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"Evaluating Asymmetric Dimethylarginine (ADMA) as a Biomarker for Preeclampsia: A Meta-Analysis"

Abhishek Bansal[1], Chetana. P. Hadimani*[2], Sadanand B Patil [3], Nik Ahmad Zuki Bin Nik Lah[4]

[1] Assistant professor, Dept. Biochemistry, The Oxford Medical College, Hospital & Research Centre, Bengaluru, Karnataka

[*2,3]Professor, Dept. Biochemistry, KLE Academy of Higher Education and Research, Jawaharlal Nehru Medical College, Belagavi, Karnataka, India

[4]Associate professor, Dept. Obstetrics and Gynaecology, Universiti Sains Malaysia Karnataka Lingayat Education Society International Medical Program, Belagavi, Karnataka India

[*]**Corresponding Author:**

[*]Email ID: chetanaph@gmail.com

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ABSTRACT

Background: Preeclampsia (PE) is a serious pregnancy-related disorder characterized by hypertension, endothelial dysfunction, and multi-organ involvement. Despite advances in understanding its pathophysiology, early diagnosis and reliable biomarkers remain critical challenges. Asymmetric dimethylarginine (ADMA) is a natural inhibitor of nitric oxide synthase (NOS) that has been implicated in endothelial dysfunction, a key feature of PE. This study aims to evaluate the potential of ADMA as an early biomarker for the detection and assessment of preeclampsia.

Methods: This systematic review and meta-analysis included 16 observational studies examining the association between serum ADMA levels and preeclampsia. Data from 767 women with PE and 896 healthy controls were analyzed to determine the mean difference in ADMA levels between the two groups. The analysis followed PRISMA guidelines, and heterogeneity was assessed using the I^2 statistic.

Results: The pooled analysis revealed that serum ADMA levels were significantly higher in women with preeclampsia compared to healthy pregnant controls (mean difference = 0.38 µmol/L, 95% CI: 0.11–0.65 µmol/L, p = 0.01). Significant heterogeneity (I^2 = 99.9%) was observed across studies. Funnel plots indicated no significant publication bias.

Conclusion: Elevated ADMA levels are associated with preeclampsia and may serve as a promising biomarker for early detection and disease severity evaluation. Despite significant heterogeneity across studies, the findings suggest ADMA's potential role in the pathophysiology of PE, particularly in endothelial dysfunction. Further prospective studies and standardization of measurement techniques are required to confirm ADMA's clinical utility in preeclampsia diagnosis and management.

Keywords: *Preeclampsia; asymmetric dimethylarginine (ADMA); meta-analysis,*

1. INTRODUCTION

Preeclampsia (PE) is a significant, pregnancy-related, multi-organ disorder characterized by a complex etiology. This condition impacts 3–6% of pregnant women globally and continues to be a primary contributor to maternal and fetal morbidity and mortality. The diagnosis of preeclampsia is clinical and relies on revised diagnostic criteria, which characterize it as new-onset hypertension occurring after 20 weeks of gestation, along with at least one of the following conditions: proteinuria, maternal end-organ dysfunction (involving renal, hepatic, hematologic, or neurological complications), or uteroplacental dysfunction indicated by fetal growth restriction (FGR).[1,2]

Preeclampsia can be clinically classified as having severe features and based on timing, it is categorized into early-onset (before 34 weeks), preterm (between 35 and 37 weeks), and term preeclampsia (after 37 weeks). Management strategies are contingent upon gestational age and disease severity, emphasizing blood pressure regulation, monitoring of maternal and fetal conditions, and timing of delivery to enhance outcomes for both mother and neonate.[3]

The initial phase of PE is asymptomatic and takes place during placental invasion and differentiation. Embryo-derived cytotrophoblasts typically invade the uterine wall and convert maternal spiral arteries into high-capacitance, low-resistance vessels. In preeclampsia, this invasion is partial and restricted to the superficial layers of the decidua, leading to inadequate access to oxygen and nutrients for the placenta and fetus. Defective placental invasion results in ischemia and reduced uteroplacental perfusion pressure.[4,5]

The second stage presents clinically and is influenced by the chronic placental hypoperfusion observed in the first stage. The placenta secretes bioactive factors into the maternal circulation, which affect endothelial cells, leading to extensive endothelial dysfunction, vasospasm, oxidative stress, inflammation, and decreased plasma volume. The overproduction of antiangiogenic proteins, including soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble Endoglin (sEng), combined with reduced levels of proangiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), leads to preeclampsia as a state characterized by antiangiogenesis.[6]

Recent theories indicate that pulmonary embolism may manifest in two distinct clinical phenotypes. The first scenario is characterized by superficial trophoblastic invasion and limited fetal growth, whereas the second is linked to maternal metabolic syndrome, normal fetal growth, and low-grade inflammation resulting from placental oxidative stress, congested placental villi.[7]

