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REVIEW

Preeclampsia: Definitions, screening tools and diagnostic criteria in the supersonic era

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Abstract

Preeclampsia is still a major risk factor for maternal-fetal health. Therefore, early identification of pregnant women at risk for preeclampsia is a big priority in obstetrics in order to decrease the mortality and morbidity associated with this disease. On the basis of well known and new pathophysiological mechanisms of preeclampsia, different biochemical and ultrasonographic parameters have been investigated in the literature, without finding an ideal marker for early screening. In this brief review, we present the best studied ultrasonographic markers and the most recent genetic factors and promising emerging biomarkers of preeclampsia, to date. We hope that in the future the combination of these tests will allow us to predict which women are at risk of preeclampsia.

Key words: Preeclampsia; Diagnosis of preeclampsia; Screening of preeclampsia; Ultrasonographic markers of preeclampsia

Core tip: Preeclampsia is a very important disease in pregnancy but substandard care has been found in its management. The core content of this paper is the review of the literature to evaluate possible markers for early diagnosis of preeclampsia.

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INTRODUCTION

Preeclampsia is still an important cause of maternal and fetal death. The 8th report of the Confidential Enquiries into Maternal Deaths in the United Kingdom reported that in the triennium 2006-2008, 261 women died from complications directly or indirectly related to pregnancy. Among these, 22 deaths were related to preeclampsia and 20 of 22 cases demonstrated substandard care[1].

Moreover, preeclampsia is an important risk for the health of the baby. The Perinatal Mortality Report of the United Kingdom[2] reports that 5% of stillbirths without congenital abnormality occurred in women with preeclampsia and that half of the women with severe preeclampsia gave birth preterm.

Then a question arises. Is the real problem to find a univocal definition of this complex disease or to find markers for the screening of preeclampsia? Or is the problem in the inadequate treatment?

In this review, we focus our attention on the possibility of screening for preeclampsia based on the data available in the literature.

However, the present report needs to include the definition of preeclampsia.

There has been confusion about the definition of hypertensive disorders in pregnancy for a long time.

In 2001, the International Society for the Study of Hypertension in Pregnancy[3] provided a consensus on classification, adopting the statement of the Australasian

Society for the Study of Hypertension in Pregnancy (ASSHP)[4] and the report of the National High Blood Pressure Education Program (NHBEP)[5].

The definition and classification is the following: hypertension in pregnancy, systolic blood pressure (SBP) ⩾ 140 mmHg and/or diastolic blood pressure (DBP) ⩾ 90 mmHg.

Four categories are identified: (1) preeclampsia: *de novo* hypertension after 20 wk gestation associated with proteinuria. Proteinuria is defined as appearance of urinary protein greater than 300 mg/d or a spot urine protein/creatinine ratio ⩾ 30 mg/mmol; (2) gestational hypertension: de novo hypertension alone after 20 gestational weeks; (3) chronic hypertension: hypertension diagnosed before 20 wk gestation or preconception hypertension; and (4) preeclampsia superimposed on chronic hypertension: in a woman with chronic hypertension, development of proteinuria and/or symptoms associated with preeclampsia after 20 gestational weeks.

In the definition of hypertension, both ASSHP and NHBPEP consider values below 140/90 mmHg as absolute values and do not provide an increase in blood pressure of 15 mmHg and 30 mmHg, respectively, for diastolic and systolic levels.

The ASSHP and NHBPEP agree on the definition and classification of hypertensive disorders during pregnancy with an important difference: the NHBPEP considers only hypertension associated with proteinuria as diagnostic criteria, whereas the ASSHP uses a clinical classification based on the pathophysiology of the disorder[4]. In fact, the definition of preeclampsia includes renal insufficiency, liver disease, neurological problems, hematological disturbances and fetal growth restriction (FGR), along with hypertension and proteinuria.

In 2009, the American Society of Hypertension (ASH) published a position paper that summarized the definitions and clinical features regarding the different forms of hypertension during pregnancy[6] and included the guidelines of the American College of Obstetricians and Gynecologists.

Like other opinions, the ASH position paper considers hypertension as a SBP ⩾ 140 mmHg and/or DBP ⩾ 90 mmHg, avoiding the dated concept of an increase in DBP of 15 mmHg or more and an increase in SBP of 30 mmHg or more. In the definition of preeclampsia, proteinuria is defined by the appearance of urinary protein greater than 300 mg/d, a spot urine protein/creatinine ratio ⩾ 30 mg/mmol or a qualitative dipstick +1. The protein/creatinine ratio is recommended in the ASH position paper because dipsticks have many false-positives and negatives and urine collection may be difficult in pregnancy.

The terminology used is that recommended by NHBPEP: preeclampsia/eclampsia, gestational hypertension, chronic hypertension and preeclampsia superimposed on chronic hypertension.

