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Abstract

Preeclampsia is a serious pregnancy condition defined as new-onset hypertension and proteinuria, commonly characterized as either early, ‘placental’, or late onset, ‘maternal’, using a cut-off of 34 weeks gestation. However, it may be more useful to differentiate between the vascular remodelling and placental invasion vs. inflammation and metabolic pathophysiology that underlie these forms of preeclampsia. Due to rising rates of obesity, the late-onset, maternal form is increasingly occurring earlier in pregnancy.

Predictive tests for preeclampsia typically include biophysical markers such as maternal body mass index and mean arterial pressure, indicating the importance of cardiovascular and metabolic health in its pathophysiology. In contrast, the placental, inflammatory, endothelial and/or metabolic biomarkers used in these tests are generally thought to indicate an abnormal response to placentation and predict the disease. However, many of these non-placental biomarkers are known to predict impaired metabolic health in non-pregnant subjects with obesity (metabolically unhealthy obesity) and coronary artery disease or stroke in people at risk for cardiovascular events.

Similarities between the performance of these markers in the prediction of cardiovascular and metabolic health outside of pregnancy suggests that they may be more indicative of maternal health than predictive for preeclampsia. This paper reviews the biophysical and biochemical markers in preeclampsia prediction and compares their performance to tests assessing metabolic health and risk of cardiovascular disease, particularly in the obese population.

Key Words

Pregnancy, preeclampsia, cardiovascular disease, metabolically unhealthy obesity, biomarkers

Introduction

Preeclampsia (PE) is one of the most common and serious complications of pregnancy, with a global prevalence ranging from 2-8% [1], and remains a leading cause of maternal death, even in developed nations [2]. PE is defined as new-onset hypertension and proteinuria developing after 20 weeks gestation [3]. PE eventually evolves to involve multiple organ systems resulting in a spectrum of clinical manifestations including pulmonary edema, myocardial dysfunction, renal failure, hepatic dysfunction, stroke, and seizures, in addition to perinatal morbidity and mortality resulting from iatrogenic prematurity, growth restriction, and placental abruption [4-7]. The prevalence of PE is increasing and this has been linked, in part, to the increasing prevalence of obesity [8].

Historically, PE has been characterized as early onset and late onset. Early onset PE develops before 34 weeks and is associated with more severe maternal and neonatal outcomes secondary to abnormal placentation, intrauterine growth restriction and abnormal uterine and umbilical artery Doppler [9]. Late onset PE develops after 34 weeks and has more favourable outcomes for both mother and fetus given the presence of non-pathologic placentation and appropriate fetal growth [9]. However, there is significant heterogeneity in the presentation of PE, and the use of an arbitrary gestational age cutoff and the presence of “normal” fetal growth are less useful in the changing demographics of the obstetric population, particularly as nearly half of pregnancies in North America are in women who are overweight or obese [10]. Thus, it may be more useful to categorize PE into primarily placental; encompassing vascular health and placental invasion, and primarily maternal, due to inflammation and metabolic pathophysiology [11].

Although the pathogenesis of PE is not fully understood, there are several well-described theories including dysregulations in immune response, placental oxygen supply, trophoblast invasion, spiral artery remodeling and angiogenesis [12]. With these mechanisms in mind, studies have attempted to identify potential markers to determine who is most at risk for developing PE. In a review of biomarkers screening for PE in 2004, the WHO stated that "there is no clinically useful screening test to predict the development of PE in either low-risk or high-risk populations" [13]. Since then, there have been multiple studies analyzing improved potential screening algorithms for PE, using combinations of demographic, biophysical and biochemical markers associated with the disease.

Most combination tests use placental, inflammatory or endothelial markers in maternal plasma, in a combination with mean arterial pressure (MAP) and body mass index (BMI). Maternal obesity, similarly to MAP, seems to be one of the strongest independent risk factors for PE and the addition of BMI to screening algorithms significantly improves the performance of the test [14, 15]. Therefore, the key argument is whether these tests screen for pathological markers associated with PE, or whether they provide information about maternal health conditions associated with an increased risk for PE.

