower odds of developing the condition, a protective effect that remained consistent across various maternal risk factors and BMI categories

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Author Contributions

NS: Conception, design of the work, and approval for final submission
KI: Validation of data, interpretation, write-up of results, and approval for final submission
HN: Revising, editing, supervising for intellectual content, and approval for final submission
MS: Writing the original draft, proofreading, and approval for final submission
SA: Manuscript writing for methodology design, investigation, and approval for final submission
SA: Data acquisition, curation, statistical analysis, and approval for final submission
NS is the nominated guarantor and takes full responsibility for the overall content and integrity of the work