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Activin A and Heart Function in Severe Preeclampsia: Insights From Global Longitudinal Strain

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LITERATURE REVIEW

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ABSTRACT

Preeclampsia, a serious pregnancy complication affecting 2–5% of women globally, is a leading cause of maternal and fetal mortality. Its prevalence in Indonesia ranges from 0.8–7% depending on parity. Associated with long-term cardiovascular risks, recent research suggests that elevated maternal activin A levels may play a causal role in linking severe preeclampsia to subsequent cardiovascular complications, particularly through mechanisms involving cellular damage, including to the heart. The aim of this study was to assess the correlation between Activin A circulating level and cardiac ventricular function as assessed by cardiac global longitudinal strain (GLS) in severe preeclampsia. A cross-sectional study was conducted at M. Djamil Hospital, Padang, West Sumatera, Indonesia with a total of 31 patients with severe preeclampsia. The Enzyme-Linked Immunosorbent Assay (ELISA) as used to determine the level of Activin A in the blood serum. Ventricular function was assessed from the global longitudinal strain using echocardiographic evaluation. The mean level of Activin A was 2.97 ± 1.91 ng/mL. From the echocardiographic evaluation, the mean cardiac GLS value was 18.01 ± 3.27%. The correlation between activin A levels and cardiac ventricular function was analyzed using Pearson's correlation test, which showed a strong negative correlation ($r = -0.718$, $p < 0.001$). This indicates that higher activin A levels are significantly associated with lower GLS values, demonstrating worse ventricular function.

Key Messages:

- Elevated circulating Activin A levels demonstrate a strong inverse correlation with cardiac Global Longitudinal Strain (GLS) in severe preeclampsia, indicating that higher Activin A concentrations are significantly associated with impaired ventricular function.

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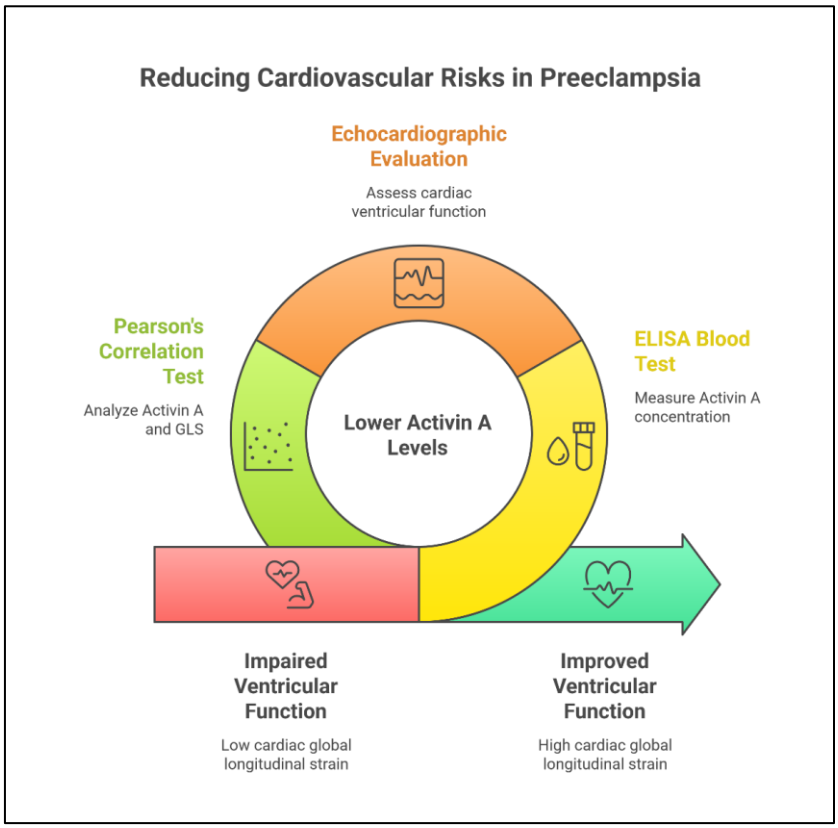
GRAPHICAL ABSTRACT



