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MINI-REVIEW

Early identification of cardiovascular health risks in pre-eclampsia: A biomarker-centric perspective

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Abstract

Pre-eclampsia is a complicated hypertensive pregnancy condition that has a major effect on the health of both the mother and the fetus and puts the affected women at risk for long-term cardiovascular (CV) problems. Despite advances in understanding its etiology, early detection of pre-eclampsia and its associated CV risks remains challenging. This mini-review emphasizes the critical role of biomarkers and advanced diagnostic techniques in addressing this gap. Emerging biomarkers, including angiogenic factors (soluble fms-like tyrosine kinase-1/placental growth factor ratio), metabolic and lipidomics markers, inflammatory cytokines, and exosomal components, provide promising pathways for early identification and risk stratification. Diagnostic techniques can be further improved by classifying these biomarkers according to their capacity to predict long-term CV risks. Technological advancements, such as omics platforms, molecular imaging, wearable health devices, and artificial intelligence (AI) and machine learning, further improve real-time detection and personalized management of pre-eclampsia. By focusing on biomarker-centric predictors of CV risks, this review highlights the integration of multi-biomarker panels and AI-driven algorithms to optimize risk prediction. The transition from association to action is explored, with an emphasis on translating knowledge into effective prevention strategies and improved risk assessment protocols. Structured postpartum follow-up is advocated to monitor and mitigate long-term CV risks in pre-eclamptic women. Practical applications, including targeted interventions and personalized risk management strategies, are discussed. By bridging cutting-edge research and clinical practice, this review aims to enhance maternal health outcomes and advance preventative measures for CV diseases in women with a history of pre-eclampsia.

Keywords: Pre-eclampsia; Hypertension; Pregnancy; Cardiovascular disease; Biomarkers; Health risk

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1. Introduction

Pre-eclampsia is a complex and potentially fatal pregnancy hypertensive condition that manifests as proteinuria and new-onset hypertension after 20 weeks of pregnancy.[1-4] It affects 5 – 15% of pregnancies worldwide and is a leading cause of maternal and perinatal morbidity and mortality.[5,6] This condition increases the risk of long-term cardiovascular

(CV) problems for the affected individuals, in addition to making pregnancy more challenging. Compared to women with normotensive pregnancies, individuals with a history of pre-eclampsia had a 2 – 4-fold increased lifetime risk of having heart failure, ischemic heart disease, stroke, and chronic hypertension.[7] Morbidity and death can be considerably decreased by early identification of pre-eclampsia and the CV health risks it entails. Pre-eclampsia is therefore a sentinel occurrence that can be used to identify women who are later at risk of CV diseases (CVDs).

Pre-eclampsia has a complicated pathogenesis that includes diminished placental angiogenesis, oxidative stress, endothelial dysfunction, and immunological maladaptation.[8] Although our understanding of the molecular pathways has advanced significantly, early diagnosis and risk assessment remain difficult. Improving the outcomes for mothers and newborns requires the search for novel and trustworthy diagnostic techniques and the exploration of biomarkers for identifying and controlling CV risks related to pre-eclampsia.[9]

In this mini-review, we focus on biomarkers and state-of-the-art diagnostic methods in pre-eclampsia that are also predictive of long-term CV risk, with a focus on their role in early intervention and prevention of CVDs. By integrating new advancements in omics technology, artificial intelligence (AI) and machine learning (ML), and molecular imaging, this review aims to provide insights into the most important indicators associated with long-term CV risk in women with pre-eclampsia.

