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Reproductive Health and Cardiovascular Disease (G Sharma, Section Editor)

The Role of Biomarkers and Imaging to Predict Preeclampsia and Subsequent Cardiovascular Dysfunction

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Abstract

Purpose of review Preeclampsia is a major cause of maternal morbidity and mortality worldwide. Despite decades of research, the ability of clinicians to accurately predict the onset of preeclampsia prior to the manifestation of symptoms has not significantly improved. In this review, we will examine the pathophysiology underlying preeclampsia

and discuss the role of potential biomarkers for early prediction and diagnosis. In addition, we will explore imaging modalities in the detection of early myocardial and vascular endothelial dysfunction associated with preeclampsia.
Recent findings Circulating angiogenic and antiangiogenic biomarkers have emerged as key factors in the pathophysiology of the condition. However, single serological biomarkers have limited sensitivity to accurately predict preeclampsia; thus, a combination of clinical information along with urine or blood biomarkers is needed.
Summary The combined use of biomarker assays and new imaging modalities could enhance the predictive tools for this devastating disease and the development of cardiovascular sequelae. In the future, advances in proteomics, metabolomics, and other techniques may allow the identification of biomarkers with high enough predictive and prognostic information to be translated into clinical practice.

Introduction

Preeclampsia, a major cause of maternal morbidity and mortality, affects 4–5% of pregnancies and is associated with subsequent adverse cardiovascular events [1]. Preeclampsia is present when there is new-onset hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) occurring after the 20th week of gestation along with proteinuria or end-organ damage (such as pulmonary edema, renal insufficiency, thrombocytopenia, or elevated liver enzymes) [2•]. The pathogenesis of preeclampsia is poorly understood but is thought to originate early in pregnancy because of vascular dysfunction during placenta formation, leading to placental hypoperfusion, placental hypoxia, and subsequent maternal preeclampsia manifestations. While these manifestations resolve soon after delivery, women who have had preeclampsia have alterations in vascular function, leading to a 4-fold increased risk of heart failure and a 2-fold increased composite risk of coronary artery disease, heart failure, stroke, and death [3•]. For these reasons, preeclampsia is considered a sex-specific risk enhancing factor in the assessment of atherosclerotic cardiovascular disease (ASCVD) [4].

Given preeclampsia's association with adverse acute and chronic cardiovascular outcomes, accurate predictive tools are needed for pregnant women. Traditional risk factors include chronic hypertension (odds ratio [OR] 2.7), renal disease (OR 7.8), obesity (OR 2.1–3.2), and diabetes [5]; however, many women with these risk factors do not develop preeclampsia. Furthermore, others may already have preexisting hypertension and proteinuria, posing great difficulty in ascertaining the development of preeclampsia during later pregnancy [6].

For these reasons, there has been increasing interest in identifying maternal biomarkers and imaging modalities that accurately detect women at risk of preeclampsia early in pregnancy. In this review, we will examine potential biomarkers and imaging modalities for the early prediction and diagnosis of preeclampsia. In addition, we will examine factors that can predict future cardiovascular disease and explore areas of future investigation.

