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Elevated values in preeclampsia: diagnostic and prognostic role of NT-proBNP and ANP

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ABSTRACT

The aim of this review is to summarize the current understanding of the cardiac dimension of preeclampsia as reflected in the PubMed database, and to provide a perspective on how NT-proBNP and ANP may play a role in the future management of this challenging condition. This narrative review synthesizes evidence from observational and clinical studies in human pregnancies, indexed in PubMed, focusing on the diagnostic and prognostic roles of the cardiac biomarkers NT-proBNP and ANP in preeclampsia. NT-proBNP primarily serves as a marker of increased ventricular afterload, whereas ANP is more indicative of diastolic dysfunction and atrial stretch. The observation that both biomarkers are significantly elevated in patients with preeclampsia, correlate with disease severity, and have the potential to predict adverse maternal outcomes underscores their clinical relevance in this condition. Multiple studies have demonstrated that both NT-proBNP and ANP levels are significantly elevated in preeclamptic pregnancies compared with healthy normotensive controls.

Keywords: Preeclampsia, hypertension, brain natriuretic peptide, atrial natriuretic peptide

INTRODUCTION

Preeclampsia is a multisystem syndrome typically manifesting after the 20th week of gestation, characterized by hypertension (systolic ≥140 mmHg and/or diastolic ≥90 mmHg) and proteinuria (≥300 mg/24 hours or a protein/creatinine ratio ≥0.3), or by hypertension accompanied by multi-organ dysfunction involving the kidneys, liver, neurological system, or hematologic system.[1,2] It is one of the leading causes of maternal and perinatal morbidity and mortality, complicating approximately 3-8% of all pregnancies.[3] Its prevalence varies according to geographic region, socioeconomic factors, and maternal risk factors such as nulliparity, advanced maternal age, obesity, chronic hypertension, and diabetes.

The clinical significance of preeclampsia stems from the serious complications it can cause. Short-term maternal risks include eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, placental abruption, acute kidney injury, pulmonary edema, and stroke. In the long term, affected women are at increased risk for chronic hypertension, cardiovascular disease, cerebrovascular events, and end-stage renal disease.[4] For the fetus and neonate, preeclampsia is associated with fetal growth restriction (FGR) due to uteroplacental insufficiency, fetal distress, preterm birth (iatrogenic or spontaneous), low birth weight, respiratory disorders such as respiratory distress syndrome, and even an elevated risk of intrauterine fetal death.[5]

The conventional criteria used for the diagnosis of preeclampsia have significant limitations. First, proteinuria does not consistently correlate with disease severity and may be minimal or even absent in some severe cases of preeclampsia.[2] Second, symptoms such as severe headache, visual disturbances, and upper abdominal pain, as well as organ dysfunction, typically manifest only after disease progression, limiting opportunities for early intervention. Third, the existing diagnostic criteria are inadequate for predicting the future course of the disease.

The pathogenesis of preeclampsia has not been fully elucidated. However, the most widely accepted model describes disease development in two stages: the first involves placental insufficiency, and the second is characterized by a maternal systemic response.[6]

Placental stage (impaired spiral artery remodeling): This represents the first and clinically silent stage of the disease. In a normal pregnancy, trophoblast cells invade the uterine spiral arteries, remodeling their structure. This process transforms the vessels into wide, low-resistance conduits, ensuring adequate blood flow to the developing fetus.[7] In preeclampsia, however, this remodeling is inadequate. The spiral arteries remain narrow and retain their vasoconstrictive properties, resulting in placental ischemia and hypoxia.[8]

Maternal stage (systemic endothelial dysfunction): The hypoxic and ischemic placenta releases a range of factors into the maternal circulation. Among these, the imbalance between anti-angiogenic factors, such as soluble Fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), and pro-angiogenic factors, including vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), plays a central role. sFlt-1 binds to VEGF and PlGF, rendering them inactive.[9] This imbalance, characterized by the predominance of anti-angiogenic factors, leads to widespread endothelial dysfunction in the maternal system.