However, the ASH position paper also introduces new entities: (1) late postpartum hypertension: usually the blood pressure returns to normal in the immediate postpartum in preeclamptic women or in women with hypertensive disorders in pregnancy. However, there is a little known entity in which the hypertension appears after delivery in women with normotensive gestation and regresses within the first post-partum year; (2) late postpartum eclampsia: the eclamptic convulsions occur from 48 h to several weeks after delivery; and (3) early gestational hypertension: a very rare entity in which patients have excessive sensitivity to progesterone due to activating mineralocorticoid reception mutations. These women develop early hypertension concomitantly with the progesterone rise in the first trimester.

Preeclampsia in the ASH position paper is usually defined by hypertension associated with proteinuria, but the American Society of Hypertension suggests the distinction between "Less Severe" and "More Severe" preeclampsia (defined by the American College of Obstetrics and Gynecology as mild and severe preeclampsia) on the basis of symptoms, hypertension level and clinical data. The "more severe preeclampsia" is defined as the presence of severe hypertension (⩾ 110 mmHg diastolic and ⩾ 160 mmHg systolic), nephrotic range proteinuria, oliguria, neurological symptoms, thrombocytopenia (< 100000/μL), hemolysis and abnormal liver function.

Despite this distinction, the American Society of Hypertension recommends that even just a suspicion of preeclampsia is a sufficient reason for hospitalization because all preeclampsia is potentially explosive.

In 2010, the National Institute for Health and Clinical Excellence (NICE)[7] published a guideline, including a classification. The definition and classifications are as follows: (1) chronic hypertension: hypertension that is present at the booking visit or before 20 wk gestation. It can be primary or secondary in etiology; (2) gestational hypertension: a new hypertension presenting after 20 wk gestation without significant proteinuria; (3) preeclampsia: a new hypertension presenting after 20 wk gestation with significant proteinuria. Significant proteinuria is defined as +1 or more in an automated reagent strip or urinary protein/creatinine ratio greater that 30 mg/mmol or greater that 300 mg protein in 24 h urine collections; (4) eclampsia: a convulsive condition associated with preeclampsia; (5) HELLP syndrome: hemolysis, elevated liver enzymes and low platelet count; (6) severe preeclampsia: preeclampsia with severe hypertension and/or with symptoms and/or biochemical and/or hematological impairment. In addition, the Guideline Development Group has defined three different levels of hypertension: mild, moderate and severe; (7) mild hypertension: diastolic BP 90-99 mmHg, systolic blood presure (BP) 140-149 mmHg; (8) moderate hypertension: diastolic BP 100-109 mmHg, systolic BP 150-159 mmHg; and (9) severe hypertension: diastolic BP 110 mmHg or greater, systolic BP 160 mmHg or greater.

In agreement with the ASH position paper, the NICE guidelines recommend hospitalization of preeclamptic women with all degrees of hypertension.

The 2010 guidelines of the Royal College of Obstetrics and Gynecologists (RCOG)[8] regarding the Manage-

Table 1 Uterine artery doppler studies for the prediction of preeclampsia

Ref.	Weeks of evaluation (wk)	Sensitivity	Specificity
Campbell *et al*[10]	16-18	68%	69%
Valensise *et al*[11]	22	74%	97.5%
Jacobson *et al*[12]	24	44%	73%
Arduini *et al*[13]	18-20	64%	94%
Ziemmermann *et al*[14]	21-24	56%	83%
Bower *et al*[15]	18-22	75%	86%
Chan *et al*[16]	20	27%	97%
North *et al*[17]	19-24	27%	90%

ment of Severe Preeclampsia substantially agree with the other definitions of preeclampsia, but there are still differences about the definition of severe preeclampsia compared to the NICE guidelines. The RCOG considers severe preeclampsia as the presence of a DBP ⩾ 110 mmHg on two occasions or a SBP ⩾ 170 mmHg on two measurements with significant proteinuria (at least 1 g/L).

In agreement with the ASH position paper, the RCOG guidelines report the evidence level I b and II b regarding the measurement of blood pressure, referred to below.

The woman should be rested and sitting at a 45 degree angle. The cuff should be an appropriate size and be placed at the level of heart. The diastolic pressure is taken at the 5th Korotkoff phase, therefore the older concept that gravid women show large differences between the 4th and the 5th Korotkoff phase has been abandoned and the 5th Korotkoff has been established as the sound of true diastolic pressure.

