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" Safety And Efficacy of Vitamin C And E in Preventing Preeclampsia in High-Risk Pregnant Women: A Randomized, Controlled Study "

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ABSTRACT:

With an impact on 2% to 7% of pregnancies, preeclampsia is a major contributor to maternal and neonatal death. This study examines the potential advantages of vitamin E and C supplements for high-risk expectant women in order to mitigate the risk of .preeclampsia

Methods: This double-arm randomized controlled trial comprised two groups: 588 primigravida women at 18-22 weeks gestation with aberrant uterine artery Doppler readings (84 of whom were identified as high-risk) and the preeclampsia history of fifty women or related conditions. Vitamins C and E, or a placebo, were given to one hundred volunteers at random. Doppler scans and levels of plasminogen activator inhibitors 1 and 2 were used to track their progress throughout the pregnancy (PAI-2).patient's preeclampsia history

Results: Preeclamptic women exhibited significantly higher PAI-1 levels than normotensive women (165 ± 72.9 vs. 110.9 ± 37.7, P = 0.03), whereas PAI-2 levels were substantially lower (104 ± 33.8 vs. 180.7 ± 66.8, P = 0.018). The intervention group had a preeclampsia prevalence of 8%, opposite of what happened in the control group because they a prevalence of 24% (P = 0.123). The occurrence of gestational hypertension (18% vs. 12%, P = 0.713) and blood pressure values between the groups were not significantly different

Conclusion: Taking preeclampsia prevention vitamins C and E did not lower the likelihood of the condition in high-risk pregnant women.. In order to investigate the potential benefits or limitations of antioxidants in the prevention of preeclampsia, it is imperative to conduct larger, multicentre trials

Keywords: Preeclampsia, Vitamin C, Vitamin E, PAI-1, PAI-2

INTRODUCTION:

With a prevalence of 2% to 7% of all pregnancies, preeclampsia is a significant cause of neonatal and maternal mortality. Women who are expectant for the first time (nulliparous) exhibit a higher incidence. There are numerous risk factors connected to preeclampsia, in this case chronic hypertension, insulin resistance, obesity, twin or multiple pregnancies, and a family history of preeclampsia: [1].

Preeclampsia is characterized by a rise in blood pressure, which may be expressed as an SBP of 140 or higher or a DBP of 90 or higher.. Proteinuria is diagnosed by a 24-hour urine collection that contains 300 mg of protein or more, and symptoms include migraines, visual disturbances, and discomfort in the upper epigastric or right upper quadrant [2].

Although the etiology and pathogenesis of preeclampsia are still unclear, some findings suggest that damage to endothelial cells induced by free radicals predisposes to the origin of this condition [3]. Oxidative stress, which results from poor blood supply to the placenta, may cause inflammation and the onset of preeclampsia [4].

Preeclampsia can lead to adverse effects on the mother's health, including cerebral hemorrhage, seizures, visual impairment, acute renal injury, coagulation disorders, and increased risk of placental abruption. All of these complications increase the risk of maternal mortality [5]. For the fetus, it can cause premature birth, intrauterine fetal growth retardation, and miscarriage [6].

The generation of free radicals has the potential to cause endothelial cell dysfunction. To protect endothelial function and lessen the likelihood of preeclampsia, antioxidants may be used to lower oxidative stress [7]. In preeclampsia, the mother's serum oxidative stress levels are higher than normal [8,9]. Vitamins C (ascorbic acid) and E, thanks to their antioxidant characteristics, may protect against preeclampsia and oxidative stress, according to recent studies [10–12].

Vitamin E is an antioxidant that dissolves in lipids, although vitamin C is water-soluble. Their complementary effects have been shown in laboratory settings. [13,14]. One process that vitamin C plays in is the synthesis of nitric oxide (NO). from L-arginine, an essential endothelial relaxing factor, through the action of the NO synthase [15]. Additionally, it has antioxidant activity. Vitamin E is utilized for its capacity to prevent or regulate diseases that are linked to oxidative stress [16,17].

We set out to determine if antioxidant supplementation had any beneficial effects on endothelium and placental function indicators. PAI is an indication of endothelial cell activity as it is mostly generated by endothelial cells. Preeclampsia is characterized by a much more rapid rise in blood PAI-1 levels than the typical course of a pregnancy. In healthy

pregnancies, the plasma concentrations of PAI-2, which the placenta produces, gradually rise; however, when placental function is disrupted, these concentrations fall. While PAI-1 to PAI-2 ratios decrease in healthy pregnancies as a result of the growing placenta, they rise in preeclampsia as a result of the insufficiency of the placenta and the activation of endothelial cells [18,19].

