Curr Hypertens Rep (2015) 17:74
DOI 10.1007/s11906-015-0584-7

PREECLAMPSIA (VD GAROVIC, SECTION EDITOR)

First Trimester Prediction of Preeclampsia

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Abstract Preeclampsia (PE) is a serious pregnancy-related condition that causes severe maternal and fetal morbidity and mortality. Within the recent years, there has been an increasing focus in predicting PE at the end of the first trimester of pregnancy. In this review, literature published between 2011 and 2015 was evaluated. In a total of six biomarker algorithms, for first and early second trimester, the prediction of preeclampsia is discussed. In addition, one randomized clinical trial was included. Several algorithms were based on placental biomarkers such as pregnancy-associated plasma protein A (PAPP-A), placental growth factor (PLGF), and soluble FMS-like tyrosine kinase 1 (s-FLT-1). The algorithms containing these biomarkers showed a high prediction rate (PR) for early onset PE, ranging from 44 to 92 % at 5 % false positive rate (FPR). New biomarkers suggest an alternative model based on free HbF and the heme scavenger alpha-1-microglobulin (A1M) with a prediction rate of 69 % at an FPR of 5 %. Interestingly, this model performs well without uterine artery Doppler pulsatility index (UtAD-PI), which is an advantage particularly if the screening method were to be implemented in developing countries. The randomized clinical trial showed a clear reduction in early onset PE as well as reducing preterm PE if identified high-risk pregnancies were treated with low-dose aspirin. In conclusion, PE prediction is now possible through several prediction algorithms and prophylaxis is beneficial in high-risk cases.

Keywords Prediction · Preeclampsia · HbF · A1M · PAPP-A · PlGF · Low-dose aspirin · Prophylaxis

This article is part of the Topical Collection on *Preeclampsia*

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Introduction

Preeclampsia (PE) is still a major obstetrical problem worldwide. It is one of three major factors causing maternal and fetal morbidity and mortality, and at the same time being one of the most important factors responsible for preterm birth [1, 2]. Especially in developing countries, there is a high incidence of maternal/fetal mortality that can be attributed to this condition [3]. Currently, there is no treatment for PE other than delivery. Furthermore, the lack of specific predictive and diagnostic tools makes clinical handling of the disease a global maternal health problem with many unmet clinical needs. PE is a syndrome of pregnancy defined by its clinical manifestations, proteinuria, and hypertension [4].

The etiology of PE is still not fully understood, but the condition is generally described as a two-stage syndrome [5]. The first stage begins in the first trimester by impaired placentation that leads to shallow trophoblast invasion of the maternal decidua and spiral arteries, resulting in insufficient remodeling of the smooth muscle wall of the arteries and consequently, inadequate perfusion of the placenta [6]. It has been suggested that maternal inflammatory cells, such as natural killer cells (NK cells) and maternal T-cells, may prevent invasion of the extravillous trophoblast cells (EVTs) if they fail to recognize paternal antigens presented by the EVTs [7, 8].

Published online: 02 August 2015

In placental PE, the uneven perfusion of the placenta leads to oxidative stress and endoplasmatic reticulum stress. The narrow vessels create higher velocity blood flow into the intravillous space leading to mechanical stress as well [6, 9]. The placenta is damaged by these stressors, which cause release of placental debris into the maternal circulation, where they induce inflammation and endothelial damage with varying degrees of organ failure. In stage two, the organ failures manifest clinically by different vague symptoms [6].

Well-described factors involved in PE are the angiogenic and anti-angiogenic factors alongside with the important inflammatory components [10, 11]. Recently, it has been suggested that oxidative stress in the placenta could lead to dysfunctional placental hematopoiesis [9]. In a gene profiling study, it was shown that genes coding for fetal hemoglobin (HbF) were significantly upregulated in women with PE [12]. Cell-free HbF was shown to be accumulated within the placental capillaries and eventually transferred to the maternal circulation [12, 13]. In fact, increased cell-free HbF levels can be detected as early as the first trimester in pregnancies later complicated by PE. Furthermore, in term pregnancy, the HbF levels correlated with the severity of the disease, i.e., blood pressure levels [14–16].