Increasingly, the *non-pregnant literature* focuses on markers of a person's health that are more sensitive than weight and height alone. Many of the endothelial, inflammatory and metabolic plasma markers that are associated with PE have also been investigated for their value in predicting the development of cardiovascular and cerebrovascular disease (CVD). Additionally, they have been used to distinguish obese patients with complications of obesity, such as hypertension, diabetes, non-alcoholic steatohepatitis (NASH) and CVD. These patients

with ‘metabolically unhealthy obesity’ (MUO) share many common features with PE, including inflammation, oxidative stress and altered levels of angiogenic factors and adipokines [16].

While not all women with a high BMI develop PE, some of the metabolic abnormalities associated with obesity are believed to contribute to the disease [17]. Furthermore, women with a history of PE have a significantly increased long-term risk of CVD [18, 19]. With so much crossover between the demographic, biophysical, and biochemical markers of PE, MUO and CVD, it becomes increasingly difficult to determine whether these biomarker algorithms measure true PE risk, or whether they assess maternal cardiovascular and metabolic health with predictable consequences for future maternal health, particularly if these women develop PE.

In this review, we aim to explore how well predictive tests for PE truly predict the obstetrical disease, or whether these tests are affected by changes in maternal cardiovascular and metabolic health. To achieve this, we searched the obstetric literature on predictive biophysical and biochemical markers for PE, and the non-obstetric literature for biomarkers of MUO and CVD. The performance of markers with significant overlap between these conditions were compared in order to gain a better understanding of the effect of maternal health on the performance of these biomarker algorithms, leading to improved screening tests for all forms of preeclampsia, whether placental or maternal in origin.

Methods

All searches were conducted prior to May, 2018 in English with no other limitations. A general PubMed search was done to obtain articles relating to potential predictive markers of PE. General search terms included ‘preeclampsia’ and similar terms such as ‘pre-eclampsia’, ‘PE’,

and ‘hypertension and pregnancy’. Other terms included in the general search were ‘marker’, ‘biomarker’, ‘screen’, ‘predict’, and ‘risk’.

Further information on any potential biomarkers was obtained through more specific PubMed searches including the general search terms along with the name of each marker or class of markers separately; for example: [(‘Preeclampsia’ OR ‘Pre-eclampsia’ OR ‘PE’) AND (‘Mean Arterial Pressure’ OR ‘MAP’) AND (‘Marker’ OR ‘Screen’ OR ‘Predict’)]. Another PubMed search was conducted to find any data on the effectiveness of these PE markers in obese populations. This was done by including the terms ‘obesity’ and ‘BMI’ in the search criteria along with the specific terms that were used.

Lastly, a PubMed search was conducted to obtain data on markers of impaired metabolic and vascular health. The first part of this search was done to find markers differentiating between healthy and unhealthy obesity with search terms such as ‘metabolically healthy obese’ (MHO) or ‘healthy obesity’ and ‘metabolically unhealthy obese’. The search for cardiovascular biomarkers included terms such as ‘vascular health’, and ‘cardiovascular disease’ along with ‘marker’ or ‘biomarker’.

Results

Biophysical Markers in PE, MUO, and CVD

Obesity has shown to be an independent factor in the prediction of PE with multiple studies demonstrating that a higher BMI correlates to an increased risk of PE [14, 20]. However, recent studies have taken into account the differences between ‘healthy’ obesity and obesity with associated metabolic abnormalities. Metabolic syndrome (MetS) is defined as a cluster of factors

such as low HDL-cholesterol, large waist circumference and elevated blood pressure, blood glucose and triglycerides, that are associated with an increased risk of CVD, kidney disease and diabetes [21]. It has been reported that MetS is associated with an increased rate of PE [22, 23] and this increased risk is positively correlated with the number of MetS components involved [22]. Obesity and MetS are both considered to be risk factors for CVD [24, 25]; conversely, it is possible that obese patients who do not have MetS should be considered to be in the MHO category. It has been argued that the severity of obesity-related complications may be a function of time, although there is limited evidence to support this statement [26]. However, studies have found that those who are considered MHO are not at an increased risk for complications such as CVD compared to metabolically healthy normal weight individuals, regardless of the duration of obesity [27].

