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Oxidative Stress and Nutrient Imbalance in Pre-eclampsia: The Roles of Homocysteine and Vitamin B12

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Abstract **Objectives:** Pre-eclampsia is a pregnancy-related disorder characterized by hypertension and organ dysfunction, posing significant risks to both mother and fetus. While the exact etiology remains unclear, evidence suggests that biochemical alterations particularly oxidative stress, homocysteine, and vitamin B12 dysregulation play a pivotal role. This study explores the interplay between oxidative stress, homocysteine, and vitamin B12 in pre-eclampsia. **Methods:** This hospital-based cross-sectional study enrolled a total of 120 patients categorized into three groups: 40 pregnant women with pre-eclampsia, 40 healthy pregnant women matched for gestational age, and 40 healthy non-pregnant women matched for age. Serum malondialdehyde (MDA) levels were assessed using the Thiobarbituric Acid Reactive Substances (TBARS) assay. Homocysteine and vitamin B12 levels were measured via chemiluminescent immunoassay. Clinical parameters including blood pressure, proteinuria, liver enzymes, platelet counts, and serum uric acid were also evaluated. Data were analyzed using SPSS version 24. **Results:** Preeclamptic women exhibited significantly elevated serum MDA (2.84±0.30 nmol/mL) and homocysteine (20.21±2.78 µmol/L), with markedly reduced vitamin B12 (179.1±31.78 pg/mL), compared to both control groups ($p<0.0001$). MDA and homocysteine showed positive correlations with blood pressure, protein-creatinine ratio, and serum uric acid, while vitamin B12 was inversely correlated with MDA. **Conclusion:** The interplay of increased oxidative stress, elevated homocysteine, and reduced vitamin B12 levels appears to play a significant role in the pathogenesis of pre-eclampsia. These findings highlight the importance of early biochemical screening to identify at-risk women and open the possibility for preventive strategies such as antioxidant therapy and vitamin B12 supplementation. However, given the multifactorial nature of pre-eclampsia, robust longitudinal and large-scale prospective studies are essential to validate these associations, clarify underlying mechanisms, and translate them into clinically effective interventions.

Key Words Preeclampsia, Oxidative stress, MDA,Homocysteine, Vitamin B12, Endothelial dysfunction, TBARS

INTRODUCTION

Preeclampsia is a pregnancy-specific, multisystem disorder primarily defined by the onset of hypertension and proteinuria after 20 weeks of gestation. It is a major contributor to maternal and perinatal morbidity and mortality worldwide [1]. Affecting approximately 2–8% of pregnancies globally, preeclampsia accounts for nearly half of all hypertensive disorders during pregnancy and ranks as the second leading cause of maternal and fetal mortality [2]. Each year, it is estimated to impact around 10 million women, resulting in approximately 76,000 maternal deaths and nearly 500,000 neonatal deaths figures that are particularly stark in low- and middle-income countries [3]. Women in developing regions are nearly seven times more likely to experience preeclampsia compared to those in high-income countries, with complications from the condition responsible for up to 20% of pregnancy-related deaths in these areas [4].

Historical records suggest that preeclampsia was recognized as early as 2,000 years ago, when Celsus described pregnancy-related seizures that resolved following childbirth a condition later termed eclampsia. It was not until the late 19th century that the association between elevated blood pressure and proteinuria in pregnancy led to the identification of preeclampsia as a distinct clinical entity [5].

Despite extensive research, the exact etiology of preeclampsia remains unclear. However, it is now widely accepted that the condition originates from placental dysfunction. Substantial evidence supports the notion that

inadequate placental vascularization and resulting endothelial dysfunction are central to its pathogenesis [6]. In particular, insufficient remodeling of the maternal spiral arteries, followed by placental ischemia and hypoxia, are believed to initiate a cascade of pathological events, including systemic endothelial injury and inflammatory responses [7].

Recent research has increasingly highlighted the role of oxidative stress in the pathophysiology of preeclampsia. Oxidative stress results from an imbalance between pro-oxidants, such as reactive oxygen species (ROS), and the body's antioxidant defense systems. This disequilibrium leads to cellular and tissue injury through mechanisms such as lipid peroxidation, protein alteration, and DNA damage, thereby amplifying the systemic inflammatory state characteristic of preeclampsia [8]. Malondialdehyde (MDA), a major end-product of lipid peroxidation, has been widely investigated as a biomarker of oxidative stress in preeclampsia, with consistently higher levels reported in affected pregnancies compared to normotensive controls [9].