Many pathophysiological events occur in early pregnancy but the clinical manifestations occur later. In fact, the definitions of PE are defined by the clinical manifestations, new onset hypertension and proteinuria presenting after 20 weeks of gestation [4]. There has been an increasing tendency of sub-classification according to other clinical manifestations. A common sub-classification is based on when in pregnancy, the maternal symptoms present, early- and late-onset PE (ePE and lPE). Early onset PE is usually defined as PE leading to delivery of the baby before 34+0 weeks of gestation and late onset PE as PE leading to the delivery after 34+0 weeks of gestation. Other authors choose to focus on preterm vs. term PE and a few studies even combine the two and classify into early (before 34+0), intermediate (between 34+0 and 36+6 weeks of gestation) and late PE (37+0 or later) [17]. A third group of authors choose to subgroup into preterm PE (leading to delivery before 37+0 weeks of gestation) vs. term PE (delivery after 37+0 weeks of gestation) [18, 19]. In general, early onset PE shows more placental pathology whereas the late onset cases depend on maternal constitutional factors. However, in most PE cases both placental and maternal factors are involved in the development of PE.

The maternal constitutional factors important for PE are obesity, diabetes, coagulation-disorders, and other chronic diseases such as kidney diseases and rheumatologic diseases (rheumatoid arthritis, systemic lupus erythematousus, etc.) [20]. Recently, maternal cardiovascular dysfunction has also been in focus as a possible risk factor that may play an important role in the development of PE, both preterm and term PE [21, 22].

Currently, there is no worldwide consensus for classification of PE. A major change has been implemented regarding how to define severe PE [23•, 24•]. This is partially due to reported inaccuracies in measurement of proteinuria [25]. In 2013, the American Conference of Obstetricians and Gynecologists (ACOG) revised their definition of severe PE in which proteinuria was not a necessity for the definition of PE. High-blood pressure (≥160/110) could be considered PE in the absence of proteinuria if it was combined with certain biomarkers or clinical signs such as thrombocytopenia (thrombocytes<100,000/ microliter), impaired liver function (liver enzymes>twice normal range), impaired kidney function (creatinine >80 μmol/l), pulmonary edema, or new cerebral or visual disturbances [24•].

In 2014, ISSHP released their newest definitions for PE [23•]. In this statement, PE could in the abcense of proteinuria be diagnosed as *de novo* hypertension in co-existence with 'other maternal organ dysfunctions' such as renal insufficiency (creatinine≥90 μmol/l), liver involvement (elevated transaminases>twice normal range), neurological complications (eclampsia, altered mental status, hyper-reflexia with foot clonus), and severe headache or hematological complications (thrombocytopenia or hemolysis). Given these differences in definitions for PE, it is clear that there is an urgent need for specific, sensitive biomarkers and objective definitions of PE. New technology allows for identification of new biomarkers, and thereby, a better understanding of the etiology.

First trimester prediction of PE is of great clinical importance, as it would allow clinicians to focus on high-risk groups and initiate prophylactic medical treatment. Health economists have calculated that it would be economically beneficial to screen for PE as long as there is an effective intervention method available [26]. Currently, several biomarkers with predictive potential for PE have been described but are not yet in use clinically.

Following the introduction of aneuploidy screening, there has been an increased interest in prediction algorithms that could be used in combination with aneuploidy screening taking place in the first trimester [27]. A new approach to maternity care has been introduced by the so-called 'pyramid of prenatal care' turned upside down. Instead of increasing the number of antenatal visits at the maternal care unit during pregnancy, this strategy advises a general screening at 11–13+6 weeks of gestation in order to identify high-risk groups and initiate prophylactic strategies [28]. This approach may lead to fewer PE cases and less unnecessary visits for low-risk pregnancies.

Here, we review first trimester screening algorithms published between 2011 and 2015 and the biomarkers used in combination with other screening methods to create predictive

algorithms that have great potential for identifying women at high risk of developing PE.