Asymmetric dimethylarginine (ADMA) is a natural metabolite and an endogenous inhibitor of nitric oxide synthase (NOS), which further hinders nitric oxide (NO) synthesis by competing with L-arginine. Increased levels of ADMA inhibit nitric oxide production, resulting in oxidative stress and endothelial dysfunction, and inflammation, which collectively worsen the clinical features of preeclampsia.[8]

Despite progress in understanding of the disease, reliable biomarkers for early diagnosis and disease monitoring continue to pose a challenge. Therefore current study seeks to assess the feasibility of ADMA as a biomarker for early detection and evaluation of PE.

2. METHODOLOGY

Study Design:

This study was a systematic review and meta-analysis of observational studies investigating the association between asymmetric dimethylarginine (ADMA) levels and preeclampsia. The study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure a comprehensive and transparent approach to the analysis.

Eligibility Criteria:

Inclusion Criteria:

- Studies that measured serum ADMA levels in pregnant women diagnosed with preeclampsia.
- Studies that compared ADMA levels between preeclampsia cases and healthy pregnant controls.
- Observational studies published in peer-reviewed journals.
- Studies that reported data sufficient for calculating effect sizes (e.g., means, standard deviations, or p-values).
- Studies published in English.

Exclusion Criteria:

- Studies not reporting sufficient data for calculating effect sizes.
- Studies focused on non-pregnant populations or other pregnancy-related complications not involving preeclampsia.
- Animal studies or studies with sample sizes less than 10 participants.

Search Strategy

A comprehensive literature search was conducted in the following databases: PubMed, Scopus, Web of Science, and Google Scholar. The search terms included combinations of keywords such as "asymmetric dimethylarginine," "ADMA," "preeclampsia," "pregnancy," "endothelial dysfunction," "serum levels," and "biomarker." Reference lists of included articles were also checked to identify additional relevant studies.

Study Selection

Two independent reviewers screened the titles and abstracts of all identified articles. Full-text articles were retrieved for studies that met the inclusion criteria. Any disagreements between the reviewers were resolved through discussion with a third reviewer.

Data Extraction:

Data were extracted independently by two reviewers using a pre-defined data extraction form. The following information was collected:

- Study characteristics: author(s), year of publication, study design, and country of origin.
- Participant characteristics: sample size, age, gestational age at diagnosis, and classification of preeclampsia.
- Outcomes: mean ADMA levels (with standard deviations or standard errors) for preeclampsia and control groups, and statistical results (e.g., p-values, correlation coefficients).

Statistical Analysis

Analysis was performed using Stata 16 software. A random-effects model was used to pool the results from individual studies due to expected heterogeneity in study designs and populations. The primary outcome was the difference in ADMA levels between preeclampsia cases and healthy controls. The pooled mean difference was calculated along with 95% confidence intervals (CIs). The degree of heterogeneity between studies was assessed using the I^2 statistic. An I^2 value greater than 50% indicated substantial heterogeneity. Funnel plots were used to assess publication bias.