SCREENING FOR PREECLAMPSIA

Ultrasounds

Uterine artery Doppler: The increase of impedance to flow in the uterine artery is evidence of impaired trophoblastic invasion of the maternal spiral arteries, a well known mechanism of the pathophysiology of preeclampsia. In fact, several studies have shown a reduction in the maternal uterine resistance index with advancing gestational age in normal pregnancy[9], while the presence of an increased resistance in maternal flow or the presence of a notch as evidence of abnormal uterine flow has been associated with the development of preeclampsia. For many years, the Doppler ultrasound evaluation of uterine arteries has been used to predict an unfavorable pregnancy outcome. However, discrepant results are described among studies in the literature (Table 1) which could be due to the different gestational age at which the women were evaluated, the different populations included, the single or two steps examination, the different cut-off of abnormal resistance index and finally the differences in ultrasound (US) Doppler technique.

In an unselected population, Bower *et al*[15] reported a sensitivity of 75% and specificity of 86% for preeclampsia in women at 18-22 wk gestation with an abnormal resistance index (above the 95th percentile and/or with the presence of a notch within the uterine artery Doppler waveform), with a better prediction for severe conditions. Valensise *et al*[11] found a sensitivity of 74% and specificity of 97.5% for the development of gestational hypertension in primigravidas at 22 wk gestation with increased impedance (resistance index more than 0.58).

Other authors report less favorable results. Chan *et al*[16] found that sensitivity of the test for preeclampsia was 27% and specificity was 97% in women at 20 wk gestation. Similar results from North *et al*[17] found a sensitivity of 27% and specificity of 90% at 19-24 wk gestation.

With the aim of reducing the number of false-positives, Steel *et al*[18] proposed a two step trial for uterine Doppler US with the first evaluation at 18 wk gestation and in the presence of increased impedance (resistance index greater that 0.58), a second Doppler evaluation at 24 wk gestation. The authors reported a sensitivity for preeclampsia of 63%. Also, Bower *et al*[19] reported an increase of positive predictive value (PPV) for preeclampsia from 12% to 28%, reanalyzing women at 24 wk with abnormal Doppler US at 20 wk gestation.

Several studies regarding the application of Doppler uterine evaluation as a screening tool have been conducted in selected populations at risk for preeclampsia. Arduini *et al*[13] evaluated women with previous gestational hypertensive disorders or essential chronic hypertension at 18-20 wk and reported a sensitivity of 64% and a specificity of 94%, but the true value of those data are still questionable. In fact, several biases and criticisms have been levelled at data from this research group. Jacobson *et al*[12] found a sensitivity of 44% and specificity of 73% for preeclampsia in women with chronic hypertension or a history of preeclampsia. Caruso *et al*[20] examined women with chronic hypertension in order to assess the predictivity power of Doppler uterine US and found a sensitivity of 78% and specificity of 45%.

Valensise *et al*[11] observed that the value of Doppler uterine evaluation as a screening test strictly depends on the studied population in his Paramount study. The PPV for hypertension is acceptable for screening in the high risk population, while in low risk pregnant women the correlation seems to be weaker. More recently, Elena Parretti from Florence[21] conducted a cross-sectional (at 24 wk gestation) and a longitudinal (at 16, 20 and 24 wk gestation) study of uterine artery Doppler in normotensive women with risk factors for preeclampsia. In agreement with other investigators, the value of 0.58 as the normal resistance index and a PPV of 44% were confirmed, still inadequate for a screening test. Instead, with a longitudinal approach, the PPV seemed to improve to 72.2% by reducing a number of false-positive results.

To improve the possibility of using the Doppler velocimetry of the uterine arteries as a screening for preeclampsia, several studies have proposed other parameters likely to be integrated with the Doppler evaluation.

Valensise *et al*[22] proposed the combination of Doppler and 24 h automated maternal blood pressure evaluation. This study stated that in the presence of abnormal Doppler and asymptomatic raised blood pressure, pa-

tients had a higher incidence of pregnancy complications with a PPV of 76% for preeclampsia.

With the aim of reducing the number of false-positive patients, other authors have proposed the use of Doppler velocimetry associated with biochemical parameters.

Elevated levels of second trimester β-human chorionic gonadotropin have been found in plasma of patients at risk for hypertensive disorders in pregnancy[23]. A study by Elsandabesee *et al*[24] demonstrated that in the presence of a diastolic notch, the association of serum screening with alpha-fetoprotein and β-human chorionic gonadotropin improves sensitivity and PPV to 91% and 41% respectively.

Initial studies showed a significant decrease in placental protein-13 (PP-13) levels in preeclamptic women[25,26], while recently Stamatopoulou *et al*[27] did not show a relationship between PP-13 levels and preeclampsia. Akolekar *et al*[28] studied PP-13 associated with PAPP-A (pregnancy-associated plasma protein A) and uterine artery Doppler US in the first trimester in 208 preeclamptic patients and in 416 normal pregnancies; a significant reduction of PP-13 level was shown in early preeclampsia but not in late preeclampsia, with a PPV for early preeclampsia of 79% and 49% for late preeclampsia. Although PAPP-A was reduced and uterine velocimetry Doppler was increased in preeclampsia, the combination of these parameters with PP-13 does not appear to improve the sensitivity of PP-13[28].