This ratio was employed in our investigation to denote the progression of the disease. One of our secondary outcomes is the prevalence of pre-eclampsia.

Forensic Medicine in Pharmaceutical Research

The fundamental principles of forensic medicine have been implemented in the study of drugs, vitamins, and dietary supplements' safety and efficacy in clinical investigations. Forensic medicine is traditionally used in death investigations, but it can also be effectively used to study the availability, distribution, metabolism, elimination (pharmacokinetics), and effects (pharmacodynamics) of chemicals and their metabolites in humans. Generally, these principles are used in investigations of high-risk chemicals, focusing on the mechanism and cause of death. However, they can also be used to study the influence of drugs, chemicals, and preparations on living human beings, i.e., their safety and efficacy. [20]

The concentrations of the chemicals studied are usually much lower than in postmortem investigations. Other aspects in setting up the study include medicinal, legal, and other conditions, such as the obligatory nature of informed consent from volunteers. [21]

The safety of the preparations is evaluated through tolerance and other studies at the beginning of the investigations. The most important of these studies is the clinical trial (the phase I study with healthy volunteers), where special emphasis is placed on the safety, tolerability, and pharmacokinetics of the preparation. [22]

It is also possible and crucial during the earlier development phase of the drug and its preparations to test their efficacy, with the basic idea still being underdosing and better control of the risks compared to later studies. [23]

The model is also an effort for the wider detection of the efficacy of vitamins, vitamin-like substances, and other over-the-counter preparations. Such investigations are presently largely and perhaps inherently impossible to carry out with the existing and traditional methodology of randomized, double-blind, placebo-controlled studies. Agents with a small therapeutic window and an unwanted side effect profile, such as antidepressant and antipsychotic medications or antibiotics, are focused on. [24]

Role of Forensic Medicine in Investigating Adverse Effects of Vitamin C and E

A review of the history of forensic medicine reveals that it approached background issues, delving into the consideration of complete criminal cases involving individual victims. With the passage of time, it began to deal with various aspects of crimes. In particular, the issue of medicines was discussed, usually dealing with poisonings and the use of medicines. The medical aspects here involved considering the mechanism of action, time of appearance and duration, and the construction of knowing some "norm" on the basis of which to ascertain whether the use of substances was lawfully disturbed. In this case, exploring the safety and efficacy of vitamins could be a basis for the eventual investigation of "adverse effects" by forensic medicine. Vitamins being natural compounds cannot "take vices" onto their own character, and in this sense, cannot be considered as poisonous. However, there might be a consideration on exceeding daily allowed intake on their recommendation either on purpose or by mistake, and in rare and anecdotal cases, doubts on their efficacy. In this regard, vitamins would remain in the domain of medicine and dietary conditions, but there would be no interest in the substantive legal aspect for law enforcement bodies to investigate such conditions by their nature. [25]

In particular, the widespread use of artificial forms of vitamins would have an e-commerce character. Such conditions raise a substantive legal aspect due to the distribution of potentially harmful products, regardless of whether they are toxicological or medicinal compounds. On such a basis, the act would be considered a crime of non-compliance with medicines and medicinal substances and regulation of medicinal drugs and auxiliary medicinal substances, etc. Given such a conjunction of circumstances, when considering the possibility and obligatory investigation of possible cases on "adverse effects" because of the use of vitamins, their safety and efficacy should be studied from the standpoint of forensic medicine. There are several pharmacological aspects based on which the eventual advisory expertise work on ascertaining the "adverse effects" by the use of vitamins could be undertaken. [26]

Patients and Methods

Study Design and Setting

A double-arm randomized controlled trial investigation was conducted at Port Said Hospitals under ERN: MED s.no (137) FCT_005 dated 4/2/2024. The study was a double arm randomized controlled trial in which we divided. The participants were divided into two categories. The first group was administered 1000 mg of vitamin C (Cevitil effervescent, EPICO) and 400 IU of vitamin E (E-viton 400 Pharco), while the second group was administered a placebo.

Participants and Procedure

Two groups were formed from us.: Group I consisted of 588 primigravida women, each of whom was between 20- and 24-weeks gestational age. The Doppler screening of the uterine artery revealed that 42 women had aberrant Doppler waveforms, which suggests an elevated risk of preeclampsia. We requested that these 84 women return for a re-scan at 24 weeks of gestation. Subsequently, 22 women (25%) withdrew from the study as a result of their routine uterine artery scans. Ultimately, 12 additional women withdrew, 8 declined to take medication during pregnancy, and 4 relocated to a different center. Group II consisted of 50 expectant women who had experienced pre-eclampsia, eclampsia, or HELLP syndrome during their previous pregnancies.