Biophysical markers of cardiovascular health have been assessed in both the prediction of PE and in risk-stratification of MUO outside of pregnancy. Overall, the most useful predictors of PE include mean arterial pressure (MAP) and uterine artery Doppler [28-30], though their performance in isolation is poor [31, 32], especially for late-onset PE where symptoms tend to be less severe and later in onset. Although these markers have shown to perform better when used to predict early-onset PE, in the obese population, the distinction of timing of PE onset is not as clearly defined. Furthermore, regardless of PE etiology, it is possible these markers are altered due to poor metabolic health associated with the increased risk for PE seen in obesity rather for PE itself. The only biophysical marker specific for PE is the uterine artery Doppler, used to measure resistance to blood flow in the uterine arteries and to identify impaired blood supply to the placenta, with limited sensitivity and specificity (Table 1A) when used as a stand-alone marker [33].

Table 2A summarizes the significant overlap of other biophysical tests in the prediction of PE, CVD and MUO. Non-invasive cardiovascular tests include EndoPAT, a measurement of endothelial vasodilation function by recording endothelial-mediated changes in the peripheral arterial tone [34-36], endothelial-dependent flow-mediated dilation (FMD), which assesses vascular function using ultrasound to measure the change in artery diameter in response to reactive hyperemia [37], and pulse wave velocity (PWV), a technique used to evaluate arterial stiffness by measuring the velocity of the blood pressure wave travelling through the arteries over time [30]. Endothelial dysfunction, as measured by the EndoPAT device, is represented by a low reactive hyperemia index (RHI) value [34]. A low FMD indicates reduced dilation of the brachial artery in response to shear stress which is suggestive of vascular dysfunction [37]. An elevated PWV value indicates an increase in arterial stiffness [38]. There is significant overlap in the prediction of PE, MUO and CVD using these tests (see Table 2A).

Biochemical Markers used in the prediction of preeclampsia

The exact pathogenesis of PE is unknown; however, several different biochemical markers have been linked to the disease. Some of the more widely studied biochemical markers for PE include pregnancy associated placental protein A (PAPP-A) and placental growth factor (PLGF). Other studies have focused on the discovery of novel markers for predicting PE through metabolomic analysis. While many researchers have determined PE predictive values for individual markers, most have concentrated on more comprehensive prediction models using multiple markers as this is associated with better prediction of PE

The most-widely studied biomarkers for PE include placental proteins, angiogenic and anti-angiogenic molecules. While the placenta-specific markers have no relevance in MUO or

CVD, there are numerous other markers, including those related to angiogenesis, inflammation, apoptosis, and oxidative stress, with considerable crossover between the conditions. Amongst the non-pregnancy specific markers, these markers were altered in PE (compared to normotensive controls) in a similar fashion to MUO (compared to MHO individuals) and CVD (compared to healthy controls). These results are summarized in Table 2B below.

Pregnancy-specific markers used in Prenatal Screening for Down syndrome

Pregnancy associated placental protein A (PAPP-A) is produced in the placenta by the syncytiotrophoblast cells [39]. Its levels increase during pregnancy and fall post-partum [40, 41]. It has been found to promote trophoblast cell proliferation and adhesion [42] and may be important in the regulation of insulin growth factor bioavailability and cell growth [43]. Decreasing levels of PAPP-A in the first trimester are predictive of aneuploidy, specifically trisomy 21 [44]. Decreased levels of PAPP-A in the presence of a normal karyotype are associated with increased risk of PE, intrauterine growth restriction, and preterm delivery [45]. There is limited literature on the associations of pregnancy-specific markers with MUO or CVD. However, elevated PAPP-A levels have been noted in patients with an increased risk of cardiovascular events and coronary artery disease [46, 47].

Placental protein 13 (PP-13) is a 32 kDa protein produced by the syncytiotrophoblast and studied as a predictive marker of preeclampsia, IUGR, and preterm birth [48, 49]. Its functions involve spiral artery remodeling, implantation of the blastocyst and placental development [48]. Placental protein 14 (PP-14), also known as glycodelin, is a 28 kDa, endocrine-related glycoprotein [50] that has been found to be involved in placental development and may also be involved in the pathogenesis of PE [51]. Increased levels of both PP13 and glycodelin have been associated with PE [50, 52].