Systemic Effects of Endothelial Dysfunction

The endothelium is the layer lining the interior of blood vessels and plays a vital role in maintaining vascular homeostasis. Endothelial dysfunction triggers the following processes, which contribute to the clinical manifestations of preeclampsia:

- **Increased systemic vascular resistance and hypertension:** In healthy endothelium, vasodilators such as nitric oxide are released to maintain vessel dilation. Endothelial injury disrupts this balance, enhancing the effects of vasoconstrictive agents such as endothelin-1. Consequently, the vessels constrict, systemic vascular resistance rises, and hypertension ensues.[10]

- **Increased vascular permeability and edema:** Disruption of endothelial integrity allows fluid and proteins to leak from the vasculature into surrounding tissues. This process contributes to edema and proteinuria, which are characteristic features of preeclampsia.

- **Multi-organ involvement:** Systemic endothelial dysfunction affects multiple organ systems.

  » Kidneys: Damage to glomerular endothelial cells leads to protein loss and renal dysfunction.

  » Liver: Endothelial injury in the liver contributes to elevated liver enzymes, right upper quadrant pain, and may predispose to HELLP syndrome.

  » Central nervous system: Cerebral edema, vasospasm, and microhemorrhages can result in severe headache, visual disturbances, hyperreflexia, and may ultimately progress to eclampsia.

  » Hematologic system: Endothelial injury triggers platelet activation and consumption, leading to thrombocytopenia.[11]

In summary, the process initiated by inadequate spiral artery remodeling progresses through placental release of anti-angiogenic factors, systemic endothelial dysfunction, and the resulting hypertension and multi-organ damage, culminating in the clinical presentation of preeclampsia. Impaired cardiovascular adaptive capacity and the consequent myocardial stress have emerged as increasingly recognized critical components in the complex pathogenesis of preeclampsia. In this context, N-terminal pro–brain natriuretic peptide (NT-proBNP) and atrial natriuretic peptide (ANP)-objective and reliable biomarkers of cardiomyocyte stress and hemodynamic load-warrant careful investigation for their potential clinical applications.

This review synthesizes evidence from human studies indexed in PubMed to examine the role of the cardiac biomarkers NT-proBNP and ANP in preeclampsia. We evaluate their contribution to pathogenesis, diagnostic accuracy, and prognostic prediction, aiming to clarify their potential for improving clinical management.

BIOLOGY AND PHYSIOLOGICAL ROLE OF NATRIURETIC PEPTIDES

ANP: Secretion and Effects

ANP is a hormone primarily synthesized and stored in the atria of the heart. The primary stimulus for ANP release is atrial stretch.[12] Atrial myocytes are stretched in response to increased blood volume and/or elevated venous return, which raises atrial pressure. Through this mechanical stimulus, ANP is rapidly secreted into the circulation.

The systemic effects of ANP are primarily directed toward reducing volume and pressure overload. These include natriuresis and diuresis: ANP relaxes the afferent arteriole and constricts the efferent arteriole in the renal glomeruli, thereby increasing the glomerular filtration rate (GFR). Additionally, it acts directly on the renal tubules to inhibit sodium (Na^+) and water reabsorption. As a result, urinary excretion of sodium and water is markedly increased, leading to a reduction in blood volume.[13]

Vasodilation: ANP acts on the smooth muscle cells of the vascular wall, promoting relaxation of the vessels. This leads to a reduction in systemic vascular resistance and blood pressure.

Inhibition of the renin–angiotensin–aldosterone system (RAAS): ANP directly suppresses renin release in the kidneys and aldosterone secretion from the adrenal glands, thereby counteracting the vasoconstrictive and fluid-retaining effects of the RAAS.[14]

Collectively, these effects of ANP play a key role in the regulation of body fluid and salt balance.