INTRODUCTION

Preeclampsia is a serious pregnancy complication affecting 2-5% of pregnant women globally, contributing significantly to maternal and fetal mortality. In Indonesia, the incidence is particularly concerning, occurring in 3-7% of nulliparas and 0.8-5% of multiparas, and is responsible for 30-40% of perinatal deaths. Activin A, a component of the Transforming Growth Factor beta TGF-β family, has been identified as a key factor in preeclampsia, with elevated levels observed in affected women. Pre-eclampsia is triggered by excessive systemic inflammation, where Tumor Necrosis Factor alpha (TNF-alpha) increases activin A secretion from peripheral blood cells in pregnant women with preeclampsia (1).

A critical issue associated with preeclampsia is the increased risk of cardiovascular problems later in life for affected women. Research has shown that Activin A may play a crucial role in this long-term cardiovascular risk. It is linked to inflammation and fibrosis in the heart, potentially serving as a mediator between preeclampsia and subsequent myocardial dysfunction. The impact on cardiac function can be assessed through global longitudinal strain (GLS) of the heart, a sensitive measure of systolic function(2).

Despite the established connection between preeclampsia and future cardiovascular risks, there is a significant research gap in the current literature. Specifically, there is limited research exploring the role of Activin A in cardiovascular disorders as a complication of preeclampsia, particularly before delivery. This study aims to address this gap by investigating the relationship between Activin A levels and cardiac function in women with severe preeclampsia prior to delivery(3).

The primary objective of this research is to analyze the correlation between Activin A levels and cardiac function in women with severe preeclampsia by assessing the GLS of the heart. By exploring this relationship, the study aims to deepen our understanding of the potential mechanisms that link preeclampsia to long-term cardiovascular risks. This could contribute to the development of improved risk assessment and management strategies for women affected by this serious pregnancy complication(4).

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Preeclampsia is a complex hypertensive disorder of pregnancy, typically emerging after the 20th week of gestation, and is characterized by high blood pressure and proteinuria. The pathophysiology of preeclampsia includes systemic inflammation, endothelial dysfunction, and altered vascular tone. Severe preeclampsia is associated with significant maternal morbidity and mortality, affecting the cardiovascular system, including impaired heart function. The pathophysiological changes in the heart are often underappreciated, yet there is emerging evidence of myocardial dysfunction, which may remain undiagnosed without proper assessment tools (5).

In recent years, biomarkers such as Activin A have been identified as potential players in the modulation of heart function in preeclampsia, and their relationship with cardiovascular outcomes is an area of active investigation(6). This literature review examines the potential role of Activin A in cardiac dysfunction associated with severe preeclampsia, with a particular focus on insights gained from global longitudinal strain (GLS), a more sensitive echocardiographic measure of myocardial function.

Activin A is a member of the transforming growth factor-beta (TGF-β) superfamily and plays crucial roles in various physiological processes, including embryogenesis, tissue remodeling, and immune regulation. In the context of preeclampsia, Activin A is believed to mediate the inflammatory response and endothelial dysfunction, which contribute to the development of cardiovascular complications in pregnancy. Elevated levels of Activin A have been observed in the serum of preeclamptic women, and its concentration correlates with disease severity, suggesting its potential as a biomarker for predicting poor maternal outcomes(7).

Furthermore, Activin A is thought to influence vascular tone and myocardial contractility, which may lead to alterations in cardiac function in women with severe preeclampsia. The protein's ability to affect both the vascular endothelium and myocardial cells points to its potential involvement in the cardiac remodeling seen in this condition. However, the exact mechanisms by which Activin A affects the heart remain poorly understood, and further research is required to clarify its role in preeclampsia-related myocardial dysfunction(8).

Traditionally, echocardiography has been the gold standard for assessing cardiac function, particularly through measurements of left ventricular ejection fraction (LVEF). Global longitudinal strain (GLS) has emerged as a more sensitive technique for detecting early myocardial dysfunction, as it measures the deformation of the myocardium during systole(9).