In addition to oxidative stress, hyperhomocysteinemia elevated plasma homocysteine concentrations has emerged as another potential factor in the development of preeclampsia. Increased homocysteine levels are associated with endothelial dysfunction, vascular injury, and inflammatory processes, closely resembling the vascular abnormalities seen in preeclampsia [10]. Importantly, homocysteine metabolism is heavily reliant on adequate levels of vitamin B12 and folate. Deficiencies in these vitamins, which are not uncommon during pregnancy, may lead to the accumulation of homocysteine and consequently heighten vascular risk [11].

Several recent studies support the hypothesis that maternal nutritional status particularly vitamin B12 levels plays a significant role in pregnancy outcomes. Deficiency in vitamin B12 during pregnancy has been linked to an increased risk of preeclampsia, intrauterine growth restriction (IUGR), neural tube defects, and preterm birth.[12] As a vital cofactor in homocysteine metabolism, vitamin B12 facilitates the clearance of homocysteine from circulation. Therefore, insufficient levels of vitamin B12 may exacerbate homocysteine-induced vascular injury and oxidative stress, thereby contributing to the complex pathophysiology of preeclampsia [13].

Despite growing evidence supporting the involvement of oxidative stress and hyperhomocysteinemia in preeclampsia, the literature remains inconclusive, with some studies failing to establish direct causal links.[14] Understanding the interaction between oxidative stress markers such as malondialdehyde (MDA) homocysteine, and essential nutritional cofactors like vitamin B12 is essential, as it may offer insights into early diagnosis, prevention, and management strategies for preeclampsia. Therefore, the hypothesis would be increased oxidative stress, elevated homocysteine, and reduced vitamin B12 levels are significantly associated with the development and severity of pre-eclampsia.

The primary aim of the study was to investigate the association between oxidative stress markers, homocysteine levels, and vitamin B12 status in pregnant women and their role in the pathogenesis of pre-eclampsia. The extent of oxidative stress in preeclamptic women was measured using MDA as a biomarker, along with assessing homocysteine and vitamin B12 levels. These parameters are compared with those of normotensive pregnant women and healthy non-pregnant women of reproductive age. The secondary aims was to assess whether vitamin B12 deficiency contributed to elevated homocysteine levels in pre-eclamptic pregnancies. The findings may contribute to a deeper understanding of the pathogenesis of preeclampsia and inform future approaches to its treatment and prevention.

METHODS

This observational, cross-sectional, hospital-based study was conducted over an 18-month period, from September 2023 to March 2025. During the study period, a total of 168 pregnant women attending the antenatal clinic were screened for eligibility. Of these, 28 women were excluded based on predefined exclusion criteria (such as pre-existing hypertension, diabetes mellitus, renal disorders, or unwillingness to provide blood samples). Among the 140 eligible women, 20 declined participation due to personal reasons or time constraints. The final study cohort consisted of 120 participants, who provided written informed consent and were included in the analysis. The entire sample was stratified into three equal groups (n=40 per group):

- **Group A (Preeclamptic Cases):** This group included pregnant women clinically diagnosed with preeclampsia, defined by new-onset hypertension systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg on at least two separate occasions accompanied by significant proteinuria (≥300 mg in a 24-hour urine sample or a protein-creatinine ratio ≥0.3). Diagnosis was established at or beyond 20 weeks of gestation.
- **Group B (Pregnant Controls):** Comprised healthy, normotensive pregnant women matched to Group A participants based on gestational age. These individuals had no known pregnancy-related complications or pre-existing medical conditions.
- **Group C (Non-pregnant Controls):** Included healthy, non-pregnant women of reproductive age, closely matched in chronological age to participants in the other two groups, with no history of major medical illnesses or conditions that could influence biochemical parameters.