Inhibins are heterodimer proteins consisting of alpha and beta subunits whereas activins are homodimeric proteins made up of beta subunits [53]. Levels of inhibin A rise until 12 weeks of pregnancy, fall and remain low until 24 weeks, and then gradually increase in the third trimester [54]. Activin A levels remain relatively constant in the first and second trimesters but rise in the third trimester with a sharp increase at term [55]. Inhibin A and activin A are involved in a feedback loop regulating human chorionic gonadotropin (hCG) levels during pregnancy. Both are produced by the placental trophoblasts, thus levels of inhibin A and activin A have been shown to rise in PE [56, 57].

The free beta subunit of β-hCG is secreted by the syncytiotrophoblast cells [58]. Its primary function is to maintain the decidual spiral arteries and the vascular supply of the placenta during pregnancy [58]. In normal pregnancies, the concentration of β-hCG increases exponentially until 8 to 10 weeks and then begins to decrease [59]. Studies have shown β-hCG levels are increased in women who develop PE [60].

Alpha-fetoprotein (AFP) is a specific globulin produced by the yolk sac, gastrointestinal tract and liver. Its function is generally unknown but it may be involved with immunoregulation during pregnancy as well as an intravascular transport protein, given its similarity to albumin [61]. Measuring elevated levels of AFP has been used as a screening tool for PE [62].

Angiogenic Factors

An imbalance between pro- and anti-angiogenic factors is thought to be crucial to the pathogenesis of PE [63]. Widely studied pro-angiogenic factors include vascular endothelial growth factor (VEGF), placental growth factor (PLGF) and angiogenin. Anti-angiogenic factors highlighted in the literature include soluble fms-like tyrosine kinase-1 (sFlt-1), soluble endoglin (sEng), and endothelin-1. In PE, levels of pro-angiogenic factors are decreased and anti-

angiogenic factors are increased [64-69]. Decreased levels of VEGF have been noted in MUO patients whereas increased levels of PLGF, sFlt-1, and endothelin-1 have been associated with CVD [70-73].

Inflammatory Markers and Adhesion Molecules

C-reactive protein (CRP) is an acute phase protein that rises in plasma in response to inflammation and is thus frequently studied as a marker of PE. In the third trimester, increased CRP levels have been noted in PE patients compared to controls [74-76]. First trimester CRP levels have also been noted to increase in patients with PE compared to controls [77, 78]. Tumour necrosis factor alpha (TNF-α) is another cytokine that contributes to a systemic inflammatory response and, similarly to CRP, increased levels of TNF- α have been measured in women with PE in the third trimester [74, 76]. Studies in the first and second trimester showed no difference between PE and control groups suggesting that TNF- α may be more useful as a diagnostic test rather than in the prediction of PE [79]. Furthermore, elevated levels of CRP and TNF-α have also been associated with both MUO and CVD [80-83].

The interleukin family of cytokines are signaling molecules involved in the inflammatory response and have been implicated in the pathological mechanism of PE. IL-6 and IL-8 are the most widely studied interleukins in the pregnant population and both have been found to increase in response to PE [74, 76, 84]. However, these studies were done in the third trimester suggesting that these interleukins may not be useful for predicting PE. A study by Chen *et al* measured serum concentrations of podocalyxin, a protein typically found to increase in the urine of PE patients, and found its levels to be increased in PE patients with IL-6 being responsible for this increase [85]. In the non-pregnancy literature, increased levels of IL-6 are associated with MUO and CVD [80-82, 86].

Other inflammatory markers have been reported, including calprotectin and transforming growth factor beta 1 (TGF-β1) which have both been shown to increase in PE [87-89]. Follistatin-like 3 (FSTL3), a glycoprotein that inhibits the TGF- β family of proteins, is elevated in obese patients who later developed PE compared to the control group with a normal BMI [90]. Decorin (DCN) is a leucine-rich proteoglycan that has also been shown to inhibit TGF- β activity [73] and DCN over-expression has been associated with an increased risk of PE [91, 92].