BNP and NT-proBNP: Secretion and Effects

BNP was first identified in brain tissue but is primarily secreted by the ventricles of the heart. Unlike ANP, it is not stored. Its synthesis and release are stimulated by increased wall tension and stress in ventricular myocytes.[15] Increases

in ventricular volume or pressure load, such as those seen in hypertension, are the main triggers for BNP production.

After secretion, BNP is divided into active BNP and inactive NT-proBNP. In clinical practice, measurement of NT-proBNP is generally preferred over BNP. The primary reasons for this preference are:

Longer half-life: The plasma half-life of NT-proBNP (60–120 minutes) is longer than that of active BNP (20 minutes). This allows NT-proBNP to remain at a more stable concentration in the circulation, making its measurement more reliable.[16]

Higher plasma concentration: Due to its longer half-life, NT-proBNP reaches higher circulating levels than BNP, facilitating laboratory measurement.

Greater stability: NT-proBNP is more stable at room temperature after sample collection, and its pre-analytical error rate is lower compared to BNP.

COMPARISON OF NT-proBNP AND ANP IN TERMS OF CLINICAL MEASUREMENT AND APPLICATION

Although both NT-proBNP and ANP are valuable biomarkers of cardiac stress, their applicability in clinical practice differs significantly. NT-proBNP is preferred and more suitable for routine use, particularly in cardiology and obstetrics clinics, due to its long half-life, high and stable plasma concentration, greater stability at room temperature, and the widespread availability of standardized commercial kits. In contrast, active ANP has a very short half-life, low basal plasma levels, and pre-analytical sensitivity requiring immediate cold-chain processing of the sample. Therefore, routine clinical measurement of ANP is more difficult and less practical compared to NT-proBNP. For this reason, ANP measurement is more commonly used in research settings, while NT-proBNP finds more use in daily practice for diagnosis, severity assessment, and prognostic prediction. However, the fact that ANP is particularly specific to atrial tension and diastolic dysfunction retains its value in terms of pathophysiological understanding.

NATRIURETIC PEPTIDE DYNAMICS IN NORMAL PREGNANCY

In a healthy pregnancy, the maternal circulatory system undergoes numerous important adaptive changes. Plasma volume increases by 40–50%, and cardiac output rises. These hemodynamic changes impose stress on the heart. Consequently, a mild elevation in natriuretic peptide levels in healthy pregnant women compared with non-pregnant women is considered physiological,[17] although this increase is generally modest.

In preeclampsia, however, the elevation in natriuretic peptides is typically much higher than the mild physiological increase observed in healthy pregnancies and is considered pathological. This excessive rise is driven by pathological afterload and cardiac dysfunction resulting from a marked increase in systemic vascular resistance. Therefore, by establishing appropriate threshold values, the pathological increase in preeclampsia can be readily distinguished from the physiological state of a healthy pregnancy.

PATHOPHYSIOLOGICAL BASIS OF CARDIAC STRESS IN PREECLAMPSIA

Hemodynamic Changes: Increased Afterload and Left Ventricular Loading

A central hemodynamic change in preeclampsia is a marked increase in systemic vascular resistance. This directly raises the afterload, defined as the pressure the left ventricle must overcome to eject blood into the aorta.[18] The elevated afterload places stress on the left ventricle, requiring it to exert greater effort with each contraction.

This increased workload has two major consequences:

- **Increased myocardial oxygen consumption:** As ventricular wall stress rises, the oxygen demand of the cardiac muscle increases.
- **Elevated left ventricular wall stress:** The mechanical stress (tension) on ventricular myocytes rises significantly as the ventricle works against high pressure to pump blood.

Increased afterload elevates left ventricular wall stress, which directly stimulates BNP synthesis and NT-proBNP release (**Figure**). Chronic pressure overload leads to left ventricular hypertrophy and diastolic dysfunction. Diastolic dysfunction increases left ventricular filling pressure, thereby raising left atrial pressure and tension. Increased atrial tension triggers ANP release. Consequently, the elevated NT-proBNP and ANP levels measured in preeclampsia are biochemical indicators of increased ventricular afterload/stress and diastolic dysfunction/atrial tension, respectively.