Ultimately, we had 100 participants, who were randomly assigned to two groups of 50 women. A placebo was administered to the other group, while one group received a combination of 1000 mg of vitamin C (Cevitil effervescent, EPICO) and 400 IU of vitamin E (E-viton 400 Pharco). During the latter half of their pregnancies, women with a history of preeclampsia and a persistent aberrant uterine artery waveform were subjected to rigorous surveillance, which included assessments every four weeks. This follow-up, in addition to standard obstetric care, guaranteed that the antenatal notes of all participants contained recordings of uterine artery Doppler results. In addition to Doppler, venous blood was collected and processed to measure PAI-1 and PAI-2. The samples were initially placed on ice and subsequently centrifuged three hours following collection. Subsequently, they were stored at -70°C until they were analyzed in more detail.

Outcome

The ratio of PAI-1 to PAI-2 in our study was the primary outcome. While PAI-1 is predominantly produced by endothelial cells, it is a marker for endothelial cell activation. PAI-2 is synthesized by the placenta and is indicative of placental function. The ratio of PAI-1 to PAI-2 diminishes as the placenta increases in size during normal pregnancies. However, in preeclampsia, this ratio is elevated as a result of placental insufficiency and increased endothelial cell activation. Secondary outcomes included preeclampsia and gestational hypertension, as well as their severity. Severe gestational hypertension was diagnosed by two DBP readings of 110 mmHg or higher with a minimum of 4 hours between them or one DBP reading of at least 120 mmHg, while gestational hypertension was diagnosed by two DBP readings of 90 mmHg or higher with a minimum of 4 hours between them. Two results of 2+ or higher on dipstick examination of urine samples or excretion of 300 mg or more in 24 hours constitute a diagnosis of proteinuria. A few examples of negative perinatal outcomes include placental abruption, spontaneous preterm birth (before 37 weeks gestation), intrauterine death, and the birth of neonates who were deemed tiny for gestational age.

Important conclusions about the efficacy of antioxidant supplementation in preventing preeclampsia were drawn from these data.

Statistical analysis

We conducted the statistical analysis using Excel and SPSS version 10 [27]. The study consisted of two main parts. In the first part, we used descriptive statistics to present data as (Mean ± SD) and frequencies in proportion. In the second part, about quantitative data, comparisons between the two groups were made using the student t-test (for mean values with SD) and the chi-square test (for median values with a range and frequency in proportion). The significance level was $p \leq 0.05$, with a confidence interval of 95%.

Results

Study population.

A Doppler assessment was performed on 588 primigravidae with gestational ages ranging from 20 to 24 weeks. 84 women from the initial cohort exhibited aberrant Doppler findings. They were requested to return for a follow-up scan at 24 weeks into their pregnancy. Out of the 84 women, 62 individuals (73.8%) continued to exhibit persistently abnormal findings. At the 24-week mark, the remaining 26% of the participants (22 women) were excluded from the study as a result of routine uterine artery examinations. Additionally, 12 women were withdrawn from the study at this juncture. Two of the women requested to transition their antenatal care to alternative locations, three opted not to continue taking medication throughout pregnancy, and one woman failed to return for subsequent visits despite receiving numerous reminders. In the second cohort, 56 expectant women who had previously experienced preeclampsia were included, and six of them were also excluded from the study. The reason for this was that one woman requested to transition her antenatal care to a different location, another preferred not to continue taking medication throughout pregnancy, and one woman did not return for further visits despite receiving multiple reminders. As a result, the investigation was eligible for a total of 50 cases.

Out of the 100 women who were included, 50 were randomly assigned to each cohort. The intervention and control groups had a mean age of 28.9 (6.4) and 29.8 (5.6), respectively. The mean SBP of the vitamins group was 112(12) at baseline, while the control group had a mean of 110(12). The mean age, body mass index, and blood pressure of both groups were statistically insignificant. Table (1) displays the baseline information.

Incidence of pre-eclampsia and gestational hypertension

Four women were diagnosed with preeclampsia in the intervention group, the incidence of which was 8%. One exhibited moderate symptom, while the other presented with a severe presentation. The control participants had an incidence of 24% (12 women), with 8 exhibiting mild disease and 4 exhibiting severe symptoms. Table (2) demonstrates that no significant

difference was observed between the two groups (P = 0.123).