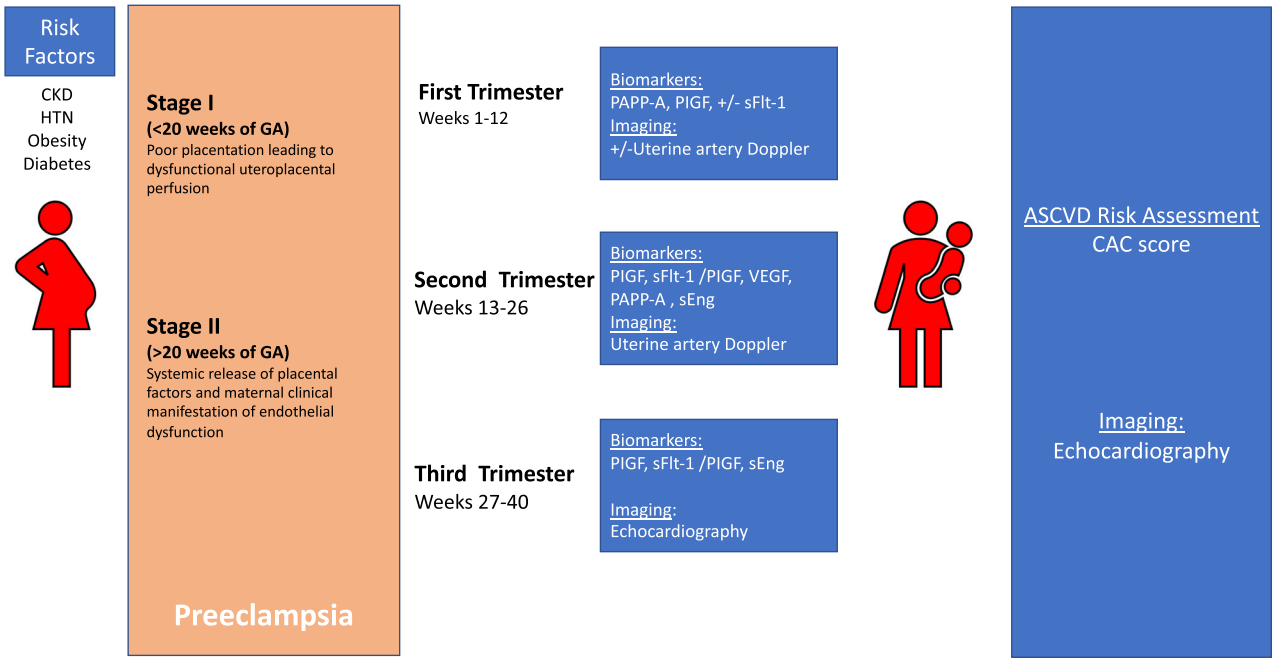
Pathogenesis of preeclampsia

The placenta has several roles in protecting and supporting the development of the maturing fetus. It is a protective barrier from the maternal immune system while also providing nutrients and oxygen to the fetus [7]. The underlying pathophysiology of preeclampsia is not fully understood; however, alterations in the tightly regulated process of placental formation and integration with the

maternal uterine system are important. Regardless of the cause, it is clear that the placenta plays a key role, because the delivery of the placenta, even in the absence of a fetus (e.g., hydatidiform mole), is the curative treatment [8].

Although it continues to be debated, the pathogenesis of preeclampsia is a two-stage process [9]. Stage I (Fig. 1) occurs early in gestation (before 20 weeks) and is characterized by abnormal placentation. In normal placental development, fetal extravillous cytotrophoblasts invade the maternal decidua and myometrium leading to remodeling of the uterine spiral arteries and increasing the capacitance of the blood vessels [9]. In preeclampsia, these changes are incomplete with the inadequate invasion of the myometrium. This aberrant placental formation subsequently leads to placental hypoxia due to poorly matured and high resistance spiral uterine arteries that are unable to meet the nutritional support and oxygenation needs of the growing fetus, especially in the second and third trimesters [7]. As a result, fetal growth restriction frequently occurs with preeclampsia [10].

Stage II occurs in the latter part of the second trimester and the third trimester when there are clinical manifestations of preeclampsia. During this stage, the diseased placenta and release of pathological circulating angiogenic factors, results in widespread endothelial dysfunction characterized by hypertension, renal injury, and other organ involvement [7, 9]. In addition, generalized vasoconstriction and subsequent uteroplacental insufficiency affect the fetus, potentially leading to placental abruption, iatrogenic premature delivery, and fetal growth restriction [9].