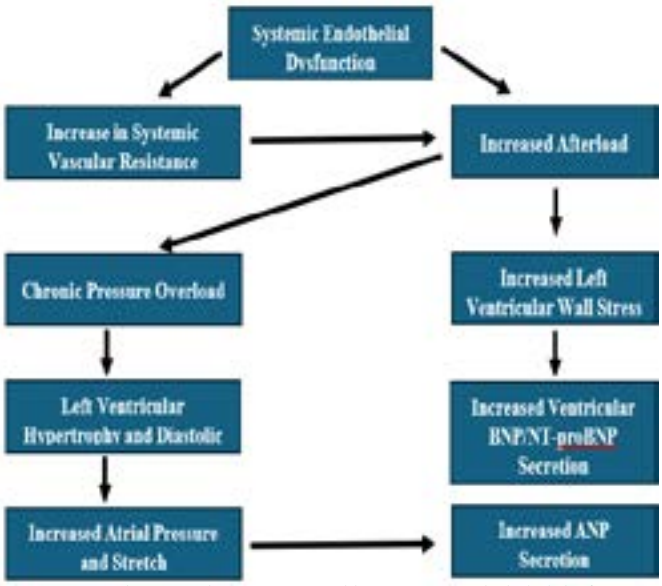

Figure. Hemodynamic changes triggered by systemic endothelial dysfunction in preeclampsia and the pathophysiological pathway of natriuretic peptide release
NT-proBNP: N-terminal pro–brain natriuretic peptide; ANP: atrial natriuretic peptide

Left Ventricular Hypertrophy and Diastolic Dysfunction

In response to increased afterload, the heart attempts to adapt over the long term. In preeclampsia, this process leads to concentric left ventricular hypertrophy, characterized

by thickening of the ventricular wall with a reduction or maintenance of the chamber volume.[19] Although this hypertrophy initially serves as a compensatory mechanism to counteract increased wall stress, it ultimately reflects a pathological process.

Myocardium that has undergone hypertrophy and exhibits increased oxygen demand is at risk for coronary microvascular dysfunction and ischemia. When these two factors—hypertrophy and ischemia-coexist, the left ventricle's ability to relax and fill is impaired, resulting in diastolic dysfunction.[20] Diastolic dysfunction means that higher pressures are required for ventricular filling. This elevated filling pressure is transmitted back to the left atrium, increasing atrial pressure and stretch, which in turn triggers ANP release[21] (**Figure**).

The elevation of both peptides indicates that preeclampsia is associated with impairments in both systolic and diastolic cardiac function.

Clinical Evaluation of NT-proBNP and ANP Levels in Preeclampsia

Numerous case-control studies have investigated this topic. Consistently, these studies have shown that both NT-proBNP and ANP levels are significantly higher in pregnant women with preeclampsia compared to healthy normotensive controls.

One of the pioneering studies on NT-proBNP, conducted by Resnik et al.,[17] reported markedly elevated BNP levels in women with preeclampsia compared to the control group. Similarly, in the study by Kale et al.,[22] NT-proBNP levels in the preeclampsia group (mean 430 pg/ml) were approximately six times higher than those in the control group (mean 74 pg/ml). Likewise, Suciu et al.,[23] in their systematic review and meta-analysis, reported significantly elevated NT-proBNP levels in the preeclamptic group, with the difference becoming more pronounced as disease severity increased.

A similar pattern is observed for ANP. Borghi et al.[24] demonstrated that ANP levels in preeclamptic women were significantly higher compared to both normotensive and chronically hypertensive pregnant women. This finding suggests that the cardiac stress observed in preeclampsia may have a dynamic profile distinct from that seen in chronic hypertension. Similarly, Pretorius et al.[25] reported markedly elevated ANP levels in the preeclampsia group compared to controls, with this increase correlating with disease severity. A comparative overview of these and other pivotal studies, including sample sizes, peptide levels, and diagnostic cut-offs, is provided in **Table**.