Participant Selection and Sample Collection

Potential participants were rigorously screened, and strict exclusion criteria were applied to ensure a homogenous study population and minimize potential confounding factors. Excluded from the study were women with chronic hypertension diagnosed prior to pregnancy, gestational

diabetes mellitus, multiple gestations (e.g., twins or higher-order pregnancies), history of malignancy, known cardiovascular or cardiac disorders, renal impairment or chronic kidney disease, hepatic dysfunction, neurologic conditions (including seizure disorders), autoimmune or endocrine disorders, as well as those receiving vitamin B12, folate, or antifolate medications at the time of enrollment. The study protocol adhered to the (STROBE) Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Following detailed counseling and the acquisition of informed written consent, 5 mL of peripheral venous blood was collected from each participant under sterile and aseptic conditions. Blood was drawn into both plain (serum) tubes and EDTA-containing tubes. Serum was separated by centrifugation at 3000 RPM for 10 minutes. The resulting serum aliquots were transferred into appropriately labeled microcentrifuge tubes and immediately stored at –20°C to prevent biochemical degradation prior to analysis.

Oxidative Stress Marker (MDA) Assessment

Serum malondialdehyde (MDA), a well-established marker of lipid peroxidation and oxidative stress, was quantified using the Thiobarbituric Acid Reactive Substances (TBARS) assay. In this method, MDA reacts with thiobarbituric acid to form a pink chromogen, the absorbance of which was measured spectrophotometrically at 530 nm. MDA concentrations were derived from a standard calibration curve prepared using known concentrations of MDA standard solutions.

Serum Homocysteine and Vitamin B12 Determination

Plasma levels of homocysteine and vitamin B12 were measured using a competitive chemiluminescent immunoassay on the automated IMMULITE 1000 analyzer. Prior to analysis, samples underwent heat denaturation and pre-treatment to dissociate homocysteine and vitamin B12 from endogenous binding proteins, thereby ensuring accuracy and consistency in measurements.

Routine Clinical Chemistry Evaluations

Additional biochemical parameters assessed included serum urea, creatinine, uric acid, random blood glucose, hepatic function markers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin as well as platelet counts. All assays were conducted using fully automated biochemical analyzers to ensure methodological consistency and reproducibility.

Urinary Protein and Protein-Creatinine Ratio

Quantitative estimation of urinary protein was performed using the pyrogallol red method. Simultaneously, urinary creatinine levels were determined using an automated biochemical analyzer. The urinary protein-creatinine ratio (UPCR), a reliable marker for assessing proteinuria, was calculated from these two parameters.

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 24.0 (IBM Corporation, USA). Continuous variables were expressed as mean±standard deviation (SD). Inter-group comparisons of clinical and biochemical parameters were performed using Student's unpaired t-test. Correlations between continuous variables, particularly between biochemical markers and clinical parameters, were examined using Pearson's correlation coefficient. Statistical significance was defined at a p-value of <0.05. All analyses were carried out in accordance with standard epidemiological and biostatistical practices to ensure the reliability and validity of the results.

Ethical Considerations

This study was conducted in accordance with ethical guidelines and approved by the Institutional Ethical Committee prior to participant recruitment with reference number: AIHMS/6/24/33. Informed consent was obtained from all participants, ensuring voluntary participation. Confidentiality was strictly maintained by anonymizing patient data, which was used solely for research purposes.

RESULTS

As shown in Table 1 and 2, women with pre-eclampsia had significantly higher systolic and diastolic blood pressure, proteinuria, liver enzymes (AST, ALT), uric acid, and malondialdehyde (MDA), along with reduced platelet counts when compared with both pregnant and non-pregnant controls ($p<0.05$). Vitamin B12 levels were markedly lower, while homocysteine concentrations were significantly elevated in the case group. Random blood sugar (RBS) was comparable between cases and pregnant controls, but significantly higher in non-pregnant controls ($p<0.001$). These results indicate a distinct biochemical profile in pre-eclampsia, characterized by oxidative stress and perturbation of the vitamin B12–homocysteine axis.

Serum malondialdehyde (MDA) levels, a marker of oxidative stress, were significantly higher in pregnant controls compared to non-pregnant women and reached their peak in pre-eclamptic cases (Figure 1, $p<0.0001$). Vitamin B12 levels followed the opposite trend, being lowest in pre-eclamptic women, intermediate in pregnant controls, and highest in non-pregnant controls, with all differences statistically significant (Figure 2, $p<0.05$). Homocysteine levels were markedly elevated in pre-eclampsia compared with both control groups, while pregnant controls showed the lowest concentrations (Figure 3, $p<0.05$).