A systematic review in 2010[29] studied the role of biochemical markers associated with ultrasonographic markers to improve the possibility of prediction for early preeclampsia. The authors included 37 articles within their review in which the most frequently studied biochemical markers were hCG (human chorionic gonadotropin), inhibin A, α-fetoprotein, sFlt-1 (soluble fms-like tyrosine kinase 1), PAPP-A, activin A, placental growth factor (PlGF) and PP-13. In some cases, markers were evaluated in the second trimester as well as the ultrasound velocimetry, in other cases the markers were assessed during the first trimester before ultrasonographic evaluation. The analysis of these papers elucidates that the addition of biochemical markers to uterine artery Doppler ultrasound scan in the second trimester or the combination of first trimester biochemical and second trimester uterine velocimetry improves the predictive performance of ultrasound alone and of markers alone. This review also suggests that the addition of maternal characteristics does improve their predictive power.

Despite these promising results, the heterogeneity between studies regarding gestational age at the study time or the selected populations (high *vs* low risk) led to uncertainty about the combination of ultrasonographic and biochemical markers as a screening procedure for preeclampsia.

Maternal echocardiography: It is well known that important changes occur in pregnancy in the hemodynamic and cardiovascular system, with initial vasodilatation adaptation of the maternal cardiovascular tree that begins in the first trimester as a consequence of invasion of the spiral arteries by trophoblasts. Indeed, the remodeling of the spiral arteries contributes 20% to 26% to the total reduction of systemic vascular resistance in the second trimester[30]. Another important change is the increase in blood volume. A study based on the multifrequency bioelectrical impedance documented that total body, extracellular and intracellular water increased significantly and progressively from the first to the second trimester[31].

Cardiovascular and hemodynamic modifications consist of an increased preload, a decreased afterload, an increased compliance of the vascular tree and a ventricular remodeling at the level of the heart. Therefore, there is an enlargement of the vascular bed and an increase in blood volume to fill the enlarged vascular bed. Conversely, an inadequate placentation and the failure of the hemodynamic adaptation were identified as the basis of the pathological process leading to pregnancy complications. In 1988, Nisell *et al*[32] showed that in preeclamptic women, independently of the cardiac output, a high peripheral resistance can be observed and in those with a low cardiac output generally, a low birth weight could occur. Duvekot *et al*[33] observed that patients with FGR had a smaller left atrial diameter and a failure of cardiac output in early pregnancy.

On this basis, Valensise *et al*[30] designed a different study to evaluate the predictive value of some echocardiographic parameters for maternal and fetal complications, alone or associated with uterine Doppler velocimetry[30,34].

The same author[30], in his first study on this topic, evaluated the relationship between cardiac systolic and diastolic function and uteroplacental resistance in a longitudinal observation of 248 patients with a normal pregnancy. He reported a significant reduction in resistance index between first and second trimester in the uterine Doppler velocimetry. The echocardiographic evaluation showed a significant increase in left atrial diameter, stroke volume and cardiac output in normal pregnant women throughout gestation, mainly from the first to the second trimester, according to the fall of the uterine resistance index that contributes to a decrease of the afterload.

Conversely, in a study[35] performed on 21 pregnancies complicated by gestational hypertension, the analysis of systolic and diastolic function associated with morphological left ventricular modifications showed that hypertensive women have an altered geometric pattern with concentric hypertrophy. Functionally, this finding is associated with higher blood pressure, higher total vascular resistance (TVR) and higher uterine resistance index compared to normotensive patients. Therefore, the use of maternal cardiac function evaluation in women presenting with an abnormal uterine Doppler resistance index in the second trimester is recommended to increase the prediction of hypertensive disorders of pregnancy. With the scope to increase the predictive values for gestational hypertension of ultrasound evaluation, Valensise *et al*[36] carried out echocardiography in 36 women with uterine Doppler abnormalities (bilateral notch and RI > 0.58)

at 24 wk gestation, showing a normal ventricular left isovolumic relaxation time (IVRT) in the normotensive women group, evidence of adequate diastolic function; while in patients with pathological outcomes, an elevated IVRT, meaning cardiac diastolic dysfunction and an altered ventricular geometric pattern was found, evidence of abnormal cardiac adaptation to pregnancy. Therefore, he proposed the association of data from maternal cardiovascular adaptation with uterine artery screening to reduce the number of false-positive diagnoses of pathological pregnancy.