Correlation with Preeclampsia Severity

The clinical utility of NT-proBNP and ANP extends beyond diagnosis, as these biomarkers can also be used to assess disease severity. Studies have demonstrated that their

Table. Summary of key studies on NT-proBNP and ANP in preeclampsia

Study (year)	Study population	Sample size (n)	Measured peptide	Peptide levels (mean±SD or median)	Cut-off value (if applicable)	Sensitivity/ specificity	Key findings
Resnik et al. (2005)	Preeclamptic vs. normotensive pregnancies	Preeclampsia: 20, Control: 20	ANP	Preeclampsia: ↑↑, control: normal	Not specified	Not reported	BNP levels significantly higher in preeclampsia; correlates with disease severity.
Kale et al. (2005)	Preeclamptic vs. normotensive pregnancies	Preeclampsia: 30, Control: 30	NT-proBNP	Preeclampsia: ~430 pg/ml, control: ~74 pg/ml	Not specified	Not reported	NT-proBNP levels ~6x higher in preeclampsia group.
Suciu et al. (2025)	Systematic review & meta-analysis	Multiple studies included	NT-proBNP, BNP	Pooled analysis showed significant elevation	Not specified	Not reported	Confirmed significant elevation in preeclampsia, especially with severity.
Borghi et al. (2000)	Preeclamptic vs. normotensive & chronic hypertensive pregnancies	Preeclampsia: 15, normotensive: 15, chronic ht: 15	ANP	Preeclampsia: ↑↑, controls: lower	Not specified	Not reported	ANP levels higher in preeclampsia than in chronic hypertension.
Pretorius et al. (2018)	Preeclamptic vs. normotensive pregnancies	Preeclampsia: 40, control: 40	ANP	Preeclampsia: ↑↑, controls: normal	Not specified	Not reported	ANP levels correlate with disease severity.
Bakacak et al. (2016)	Severe vs. non-severe preeclampsia	Severe PE: 25, non-severe PE: 25	NT-proBNP	Severe PE: higher levels	Not specified	Not reported	NT-proBNP higher in severe preeclampsia; useful for severity grading.
Álvarez-Fernández et al. (2016)	Preeclamptic vs. normotensive pregnancies	Total: 120	NT-proBNP	Not specified	219 pg/ml	84%/76%	Good diagnostic accuracy; improves when combined with sFlt-1/PlGF.
Nan et al. (2025)	Preeclamptic vs. normotensive pregnancies	Total: 200	NT-proBNP	Not specified	116 pg/ml	90.9%/94.3%	High diagnostic accuracy for preeclampsia and maternal-fetal complications.
Reyna-Villasmil et al. (2018)	Preeclamptic vs. normotensive pregnancies	Total: 100	ANP	Not specified	0.66 ng/ml	87.8%/83.3%	Good diagnostic performance for ANP in preeclampsia.

SD: Standard deviation, ANP: Atrial natriuretic peptide, BNP: Brain natriuretic peptide, NT-proBNP: N-terminal pro–brain natriuretic peptide, HT: Hypertension, PE: Preeclampsia, sFlt-1: Soluble Fms-like tyrosine kinase-1, PlGF: Placental growth factor

concentrations are significantly higher in severe preeclampsia compared to mild cases.

In a study conducted by Bakacak et al.[26] in 2016, NT-proBNP levels were found to be higher in the severe preeclampsia group, suggesting that NT-proBNP could be used to grade the severity of preeclampsia. A similar pattern has been observed for ANP. In a study by Adam et al.,[27] serum ANP levels were reported to be significantly elevated in patients with severe preeclampsia and eclampsia.

These findings suggest that NT-proBNP and ANP can serve as measures of the pathophysiological impact of preeclampsia on cardiac load. As afterload and diastolic dysfunction worsen with disease progression, the serum levels of these peptides increase correspondingly. Therefore, these biomarkers are considered capable of reflecting the severity of preeclampsia in an objective and quantitative manner.

