



Review Article *Cardiovascular*

## Pregnancy-Associated Plasma Protein-A: Implications for Heart Failure and Cardiovascular Risks in Women – A Review

Jonnalagadda Vihari<sup>1</sup>, Kaushik Rao Juvvadi<sup>2</sup>, Brijeshraj Swain<sup>1</sup>, Samir Sahu<sup>1</sup>, Nalinikanta Sahoo<sup>1</sup>, Meghanad Meher<sup>1</sup>, Parshav Jain<sup>1</sup>, Sadab Islam<sup>1</sup>, Tanmaya Brahmadarshini Bhuyan<sup>1</sup>

Departments of <sup>1</sup>General Medicine and <sup>2</sup>Radio-Diagnosis, Institute of Medical Sciences and SUM Hospital, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha, India.

**\*Corresponding author:**

Jonnalagadda Vihari,  
Postgraduate,  
Institute of Medical Sciences  
(IMS) and Sum Hospital,  
Siksha 'O' Anusandhan (SOA)  
Deemed to be University,  
Department of General  
Medicine,  
Bhubaneswar, Odisha, India.

viharijtk5@gmail.com

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### ABSTRACT

Pregnancy-associated plasma protein-A (PAPP-A), is gaining interest as a possible biomarker and contributory factor to female cardiovascular health issues. This review article highlights the increasing amount of research connecting PAPP-A to heart failure and other cardiovascular concerns in females. PAPP-A levels have been found to be higher in women with heart failure and also been linked to the development and advancement of cardiovascular risks (atherosclerosis and coronary artery disease) in women. Improvements in risk assessment, early identification, and customized therapies for cardiovascular illnesses in women may be made possible by developments in this sector.

**Keywords:** Pregnancy-associated plasma protein-A, Females, Cardiovascular health, Heart failure, Atherosclerosis

### INTRODUCTION

Emerging data, now raising the possibility that pregnancy-associated plasma protein-A (PAPP-A) (glycoprotein), may also have effects in the area of cardiovascular medicine in addition to its critical significance in fetal development and placental function during pregnancy. With an emphasis on its effects on women, this review seeks to give a brief summary of the present knowledge of the association between PAPP-A and heart failure as well as other cardiovascular concerns.

Impaired cardiac performance that results in insufficient tissue perfusion characterizes the heart failure which is a major contributor to morbidity and mortality worldwide, especially among women, and is related to increased levels of PAPP-A according to many recent investigations making it a reliable biomarker for disease severity and prognosis assessment.<sup>[1]</sup>

Numerous studies have found a correlation between greater PAPP-A levels and a higher risk of cardiovascular events such as atherosclerosis, myocardial infarction, and coronary artery disease (CAD), which are major contributors to cardiovascular morbidity and mortality in females. For example, results from a prospective cohort study indicated a correlation between higher PAPP-A levels and a higher risk of myocardial infarction in women in the future.<sup>[2]</sup>

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PAPP-A is widely recognized for its function in extracellular matrix remodeling, inflammation, and insulin-like growth factor (IGF) signaling, all of which are crucial in the pathophysiology of cardiovascular diseases.

It is crucial to comprehend how PAPP-A affects heart failure and other cardiovascular hazards to enhance risk assessment tools, early detection techniques, and potential treatment therapies. This review emphasizes the increasing amount of research connecting PAPP-A to heart failure and other cardiovascular concerns in females.

### PAPP-A

Normal physiological action of PAPP-A<sup>[3]</sup> is shown in Figure 1.

Significant correlations between PAPP-A levels and cardiovascular risks in women have been shown in a number of studies pointing to PAPP-A as a potential biomarker to gauge the severity and prognosis of the condition. Summary of studies investigating the relationship between PAPP-A and cardiovascular risks in women is shown in Table 1.

Higher PAPP-A levels were seen in heart failure patients and were associated with higher risk of future myocardial