A few studies have focused on different adhesion molecules as potential biomarkers of PE. Intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin have been shown to be elevated in women with PE compared to normal controls [93]. Increased levels of E-selectin have been noted in MUO patients [94] and elevated levels of both ICAM-1 and E-selectin have been seen in patients with CVD [95, 96]. A Disintegrin and Metalloprotease 12 (ADAM12) is a glycoprotein known to be involved in cell-cell signaling processes and cell surface receptor proteolytic activity [97]. It is derived from the placenta and increases from 8 weeks gestation until term. Studies have shown that ADAM12 levels are decreased in women with PE [98-100].

Adipokines

Adipokines are involved in inflammation and metabolic processes and have been associated with both obesity and PE [101]. Leptin is an adipokine expressed in adipose tissue and is involved in energy expenditure, modulation of satiety and insulin resistance [102]. It is also produced by placental trophoblastic cells [103]. Studies measuring leptin in the second and third trimesters showed an increase in leptin levels in PE versus control patients [103-106]. In one study, levels of leptin were found to increase in PE and were increased further depending on disease severity [107]. Despite seemingly promising results, these studies had small sample sizes

and did not measure leptin levels in the first trimester, therefore limiting its clinical utility for early detection of PE. When preeclamptic patients were stratified by weight, studies reported increased leptin levels in obese preeclamptic patients compared to normal weight preeclamptic patients [108, 109], suggesting that leptin may be predictive of PE in the obese population. Increased leptin levels have also been associated with MUO and CVD [110, 111].

Adiponectin is an anti-inflammatory, insulin sensitizing, and anti-atherogenic adipokine that is implicated in the pathophysiology of PE [112]. Several authors have studied the association between adiponectin and PE and found conflicting results. Most studies report an increase in adiponectin in the third trimester in patients with PE compared with control [104, 113]. However, other studies report the opposite, i.e. adiponectin decreased in patients with PE [114, 115]. In the non-pregnancy literature, decreased levels of adiponectin are associated with both MUO and CVD [80, 111, 116, 117]. Although a decrease in adiponectin would be expected in PE, as it has been linked to metabolic and cardiovascular complications, studies suggest the increase may be due to a feedback loop in order to improve insulin sensitivity and vascular function which are significantly affected by the disease [113]. Furthermore, the leptin/adiponectin ratio, a parameter of insulin resistance, is significantly elevated in PE, suggesting that the imbalance in the levels of these adipokines plays a role in the pathophysiology of the disease [118].

Other adipokines that have been identified as potential predictors of PE include resistin, visfatin and lipocalin-2, all of which are elevated in the presence of PE [104, 119-121]. Increased levels of resistin have been seen in PE patients between 33-38 weeks [104] while visfatin levels were found to rise in the first trimester in women who developed PE [119]. Resistin levels have

also been found to decrease in patients with CVD [111]. However, studies on these markers are limited and further research is warranted.

Markers of Oxidative Stress and Apoptosis

It is widely accepted that endothelial dysfunction is involved in the mechanism of PE [63]. Evidence supports a generalized systemic inflammatory response and oxidative stress that precedes the endothelial dysfunction [122]. Free radicals resulting from oxidative stress cause damaging alterations to lipids, protein and DNA, eventually resulting in vascular endothelial dysfunction and features of PE [122]. Oxidative stress markers that have been evaluated in the prediction of PE include malondialdehyde (MDA), 8-isoprostane, prostaglandin F2α (PGF2α), and oxidative low-density lipoprotein (ox-LDL), all of which have been found to increase in response to PE [74, 123, 124]. Oxidative stress is also increased in MUO and CVD with studies noting increased levels of ox-LDL in both conditions [125, 126].

It is believed that apoptosis is involved in every step of the pathogenesis of PE [127]. Increased apoptotic activity in placental trophoblasts of women with PE compared to normotensive controls has been described; suggesting that increased apoptosis contributes to poor trophoblast invasion and spinal artery remodeling [128]. PE correlated with increased caspase-9 activity and DNA fragmentation, which are both indicators of apoptosis [129]. Increased DNA fragmentation has also been seen in patients with CVD [130].