GLS has been shown to be a powerful predictor of cardiac outcomes in various cardiovascular conditions, and its application to preeclampsia has garnered significant interest. Studies have demonstrated that women with severe preeclampsia exhibit impaired GLS, even when LVEF remains normal. The sensitivity of GLS makes it particularly useful in identifying cardiac involvement in preeclampsia, where myocardial dysfunction may occur despite a lack of overt symptoms or changes in conventional echocardiographic parameters. The aim of this study was to investigate the correlation between circulating Activin A levels and cardiac ventricular function, as assessed by global longitudinal strain (GLS), in patients with severe preeclampsia.

METHODS

Study design and patients

This cross-sectional study was conducted at Dr. M. Djamil General Hospital, Padang, West Sumatra, Indonesia, between October and December 2023. The inclusion criteria were pregnant women who presented to the emergency department or outpatient clinic and provided informed consent to participate. Eligible participants had a gestational age of above 20 weeks, determined using the Naegele formula based on the last menstrual period or confirmed by ultrasound examination, and were diagnosed with severe preeclampsia based on clinical examination and laboratory findings. Exclusion criteria included chronic diseases such as diabetes mellitus, atherosclerotic cardiovascular disease, acute or chronic renal failure, superimposed preeclampsia, and malignant tumors, based on medical history and clinical diagnosis(10).

During the study period, a total of 54 patients with severe preeclampsia were admitted. Of these, 23 patients were excluded: 2 with cardiac complications, 1 with chronic renal failure, 2 with

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superimposed preeclampsia, 3 without GLS results, and 15 who did not undergo echocardiography because the procedure fell on a hospital holiday. After patient selection using these inclusion and exclusion criteria, a total of 31 samples were obtained, in which serum Activin A levels and cardiac GLS were measured.

The enzyme-linked immunosorbent assay (ELISA) method was used to measure the levels of Activin A. Serum Activin A levels were measured using an enzyme-linked immunosorbent assay (ELISA), following the manufacturer's instructions (BT Lab Human Activin A Kit, code: A4D1w7). This biomarker examination was carried out in the Biomedical Laboratory of Andalas University, Indonesia.

Assessment of left ventricular function was performed using echocardiography (General Electric Echocardiography Vivid T8). Speckle-tracking echocardiography can be performed offline in two-dimensional echocardiography by tracking myocardial features throughout the cardiac cycle. Strain can be measured in different directions (longitudinal, circumferential, and radial) and is conventionally expressed as a percentage, defined as the relative change in length or thickness of the left ventricular (LV) myocardium in relation to its original length or thickness (without units). Left ventricular GLS was calculated from four-chamber (4CH), three-chamber (3CH), and two-chamber (2CH) apical views, while global LV circumferential and global LV radial strains were calculated from short-axis views. The average interpretation of GLS is normal (>18%), borderline (16–18%), and abnormal (<16%) (11).

Statistical analysis

Data were analyzed using inferential statistical methods to assess the correlation between serum Activin A levels and cardiac GLS using the software SPSS version 27. The relationship between GLS and activin A was determined using the Pearson correlation test for normally distributed data or Spearman's rank correlation test for non-normally distributed data. Statistical significance was defined as a p-value of less than 0.05.

The ethical aspects of this study were conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Dr. M. Djamil General Hospital, Padang (approval number: LB.02.02/5.7/240/2023).

RESULTS

A total of 31 patients were included in this study, and their characteristics are presented in Table 1. The average age of the patients was 32.03 ± 6.3 years. Overweight BMI is the most common. The mean serum Activin A levels were 2.97 ± 1.91 ng/mL. From the echocardiography evaluation, GLS was 18.01 ± 3.27.

Table 1. Demography, comorbidities, echocardiography characteristics, and activin A levels were included in the study.