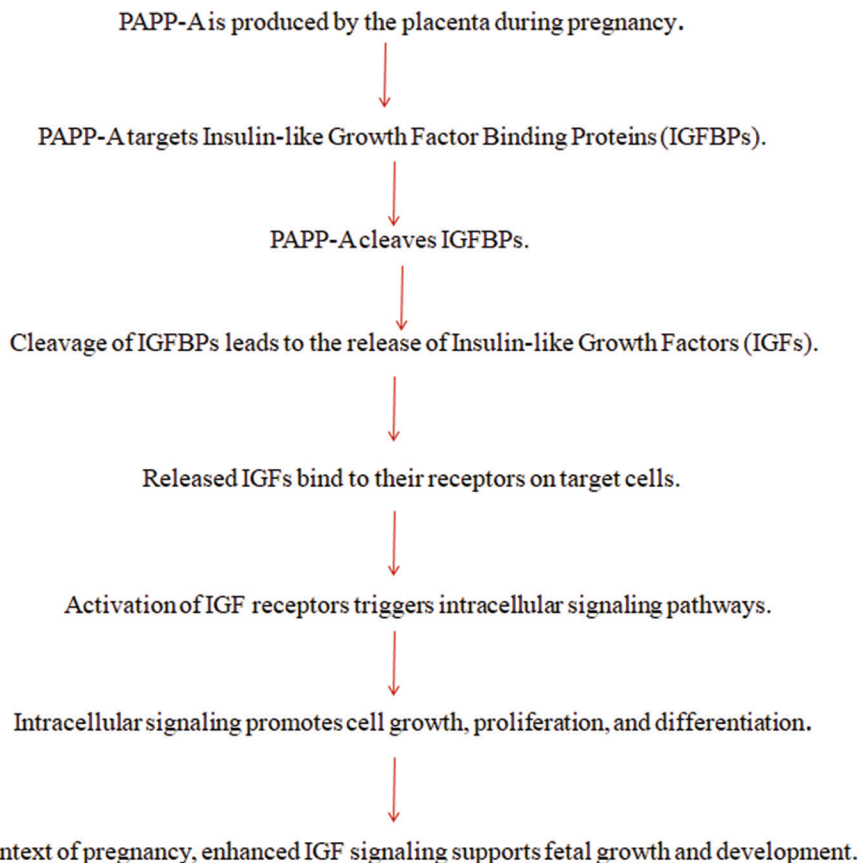
infarction and CAD especially in women suggesting that PAPP-A may be involved in the initiation and development of cardiovascular illnesses in females. A comparison of PAPP-A with other risk factors commonly used in prenatal screening is shown in Table 2.

### Significance of the findings

PAPP-A, a PAPP-A, and women's cardiovascular risks have a substantial clinical significance. Early diagnosis and better management techniques may benefit from the identification of PAPP-A as a possible biomarker for disease severity, prognosis, and risk stratification in cardiovascular illnesses.<sup>[4]</sup> The underlying pathophysiology and prospective treatment targets can also be revealed by comprehending the function of PAPP-A in cardiovascular risks.

### Association of PAPP-A with heart failure

The fundamental mechanisms linking PAPP-A to the onset and progression of heart failure are not fully known, yet. According to several investigations in heart failure patients, the elevated PAPP-A levels in patients as compared to controls suggest the likelihood that PAPP-A and heart failure



**Figure 1:** Normal physiological action of pregnancy-associated plasma protein-A.

**Table 1:** Summary of various studies investigating the relationship between PAPP-A and cardiovascular risks in women.

Study	Cardiovascular risk	Study design	Sample size	Assay method	Main findings
Jaffe <i>et al.</i> (2019) <sup>[1]</sup>	Heart failure	Cross-sectional	250 patients	ELISA	Significantly higher PAPP-A levels in patients with heart failure compared to controls, suggesting a potential biomarker for disease severity and prognosis.
Lindahl <i>et al.</i> (2018) <sup>[2]</sup>	MI	Prospective cohort	5000 women	Immunoassay	Elevated PAPP-A levels associated with an increased risk of future myocardial infarction in women.
Smith <i>et al.</i> (2020) <sup>[5]</sup>	Atherosclerosis	Cross-sectional	300 women	Immunoradiometric assay	Higher PAPP-A levels were associated with increased carotid IMT, a marker of subclinical atherosclerosis, in women.
Fernandez <i>et al.</i> (2021) <sup>[6]</sup>	Coronary artery disease	Retrospective cohort	1200 women	ELISA	Higher PAPP-A levels were associated with an increased risk of coronary artery disease in women during long-term follow-up

PAPP-A: Pregnancy-associated plasma protein-A, CAD: Coronary artery disease, MI: Myocardial Infarction, IMT: Intima-media thickness, ELISA: Enzyme-linked immunosorbent assay