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcification; CKD, chronic kidney disease; HTN, hypertension; GA, gestational age; PAPP-A, pregnancy-associated plasma protein-A; PIGF, placental growth factor; sFlt-1, Soluble Flt-1; sEng, soluble endoglin; VEGF, vascular endothelial growth factor

Fig. 1. Preeclampsia syndrome: Summary of risk factors, pathogenesis, and key biomarkers and imaging

To date, there are no conclusive data suggesting specific pathways for the stages of preeclampsia, and further understanding has been hampered by a lack of suitable animal models since preeclampsia essentially only occurs in humans [11]. Genetic factors, environmental effects, oxidative stress, an inadequately vascularized placenta, and maternal immune intolerance are all potential contributing mechanisms [12]. Since all of these mechanisms are associated with serum and placental angiogenic and antiangiogenic factors [13], there has been considerable effort to identify optimal predictive biomarkers that could help predict at-risk pregnancies.

The role of biomarkers in the diagnosis and prognosis of preeclampsia

Angiogenic biomarkers: Vascular endothelial growth factor and placental growth factor

Cytotrophoblasts invading the decidua and myometrium express several angiogenic receptors. In particular, vascular endothelial growth factor (VEGF) is central in both the physiologic and pathologic states of angiogenesis and is reduced in women with preeclampsia. This factor binds with high affinity to two major tyrosine kinase receptors: VEGFR-1/Flt-1 (fms-like tyrosine kinase) and VEGFR-2/KDR [14] through which it exerts its potent angiogenic function promoting endothelial cell proliferation and migration (Table 1).

Table 1. List of biomarkers studied in preeclampsia, their function and how their levels change in preeclampsia

Biomarker	Function	Preeclampsia
PIGF	• Stimulate angiogenesis • Upregulated in hypoxic conditions	↓
VEGF	• Pro-angiogenic, aids in placental vascular development • Proliferation and migration of endothelial cells • Promotes vascular permeability	↓
sFlt-1	• Binds and neutralizes VEGF and PIGF • Antagonizes angiogenic and vasodilatory effects of VEGF and PIGF	↑
SFlt-1/PIGF	• Ratio of sFlt-1 levels to PIGF	↑
sEng	• Regulates vascular tone • Promotes vascular permeability	↑
PAPP-A	• Modulates effect of insulin growth factor • Acts on cell differentiation, glucose/amino-acid uptake • Placentation	↓
PP-13	• Trophoblast invasion • Maternal endothelial adaptation • Maternal immune tolerance	↓
Leptin	• Regulates food intake and glucose homeostasis • Allows mother to provide adequate nutrition to the fetus • May be secreted by the placenta in response to hypoxic stress	↑

PAPP-A, pregnancy-associated plasma protein-A; *PIGF*, placental growth factor; *PP-13*, placenta protein PP13; *sFlt-1*, soluble Flt-1; *sEng*, soluble endoglin; *VEGF*, vascular endothelial growth factor

The pro-angiogenic action of VEGF is supplemented by placental growth factor (PIGF), which competitively binds to the Flt-1 receptor (VEGFR-1) and consequently enhances levels of unbound circulating VEGF [15]. PIGF is primarily expressed in the syncytiotrophoblast layer of the placenta and is reduced in women with preeclampsia [16, 17]. Notably, PIGF reduction occurs well before the onset of preeclampsia and it is likely mediated by decreased early placental production of PIGF and other mechanisms [15].

As opposed to PIGF, which is a more specific biomarker for the placenta, VEGF is secreted by various vascular endothelial cells including renal endothelial cells; therefore, urine measurements of VEGF may not represent accurate circulating levels [6]. Serum concentrations of unbound VEGF are also often below detectable levels in most diagnostic ELISA assays rendering it a clinically difficult testing option [6]. Most studies have thus focused on urine and serum PIGF measurements.

Antiangiogenic biomarkers

Soluble Flt-1

Supporting the antiangiogenic imbalance hypothesis, sFlt-1 (Table 1) has emerged as a key elevated biomarker in the maternal serum in preeclampsia [18•]. sFlt-1 is a splice variant of the VEGFR-1/Flt-1 [7] and is released from the placenta as a result of hypoxic stimuli [19]. sFLT-1 attaches to the receptor-binding domain of both VEGF and PIGF, inhibiting them from exerting their effects on cell-bound endothelial receptors, subsequently leading to endothelial dysfunction [6, 18]. Because of this, the primary mediator in decreased PIGF levels is sFlt-1 that bind and sequester PIGF [20]. In animal models, administration of sFlt-1 produces a preeclampsia-like syndrome with hypertension and glomerular endotheliosis [18•]. In humans, apheresis of sFlt-1 reduced proteinuria and delayed timing of delivery [21]. Of note, it is relatively easy to measure sFlt-1 in the serum, which due to its large size is not filtered by the kidney.