In a subsequent study[37], the same research group evaluated the predictive value for maternal and fetal complications of TVR and left ventricular morphology in normotensive high risk primigravidas with a bilateral notch of uterine artery at 24 wk. They reported that the increase of TVR above the cut-off had a sensitivity at 89%, specificity at 94%, PPV at 77% and negative predictive value at 97%. Considering the importance of the assessment of the cardiac function in pregnancy, another study[34] was conducted to evaluate the significance of myocardial function associated with abnormal uterine Doppler velocimetry in women with hypertensive complications and in normal pregnancy. The results showed that in pregnancy with abnormal uterine artery Doppler and complicated outcomes, the myocardial function is impaired prior to the development of complications and remains depressed 6 mo postpartum; in women with normal uterine artery and normal pregnancy, the myocardial function was unchanged compared to the postpartum; in patients with bilateral notching and a normal outcome of pregnancy, an enhanced myocardial function is reported and the authors hypothesize that it is a crucial mechanism to maintain normal hemodynamic parameters.

Echocardiographic parameters of cardiac performance during pregnancy could be an important predictor of pregnancy complications and a predisposition to cardiovascular disease in normotensive women.

Genetic assessment

Preeclampsia is a complex multisystem and multifactorial disorder with an unclear genetic component. However, it can be hypothesized that well known etiological factors may have a genetic implication[38]. In the past, it has been suggested that Mendelian or mitochondrial gene transmission could be a cause of preeclampsia; however, studies conducted on monozygotic twins did not confirm this hypothesis. Fetal genotype was also investigated without demonstrating a clear role in determining an increased risk of preeclampsia[38].

Not only the genotype but also the m-RNA expression of specific genes seems to be associated with the development of preeclampsia[38]. Indeed, Rajakumar *et al*[39] identified 368 genes differentially expressed in preeclamptic women and normotensive patients in a recent study analyzing leukocyte gene expression. Particularly, he observed that this different expression concerns genes that play a central role in functions, such as cell proliferation, inflammation, apoptosis, immune function and angiogenesis that are involved in the pathogenesis of preeclampsia.

Therefore, it appears that preeclampsia is a complex multifactorial and multigenic disease.

In a systematic review, Mütze *et al*[38] reported more than 50 candidate genes as predisposing factors for preeclampsia but only a few genes account for about 70% of research.

Evaluating the current state of the literature regarding the role of gene polymorphisms in preeclampsia, we distinguish different genes on the basis of their pathophysiological role in this disease: endothelial dysfunction, oxidative stress and placental thrombosis.

Genes involved in endothelial dysfunction: Different genes were identified in endothelial remodeling and their polymorphisms have been associated with endothelial dysfunction, although with controversial results.

For example, it is well known that endothelin-1 (ET-1) is an important vasoconstrictor produced by endothelial and smooth muscle cells and that endothelial-1 converting enzyme (ECE-1) is connected with ET-1 concentration. However, one study examined the role of polymorphism Lys198As in the ET-1 in preeclamptic women but found no significant association[40]. Another recent study[41] evaluated the polymorphism Lys198Asn of ET-1 and Thr34IIe of ECE-1 and no statistically significant differences in polymorphic frequencies between hypertensive pregnant women and the control group were found. Moreover, the gene encoding for endothelin-1 receptor was investigated but the polymorphism considered (231G>A) was not found to be related to the risk of preeclampsia[42].

Genes encoding for information regarding blood pressure, hemodynamic changes and vascular remodelling as gene components of the renin-angiotensin systems have been investigated to evaluate the presence of polymorphism candidates for involvement in preeclampsia.

The polymorphism in intron 16 (insertion/deletion) of angiotensin converting-enzyme (*ACE* gene) is associated with changes in ACE activity. A large study by Serrano *et al*[43] in 665 preeclamptic women and 1046 controls did not find a significant association of a deletion form with preeclampsia. Li *et al*[44] investigated polymorphism of the *ACE* gene and the polymorphism A1166C of angiotensin Ⅱ receptor type 1 gene (*AT1R*) in a Chinese population. He found no significant differences in the frequency of genotypes of the *ACE* gene and *AT1R* gene in preeclampsia and normal pregnancy; however, preeclamptic women carrying the deletion form are more susceptible to developing renal dysfunction.

Another recent study investigated the association of both polymorphisms with the risk of preeclampsia[45] and showed that the polymorphisms of the renin angiotensin system could be associated with elevated oxidative stress involved in preeclampsia development. Although is well known that the renin angiotensin system contributes to fetoplacental blood flow regulation, there are still no conclusive studies regarding the association of genetic polymorphisms of this system and preeclampsia.

Nitric oxide is an important regulator of vasodilatation and vascular remodeling and its production by nitric oxide synthase (eNOS) is known to be decreased in preeclampsia.