2. Biomarker predictors of long-term CV risk

One of the most important indicators of a woman's long-term CVD is pre-eclampsia. A promising method for identifying CV health problems early on is biomarker profiling, which enables focused preventative measures.[10] Strong predictive value for CV outcomes has been shown by biomarkers, such as soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), endothelin-1, and asymmetric dimethylarginine (ADMA). Endothelial dysfunction is reflected in elevated sFlt-1/PlGF ratios during pre-eclampsia,[11] whereas vascular injury and decreased nitric oxide generation are associated with ADMA. Particularly vulnerable are women who have severe pre-eclampsia or early-onset pre-eclampsia, as CV problems may appear 5 – 10 years after giving birth. These indicators' continuous to rise after pregnancy indicates ongoing inflammation, metabolic dysregulation, and endothelial damage, all of which greatly heighten the risk of CVDs. Early subclinical atherosclerosis and increased rates of hypertension, dyslipidemia, and diabetes are common in women with severe pre-eclampsia, and these conditions hasten the degradation of the CV system.[12] Crucially, the severity and timing of each biomarker during pregnancy should be taken into consideration when performing risk stratification. During and following pre-eclampsia, a number of new biomarkers/predictors have been identified (Table 1).

3. Emerging biomarkers in pre-eclampsia and CV risk

Our understanding of the pathophysiology of pre-eclampsia and its consequences on the CV system has radically transformed as a result of biomarker research. Angiogenic factors, metabolic indicators, and endothelial dysfunction markers are biomarkers that have shown promise in the early identification and risk classification of pre-eclampsia.[13,14] Below is a list of some significant novel biomarkers and descriptions of how they relate to CV health problems:

3.1. Metabolomics and lipidomics biomarkers

Metabolomics and lipidomics are emerging as groundbreaking methods for the early identification of CV health risks in pre-eclampsia, a pregnancy syndrome marked by hypertension and organ failure. Novel metabolic and lipid biomarkers that indicate the state of CV health have been discovered by advanced omics technologies.[15] Modern omics methods enable comprehensive lipid and metabolite profiling, revealing subtle biochemical alterations connected to the onset and progression of pre-eclampsia. Information regarding disrupted vascular and metabolic pathways can be obtained through metabolomics, including organic acids and amino acid derivatives, as well as specific lipids and lipid ratios.[16]

(i) Lipid peroxidation products. Pre-eclampsia is associated with increased levels of isoprostanes and malondialdehyde, which are indicators of oxidative lipid damage
(ii) Ceramides and sphingolipids. Atherosclerosis and the risk of CVD are linked to dysregulated lipid metabolism in pre-eclampsia.

By enabling early diagnosis, risk assessment, and customized treatment, these biomarkers may enhance maternal and fetal outcomes. Combining metabolomics and lipidomics with state-of-the-art analytical technologies, such as mass spectrometry and ML improves the predictive accuracy and mechanistic understanding of CV risks linked to pre-eclampsia.

Table 1. Categorization of pre-eclampsia biomarkers/predictors

Pre-eclampsia	During pre-eclampsia	After pregnancy
Biomarkers/Predictors	• Soluble fms-like tyrosine kinase-1 • Placental growth factor • Proteinuria • Blood pressure	• Persistent hypertension • Dyslipidemia • Insulin resistance • Increased body mass index (BMI)
Timing for assessment	Evaluated during pregnancy (when preeclampsia first appears or is diagnosed)	Evaluated after pregnancy (usually 6 weeks after delivery and during annual follow-ups)
Associated risk insight	Determines the severity and biomarker levels of women who are at immediate and long-term cardiovascular risk	Represents ongoing cardiovascular risk; changes might be brought on by interventions, aging, or changes in lifestyle
Intervention plan	• Enhanced maternal monitoring during pregnancy • Stabilization of blood pressure and proteinuria • Early delivery if necessary	• Lifestyle modifications (diet, exercise) • Pharmacological intervention (e.g., antihypertensives, statins) • Regular cardiovascular screenings
Instigation time	During pregnancy, immediately upon diagnosis of preeclampsia	Post-partum, beginning with the 6-week check-up and continuing with follow-ups every year afterward
Potential impact	Aids in predicting long-term risk and minimizing pregnancy problems	Focuses on preventing long-term cardiovascular disease and modifying risk

3.2. CV stress and myocardial injury biomarkers

Early detection and management of CV health risks in pre-eclampsia depend on biomarkers for CV stress and myocardial injury. Pre-eclampsia poses major risks to the mother's and the fetus's health and may have long-term CV consequences. Brain natriuretic peptide (BNP), high-sensitivity C-reactive protein (hs-CRP), and cardiac troponins are biomarkers that provide information on endothelial dysfunction, inflammation, and myocardial stress.