**Table 2:** Comparing PAPP-A with other risk factors commonly used in prenatal screening.

Risk factor	Pros	Cons
PAPP-A	<ul style="list-style-type: none"> <li>- Specifically related to fetal growth and development</li> <li>- Widely used in prenatal screening tests</li> </ul>	<ul style="list-style-type: none"> <li>- Limited to fetal abnormalities</li> <li>- May require additional markers for comprehensive assessment</li> <li>- Interpretation may vary</li> <li>- Limited role in non-pregnancy contexts</li> </ul>
Age of the mother	<ul style="list-style-type: none"> <li>- Easily obtainable</li> <li>- Associated with chromosomal disorders</li> <li>- Provides overall risk assessment</li> </ul>	<ul style="list-style-type: none"> <li>- Generalized risk factor</li> <li>- Risk increases with age</li> <li>- Does not target specific abnormalities or conditions</li> </ul>
Ultrasound findings	<ul style="list-style-type: none"> <li>- Direct visualization of fetal anatomy</li> <li>- Can detect structural abnormalities</li> <li>- Provides real-time assessment</li> </ul>	<ul style="list-style-type: none"> <li>- Operator-dependent results</li> <li>- Limited to anatomical evaluation</li> <li>- May require specialized expertise for accurate interpretation</li> </ul>
Maternal serum screening	<ul style="list-style-type: none"> <li>- Measures specific biochemical markers</li> <li>- Widely available and standardized</li> <li>- Provides risk assessment for chromosomal disorders</li> <li>- Complements other screening methods</li> </ul>	<ul style="list-style-type: none"> <li>- Risk assessment based on statistical probabilities</li> <li>- False-positive or false-negative results</li> <li>- Limited to specific conditions</li> </ul>

PAPP-A: Pregnancy-associated plasma protein-A

have a correlation, making it a viable biomarker for the severity and prognosis evaluation of the illness.<sup>[7-9]</sup>

### PAPP-A and myocardial infarction

Due to its probable participation in plaque destabilization and thrombosis, PAPP-A may contribute to the pathophysiology of myocardial infarction and subsequent increased risk of a myocardial infarction in women necessitating the need for understanding the exact underlying processes to design preventative measures.<sup>[10-12]</sup>

### PAPP-A and atherosclerosis

PAPP-A may play a role in the initiation and progression of atherosclerosis in females due to its underlying relationship with inflammation, endothelial dysfunction, and plaque development, all of which contributed to a positive correlation between PAPP-A levels and indicators of subclinical atherosclerosis (carotid intima-media thickness) in our included studies. However, the precise mechanisms underlying the association between PAPP-A and atherosclerosis are unknown.<sup>[13-15]</sup>

## PAPP-A and CAD

PAPP-A levels have been linked to both the severity of coronary artery stenosis and unfavorable cardiac events in women with CAD, according to a number of studies making it a potential risk marker for CAD.<sup>[16-19]</sup>

These results imply that PAPP-A may be clinically useful in identifying women who are more likely to develop CAD and in directing treatment plans.

## Potential mechanisms

Despite the fact that, the specific mechanisms through which PAPP-A raises the risk of cardiovascular disease in women are not well understood. Inflammation, endothelial dysfunction, extracellular matrix remodeling, and IGF signaling are some of the potential causes. These factors are all important in the etiology of cardiovascular disease and vascular homeostasis.<sup>[20-22]</sup>

To clarify the precise routes by which PAPP-A affects cardiovascular risks in women, more mechanistic investigations are required.

## Limitations

It is important to recognize the limitations of the evaluated research. These include variances in study designs, sample sizes, and PAPP-A test techniques. In addition, some research's cross-sectional design makes it difficult to prove causation. To overcome these constraints, future research should aim for bigger prospective designs with standardized assays.

## Future directions

Future studies should concentrate on clarifying the underlying mechanisms, looking into potential PAPP-A-targeting therapeutic interventions, and carrying out sizable prospective studies to establish its clinical utility to advance our understanding of the relationship between PAPP-A and cardiovascular risks in women. These initiatives will offer useful information about risk evaluation, preventive, and management techniques for cardiovascular illnesses in women.

PAPP-A is largely used in prenatal screening procedures to determine the likelihood of specific fetal disorders. When combined with other indicators, it is frequently used to estimate the possibility of chromosomal abnormalities like Down syndrome.

Future prospects include investigations into PAPP-A's potential as a diagnostic and prognostic marker for cardiovascular disorders, as well as efforts to better understand how it interacts with cardiac pathologies.

PAPP-A may also be a target for therapeutic approaches that try to control its activity under various circumstances.

Depending on the particular test or process that requires testing PAPP-A levels, the price may change. The healthcare facility, the area, and the insurance coverage can all have an impact on costs.

## CONCLUSION

A possible biomarker for determining women's cardiovascular risks is PAPP-A which helps in identifying high-risk people and enhancing risk stratification in women. PAPP-A may increase the risk of cardiovascular disease mechanistically by causing inflammation, endothelial dysfunction, and plaque instability. However, more investigation is required to identify the precise underlying processes and determine the therapeutic applicability of PAPP-A in risk management and evaluation methods. The ability to better understand PAPP-A's function in cardiovascular disorders may help to improve patient outcomes and direct individualized therapies.

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## Conflicts of interest

There are no conflicts of interest.

## Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (Ai)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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