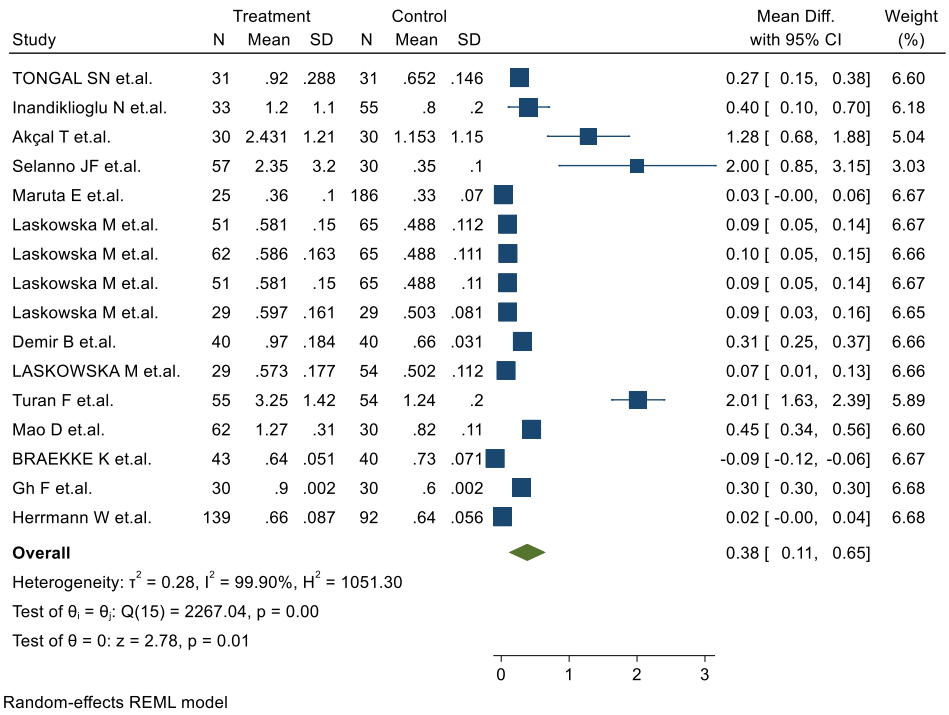
Ethical Considerations

As this study was based on published data, no ethical approval was required. All data were obtained from peer-reviewed articles, ensuring that ethical standards had been followed in the original studies.

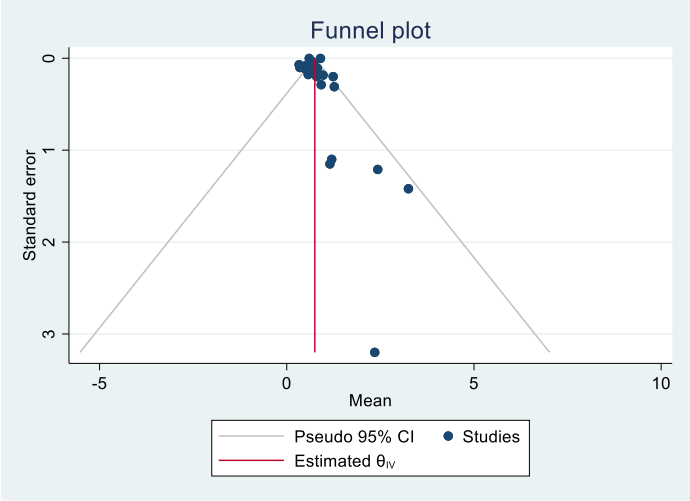
Results:

This study included 16 observational studies, covering 767 participants with preeclampsia (PE) and 896 healthy pregnant controls (Table 1). The studies were conducted in various countries and employed different methodologies to measure serum ADMA levels in both PE and control groups.

Author	Year	Case			Control		
		n	Mean	SD	n	Mean	SD
TONGAL SN et.al.[9]	2023	31	0.920	0.288	31	0.652	0.146
Inandiklioglu N et.al.[10]	2021	33	1.200	1.100	55	0.800	0.200
Akçal T et.al.[11]	2021	30	2.431	1.210	30	1.153	1.150
Selanno JF et.al.[12]	2020	57	2.350	3.200	30	0.350	0.100
Maruta E et.al.[13]	2017	25	0.360	0.100	186	0.330	0.070
Laskowska M et.al.[14]	2014	51	0.581	0.150	65	0.488	0.112
Laskowska M et.al.[15]	2013	62	0.586	0.163	65	0.488	0.111
Laskowska M et.al.[16]	2013	51	0.581	0.150	65	0.488	0.110
Laskowska M et.al.[17]	2012	29	0.597	0.161	29	0.503	0.081
Demir B et.al.[18]	2012	40	0.970	0.184	40	0.660	0.031
LASKOWSKA M et.al.[19]	2011	29	0.573	0.177	54	0.502	0.112
Turan F et.al.[20]	2010	55	3.250	1.420	54	1.240	0.200
Mao D et.al.[21]	2009	62	1.270	0.310	30	0.820	0.110
BRAEKKE K et.al.[22]	2009	43	0.640	0.051	40	0.730	0.071
Gh F.[23]	2009	30	0.900	0.002	30	0.600	0.002
Herrmann W et.al.[24]	2005	139	0.660	0.087	92	0.640	0.056



The pooled analysis as shown in figure 1 revealed that serum ADMA levels were significantly higher in women with preeclampsia compared to healthy pregnant controls (MD = 0.38 µmol/L, 95% CI: 0.11 to 0.65 µmol/L, p =0.01). This suggests that elevated ADMA levels are associated with the pathophysiology of preeclampsia, supporting its potential role as a biomarker. Significant heterogeneity was observed between studies (I^2 = 99.9%), indicating variability in the results across different populations and methodologies.



Publication Bias

Funnel plots (figure 2) suggested no significant publication bias which support the reliability of the findings.