(i) N-terminal pro-B-type natriuretic peptide (NT-proBNP). The risk of heart failure is indicated by elevated NT-proBNP in pre-eclampsia, which implies myocardial strain.
(ii) Troponins. In situations of severe pre-eclampsia, cardiac troponins are investigated due to their capacity to detect myocardial damage.

These markers facilitate early identification, risk assessment, and tracking the evolution of disease, allowing for timely action to prevent adverse outcomes. Innovative diagnostic technologies that enhance the accuracy of biomarker assessment and offer real-time clinical decision support include point-of-care assays and advanced imaging modalities.[17] Improved CV health outcomes for pre-eclamptic women are made possible by predictive algorithms, tailored medicine approaches, and biomarker screening. This combination of biomarkers and technology highlights the potential for transformative advancements in CV risk management and maternal-fetal medicine.

3.3. Angiogenic and anti-angiogenic factors

Pregnancy-specific pre-eclampsia, which is marked by organ malfunction and hypertension, poses serious health risks to both the mother and the fetus. The vascular remodeling necessary for a healthy pregnancy depends on angiogenesis and anti-angiogenic factors, such as vascular endothelial growth factor and PlGF.[18] Because these variables are dysregulated and anti-angiogenic proteins such as sFlt-1 are elevated, pre-eclampsia is linked to endothelial dysfunction and reduced placental blood flow. Decreased PlGF and elevated sFlt-1 are early indicators of placental dysfunction, which is crucial to the pathophysiology of pre-eclampsia and reflects an imbalance between the two factors.[19] An anti-angiogenic condition linked to endothelial dysfunction and unfavorable outcomes in pre-eclampsia is also reflected by an elevated sFlt-1/PlGF ratio.[20] Elevated levels of soluble endoglin, a co-regulator of angiogenesis, have been connected to hypertension and vascular inflammation, making it a possible biomarker for identifying women who are at risk of CVDs. The sFlt-1/PlGF ratio has demonstrated usefulness in predicting CV problems after pregnancy and differentiating pre-eclampsia from other hypertensive disorders.

Early detection of anomalies in these biomarkers can lead to timely treatments and useful information regarding CV risks. Emerging technologies, such as sophisticated biosensors and point-of-care diagnostic tools, provide accurate quantification of angiogenic factors, aiding in risk assessment and customized treatments. Incorporating these indications into predictive algorithms may also improve outcomes for both mothers and fetuses and revolutionize the assessment of CV risk. Further investigations into new medicines that target these pathways to mitigate the long-term effects of pre-eclampsia on CV health are warranted.

3.4. Inflammatory and oxidative stress biomarkers

The disease's defining characteristics include systemic inflammation and elevated oxidative stress, which worsen

vascular endothelial dysfunction and increase the risk of CVDs. For risk assessment and early detection, reliable biomarkers associated with these processes must be found. Tumor necrosis factor-alpha, interleukins (IL-6, IL-8), and hs-CRP are important inflammatory indicators that reveal status about the chronic inflammatory milieu of pre-eclampsia.[21] At the same time, increased levels of oxidative stress indicators such as malondialdehyde, nitric oxide, endothelin-1, ADMA and 8-isoprostane, along with reduced antioxidant defenses, such as glutathione levels, indicate oxidative burden in affected individuals.[22]

The assessment of CV risk in pre-eclampsia could be revolutionized by predictive algorithms, advanced imaging, and innovative diagnostic techniques that utilize these indicators. By integrating these biomarker profiles with clinical data, healthcare providers can implement targeted interventions that will ultimately enhance maternal CV health outcomes and reduce long-term problems.