Correlation analysis demonstrated that MDA and homocysteine were positively associated with systolic and diastolic blood pressure, protein-creatinine ratio, and uric acid levels (all $p<0.001$), highlighting their contribution to endothelial dysfunction in pre-eclampsia. In contrast, vitamin B12 showed a strong inverse correlation with MDA ($r = –0.574$; $p<0.001$), suggesting

Table 1: Clinical and biochemical data of cases vs Control group I

Variable	Case Group (n = 40) (Mean±SD)	Control group I (n = 40) (Mean±SD)	p -value (with 95% C.I.)
Age (years)	26.83±3.23	25.78±3.62	0.175 (NS)
SBP (mm of Hg)	150.10±5.78	118.55±9.28	<.0001 *
DBP (mm of Hg)	95.40±3.77	75.45±5.36	<0.0001 *
Urine Protein (mg/dl)	15.77±5.58	7.37±1.84	<0.0001 *
Urine creatinine (mg/dl)	25.51±6.67	28.99±4.78	0.009 *
Protein creatinine ratio	0.64±.26	0.25±.05	<0.0001 *
Serum Urea (mg/dl)	26.08±9.19	22.83±6.60	0.073 (NS)
Serum Creatinine (mg/dl)	0.86±.21	0.80±.17	0.172 (NS)
RBS (mg/dl)	96.90±12.84	99.98 ±15.75	0.520 (NS)
Total Bilirubin (mg/dl)	0.87±.26	0.76±.24	0.064 (NS)
AST (U/L)	66.23±30.27	27.65±8.53	<0.0001 *
ALT (U/L)	64.38±29.36	26.50±8.01	<0.0001 *
ALK. PHOSP. (U/L)	71.95±20.31	62.25±13.93	0.015 *
Platelet Count (lakh/µl)	2.54 ±.93	3.02 ±.60	0.008 *
Uric acid (mg/dl)	4.63±.91	2.99±.25	<0.0001 *
MDA (nmol/ml)	2.84±.30	1.89±.16	<0.0001 *
Vitamin B12 (pg/ml)	179.1±31.78	232.5±70.01	<0.0001 *
Homocysteine (µmol/L)	20.21±2.78	8.41±3.10	<0.0001 *

*Student's unpaired t-test done, p<0.05 is considered significant

Table 2: Clinical and biochemical data of Case Group vs Control group II

Variable	Case Group (n = 40) (Mean±SD)	Control group II (n = 40) (Mean±SD)	p -value (with 95% C.I.)
Age (years)	26.83±3.23	26.38±4.55	0.612 (NS)
SBP (mm of Hg)	150.10±5.78	118.70±8.84	<.0001 *
DBP (mm of Hg)	95.40±3.77	77.05±5.44	<0.0001 *
Urine Protein (mg/dl)	15.77±5.58	7.01±2.48	<0.0001 *
Urine creatinine (mg/dl)	25.51±6.67	28.96±5.45	0.013 *
Protein creatinine ratio (PCR)	0.64±.26	0.24±.68	<0.0001 *
Serum Urea (mg/dl)	26.08±9.19	22.35±4.60	0.025 *
Serum Creatinine (mg/dl)	0.86±.21	0.79±.16	0.101 (NS)
RBS (mg/dl)	96.90±12.84	109.20±16.72	<0.0001 *
Total Bilirubin (mg/dl)	0.87±.26	0.77±.21	0.088 (NS)
AST (U/L)	66.23±30.27	25.95±9.09	<0.0001 *
ALT (U/L)	64.38±29.36	24.48±7.92	<0.0001 *
ALK. PHOSP. (U/L)	71.95±20.31	59.62±14.24	0.002 *
Platelet Count (lakh/µl)	2.54 ±.93	3.12 ±.46	0.001 *
Uric acid (mg/dl)	4.63±.91	2.98±.23	<0.0001 *
MDA (nmol/ml)	2.84±.30	0.93±.20	<0.0001 *
Vitamin B12 (pg/ml)	179.1±31.78	271.08±47.60	<0.0001 *
Homocysteine (µmol/L)	20.21±2.78	18.68±2.92	0.018 *

* Student's unpaired t-test done, p <.05 is considered significant.