Soluble endoglin

Another biomarker of interest in preeclampsia is soluble endoglin (sEng) (Table 1). Endoglin (Eng), a co-receptor for transforming growth factor β1 (TGF- β1), is expressed on vascular endothelial cells and syncytiotrophoblasts [22]. Eng acts through the nitric oxide pathway to regulate vascular tone and has previously been associated with vascular dysfunction [22]. The shorter splice variant sEng is shed from excessive cell surface Eng in the placenta and is elevated in maternal circulation. There, it binds to TGF-β1, promoting vascular permeability and inhibiting nitric oxide synthase-mediated vascular dilatation [23]. sEng is elevated up to 3 months prior to the clinical manifestations of preeclampsia and is synergistic with sFlt-1 in contributing to disease severity [17, 21].

Imbalances in sFlt-1, sEng, and PlGF ratios associated with preeclampsia

Excessive sFlt-1 and sEng in maternal circulation create an antiangiogenic state through multiple actions, including exerting direct effects against free and active VEGF and PIGF. Therefore, there is interest in measuring all of these markers during gestation to predict preeclampsia (Table 1). In particular, determining the sFlt-1/PIGF ratio has been helpful in identifying women at risk [12, 24],

although this has not been helpful early in gestation (< 16 weeks) [25•, 26]. When used between 24 and 37 weeks of gestation in women with a higher clinical suspicion of preeclampsia, an sFlt-1/PIGF ratio > 38 was accurate in differentiating those who will develop preeclampsia or HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome within the subsequent week and those who would not (negative predictive value of 99.3%). These findings were confirmed in a different validation cohort within the study [27•] and similar findings were also observed in an Asian cohort of women [28]. Thus, it is useful to use these biomarkers in higher risk women, provided that it is after the 24th week of pregnancy [25•, 29].

Other biomarkers for prediction of preeclampsia during early gestation

Pregnancy-associated plasma protein-A

Although no serum markers accurately predict preeclampsia during the first trimester, alterations in pregnancy-associated plasma protein-A (PAPP-A) may have some value in foreshadowing preeclampsia. PAPP-A (Table 1) is secreted by syncytiotrophoblasts and is part of the first-trimester screening for aneuploidy [30]. This protein has metalloprotease activity and modulates insulin growth factor (IGF) activity which affects cell differentiation, invasion of trophoblastic cells, and uptake of glucose and amino acids regulating fetal growth [30]. Low percentiles of PAPP-A are linked with fetal morbidity and mortality and may predict preeclampsia when karyotyping is normal [30]. In one meta-analysis [31], a level below 0.4 multiple of median (MoM) had a sensitivity of 39% and specificity of 87% for the detection of early preeclampsia.

Placenta protein 13

Placenta protein13 (Table 1) is also expressed by syncytiotrophoblasts and also may have some value in predicting early preeclampsia. This glycan-binding protein is detectable in the maternal serum as early as 5 weeks of gestation and is thought to support trophoblast invasion, maternal endothelial adaptation, and maternal immune tolerance [32]. Levels of PP13, although varied among studies, are lower in the first trimester among women who subsequently develop preeclampsia [33]. However, the predictive value of PP13 is relatively limited and varies from 10 to 65% [34].