Häkli *et al*[46] evaluated the polymorphism Glu298Asp of *eNOS* gene in 132 preeclamptic women and 113 controls and found a similar distribution in both populations. A systematic review[38] on genes and preeclampsia regarding the eNOS E298D polymorphism concludes that this polymorphism does not seem to be related to a significantly increased risk of preeclampsia.

The production of vasoactive substances regulating the vascular tone is mediated by estrogen receptors α and β (ER α/β). Polymorphisms for these receptors have been reported to be associated with vascular disorders and the pathogenesis of hypertension[47]. Maruyama *et al*[47] found a similar distribution of polymorphisms in preeclamptic women and the control group when considering the relationship between four SNPs (single nucleotide polymorphisms) in ER β and preeclampsia. Another study[48] investigated two polymorphisms of the *ER α* gene (c.454 -397T>C and c.454 -351A>G) in 119 women with severe preeclampsia and 103 normotensive women and found no association between severe preeclampsia and single gene polymorphism; however, the presence of both polymorphisms (TT/AA genotypes) was significantly more frequent in severe preeclamptic patients than in the normotensive population. However, Zhang[49] did not confirm these data in a study in a Chinese population conducted on 204 preeclamptic subjects and 236 normal women, reporting a similar distribution of combined polymorphisms of *ER α* gene in both groups.

In recent years, the attention has been focused on binding of vascular endothelial growth factor (VEGF) and PlGF and their receptor Fms-like tyrosine kinase-1 receptor (sFlt-1) that stimulates placental vasculogenesis and angiogenesis; this interaction leads to decreased circulating levels of PlGF and in preeclamptic women an increase in sFtl-1 and a corresponding decrease in PlGF is observed. A recent meta-analysis[50] of 11 case-control studies analyzing 1069 preeclamptic women and 1315 normal pregnancies concluded that VEGF polymorphisms +936C/T and -634G/C were associated with preeclampsia and there was no evidence of the association between them. Only one study, to the best of our knowledge, has been published regarding the polymorphisms in Flt-1 receptor, based on the observation that a misregulation of Flt-1 results in over-expression of sFlt-1, and could contribute to pathophysiology of preeclampsia. Kim *et al*[51] did not find a significant difference in frequencies of the dinucleotide repeat polymorphism in preeclamptic women and the normotensive group.

Genes implicated in oxidative stress: It has been reported that oxidative stress plays an important role in the etiology of preeclampsia. Indeed, in an imbalance between reactive oxygen species (ROS) production and antioxidant defence, placental oxidative stress may stimulate syncytiotrophoblast apoptosis resulting in impaired placental function characteristic of preeclampsia[52].

In recent years, the expression of *OLR1* gene encoding for LOX-1 receptor (low-density lipoprotein oxidized) has been investigated in preeclamptic women. Indeed, LOX-1, extensively studied for its role in myocardial ischemia, is a powerful mediator of endothelial dysfunction through generation of superoxide, induction of chemokine expression and inhibition of nitric oxide production leading to cell apoptosis[53]. An immunohistochemical study in preeclamptic placentas showed LOX-1 positive specimens in syncytiotrophoblasts significantly upregulated compared with normal placentas, confirming the elevated apoptotic activity of syncytiotrophoblasts in preeclampsia[53].

The Western blot examination of OLR-1 expression in syncytiotrophoblasts had a higher expression in cases of preeclampsia and other pregnancy diseases[54]. OLR1 is the main scavenger receptor responsible for up-take of LDL-ox within placental cells. The high level of OLR1 expression is evidence of enhanced oxidative stress in preeclamptic placentas, in agreement with previous observations of elevated levels of serum lipid peroxides in preeclampsia[55,56].

Polymorphisms in genes involved in the production of ROS or in the metabolism of these reactive species can also lead to placental dysfunction.

Among anti-oxidant systems, an important role is played by placental glutathione S-transferase (GST) which contributes to placental detoxification. Zusterzeel *et al*[57] reported that homozygous genotype GST 1b/1b was significantly more represented in preeclamptic women than in normotensive controls (OR = 3.4), which could result in a lower detoxification capacity.

Conversely, Kim *et al*[58] showed that *GST* gene polymorphisms, as well as polymorphisms in the oxidative stress related genes, do not seem to be factors of susceptibility to preeclampsia in their study of 214 normotensive pregnant women and 121 preeclamptic patients.

Cytochrome P4501A1 (CYP1A1) was also related to preeclampsia; however, no study demonstrated the association between the single CYP4501A1 and preeclampsia[58].

Although single polymorphism does not seem to increase susceptibility to gestational hypertensive disorders, Zusterzeel *et al*[59] described a significant association between higher ROS production or a lower detoxification pattern and preeclampsia development when studying the simultaneous occurrence of severe genetic polymorphisms (GST, epoxide hydrolase and CYP1A1) in women developing preeclampsia.