Table (2) illustrates that there were no statistically significant differences between the intervention and the placebo in terms of gestational hypertension (20% vs. 14%, respectively, P = 0.713).

Blood pressure values during pregnancy (mmHg)

In patients who developed preeclampsia, no significant difference was observed between the intervention and control groups in terms of the mean SBP (160 ±20.3 vs 156±3.13 respectively, P = 0.42) and the mean DBP (110 ±13.7 vs 105±15.7 respectively, P = 0.27) (Table 3).

Table (4) also indicates that there was no statistically significant difference between the two groups in terms of SBP and DBP among women who developed gestational hypertension (P = 0.26 and P = 0.96, respectively).

PAI-1 and PAI-2 values (ng/ml)

PAI-1 was significantly elevated in women who developed preeclampsia compared to normotensive women (165±72.9 vs 110.9±37.7, respectively, P = 0.03). In contrast, the level of PAI-2 was markedly lower in women who developed preeclampsia than in normotensive women (104±33.8 vs 180.7±66.8, respectively, P=0.018).

Discussion

In this trial, the administration of daily doses of vitamin C and E to women with consistently abnormal Doppler waveforms and those who had previously experienced pre-eclampsia resulted in a statistically insignificant decrease in the incidence of pre-eclampsia and a negligible increase in the occurrence of gestational hypertension, taking into account the impact of antioxidants. When the mean SBP and DBP during pregnancy were analyzed, no significant differences were observed between these groups. In addition, the trial demonstrated a significant increase in PAI-1 levels among women who developed preeclampsia in comparison to those who remained normotensive. Conversely, women who developed preeclampsia exhibited a substantial decrease in PAI-2 levels when contrasted with those who did not.

Various methodologies were implemented in this paper to identify expectant women who are at an increased risk of developing preeclampsia. Primarily, primigravidas are at an elevated risk of developing preeclampsia [28]. The second method is uterine artery Doppler, which is a surrogate marker of placental perfusion, as investigated by Ochi et al. [29]. 8000 pregnant women were examined in a multicenter cohort study conducted by Papageorghiou et al. to assess the efficacy of transvaginal color Doppler assessment of the uterine artery in predicting the occurrence of pre-eclampsia and intrauterine growth restriction. The study did not specify any selection criteria. They determined that the most advantageous method for

identifying more severe cases of these conditions is to conduct a uterine artery Doppler screening at 23 weeks gestation [30].

The hypothesis that administering vitamin C and E supplements during the mid-trimester could potentially reduce the likelihood of preeclampsia development in women at elevated risk for this condition was first proposed by chapel et al. in 1999 [19]. The intervention group exhibited a substantially lower incidence of preeclampsia (8%) than the placebo group (17%), as reported. The incidence of preeclampsia was 7.5% in the cohort that received vitamins and 25% in the control group in a separate trial conducted in the United Kingdom, which involved 160 women at an elevated risk of developing preeclampsia [31]. In Iran, Mostajeran and colleagues also observed a lower incidence of preeclampsia in the treated group than in the control group (9.1% and 22.3%, respectively). This observation was made during their investigation of the therapeutic effects of vitamins C and E on 160 expectant women who were at an increased risk of developing preeclampsia [32].

However, it is crucial to bear in mind that the consumption of these vitamins in excess may be detrimental. Another name for vitamin C is ascorbic acid, a water-soluble vitamin that is generally harmless to consume in large quantities. Conversely, gastrointestinal issues, including diarrhea and cramping, may arise as a consequence of excessive vitamin C intake—typically exceeding 2,000 mg per day. In contrast, vitamin E, a fat-soluble vitamin, has the potential to accumulate in the body over time. Consuming an excessive amount of it may increase the likelihood of hemorrhaging and disrupt blood coagulation. It is generally recommended to follow the daily recommendations for both vitamins and consult with a physician before utilizing megadose or high-dose supplements to mitigate the risk of toxicity [33].

However, several studies failed to find any significant difference in the incidence of preeclampsia in women who had taken vitamin E and C as a preventative measure. In the VIP study, there was no significant difference between the control group and the group that received vitamin treatment. The number 33. Also, a big Australian experiment that compared the vitamin group to the placebo group found no statistically significant change in preeclampsia risk. [RR 1·2, CI (0.82–1.75)]. [34].

In a manner similar to these findings, we were also unable to identify any statistically significant difference in the incidence of gestational hypertension or preeclampsia. The research results may be explained by variations in dietary habits, genetic background, and ethnicity. The development and progression of preeclampsia can be substantially impacted by these factors [35].