Monitoring indicators of endothelial dysfunction facilitates the assessment of the long-term CV risks in affected women. These biomarkers may be used to predict CV risks following childbirth and to shed light on systemic inflammation. Together, these biomarkers demonstrate the complex relationship between CV risks and pre-eclampsia, opening the door to focused prevention measures.

3.5. Exosomal, epigenetic, and proteomic biomarkers

Exosomal, epigenetic, and proteomic biomarkers have become novel approaches to address this problem. Cells release exosomes, which are nanovesicles containing bioactive substances, such as lipids, proteins, and RNA. These molecules reflect physiological parameters and offer information on pathological alterations. Placenta-derived exosomes contain proteins, lipids, and microRNAs that reveal the placenta's health and dysfunction.[23] Past research highlights the role that epigenetic changes play in the CV risks linked to pre-eclampsia:

(i) miRNAs or microRNAs. Circulating and specific miRNAs, including miR-210 and miR-155, control immunological and angiogenic pathways and serve as non-invasive biomarkers for pathophysiology, pre-eclampsia, disease development, and CV risk prediction. Examples of epigenetic biomarkers that shed light on gene-environment interactions that raise the risk of pre-eclampsia development include DNA methylation and histone modifications.

(ii) Proteomic signatures. By analyzing plasma proteomically, distinct protein signatures associated with endothelial dysfunction and CV risk have been found. Across the proteomics approach, dysregulated pathways and potential therapeutic targets can be revealed by identifying and quantifying proteins in biological materials.

Together, these biomarkers increase the precision of CV risk assessment in pre-eclampsia, enabling personalized treatment and early intervention. Their integration into clinical practice has the potential to revolutionize maternal healthcare by improving diagnosis accuracy and promoting creative preventative strategies for CV problems in pre-eclampsia.

4. From association to action: Translating knowledge into prevention and risk assessment

Pre-eclampsia is becoming more widely acknowledged as a risk factor for women's long-term CV health. A thorough framework for risk assessment and prevention is necessary to close the gap between this association and workable solutions. To convert scientific discoveries into significant public health results, this framework should include risk categorization, preventative measures, and healthcare integration.

(i) Risk stratifications. Utilizing clinical and biochemical indicators identified during pregnancy is essential for identifying patients at increased CV risk after pre-eclampsia.[24] Future risk can be inferred from markers including dysregulated lipid profiles, proteinuria, and high blood pressure. Categorization into high- and low-risk groups allows for customized post-partum treatment. Women who have severe or recurring pre-eclampsia, for example, may be deemed high-risk and require close observation.[25] Risk prediction models can be further improved by emerging biomarkers, such as angiogenic factors, such as PlGF and sFlt-1. Predictive analytics and electronic health records can expedite this stratification procedure, guaranteeing the early and methodical identification of high-risk individuals.

(ii) Preventative interventions. Specific prophylactic actions can reduce long-term CV morbidity in high-risk women. The cornerstone tactics are lifestyle changes, such as diet adjustments, exercise, and stress reduction. In accordance with individual risk profiles, pharmacological therapy with medications such as statins or antihypertensives can be used to treat chronic dyslipidemia or hypertension. Establishing routine CV screenings after pregnancy is also essential.[26] Early identification of endothelial dysfunction, subclinical atherosclerosis, and other risk factors for CVDs should be the main goal of such examinations. Effective implementation of evidence-

based therapies can be ensured by collaboration with specialized care teams and cardiologists.

(iii) Healthcare integration. Transforming information into practice requires the incorporation of CV follow-up measures into post-partum care programs. It is crucial to implement a systematic strategy that includes post-partum visits specifically aimed at CV health. Scheduled screenings, lifestyle counseling, and risk stratification evaluations may be included in these sessions. It is equally crucial to educate primary care physicians, midwives, and obstetricians on the long-term CV consequences of pre-eclampsia. Support at the policy level to guarantee the long-term viability of these integrated care models can improve results and compliance. Longitudinal monitoring can be further facilitated by telemedicine and digital health platforms, which can close gaps in treatment delivery and access.