Polymorphisms of the gene encoding for superoxide dismutase (SOD) were also investigated, with SOD acting as a cell protector from superoxide radicals. Kim *et al*[58] reported no association between gene polymorphisms and susceptibility for preeclampsia. More recently, two missense polymorphisms of extracellular SOD (Arg-213Gly and Ala40Thr) were investigated in 114 normotensive women and 159 preeclamptic patients and no significant differences were found, but it has been demonstrated that women carrying these polymorphisms do

Table 2 Biochemical markers predicting preeclampsia

Markers	Ref.	Age of testing	Sensitivity	Specificity
hCG	Jauniaux *et al*[73]	2nd trimester	72.7%	90%
	Merviel *et al*[74]	2nd trimester	54.5%	93.5%
Inhibin A	Spencer *et al*[75]	1st or 2nd trimester	68%	95%
	Florio *et al*[76]	2nd trimester	38.9%	92.5%
PP-13	Nicholaides *et al*[77]	1st trimester	90%	90%
AFP	Jauniaux *et al*[73]	2nd trimester	72.7%	70%
	Kuo *et al*[78]	2nd trimester	61.5%	47.3%
Activin A	Florio *et al*[76]	2nd trimester	61.1%	77.5%
	Spencer *et al*[75]	2nd trimester	63%	95%
PAPP-A	Poon *et al*[79]	1st trimester	20.5%	95%
	Spencer *et al*[80]	1st trimester	62.1%	95%

hCG: Human chorionic gonadotrophin; PP-13: Placental protein-13; AFP: α-fetoprotein; PAPP-A: Pregnancy-associated plasma protein A.

present with a higher risk of severe preeclampsia complicated by FGR[60]. Another recent study[61] in Romanian women described that the genotype Val/Val was significantly associated with preeclampsia and a more clinically severe disease.

Inherited thrombophilias: The observation that women developing preeclampsia subsequently have a higher risk of thromboembolism has often suggested the existence of a correlation between inherited thrombophilias and preeclampsia[62,63]. The occurrence of villous thrombosis is also considered an important mechanism in the pathogenesis of preeclampsia. The condition of inherited thrombophilias is generated by specific polymorphisms in genes encoding for specific coagulation factors. These polymorphisms include factor V Leiden mutation (G1691G>A mutation Factor V), methylenetetrahydrofolate reductase (MTHFR) (MTHFR 677C>T), the prothrombin mutation (G20210G>A) and the plasminogen activator inhibitor-1 mutant genotype (PAI-1 4G/4G>5G/5G).

In 1995, Dekker *et al*[64] described an association between inherited thrombophilias and severe preeclampsia. Since then, many studies have followed on the role of thrombophilic mutations in gestational hypertensive disorders, with contradictory results. In a 2005 review, Calderwood *et al*[65] report inconclusive results due to the absence of large scale, randomised controlled studies. However, he did underline a feasible association between placental troubles and factor V Leiden. A large meta-analysis by Kosmas *et al*[66] with almost 3000 women focused on factor V Leiden reports an odds ratio of 2.3, showing the important role of this polymorphism as a risk factor for preeclampsia. The same author reports[67] a moderately increased risk of preeclampsia in carriers of heterozygous and homozygous mutation of MTHFR 667 (OR = 1.3). However, a subsequent review by Pabinger[68] of several interesting studies reports no association between factor V Leiden and prothrombin mutation (G20210G>A) compared to hypertensive gestational disorders.

Our study group analyzed a link between inherited thrombophilias and preeclampsia with preeclamptic and normal pregnant women and no evidence of an association between preeclampsia and factor V Leiden or prothrombin gene mutation[69] was found. Given the low PPV of a single thrombophilia in the detection of preeclamptic risk, we conducted another study considering the association of double inherited thrombophilias and risk of adverse pregnancy outcomes. We found a slight but significant association between the combination of MTHFR C677T with Factor Ⅷ and the combination of factor Ⅱ and factor V mutations and the occurrence of abruptio placentae; however, we did not find an increased incidence of adverse pregnancy outcomes in subjects with a combination of MTHFR C677T and factor V Leiden or in patients with the simultaneous presence of factor Ⅱ mutation and PAI-1 (G5/G5)[70].

A recent review[71] of preeclampsia and inherited thrombophilias reports that mild preeclampsia is unlikely to be associated with thrombophilias, but severe and early onset preeclampsia seems to be significantly related to inherited thrombophilias, and preeclamptic patients carrying gene mutations are at greater risk of developing more severe forms and sequelae.