3. DISCUSSION

Preeclampsia is a complex and multifactorial pregnancy-related disorder that continues to pose significant challenges in maternal and fetal health. Affecting approximately 3–6% of pregnant women globally, PE remains a major cause of maternal morbidity and mortality, and it significantly impacts neonatal health, often contributing to preterm birth, fetal growth restriction, and other complications.[5–7]

The pathophysiology of preeclampsia involves a combination of placental abnormalities, impaired endothelial function, and systemic inflammation. During normal pregnancy, trophoblasts invade the maternal uterine vasculature to remodel the spiral arteries, allowing for increased blood flow to the placenta.[5] However, in preeclampsia, this process is incomplete, leading to

shallow placental invasion and inadequate blood supply to the placenta. This placental hypoperfusion triggers the release of bioactive molecules which disrupt vascular homeostasis by promoting endothelial dysfunction, vasoconstriction, and oxidative stress. These processes collectively contribute to the elevated blood pressure and other clinical manifestations seen in PE.[25] Despite advances in understanding its underlying mechanisms, the identification of reliable biomarkers for the early detection and monitoring of PE remains a critical area of intrest.

Asymmetric dimethylarginine is an endogenous inhibitor of nitric oxide synthase (NOS), the enzyme responsible for producing nitric oxide, a molecule essential for maintaining endothelial function and vasodilation.[26,27] Therefore this study sought to investigate the potential of asymmetric dimethylarginine as a biomarker for the early detection and evaluation of preeclampsia.

The current study, which pooled the data from 16 observational studies involving 767 participants with preeclampsia and 896 healthy pregnant controls shows strong evidence that ADMA levels are significantly elevated in women with PE. The pooled analysis revealed a mean difference of 0.38 µmol/L (95% CI: 0.11 to 0.65 µmol/L, p = 0.01), indicating a strong association between elevated ADMA levels and preeclampsia. This finding aligns with previous studies suggesting that elevated levels of ADMA impair NO production, leading to endothelial dysfunction, vasoconstriction, and increased oxidative stress which pathophysiological processes that contribute to the development of preeclampsia. This association suggests that ADMA could serve as an early biomarker for preeclampsia, particularly in identifying women at risk for developing the condition before clinical symptoms appear.[12,15,21,28–37]

Endothelial dysfunction is a hallmark of preeclampsia, and the findings from this analysis provide further support for the role of ADMA in worsening this dysfunction. The placenta, which serves as the interface between the mother and fetus, is central to the development of preeclampsia. In normal pregnancy, the trophoblasts invade the uterine wall to convert maternal spiral arteries into low-resistance vessels, thereby facilitating adequate placental perfusion. In preeclampsia, this process is impaired, leading to chronic placental hypoperfusion and the release of antiangiogenic factors that disrupt endothelial function. Elevated ADMA levels may further amplify these endothelial disturbances by inhibiting NO production, which is critical for maintaining vascular homeostasis and preventing excessive vasoconstriction.[33,35,37–39]

Although the pooled results were significant, the study also revealed substantial heterogeneity among the included studies (I^2 = 99.9%), suggesting variability in study populations, methodologies, and diagnostic criteria. This variability may be due to differences in the populations studied as well as methodological differences in measuring ADMA levels. Preeclampsia is a heterogeneous condition, and the variability observed in the meta-analysis highlights the need for standardized diagnostic criteria and measurement techniques in future studies.[40]

Preeclampsia is traditionally diagnosed based on blood pressure measurements and proteinuria, these indicators are not always reliable for early detection, particularly in the absence of symptoms. ADMA could complement current diagnostic methods by providing an additional early marker of endothelial dysfunction, allowing clinicians to identify women at higher risk for PE earlier in pregnancy.[40–42] In conjunction with other clinical assessments, ADMA could improve risk stratification and enable more personalized management strategies.

However, several important limitations should be considered when interpreting these results. The most significant limitation is the observational nature of the included studies. While the association between ADMA and preeclampsia is strong, causality cannot be established from observational data alone. Further research, including prospective cohort studies and randomized controlled trials, is needed to confirm the role of ADMA in the development and progression of preeclampsia. Longitudinal studies that assess ADMA levels at various points throughout pregnancy could help determine whether elevated ADMA levels precede the onset of preeclampsia or are a consequence of the disease. Another limitation is the variability in study designs and measurement techniques across the included studies. Differences in laboratory methods for measuring ADMA and the populations studied could have influenced the results. Standardized protocols for measuring ADMA and consistent diagnostic criteria for preeclampsia would enhance the reliability and comparability of future studies.

Conclusion:

This meta-analysis provides compelling evidence that elevated serum ADMA levels are associated with preeclampsia and may serve as a promising biomarker for early detection and monitoring of the disease. However, due to the observed heterogeneity and the observational nature of the studies included, further research is needed to validate these findings and explore the clinical utility of ADMA in the diagnosis and management of preeclampsia. Standardizing methodologies for ADMA measurement and conducting larger, multicenter studies will be essential to confirm its potential as a diagnostic tool and to better understand its role in the pathophysiology of preeclampsia. The identification of reliable biomarkers such as ADMA could significantly improve clinical outcomes for both mothers and infants affected by preeclampsia.

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