5. Pragmatic approaches

Several pragmatic approaches are presented in the following:

(i) Proposed program of testing. It is crucial to evaluate CV risk factors, such as blood pressure, lipid profiles, and glucose tolerance as soon as possible after giving birth. The link between delivery and long-term CV health can be closed with annual physicals that concentrate on these metrics and the use of home blood pressure monitoring for early identification.

(ii) Financial implications. It is important to stress how cost-effective early detection and preventative care are. Evidence indicates that systematic post-partum follow-up could significantly lower the long-term financial burden associated with controlling CVDs, despite the initial investment appearing hefty. Existing post-partum care programs' insights highlight how feasible such a strategy is.

(iii) Implementation and oversight. For implementation to be successful, an integrated care route involving cardiologists, obstetricians, and primary care doctors is essential. To ensure fair access and participation, community health workers and digital health platforms can help with adherence and continuity of care.

(iv) Future trial. To validate these suggested therapies, extensive, long-term studies are necessary. Pre-eclampsia women's existing registries are a useful tool for obtaining sufficient samples and carrying out long-term follow-up research. Evidence-based guidelines would be informed by these trials, improving post-partum care and lowering long-term CV morbidity in this susceptible group.

6. Practical applications for post-partum care

This section describes useful applications that close the knowledge gap between science and practical application, with an emphasis on enhancing post-partum care for women who have previously experienced pre-eclampsia.

(i) Home blood pressure monitoring. All women with pre-eclampsia who receive a home blood pressure monitor are better equipped to monitor their CV health on their own. Accurate readings are guaranteed and early hypertension detection can be realized through sufficient training on correct usage and interpretation. By providing prompt medical advice based on patient-reported data, telehealth services can further complement this strategy.

(ii) Post-partum care packages. Long-term CV health can be improved with a structured care package designed for pre-eclamptic women. These packages ought to contain structured physical activity suggestions, mental health support, and dietary instructions that prioritize cardioprotective diets and lower sodium intake. Regular check-ins can be made easier with the help of telehealth services, guaranteeing adherence and quickly resolving new issues.

(iii) Community-based follow-up programs. Collaborations with local healthcare professionals provide regular and easily accessible follow-up care. Programs could consist of community support groups, educational courses, and recurring health evaluations. These programs encourage participation and remove obstacles to care, especially for marginalized groups.

7. Innovative diagnostic tools

7.1. Point-of-care testing (POCT)

A major development in early diagnostic techniques is POCT, which provides quick and accurate identification of biomarkers linked to pre-eclampsia and CV health risks. Real-time evaluation of vital parameters, such as blood pressure, proteinuria, and new biomarkers, such as PlGF and sFlt-1 is made possible by POCT equipment, which are portable and easy to use.[27] Previous research has demonstrated the effectiveness of POCT in environments with low resources, where traditional laboratory infrastructure might not be available.

To mitigate maternal and fetal problems, for example, the incorporation of POCT for sFlt-1/PlGF ratio testing has shown promise in stratifying the severity of pre-eclampsia. POCT promotes personalized medicine methods by promoting early detection and intervention, which improves outcomes for women who are at risk of pre-eclampsia and related CV disorders.[27] POCT will

become more useful in the future as biosensor technology and digital health integration advance, guaranteeing prompt, precise, and easily accessible diagnostics for maternal healthcare.