Diagnostic Accuracy and Threshold Values

Studies in the literature generally report high sensitivity and specificity for NT-proBNP in distinguishing preeclampsia from healthy pregnancies.

In a study by Álvarez-Fernández et al.,[28] using a cut-off value of 219 pg/ml, NT-proBNP demonstrated 84% sensitivity and 76% specificity for detecting preeclampsia, with even higher sensitivity and specificity when combined with sFlt-1/PlGF. A more recent study identified an optimal cut-off of 116 pg/ml, reporting a sensitivity of 90.9% and specificity of 94.3% for NT-proBNP alone.[29]

Reyna-Villasmil et al.,[30] in their study on the role of ANP in detecting preeclampsia, reported 87.8% sensitivity and 83.3% specificity at a cut-off value of 0.66 ng/ml.

There is no universally accepted threshold value for these peptides. Different studies have proposed varying cut-off ranges, with the main reasons for this variability being:

- Population differences: Variations in study populations, including gestational age, body-mass index (BMI), comorbidities, and race/ethnicity.
- Commercial kits and analyzers used: Differences in measurement standards across laboratories due to the use of various kits and analytical devices.
- Patient selection criteria: Heterogeneity in the severity distribution of preeclampsia cases included in the studies.

Due to these variations, establishing a universal reference range is challenging. Instead, it appears more appropriate for each laboratory to validate the biomarkers within its own population and using its specific methods, and to establish laboratory-specific reference ranges.

PROGNOSTIC ROLE OF NT-proBNP AND ANP

Prediction of Maternal Complications

The primary clinical potential of NT-proBNP and ANP lies less in diagnosis and more in their capacity to predict life-threatening maternal complications. Emerging studies suggest that elevated levels of these biomarkers may serve as indicators of a more severe disease course.

HELLP syndrome and eclampsia: In a study by Nan et al.,[29] patients who developed HELLP syndrome or required intensive care exhibited significantly higher baseline NT-proBNP levels compared to those with uncomplicated preeclampsia. Similarly, elevated ANP levels are thought to be associated with severe hypertensive crises and eclampsia. This is because these peptides indirectly reflect the severe hypertension and vascular dysfunction underlying cardiac decompensation and neurological involvement.

Pulmonary edema and cardiac complications: In preeclampsia, pulmonary edema typically arises as a consequence of diastolic dysfunction and increased capillary permeability. Both NT-proBNP (an indicator of diastolic dysfunction) and ANP (a marker of elevated atrial pressure) are directly linked to these pathophysiological processes. Therefore, elevated levels of these peptides may help identify patients at risk of developing pulmonary edema at an early stage.

Acute kidney injury: Reduced cardiac output and impaired renal perfusion can lead to kidney injury. As NT-proBNP is a sensitive marker of decreased cardiac output, it may have prognostic value in identifying the risk of preeclampsia-associated acute kidney injury.

Association with Fetal and Neonatal Outcomes

Maternal cardiovascular stress directly affects uteroplacental perfusion. Consequently, elevated maternal serum NT-proBNP and ANP levels are likely associated with fetal and neonatal complications.

FGR and preterm birth: Placental insufficiency is associated with both preeclampsia and FGR. Maternal hypertension and cardiac dysfunction further impair uteroplacental blood flow. Therefore, elevated NT-proBNP levels may serve as indicators of more severe placental dysfunction and, consequently, an increased risk of FGR and iatrogenic preterm birth.[30]

Low birth weight and fetal distress: Similarly, deterioration of maternal hemodynamics can contribute to the development of fetal distress. Several studies in the literature have reported associations between high maternal NT-proBNP levels and adverse neonatal outcomes, including low 5-minute Apgar scores, umbilical artery acidosis, and the need for neonatal intensive care unit admission.[29,30]

Monitoring Postpartum Cardiac Recovery

The adverse effects of preeclampsia on the maternal cardiovascular system do not resolve immediately after delivery. The postpartum period represents a recovery phase during which cardiac remodeling and hemodynamics gradually return to normal. NT-proBNP and ANP may serve as useful biomarkers for monitoring this process.