Vitamin D and Uric Acid

Recent studies have identified differences in vitamin D levels between MHO and MUO individuals. Metabolic abnormalities in obese patients have been found to be associated with low

levels of vitamin D [131]. Several studies have revealed that vitamin D deficiency has also been associated with PE and CVD [132-135].

Uric acid has also been suggested at a predictor of PE as well as CVD and unhealthy obesity. Studies have shown that, when compared to normotensive controls, patients with either PE or CVD have elevated uric acid levels [136, 137]. Likewise, MUO individuals have been found to have higher uric acid levels than MHO individuals [138].

Metabolomics

Metabolomics is a promising new field of research specializing in the analysis of small molecule metabolites (< 1500 Daltons) [139]. It utilizes analytical chemistry techniques such as nuclear magnetic resonance, mass chromatography, lipidomics and others to characterize metabolites including amino acids, lipids, sugars and other complex organic molecules [139]. Work in this field is being applied to the development of new biomarkers to screen for disease processes, including PE and obesity-related morbidities [140].

Altered metabolic profiles have been noted in patients with PE, MUO and CVD. Several studies comparing women with and without PE have noted differences in several amino acid compounds including methionine, phenylalanine, alanine, asparagine, glutamate, homocysteine and glycylglycine [141-146]. Other metabolites that have been identified as potential markers of PE include acylcarnitines, stearoylcarnitine, hydroxyhexanoylcarnitine, and taurine [143, 144, 147, 148].

When comparing metabolic profiles of MHO and MUO patients, differences have been seen in several metabolites including aspartate, glutamine, histidine, spermidine, phosphotidylcholines, and arachidonic acid [149]. One study compared metabolites in lean and overweight/obese patients with and without MetS and determined that a number of branch

chained amino acids and acylcarnitines are associated with metabolic health [150]. Decreased levels of glycine have also been linked to the metabolically unhealthy phenotype [151].

Metabolomics has also been used to determine a metabolic signature of those at risk for CVD. Altered levels of acylcarnitines have been associated with an increased risk of CVD [152, 153]. Several amino acids, including leucine, isoleucine, tyrosine, phenylalanine and homocysteine, have also been identified as potential indicators of CVD [153-155].

Abnormal lipid profiles have also been associated with both PE and impaired metabolic health in obesity. Higher levels of triglycerides and low-density lipoprotein (LDL) have been observed in PE patients in the third trimester compared to normotensive controls, even when matched for gestational age and BMI [156]. Studies have also found that the MUO patients had higher triglycerides and lower high-density lipoprotein (HDL) than those who were MHO [157, 158]. Finally, poor cardiovascular health has been associated with increased triglycerides and LDL as well as decreased HDL [159, 160].

Discussion

PE is a serious pregnancy-related condition with significant maternal and fetal implications. A first trimester screening test would help to identify patients who are at an increased risk and, therefore, may benefit from an individualized approach to antenatal care. These selected patients may be incorporated into randomized studies to better investigate preventative strategies for PE.

On reviewing the available evidence, it is clear that there is no single test that has outperformed others in the prediction of PE. Even the most promising markers, including uterine artery Doppler, PP-13, and PLGF, do not independently predict PE. Models for screening have

combined biomarkers with biophysical findings and maternal characteristics to improve detection rates. However, these models have been deemed insufficient for application to clinical practice with limited sensitivity and specificity (Table 1B). It is important to note that these detection rates are only true at a specificity of 90%, which is not considered adequate when developing a valid screening test for a disease process. It is generally accepted that, in order to develop a valid screening test, a false positive rate of 5% is required, as per WHO criteria. There are several reasons why these biomarkers have been so unsuccessful when used to predict PE. The ability to differentiate between the early and late (placental and maternal) forms of PE is difficult, especially when defined based on gestational age. Furthermore, the prediction of PE becomes increasingly difficult in the obese population because of hemodilution related to their relatively greater blood volume [161]. Obesity itself is a risk factor for poor maternal metabolic and cardiovascular health [162] and should be considered when evaluating predictive markers of PE; especially since the same markers that are associated with PE are similarly affected by obesity.