PAI-1 is a primary inhibitor of tissue plasminogen activators and other enzymes that are responsible for the activation of plasminogen in the circulation. Its function is to regulate and

control the process of fibrinolysis by restricting plasmin generation [36]. The PAI-1 to PAI-2 ratio should diminish during pregnancy due to the placental growth, as PAI-2 is synthesized by the trophoblast. Nevertheless, this ratio is elevated in pre-eclampsia as a result of the increased activation of endothelial cells and placental insufficiency [36]. Our findings corroborate this assertion, as we observed a substantial increase in PAI-1 and a decrease in PAI-2 in the experimental group in comparison to the control group.

In summary, our investigation did not produce substantial evidence to substantiate the efficacy of vitamin C and E supplementation in reducing the prevalence of preeclampsia in high-risk expectant women. Although the biological plausibility and prior research have suggested potential benefits, our results suggest that there are no significant differences in preeclampsia or gestational hypertension between the intervention and placebo groups. The multifactorial nature of preeclampsia development and the complexity of its etiology are underscored by the observed outcome variations, which may be influenced by disparities in ethnicity, genetic background, and consumption patterns among the participants.

The results emphasize the necessity of conducting more extensive, multicenter trials to comprehensively assess the role of antioxidants in the prevention of preeclampsia. The objective of such studies should be to identify the true potential of vitamin C and E in reducing the risk of this condition by incorporating a variety of confounding factors and including a diverse population. Furthermore, future research should investigate the precise mechanisms by which these antioxidants may affect placental and endothelial function, as an understanding of these pathways could result in more effective and specifically targeted interventions.

Although our research contributes to the ongoing discussion regarding the prevention of preeclampsia, it also underscores the importance of ongoing research to comprehend the complex mechanisms of preeclampsia and to create effective prevention strategies. Until more conclusive evidence is available, clinicians should continue to rely on established methods for managing and mitigating the risk of preeclampsia while taking the individual patient's risk factors and overall health profile into account.

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Declaration of Competing Interests

Neither the writers' personal ties nor their financial interests have any bearing on the results presented in this study, as far as the authors are aware.

Data Accessibility

Data will be accessible upon request.

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Informed Consent

All individual participants who were enrolled in the investigation provided informed consent.

Authorization for publication.

The publishers are granted permission by the authors to produce and publish the work.

Table (1): Patient demographics used for the analysis

PATIENT PROFILE	CONTROL (N=50)		VITAMINS C AND E (N=50)	
	Mean	**SD**	**Mean**	**SD**
AGE (YEARS)	29.8	5.6	28.9	**6.4**
BODY MASS INDEX	25.6	5.6	23.3	**6**
SYSTOLIC Blood pressure (MMHG)	110	12	112	**12**
DIASTOLIC Blood pressure (MMHG)	68	10	67	**11**
SMOKER	**1**		**0**	

The data is shown in a (Mean ± SD).

Table (2): Preeclampsia and gestational hypertension incidence rate between the control and study groups.

Blood pressure status	Control (n=50)	Vitamins C and E	Total (n=100)	P value
Normotensive	30 (60%)	36 (72%)	66 (66%)	**0.370**[1]
Gestational Hypertension	8 (16%)	10 (20%)	18 (18%)	**0.713**[1]
Mild preeclampsia	8 (16%)	2 (4%)	10 (10%)	**0.16**[1]
Severe preeclampsia	4 (8%)	2 (4%)	6 (6%)	**0.55**[1]
Total Preeclampsia	**12 (24%)**	**4 (8%)**	**16(16%)**	**0.123**[1]

1. Pearson's Chi-squared test

Table (3): Average systolic blood pressure during pregnancy (mm Hg)

Systolic blood pressure	Control (n=50)	Vitamins C and E (n=50)	P value
Normotensive	120 (12.5)	125 (11.3)	**0.32[1]**
Gestational hypertension	145 (15.6)	150 (14.6)	**0.26[1]**
Preeclampsia	**156 (3.13)**	**160 (20.3)**	**0.42[1]**

1. A t-test for students. The data is shown in a (Mean ± SD).

Table 4 compares the two groups' average diastolic blood pressure readings (mmHg) during pregnant.

Diastolic blood pressure	Control (n=50)	Vitamins C and E (n=50)	P value
Normotensive	75 (7.3)	80 (6.5)	**012[1]**
Gestational hypertension	100 (10.2)	100 (9.6)	**0.96[1]**
Preeclampsia	**105 (15.7)**	**110 (13.7)**	**0.27[1]**

1. A t-test for students. The data is shown in a (Mean ± SD)

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