Limited studies have provided promising data in this regard. Research has shown that postpartum NT-proBNP levels in preeclamptic women decline rapidly, although this reduction may occur more slowly compared to normotensive women.[31] Persistently elevated NT-proBNP levels may indicate

incomplete cardiac recovery or permanent myocardial damage during the postpartum period.[32]

These findings support the potential utility of these cardiac biomarkers in assessing long-term cardiovascular risk in preeclampsia patients and in monitoring their postpartum recovery. However, further prospective studies are needed to establish postpartum-specific cut-off values and to delineate normal recovery dynamics.

DISCUSSION

The evidence presented in this review demonstrates that NT-proBNP and ANP serve as sensitive and objective biomarkers of cardiac stress and dysfunction, which play a central role in the pathophysiology of preeclampsia. NT-proBNP primarily reflects increased ventricular afterload, whereas ANP is more indicative of diastolic dysfunction and atrial stretch. Studies consistently report markedly elevated levels of both biomarkers in preeclamptic patients, their correlation with disease severity, and their potential to predict adverse maternal outcomes, highlighting their clinical value.

Routine use of these biomarkers in clinical practice could inform patient management in several ways:
Patient risk stratification: NT-proBNP, in particular, can be used to differentiate between "high-risk" and "low-risk" preeclampsia cases at the time of clinical presentation. Patients with elevated serum levels may warrant closer maternal monitoring (e.g., frequent blood pressure checks, laboratory assessments) and enhanced fetal surveillance (e.g., non-stress tests and ultrasonography). These biomarkers may even help anticipate the need for hospitalization.

Individualization of follow-up protocols: Serial measurements of these biomarkers can provide an objective assessment of preeclampsia progression or stabilization. Declining or stable levels may be interpreted as reassuring, whereas rising levels could prompt reconsideration of the therapeutic strategy.

CONTRADICTIONS AND METHODOLOGICAL DIFFICULTIES

In the literature, there is a general consensus regarding the diagnostic performance of NT-proBNP and ANP in preeclampsia. Nevertheless, inconsistencies remain among studies concerning the proposed cutoff values and certain prognostic associations. These discrepancies are largely attributable to methodological differences and the influence of confounding factors.

These include:
Gestational age: NT-proBNP and ANP levels may vary across different trimesters of pregnancy. Since the populations examined in various studies often include patients at different gestational stages, this heterogeneity can distort the results.

Preexisting cardiovascular and metabolic disorders: Conditions such as obesity, chronic hypertension, diabetes, or preexisting cardiac disease may independently influence these peptide levels; therefore, the observed elevations may not be specific to preeclampsia alone.

Population heterogeneity: Differences in ethnicity, age, and BMI distributions among study populations can affect the generalizability of findings.

Analytical variability: The lack of standardization among commercially available assay kits and measurement platforms makes it difficult to compare cutoff values across studies.

Clinical practice applicability and marker selection: While evidence in the literature suggests that both NT-proBNP and ANP reflect cardiac stress in preeclampsia, NT-proBNP has a clear advantage when it comes to translating these markers into clinical practice. Technical challenges in measuring ANP and the limited availability of standardized, widely accepted test kits make its integration into routine diagnostic or prognostic algorithms difficult. In contrast, automated, rapid, and reliable measurement systems have been developed for NT-proBNP, and its use in clinical laboratories is becoming increasingly common. This practical advantage increases the potential for NT-proBNP to be considered as a first-line biomarker in the management of preeclampsia. ANP, on the other hand, may play a more central role in mechanistic studies or as a complementary marker that can further clarify the pathophysiological picture when used in conjunction with NT-proBNP.

Lack of detailed subgroup analyses: The current literature and the scope of this review do not include detailed subgroup analyses of key confounding factors that may have significant effects on NT-proBNP and ANP levels. Specifically:

- **Gestational age:** Understanding how NT-proBNP and ANP levels vary across trimesters and even specific weeks of pregnancy is critical for establishing gestational week-specific reference ranges for these markers. Current studies often analyze heterogeneous groups of patients at different gestational weeks, making interpretation of results challenging.