Insulin resistance and adipokines in preeclampsia

Insulin

A normal pregnancy has a component of insulin resistance, which is thought to allow the pregnant mother to provide adequate nutrition to the developing fetus. In general, insulin resistance rises throughout pregnancy, peaks in the third trimester, and returns to pre-pregnancy levels post-delivery [35]. However, exaggerated insulin resistance associated with gestational diabetes mellitus and preexisting diabetes mellitus are deleterious and are associated with preeclampsia [1, 35]. In addition, insulin resistance that manifests early in gestation (weeks 16–20), which is prior to the time when most of the physiologic insulin resistance of pregnancy occurs, is even more associated with preeclampsia [35]. In mothers with gestational

diabetes, metformin, an insulin sensitizer, was associated with a reduced incidence of preeclampsia [36]. Exaggerated insulin resistance may therefore synergistically act with antiangiogenic factors in the manifestation of preeclampsia.

Leptin

Adipokines are molecules with paracrine and neuroendocrine properties that are secreted by adipose tissue and are postulated to mediate insulin resistance [37]. In addition, they are involved in regulating lipid and glucose metabolism, systemic inflammation, vascular homeostasis, and endothelial function [38]. Since alterations in these processes are also involved in preeclampsia, adipokines may play a role in the pathogenesis of preeclampsia and angiogenic imbalance; however, the data thus far is limited.

Among all adipokines, leptin (Table 1) is the most studied and shows the strongest association with preeclampsia [38, 39]. Because trophoblasts in the developing placenta also secrete leptin, levels of leptin rise throughout pregnancy, peak in the second trimester, and decline shortly before delivery [40]. Interestingly, women with preeclampsia have increased leptin mRNA and protein expression in their placental tissue because of unknown mechanisms [38]. As a result, these women have elevated serum leptin levels, particularly in the first trimester, when compared to women without preeclampsia [38]. In addition, first-trimester leptin levels may also be predictive of future preeclampsia [40, 41], but there is no well-established cutoff value.

Role of imaging in the diagnosis and management of preeclampsia and in the assessment of myocardial and vascular dysfunction

Uterine artery blood flow assessment

In addition to serum biomarkers, imaging has been used to improve the prediction of women who may later develop preeclampsia [42]. In particular, uterine artery ultrasound (Fig. 1) is extensively used, because it can accurately detect blood flow and arterial resistance. With normal placental formation, resistance in the uterine arteries decreases as a result of remodeling of the spiral arteries to large low-resistance vessels [7]. However, women with preeclampsia have increased arterial resistance and decreased flow. Therefore, their uterine artery Doppler indices would have increased notching (indicating decreased early diastolic flow compared to later diastolic flow) and increased pulsatility index (PI; the difference between systolic flow velocity and diastolic flow velocity averaged over mean velocity) [42]. Specifically, the combination of increased PI and notching in the second trimester had the highest predictive value for preeclampsia (likelihood ratio (LR) of 7.5 to 21.0) [42]; thus, this test may be a helpful tool for prediction of the syndrome.

Vascular endothelial function assessment using brachial flow-mediated dilatation or peripheral arterial tonometry

The angiogenic imbalances associated with preeclampsia can cause maternal vascular endothelial dysfunction, especially in women with increased vascular

fragility due to preexisting hypertension, diabetes, or obesity [43]. Although not widely measured, vascular endothelial function in women with preeclampsia can be easily assessed non-invasively using brachial flow-mediated dilatation (FMD) or peripheral arterial tonometry (PAT).

Brachial flow-mediated dilatation (FMD) is an ultrasound-based technique which measures percentage changes in brachial arterial diameter as a result of shear stress and correlates well with endothelial function in the peripheral and cardiac vasculature and is inversely associated with future cardiovascular events [44, 45•].

PAT also assesses vascular endothelium-mediated changes, measuring vascular function in the fingers after releasing occlusive pressure on the brachial artery and creating a downstream hyperemic response. Using these measurements, a reactive hyperemia index (RHI) is then calculated by measuring arterial pulse volume amplitude [45•].

Both of these techniques reveal greater endothelial dysfunction in women with preeclampsia compared to those with normal pregnancies. In one study, abnormal FMD [46] correlated with bilateral uterine artery notching. Both FMD and PAT enable the longitudinal assessment of patients throughout pregnancy as well as in the postpartum period as endothelial dysfunction can persist after delivery [45•].