As the obesity rates continue to increase, so do the related metabolic and cardiovascular complications leading to impaired maternal health. This review highlights the considerable overlap between markers of obesity, PE and other metabolic and vascular diseases. In such patients, vascular health and endothelial function are reduced while inflammation and oxidative stress are increased. With the significant overlap between these conditions, it is possible that these markers of PE may not be predictive of the disease itself but instead are indicative of pre-existent poor vascular and metabolic health.

Table 1A: Predictive Values of Preeclampsia Markers

Marker	Onset: Early, Late, Not Specified (NS)	Predictive Value(s) at 5% FPR	Predictive Value(s) at 10% FPR	
Mean Arterial Pressure	Early	49 – 58.4%	59.5 – 72.9%	[163-165]
	Late	30 – 44%	36.7 – 59.3%	[165]
	NS	15 – 37.3%	30-53.5%	[28, 164, 166]
Uterine Artery Doppler	Early	15 – 86%	21.4 – 95.7%	[163, 164, 167, 168]
	NS	7 – 30.8%	19 – 51%	[77, 164, 167, 169]
Pulse Wave Velocity	Early		82%	[170]
	Late		20%	[170]
	NS		81%	[170]
PAPP-A	Early	5 – 50%	19 – 59%	[52, 164, 169]
	NS	9.6 – 31.5%	15.4 – 50%	[164, 169, 171, 172]
PP-13	Early	10 – 65%	36 – 80%	[167, 173-175]
	NS	10 – 55%	45 – 79%	[167, 169, 173, 176]
PP-14	Early		83.6% *	[50]
	NS	59% **		[50]
Inhibin A	Early	23.1%	30.8%	[56]
	NS	16 – 37%	32 – 47%	[177-179]
Activin A	Early	11.1%	25.9%	[57]
β-hCG	NS	11 – 15%	18 – 22%	[177, 178]
AFP	NS	7%	13%	[178]
PLGF	Early	25.9 – 59.3%	41 – 72.4%	[164, 175, 180, 181]
	NS	29.1 – 32%	40.1 – 61.5%	[67, 164, 171]
sEng	Early	18 – 30%	46.7%	[67, 180]
sFlt-1	NS	26%	30.8%	[67, 171]
CRP	NS	22%	33%	[182]
TNF- α	NS		78%	[79]
Podocalyxin	NS		81% ***	[85]
Decorin	NS		89% ****	[91]
E-selectin	NS		68% #	[183]
ADAM12	NS	30%	38%	[98]
Leptin	NS	91% ##		[107]

Table 1B: Predictive Values of Combined Preeclampsia Screening Models

Screening Model	Onset: Early, Late, Not Specified (NS)	Predictive Value(s) at 5% FPR	Predictive Value(s) at 10% FPR	
MC, Doppler, PAPP-A, sEng	Early	63%	83.3%	[180]
MC, Doppler, PAPP-A, Inhibin A	Early	81%	88.5%	[56]
MC, Doppler, PLGF, sEng	Early	78%	96.3%	[180]
MC, Doppler, PLGF, MAP	Early	86%	92.3%	[184]
MC, Doppler, PAPP-A, MAP	Early	84%	94.6%	[185]
MC, Doppler, PAPP-A, PLGF	Early	75.9%	86.2%	[181]
MC, Doppler, PAPP-A, PLGF, MAP	Early	93.4%	96.3%	[164]
	NS	37.8%	53.6%	[164]
MC, Doppler, PAPP-A, PLGF, Inhibin A	Early	NA	100%	[186]
	NS	NA	40%	[186]
MC, Doppler, β-hCG, PAPP-A, PLGF	Early	67%	75%	[187]
MC, Doppler, β-hCG, PAPP-A, PLGF, PP-13	Early	58%	67%	[187]

Table 1 summarizes published predictive values of preeclampsia (A) markers and (B) screening models. Studies that distinguished between early and late preeclampsia are indicated as such (or NS: not specified). Values represent sensitivity (%) at a false positive ratio (FPR) of either 5% or 10%; exceptions: * specificity = 80%, ** specificity = 93.3%, *** specificity = 84%, **** specificity = 61%, # specificity = 58%, ## specificity = 100%.