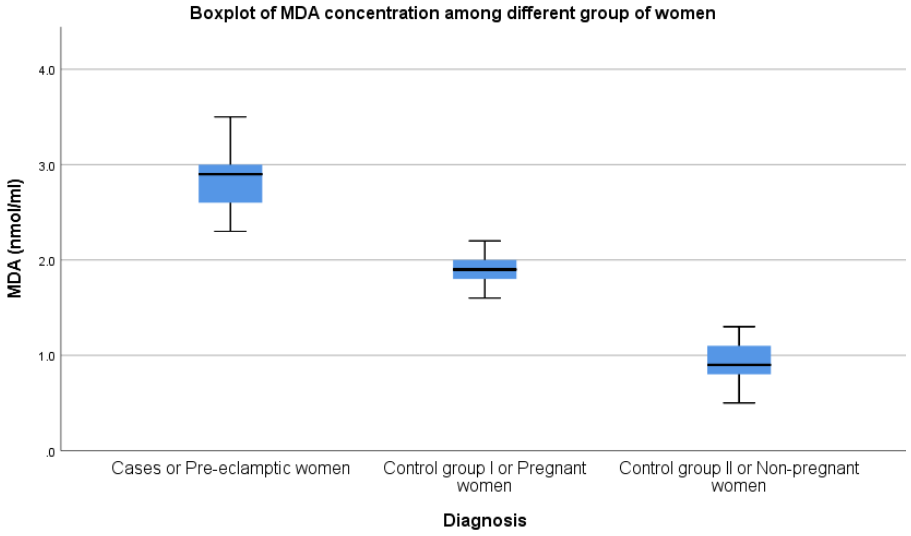

Figure 1: Comparison of Serum MDA Levels Across Study Groups

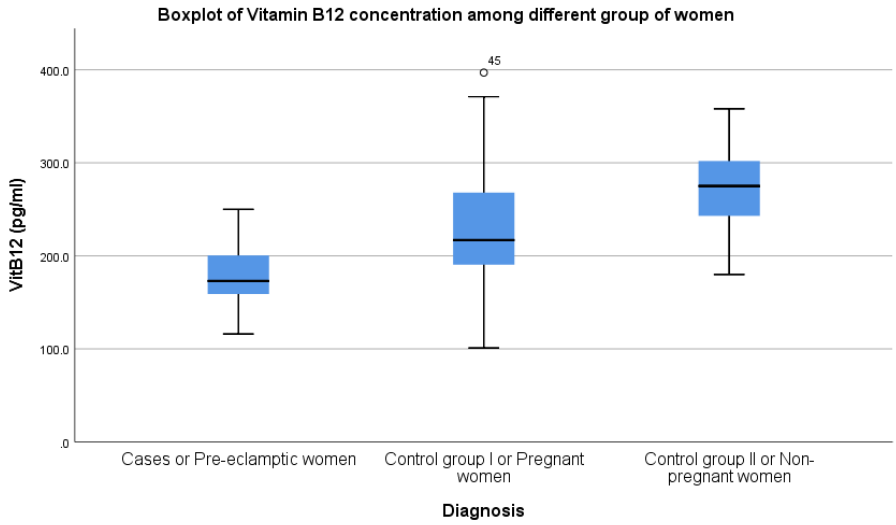

Figure 2: Comparison of Serum Vitamin B12 Levels Across Study Groups

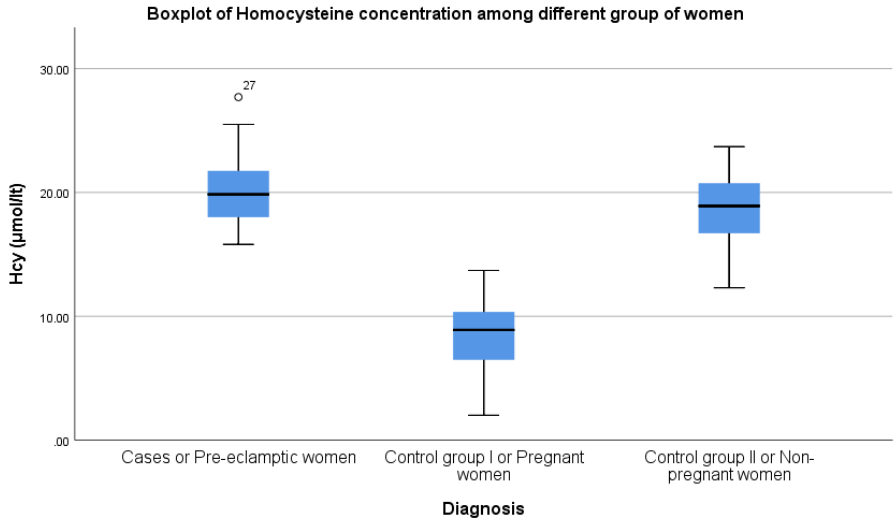

Figure 3: Comparison of Serum Homocysteine Levels Across Study Groups

a protective role against oxidative stress. Collectively, these findings point to an interlinked pathway of heightened oxidative stress, reduced vitamin B12, and elevated homocysteine as key biochemical signatures of pre-eclampsia.

DISCUSSION

The present study aimed to assess serum levels of oxidative stress markers specifically malondialdehyde (MDA) along with homocysteine and vitamin B12 in preeclamptic pregnant women, comparing them to levels in normotensive pregnant women and healthy non-pregnant controls. The findings reveal notable biochemical disparities and offer valuable insights into the complex pathophysiology of preeclampsia.

A marked increase in serum MDA levels was observed in preeclamptic women compared to both control groups, highlighting the pivotal role of oxidative stress in the disease's development. This observation is consistent with the findings of Al-Kuraishy *et al.* [15], who also reported elevated oxidative stress markers, including MDA, in preeclamptic individuals, emphasizing oxidative imbalance as a driver of endothelial dysfunction and systemic inflammation. Similarly, Jin *et al.*, in a recent case-control study, found significantly higher levels of oxidative stress biomarkers in preeclamptic subjects. They proposed that excessive reactive oxygen species (ROS) production contributes to endothelial damage, impaired vasodilation, and reduced placental perfusion key elements in the progression of preeclampsia.

Beyond endothelial dysfunction, oxidative stress may also contribute to broader adverse outcomes. For instance, Liu *et al.* [16] demonstrated a link between increased oxidative stress and placental apoptosis in preeclampsia,

suggesting that excessive ROS can induce trophoblastic cell death and hinder fetal development. Such mechanisms are associated with complications like intrauterine growth restriction (IUGR) and preterm delivery.