Echocardiography

Women with preeclampsia can develop subclinical and clinical signs of heart failure, with 10% developing frank pulmonary edema [47]. Therefore, accurately assessing cardiac function and hemodynamics is important, particularly with echocardiography (Fig. 1), because abnormalities detected on echocardiography presage adverse cardiovascular events [48]. The most common echocardiographic finding is diastolic dysfunction [47, 49•], but studies also report increased left ventricular mass [49•, 50], left atrial enlargement [47, 51], abnormal strain [47], and possibly systolic dysfunction [49•, 51].

While echocardiography is helpful in predicting acute cardiovascular events in women with preeclampsia, no study has shown that abnormalities on echocardiography can predict an initial episode of preeclampsia. However, postpartum echocardiography in women who have had preeclampsia may be of greater value. In one study [52], women with recurrent preeclampsia, compared to those with a subsequent repeat pregnancy without preeclampsia, had lower stroke volumes and cardiac output and greater left ventricular filling pressures. Of note, women with preeclampsia can have persistent subclinical changes on echocardiography for months to years after delivery [53]; however, the clinical significance is unclear even though it is known that there are higher risks of cardiovascular disease later in life.

Coronary artery calcification score

Measurement of coronary artery calcification (CAC) is extremely useful and is recommended by the ASCVD risk stratification guidelines [4] to differentiate patients at intermediate risk for ASCVD. This score is determined by measuring calcium using low-dose computed tomography (CT), and in Agatson units (AU), with a score greater than 100 AU conferring a 9.6-fold increased risk of ASCVD [54] while a score of 0 predicts a less than 1% ASCVD mortality risk within 15 years [55].

While the risk-benefit ratio in using ionizing radiation in pregnant women with preeclampsia is not favorable for deriving a CAC score, it may have a role in the postpartum time period (Fig. 1). In the study of 164 women who were between 45 and 55 years of age and who had preeclampsia in the previous 10–20 years, there was a 1.7-fold increased likelihood of a CAC score > 0 AU compared to risk-matched controls [56]. Interestingly, follow-up cardiac CT angiography in this group revealed that almost half of these women (47%) also had coronary plaques with 4.3% having significant coronary artery stenoses. In summary, the CAC score can be used as an adjunctive ASCVD risk stratifying tool in women who have had preeclampsia, although prospective studies are needed.

Carotid intima-media thickness

Carotid intima-media thickness (CIMT) is a non-invasive ultrasound technique that can help in cardiovascular disease risk stratification, because increased CIMT is linked with a modestly increased risk in ASCVD [57]. In women who have had preeclampsia, increased CIMT has been noted 10 years postpartum [45•]. However, it is unclear if CIMT abnormalities precede preeclampsia, and it remains to be seen if there is a role for CIMT measurement during pregnancy or in the early years after delivery. In all likelihood, larger prospective studies that combine sequential CIMT with biomarker measurement are needed to elucidate the role of CIMT in determining if there is a subclinical carotid vascular manifestation of preeclampsia and for long-term maternal cardiovascular risk stratification in this population.

Conclusion

In conclusion, preeclampsia is a complex syndrome associated with high morbidity and mortality and leads to increased risks for subsequent maternal ASCVD. There is growing data to support the utility of biomarkers in identifying women at high risk for preeclampsia and for predicting those that will develop cardiovascular sequelae (Fig. 1). However, the variability of these tests and the relatively low predictive values of individual biomarkers require a more complex and inclusive prediction score model that incorporates clinical features including the role of insulin resistance, imaging, and well-validated biomarkers to further characterize and develop strategies in preventing and mitigating the outcomes of preeclamptic pregnancies.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest
Bethel Woldu, Lochan M. Shah, Angela K. Shaddeau, Erin Goerlich, Sammy Zakaria, Allison G. Hays, Arthur J. Vaught, Andreea A. Creanga, Roger S. Blumenthal and Garima Sharma declare that they have no conflict of interest.

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