MC = maternal characteristics (i.e. prior risk), Doppler = uterine artery Doppler

Table 2A: Biophysical Markers of Preeclampsia, Metabolically Unhealthy Obesity and Cardiovascular Disease

Predictive Biophysical Markers	Preeclampsia	Metabolically Unhealthy Obese	Cardiovascular Disease
Obesity	↑ [14, 20]	NA	↑ [24]
Metabolic Syndrome	↑ [22, 23]	↑	↑ [25]
Mean Arterial Pressure	↑ [28, 65]	↑ [188]	↑ [189]
Uterine Artery Doppler	↑ [65, 190]	NA	NA
Endothelial Function (EndoPAT - RHI)	↓ [35, 36]	↓ [191]	↓ [192]
Endothelial-dependent FMD	↓ [193]	↓ [194]	↓ [195]
Pulse Wave Velocity	↑ [35, 36]	↑ [196]	↑ [197]

Table 2B: Biochemical Markers of Preeclampsia, Metabolically Unhealthy Obesity and Cardiovascular Disease

Biomarker Group	Biomarkers	Preeclampsia	Metabolically Unhealthy Obese	Cardiovascular Disease
Markers for Prenatal Screening of Down Syndrome	PAPP-A	↓ [45]		↑ [46, 47]
	PP-13	↓ [52]		
	PP-14	↑ [50]		
	Inhibin A	↑ [56]		
	Activin A	↑ [57]		
	B-hCG	↑ [60]		
	AFP	↑ [62]		
Angiogenic Factors	PLGF	↓ [64, 65, 67]		↑ [71]
	VEGF	↓ [64, 65, 67]	↓ [70]	
	Angiogenin	↓ [66]		
Anti-angiogenic Factors	Sflt-1	↑ [67-69]		↑ [72]
	sEng	↑ [67, 69]		
	Endothelin-1	↑ [69]		↑ [73]
Inflammatory Markers	CRP	↑ [74-76]	↑ [80, 81]	↑ [82]
	TNF-α	↑ [74, 76]	↑ [80, 81]	↑ [83]
	Interleukins	↑ [74, 76, 84]	↑ [80, 81, 86]	↑ [82]
	Podocalyxin	↑ [85]		
	Calprotectin	↑ [87]		
	TGF-β1	↑ [88, 89]		
	FSTL3	↑ [90]		
	Decorin	↑ [91, 92]		
Adhesion Molecules	ICAM-1	↑ [93]		↑ [95, 96]
	VCAM-1	↑ [93]		
	E-selectin	↑ [93]	↑ [94]	↑ [96]
	ADAM-12	↓ [98-100]		
Adipokines	Leptin	↑ [103-106]	↑ [110]	↑ [111]
	Adiponectin	↓/↑ [104, 113-115]	↓ [80, 116]	↓ [111, 117]
	Resistin	↑ [104]		↑ [111]
	Visfatin	↑ [119]		
	Lipocalin-2	↑ [120, 121]		
Oxidative Stress Markers	MDA	↑ [123]		
	PGF2α	↑ [123]		
	8-isoprostane	↑ [74]		
	Ox-LDL	↑ [124]	↑ [125]	↑ [126]
Apoptotic Markers	Caspases	↑ [129]		
	DNA fragmentation	↑ [129]		↑ [130]
Other	Vitamin D	↓ [132-134]	↓ [131]	↓ [135]
	Uric Acid	↑ [136]	↑ [138]	↑ [137]

Table 2 summarizes (A) biophysical and (B) biochemical markers of preeclampsia, metabolically unhealthy obesity and cardiovascular disease. The arrows represent the most published effect (↑ increase, ↓ decrease) with [citations]. Those markers with no effect indicated, to our best knowledge, have not yet been studied in this context.

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