In addition, our study revealed significantly elevated serum homocysteine levels in preeclamptic women compared to normotensive pregnant controls. This finding aligns with recent work by Razavi *et al.* [17], who identified elevated maternal homocysteine as an independent risk factor influencing both the onset and severity of preeclampsia. Homocysteine is known to contribute to endothelial dysfunction, stimulate pro-inflammatory cytokine release, and exacerbate oxidative stress.

Supporting this, a comprehensive meta-analysis by Neuman *et al.* [18] recognized hyperhomocysteinemia as a strong predictor of adverse maternal and fetal outcomes, including preeclampsia, underscoring the potential value of routine homocysteine screening in prenatal care.

Our findings also demonstrated a significant positive correlation between homocysteine levels and key clinical markers of preeclampsia, including systolic and diastolic blood pressure as well as proteinuria. This relationship reflects the vascular injury associated with elevated homocysteine levels. Consistent with our results, Singh *et al.* [19] reported a direct link between hyperhomocysteinemia and increased vascular resistance in pregnancy-related hypertensive disorders. These insights highlight the importance of early detection and monitoring of homocysteine levels as part of a comprehensive strategy to identify high-risk pregnancies and improve clinical management of preeclampsia.

Our study also identified significantly lower serum vitamin B12 levels in preeclamptic women compared to normotensive pregnant controls. This finding supports growing evidence that maternal vitamin B12 status plays a crucial role during pregnancy, particularly in the one-carbon metabolic pathway, which is vital for homocysteine metabolism and DNA methylation [20]. In line with our results, Sukumar *et al.* [21] reported a strong association between maternal vitamin B12 deficiency, preeclampsia, and fetal growth restriction, emphasizing the vitamin's essential contribution to favorable pregnancy outcomes.