7.2. AI and ML

With their potential for early detection and risk assessment of CV problems linked to pre-eclampsia, AI and ML have become revolutionary tools in the healthcare industry. For prompt intervention, CV risks must be identified early. Large and complex datasets, such as biochemical, genetic, proteomic, clinical biomarker, and imaging data, can be analyzed with algorithms driven by AI and ML to predict the development and course of pre-eclampsia. Furthermore, integrating wearable health monitoring technology with AI-powered platforms improves the monitoring of blood pressure and heart rate variability in real-time, resulting in a personalized risk profile. AI models that take into account biomarker levels, blood pressure trends, and maternal history have shown superior predicted accuracy.[28] In addition, ML models, such as random forests and support vector machines have shown excellent accuracy in predicting hypertensive disorders during pregnancy by analyzing patient history and physiological data.[29] These tools outperform traditional statistical methods by detecting non-linear patterns and interactions between variables. AI and ML developments have the potential to revolutionize pre-eclampsia care by enabling the early detection of CV risks, enhancing maternal-fetal outcomes, and reducing medical expenses.

7.3. Advanced imaging techniques

Cutting-edge imaging methods have become essential for the early detection and risk assessment of CV problems in pre-eclampsia. In patients with pre-eclampsia, early indicators of CV dysfunction are detectable using methods including echocardiography (ECG) and cardiac magnetic resonance imaging (MRI). For example, Doppler ultrasound is frequently used to evaluate anomalies in uteroplacental blood flow, which are early markers of pre-eclampsia and its development into CV disorders.[5] In addition, high-resolution insights into the placental function and structural alterations linked to pre-eclampsia have been demonstrated using MRI.[30] Furthermore, a thorough assessment of the hemodynamic changes and cardiac remodeling in afflicted patients is made possible by three-dimensional ECG.

Recent advancements, such as the integration of computed tomography angiography for vascular imaging, have enhanced the precision of identifying endothelial dysfunction and vascular stiffness, which are both critical biomarkers of long-term CV risks. Innovations in imaging-based AL algorithms further enable predictive modeling, improving early detection and personalized management strategies. Collectively, these advanced imaging techniques offer a non-invasive, reproducible, and highly sensitive approach for identifying CV risks in pre-eclampsia, significantly improving maternal and fetal outcomes.

7.4. Wearable health technology

In the early detection of CV health problems, wearable health technology has become a game-changer, especially in circumstances, such as pre-eclampsia. These cutting-edge tools make it easier to continuously monitor physiological indicators and provide real-time data that helps identify risk biomarkers. Wearable sensors have been shown to be useful in monitoring heart rate variability and blood pressure.[31] Furthermore, improvements in non-invasive biosensors have made it possible to assess circulating biomarkers, such as sFlt-1 and PlGF, improving predictive powers.

ML algorithms have been incorporated into smart wearable devices, such as smartwatches and patches, to forecast the course of diseases and send out tailored notifications. A recent analysis showed that by identifying minute hemodynamic changes weeks before clinical symptoms, wearable devices could enhance early diagnosis and treatment results.[31] This demonstrates how wearable technology may help prevent long-term CV problems by changing the management of pre-eclampsia from reactive to proactive. When paired with developments in biomarker research, these technologies constitute a major breakthrough in the treatment of problems related to maternal and fetal health.

8. Conclusion

A paradigm change in maternal healthcare is provided by the early detection of CV health risks in pre-eclampsia through the development of biomarkers and creative tools, which also present new chances for risk prediction and appropriate risk management. Combining these indicators with cutting-edge diagnostic technologies, such as wearable technology and ML algorithms, has the potential to completely transform personalized medicine methods in CV and maternal-fetal health. To ensure prompt and efficient therapy of pre-eclampsia and associated CV after-effects, translational efforts are crucial in bridging the gap between research and clinical practice.

The integration of multi-biomarker panels, advanced diagnostic tools, and AI-driven technologies holds promise for revolutionizing the management of pre-eclampsia. Further research is required to: (i) validate

novel biomarkers in large, diverse populations, and explore their potential to guide targeted interventions; (ii) enhance the accessibility and affordability of innovative tools in low- and middle-income countries; and (iii) investigate the long-term CV outcomes in women with a history of pre-eclampsia using advanced diagnostics.

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