Characteristics (n=31)	Mean ± SD
Demography	
Age, years	32.03 ± 6.3
Parity	
Primiparity, n (%)	10 (32.25%)
Multiparity, n (%)	18 (58.07%)
Grandmultiparity, n (%)	3 (9.68%)
Gestational Age	
20-34 weeks, n (%)	23 (74.19%)
≥34 weeks, n (%)	8 (25.81%)
Body Mass Index (BMI), kg/m^2	
Normoweight, n (%)	10 (32.25%)
Overweight, n (%)	12 (38.72%)
Obesity, n (%)	9 (29.03%)
Systolic blood pressure (mmHg)	
160-200, n (%)	25 (80.65%)
>200, n (%)	6 (19.35%)

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Characteristics (n=31)	Mean ± SD
Fetal Outcomes	
Birth weight (g)	1931.82 ± 860.76
Mild Asphyxia, n (%)	16 (51.62%)
Moderate asphyxia, n (%)	9 (29.03%)
Severe asphyxia, n (%)	4 (12.90%)
Death, n (%)	2 (6.45%)
Echocardiography findings	
GLS	18.01 ± 3.27
Normal (>18%), n (%)	11 (35.48%)
Borderline (16-18%), n (%)	14 (45.16%)
Abnormal (<16%), n (%)	6 (19.36%)
E.F (%)	58.68 ± 7.66
Global hypokinetic, n (%)	2 (6.45%)
LV concentric hypertrophy, n (%)	31 (100%)
Mild TR, n (%)	18 (58.06%)
Diastolic dysfunction, n (%)	15 (48.38%)
Minimal pericardial effusion, n (%)	15 (48.38%)
Activin A Result (ng/mL)	2.97 ± 1.91

Table 2. Correlation between Activin A and Global Longitudinal Strain (GLS) of Heart in severe preeclampsia

Correlation	r (Pearson correlation)	p-value
Activin A with GLS (Global Longitudinal Strain)	-0.718	0.000

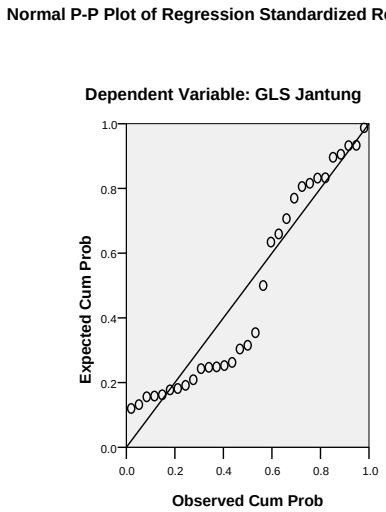

Figure 1. Normal P-P Plot of Regression Standardized Residual for Cardiac GLS.

DISCUSSION

Based on Table 1, Pearson correlation analysis demonstrated a significant inverse relationship between serum Activin A levels and cardiac GLS ($r = -0.718$, $p < 0.001$). This inverse relationship indicates that higher levels of Activin A are associated with lower GLS values, suggesting impaired myocardial function. This finding aligns with previous studies demonstrating that elevated Activin A levels are associated with impaired myocardial function. Long-term studies in women with a history of preeclampsia have also demonstrated that higher Activin A levels are consistently linked to worse GLS values, even after adjustment for confounding factors. These findings further support the role of Activin A as a potential marker of cardiac dysfunction(3).

In this study, the average activin A value of severe preeclampsia patients was 2.97±1.9 ng/ml. Previous studies, such as that, have also reported elevated maternal serum Activin A concentrations in

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women with preeclampsia. This increase is hypothesized to result from enhanced cytotrophoblast proliferation in response to placental ischemia. The accuracy of Activin A for predicting preeclampsia was estimated through analysis of 10 trials (n = 1,985). The results showed that the range of sensitivity values was 11 to 93%, specificity was 71 to 95%, and the range of positive and negative likelihood ratios was 2.2 to 11.0 and 0.1 to 0.9, respectively. Preeclampsia may exhibit alterations in the activin A system, as the diverse data generally imply that activin A may influence trophoblasts, whose aberrant migration is crucial to the development of preeclampsia. Both genetic polymorphisms in the Activin A receptor gene (ACVR2A) and variations in circulating and placental Activin A levels have been proposed as factors influencing the pathophysiology of preeclampsia. Polymorphisms in ACVR2A may be a genetic risk factor for pre-eclampsia, according to recent research. Furthermore, preeclampsia is associated with considerably elevated serum and placental activin A levels, indicating that activin A may serve as a biomarker for the illness (12).