In agreement with these findings, our study group highlighted that in preeclamptic patients with inherited thrombophilias, a more severe involvement of kidneys and a more severe damage in the course of hypertensive gestational disease might occur[72].

It is therefore clear that there are contradictory results regarding the association between thrombophilic gene mutations and preeclampsia and there are no consistent data to suggest mandatory thrombophilic screening as predictive of preeclampsia.

New biochemical markers

In obstetrical practice, a long-term objective is to identify ideal maternal biomarkers for preeclampsia but it is very difficult because the "ideal marker" requires the coexistence of different characteristics: noninvasiveness, high sensitivity and specificity and a high PPV to predict disease prognosis. We currently have a plethora of studies intended to identify an ideal biomarker; however, differences in the studied populations, the methodologies and the interpretation of results make it difficult to perform a systematic analysis of all the markers (Table 2). Therefore, in this review we only consider markers that have been proposed more recently as potential new biomarkers.

Research of these new emerging biomarkers arises from the new model of pathogenesis of preeclampsia which focuses on the angiogenesis process rather than the vasoconstrictive phenomenon[81].

VEGF and PlGF are among the proangiogenic factors, soluble endoglin (sEng) and soluble fms-like tyrosine kinase 1 receptor(sFlt-1) are among the antiangiogenic factors.

Cells expressing VEGF are located near fenestrated endothelia and the inhibition of VEGF leads to pathological conditions in many organs with fenestrated endothelia (*e.g.*, liver, kidney, choroid plexus, *etc.*), as observed in se-

vere preeclampsia. PlGF is expressed mainly by placental cells and its levels increase from the second to third trimester. Both VEGF and PlGF bind to the VEGF receptor family, named Flt-1 and kinase insert domain receptor (KDR). PlGF binds more actively to Flt-1, while VEGF binds to KDR. It has been suggested that sFlt-1 acts to modulate VEGF availability[82].

This evidence confirms the antiangiogenic role of soluble form of VEGF-PlGF receptor sFlt-1.

sFlt-1 binds these angiogenic factors and inhibits their vasodilatory effect. The other antiangiogenic factor is sEng. In animal studies, it allows the formation of the endothelial tube, increases capillary permeability and could be responsible for hypertension, nephrotic syndrome and liver dysfunction during preeclampsia[83].

A recent review reported significant changes in the levels of sFlt-1, PlGF and sEng in preeclamptic patients with a different time course, the earliest in the first trimester for PlGF and later for sFlt-1 and sEng.

Levine *et al*[84,85], in two studies from 2004 and 2006, demonstrated that levels of sFlt-1 increased 5 wk before the onset of clinical disease and parallel levels of PlGF and VEGF decreased due to the binding by sFlt-1, while the levels of sEng increased 2-3 mo before clinical disease.

More recently, the level of PIGF has been evaluated in pregnancy complicated by hypertension disease[86] and it has been found that a positive PIGF test can predict delivery before 37 wk in over 90% of pregnant women with hypertensive disease. Therefore, a low level of PIGF could be used before 35 wk in hypertensive women to evaluate the risk of pregnancy complications. sEng level also seems to be prognostic and its level appears to be correlated with severe preeclampsia or eclampsia[87]. Despite this evidence, there are no conclusive data yet on their diagnostic capability, the cut-off of normality and the time or strategy to measure these markers.

Regarding diagnostic capability, a recent extensive study conducted on 2200 patients with PlGF and sFlt-1 in the first trimester found a sensitivity of 55% and 57% respectively and a specificity of 43% and 40% respectively[88]; this result does not improve later in pregnancy. It is evident that the predictive positive value is too low to use this marker in the first trimester for screening for preeclampsia. Other strategies in measuring angiogenic factors have been proposed: a longitudinal evaluation and a ratio between two factors.

Indeed, an increase from first to second trimester of sFlt-1, sEng and PlGF[89] has been demonstrated in preeclamptic women. On the other hand, several studies have proposed a ratio between sFlt-1 and PlGF (sFlt-1: PlGF)[90] and between PlGF and sEng (PlGF:sEng)[91] based on the observation that levels of PlGF and sFlt-1 are altered together in preeclampsia, reporting an important improvement in sensitivity (88.5% and 100% respectively) and specificity (88.5% and 98% respectively). Despite these promising results, larger studies are needed to confirm these finding.

Our brief review of the possibility of early screening for preeclampsia analyzed the most recent literature and highlighted the lack of a single certified method able to predict the risk. However, despite the complexity of clinical and pathophysiological behavior of preeclampsia, it is possible that in the future the combination of several tests will allow us to predict women at risk of preeclampsia.

One point needs to be underlined: we started from ultrasonic evaluations (uterine arteries Doppler US) and in a relatively short period we arrived at a supersonic era in which more promising and accurate tests seem to come from the laboratory.

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