While our data showed a negative correlation between vitamin B12 and homocysteine levels, this association did not reach statistical significance. However, numerous recent studies have documented a significant inverse relationship. For example, Selhub *et al.* [22] demonstrated that lower serum vitamin B12 levels are significantly associated with elevated plasma homocysteine, suggesting that adequate B12 supplementation could help reduce homocysteine concentrations and, in turn, lower the risk of preeclampsia and its complications. Future research involving larger cohorts and longitudinal study designs is warranted to further clarify this relationship across diverse populations and pregnancy settings.

Notably, our study also reveals a significant inverse correlation between serum vitamin B12 levels and oxidative stress, as indicated by malondialdehyde (MDA). This relationship, though relatively underexplored in pregnancy-related research, opens new avenues for understanding the antioxidant potential of vitamin B12. Supporting this, experimental studies in animal models by Gao *et al.* [23] suggest that vitamin B12 may exert antioxidant effects by scavenging free radicals, thereby reducing oxidative damage. Such properties could play a protective role in preeclampsia by limiting endothelial injury. Nonetheless, human clinical trials are essential to validate these findings and establish the therapeutic relevance of vitamin B12's antioxidant capacity.

Collectively, our findings contribute to the growing body of evidence highlighting the complex biochemical landscape of preeclampsia. The concurrent presence of elevated oxidative stress, hyperhomocysteinemia, and vitamin B12 deficiency underscores key disruptions in maternal vascular and metabolic health that influence pregnancy outcomes. This study was limited by its relatively small sample size and cross-sectional design, which restrict causal inference and generalizability. Larger prospective randomized trials are needed to confirm these findings and evaluate the clinical effectiveness of antioxidant and vitamin supplementation. Further exploration of broader nutritional and oxidative stress markers may yield deeper insights into the metabolic basis of pre-eclampsia and guide more targeted preventive strategies.

CONCLUSION

This study highlights a significant elevation in serum malondialdehyde (MDA) levels a well-established marker of oxidative stress in women with preeclampsia when compared to both normotensive pregnant women and healthy non-pregnant controls. The marked increase in MDA suggests enhanced lipid peroxidation and oxidative damage, likely stemming from an imbalance between the generation of reactive oxygen species (ROS) and the body's antioxidant defenses. This oxidative environment may contribute substantially to the endothelial dysfunction and vascular complications that characterize preeclampsia.

In addition to oxidative stress, the findings reveal significantly elevated homocysteine levels and decreased vitamin B12 concentrations in preeclamptic women. These biochemical alterations appear to be interrelated, forming a triad of risk factors that may play a synergistic role in the pathogenesis of preeclampsia. The inverse correlation observed between MDA and vitamin B12 further supports the hypothesis that nutritional deficiencies may exacerbate oxidative stress and vascular damage during pregnancy.

Taken together, the results underscore the potential value of incorporating the assessment of oxidative stress markers, homocysteine, and vitamin B12 into routine prenatal screening protocols. Such monitoring may enable early identification of women at increased risk for preeclampsia, allowing for timely preventive or therapeutic interventions aimed at reducing maternal and fetal morbidity.

Future Directions for Research

To build upon the current findings, future research should focus on prospective longitudinal studies that track changes in oxidative stress markers, homocysteine, and vitamin B12 levels throughout pregnancy. This would help clarify the temporal relationship between these biomarkers and the onset or progression of preeclampsia. Furthermore, interventional studies evaluating the efficacy of antioxidant supplementation, vitamin B12 replacement, or combined nutritional strategies in high-risk pregnant populations are warranted. These trials could determine whether targeted therapeutic approaches can reduce the incidence or severity of preeclampsia and improve pregnancy outcomes.

Additionally, mechanistic studies exploring the molecular pathways linking oxidative stress, endothelial dysfunction, and micronutrient imbalance in preeclampsia would offer valuable insights. Expanding the biomarker panel to include other antioxidants and inflammatory markers may also help identify more robust predictive profiles. Ultimately, integrating biochemical surveillance with clinical risk assessment could pave the way for more personalized and preventive prenatal care strategies.

Conflicts of Interest

The author declares no conflicts of interest.

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