Experimental research conducted on experimental mice showed that increased levels of activin A were associated with endothelial cell dysfunction and maternal systemic inflammatory responses in preeclampsia. Elevated maternal Activin A levels in preeclampsia were primarily reflective of increased placental production (12). Further research is needed to fully understand the mechanisms underlying the involvement of activin A in preeclampsia. Activin A has been shown to play a role in endothelial cell dysfunction in preeclampsia. Studies have found that activin A and preeclampsia serum upregulate endothelin-1 (ET-1), Intercellular Adhesion Molecule-1 (ICAM-1), and Vascular Cell Adhesion Molecule-1 (VCAM-1) in human umbilical vein endothelial cells (HUVECs), which are markers of endothelial activation. Additionally, in HUVECs exposed to activin A or preeclampsia serum, follistatin, a particular binding protein for activin, reduced the upregulation of ET-1, ICAM-1, and VCAM-1. These findings suggest that activin A contributes to the pathophysiology of preeclampsia by increasing endothelial cell dysfunction(13).

Abnormal findings on echocardiography examination generally include concentric hypertrophy in the left ventricle, mild tricuspid regurgitation, diastolic dysfunction, and pericardial effusion. Variations in pressure load dramatically rise in preeclampsia, but variations in volume load decrease. Concentric remodeling, diastolic dysfunction, reduced left ventricular strain, and elevated right ventricular systolic and diastolic pressure are the hallmarks of preeclampsia, in which concentric remodeling occurs in parallel sarcomere replication. It has been agreed that much of the collagen and extracellular fibrotic matrix composition decreases the work of the heart. After preeclampsia, the incidence of diastolic dysfunction, left and right ventricular strain damage, and subclinical heart failure will increase. These changes can change, persist, or even worsen, especially with metabolic disorders, poor lifestyles, or blood pressure factors, and can contribute to a 2- to 7-fold increase in cardiovascular risk, including heart failure. In conditions of increased heart load due to severe preeclampsia resulting in hyperdynamic ventricular function. This is accompanied by increased pressure in the pulmonary capillaries, and pulmonary edema may occur despite normal ventricular function. This occurs in part due to alveolar endothelium-epithelial leakage and is exacerbated by reduced oncotic pressure from low serum albumin(14).

In this study, the mean GLS value was 18.01% with a standard deviation of 3.27%. The majority of patients (45.16%) fell within borderline values. In addition, all samples also showed left ventricular concentric hypertrophy, and almost half of them had diastolic disorders and minimal pericardial effusion. Our findings are consistent with those who reported significantly reduced GLS values in women with preeclampsia compared to normotensive pregnant controls. Cohort study by Clemmensen et al. In 2018, a study involving 93 women in Denmark (with a history of preeclampsia and a control group) who were evaluated with echocardiography 12 years after delivery found no difference in LVEF between preeclampsia and non-preeclampsia patients. However, GLS was significantly lower in the preeclampsia group (15). This is associated with severe restrictions during ventricular filling (diastole), especially in early-onset preeclampsia. In contrast, relatively preserved GLS values were found in both preeclamptic and control groups at 2.3 years postpartum, suggesting that cardiac strain alterations may normalize

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over time. This difference appears to be due to variations in the timing of cardiac GLS examinations and the progression of subclinical damage over time.

According to previous research, women with preeclampsia exhibit lower global longitudinal strain (GLS), a sensitive echocardiographic indicator of systolic function that can reflect early myocardial tissue damage and fibrotic remodeling. Activin A may play a causal role in the etiology of preeclampsia, as elevated maternal Activin A levels have been detected several months before the clinical manifestation of the disease. Consistent with these findings, Shahul et al. (2018) (16) and Bakrania et al. (2022) (17) show that women with preeclampsia show reduced GLS, indicating subclinical systolic dysfunction and possible myocardial fibrosis. Furthermore, sustained elevation of activin A was associated with, and experimentally shown to induce, impaired cardiac function during pregnancy, suggesting its involvement in the pathogenesis of preeclampsia and related cardiac complications.