- **BMI:** Obesity is thought to independently influence natriuretic peptide levels due to its known effects on cardiac structure and function. However, comprehensive analyses comparing the behavior of these markers in obese and normal BMI pregnant women with preeclampsia are limited.

- **Pre-existing cardiovascular and metabolic diseases:** Conditions such as chronic hypertension, diabetes, or subclinical heart disease can elevate natriuretic peptide levels independently of pregnancy. To differentiate the preeclampsia-specific increase from the increase caused by these underlying conditions, controlled subgroup analyses are needed in preeclampsia groups with and without these comorbidities.

In studies where these confounding factors are not systematically controlled for or isolated, it is difficult to determine the extent to which measured natriuretic peptide elevation is specific to preeclampsia and to what extent it is due to these other factors. This leads to uncertainty both in determining diagnostic thresholds and in prognostic interpretation.

Future research directions: The methodological challenges and shortcomings highlighted above underscore the need for further research in the following areas:

- **Large-scale, prospective, multicenter cohort studies:** Well-designed, multicenter cohort studies involving diverse populations are needed to establish gestational age–specific reference ranges for NT-proBNP and ANP, and to validate their diagnostic and prognostic accuracy after adjustment for confounding factors.

Multi-Marker Approaches

Rather than relying on a single biomarker, panels that reflect different pathophysiological pathways may offer greater clinical insight. For instance, combining markers of cardiac stress (NT-proBNP/ANP) with those of placental dysfunction (sFlt-1/PlGF ratio) could substantially improve both diagnostic precision and prognostic performance compared to using each marker in isolation.

Despite the theoretical advantages of the multi-marker approach, its integration into routine clinical practice should also be evaluated in terms of cost-effectiveness, test accessibility, and workflow. Measurement of angiogenic markers such as the sFlt-1/PlGF ratio can often be more expensive than NT-proBNP and may not be routinely used in all centers, especially those with limited resources. NT-proBNP, on the other hand, is an automated and relatively low-cost test already available in many hospitals due to its widespread use in the diagnosis and monitoring of heart failure. Therefore, NT-proBNP alone can be a valuable screening or risk stratification tool, especially in settings where the sFlt-1/PlGF test is not routine. In an ideal scenario, combining markers from both pathways (placental and cardiac) would provide the highest diagnostic and prognostic accuracy. However, it is thought that the cost-benefit ratio of this combination can only be justified in high-risk pregnancy centers or in cases of significant clinical suspicion. Widespread adoption of this approach as a routine measure will depend on lower testing costs, standardization, and robust evidence demonstrating that these panels improve clinical outcomes.

Interventional studies: The highest level of evidence required for the clinical implementation of these biomarkers will come from randomized controlled trials. Future studies could investigate whether biomarker-guided risk stratification-such as more intensive management or closer monitoring of patients with elevated NT-proBNP and ANP levels-can effectively reduce maternal and neonatal morbidity.

CONCLUSION

As a result, evidence indicates that both NT-proBNP and ANP levels are significantly elevated in women with preeclampsia compared to healthy normotensive pregnancies. This elevation is directly and causally linked to the hemodynamic alterations characteristic of preeclampsia, including increased systemic vascular resistance, elevated left ventricular afterload, and the resulting diastolic dysfunction-all reflecting heightened cardiac stress and dysfunction. NT-proBNP and ANP thus emerge as promising biomarkers for understanding and managing the cardiac dimension of preeclampsia.

However, for their integration into routine clinical practice, several prerequisites remain essential: the standardization of measurement methodologies, the establishment of gestational age–specific cutoff values through large-scale prospective studies, and stronger evidence derived from multi-marker and interventional trials. Conducting such studies will substantially contribute to reducing the maternal and fetal complications associated with preeclampsia.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

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Author Contributions

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