The pathogenesis of maternal preeclampsia is thought to involve an exaggerated systemic inflammatory response, characterized by endothelial activation and cytokine release, such as TNF-α, which has been shown to increase Activin A secretion from peripheral blood mononuclear cells(16). In vivo research in mice by Bakrania showed an increase in circulating activin A associated with GLS disorders(13). The expression of beta-myosin heavy chain was elevated in heart tissue upon activin A infusion (6 μg/day), suggesting myocardial damage, so it was concluded that activin A functions as a mediator related to cardiac dysfunction due to PE.

In order to create phosphorylated heteropolymers, activin A first attaches to type II receptors and encourages their phosphorylation. It next recruits type I receptors. SMAD (Suppressor of Mothers Against Decapentaplegic) 2 and 3 will be phosphorylated by the active receptor complex in a carboxyl terminal chain pattern. Next, SMAD4 is recruited to help form the transcription complex. Meanwhile, the noncanonical pathway involves ERK (extracellular signal-regulated kinase), p38, Wnt (wingless and Int-1), the PI3K complex (*phosphoinositide 3-kinase*), Akt (protein kinase), and mTor (*mammalian targets of rapamycin*)(17). Following their translocation to the nucleus, these two pathways impact the transcription of the target cells' Pax-6, FSH, p21, and follistatin genes.

Previous studies indicate that activin A, a pathophysiologically significant member of the TGF-β (transforming growth factor-β) superfamily, may be a key player in the development of heart failure. Abnormal cardiomyocyte remodeling, endothelial dysfunction, and myocardial fibrosis—which causes concentric remodeling of the heart muscle—are the mechanisms that connect activin A to heart failure(18).

The results demonstrate a statistically significant correlation between elevated serum activin A levels and impaired cardiac function, as quantified by reduced Global Longitudinal Strain (GLS), in patients with severe preeclampsia. Furthermore, the study suggests that these preeclampsia-induced cardiac alterations may persist or progress over time, potentially contributing to a 2- to 7-fold increase in long-term cardiovascular risk, including the development of heart failure.

Based on the current findings, future studies could focus on several areas to further understand the role of Activin A in the pathophysiology of preeclampsia and related cardiac dysfunction. First, it is important to explore the relationship between Activin A levels and the type of preeclampsia onset, whether early or late onset, and its impact on cardiac function, specifically regarding differences in the reduction of Global Longitudinal Strain (GLS). Larger longitudinal studies could help identify differences in the long-term progression of heart dysfunction in women with preeclampsia based on the onset timing of the disease.

Additionally, further studies could explore the molecular mechanisms underlying how Activin A affects endothelial function and cardiomyocyte remodeling in the long term. Research on more specific animal models, such as using transgenic mice that focus on the ACVR2A gene or other genetic variations, could provide deeper insights into the expression patterns and their impact on the progression of heart disease after preeclampsia (19).

Research should also investigate the potential use of Activin A as a biomarker for early detection of preeclampsia and predicting the likelihood of subsequent cardiac damage post-preeclampsia. By adding more data from control groups and preeclamptic patients with varying symptoms, future studies

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could improve strategies for the prevention and management of cardiovascular risks in women with preeclampsia.

CONCLUSION

There are differences in ventricular function, as assessed by global longitudinal strain of the heart, in patients with severe preeclampsia based on activin A levels, which indicate both systolic and diastolic dysfunction, along with structural changes characterized by concentric hypertrophy and minimal pericardial effusion. A statistically significant relationship exists between levels of activin A and ventricular function, as assessed by global longitudinal strain of the heart, in pregnancies with severe preeclampsia. Elevated levels of activin A are associated with deteriorating ventricular function, characterized by reduced GLS and cardiac structural alterations.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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