Methods

Literature in the PubMed database was searched using the terms 'prediction' and 'preeclampsia'. Prediction algorithms that included one or more biochemical markers, in combination with maternal characteristics, and one or more biophysical markers were chosen. Only original articles published between 2011 and 2015 were included. Articles lacking Prediction Rates (PR) (for example, articles that only presented odds ratios or likewise) were excluded. Older literature, published before 2011, was used as background material to present the syndrome of PE and the relevant biomarkers.

Results

In total, seven articles met the inclusion criteria; six case cohort studies and one randomized clinical trial.

Maternal Characteristics

Maternal characteristics, such as age (<20 years or >40 years), primiparity, ethnical background, twin pregnancies, chronic diseases, are all known risk factors for PE [20]. Several prediction models have been developed based on maternal risk factors alone, and in general, they have a PR for all PE subtypes of about 30 %, at a False Positive Rate (FPR) of 5 %. The PR is somewhat better for ePE [17].

Biochemical Markers

Pregnancy associated plasma protein A (PAPP-A) is a glycoprotein primarily synthesized in the placenta. It has been studied as a biomarker for placental function for almost three decades [29]. PAPP-A is well established as a predictive first trimester marker in aneuploidy screening (trisomy 13, 18, and 21) where it is combined with human chorionic gonadotropin (hCG) and neck-translucency ultrasound [30]. The function of PAPP-A is not completely clear, but it is suggested to be important for placental development. In fetuses with normal chromosome number, low levels of PAPP-A have been associated with the development of PE, intrauterine growth restriction (IUGR), placental abruption and stillbirth [31, 32]. As a single biomarker for PE, PAPP-A only predicts 22 % of the ePE cases in the first trimester of pregnancy at an FPR of 5 %. When combined with Doppler ultrasound uterine artery measurements, the predictive capacity for ePE increases, reaching PR 62.5 % at 5 % FPR; but still, it only predicts 32 % of all PE at 5 % FPR [33].

The angiogenic/anti-angiogenic factor imbalance is suggested to be important for the progression from stage one to stage two of PE [10]. Attempts to re-define PE by using these biomarkers have been published [34, 35]. Briefly, the predictive strategy is based on the well-established findings that the stressed placenta is producing increased amounts of the anti-angiogenic factor soluble FMS-like tyrosine kinase 1 (sFLT-1) that binds the pro-angiogenic factors in the maternal circulation (mainly vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). This leads to decreased angiogenic stimulation of the endothelium and consequently to endotheliosis [36, 37]. Endotheliosis is also present in the kidneys, which leads to glomerular endotheliosis, podocyte injury and eventually proteinuria, hallmarks of PE [38].

The placental growth factor PlGF has been shown to be lower in PE as early as 11–13+6 weeks of gestation and has therefore been included in several prediction algorithms. In contrast, sFLT-1 has not been shown to have any clinical value as a biomarker for PE in early pregnancy. However, sFlt-1 is significantly elevated in the second trimester and therefore suggested as a diagnostic biomarker [39]. As a single biomarker, PlGF has a PR of 47 % at a 5 % FPR [17]. Today, PlGF is used as part of several larger prediction algorithms where it has been shown to increase the overall prediction rate as listed below (Table 1) [18, 19, 40, 41].

The increased production of cell-free HbF in PE placentas has been suggested as an etiological factor [9]. Furthermore, HbF has been studied as a predictive biomarker for PE in combination with the heme scavenger α_1-microglobulin (A1M) [16]. In a cohort of 96 high-risk patients, serum collected at 10–16 weeks of gestation showed significantly higher concentrations of HbF and A1M in patients that subsequently developed PE [16]. A logistic regression analysis revealed a PR of 69 % at 5 % FPR [16].

Most predictive biomarkers are measured in plasma or serum. Currently, there are no urine markers for prediction of PE in the first trimester. In the second trimester however, the determination of cultured podocyte fragments has been shown to have a high predictive value for PE [42].

Biophysical Markers

Mean arterial pressure (MAP) is defined as the average arterial pressure during one cardiac cycle [43] and can easily be measured with standardized blood pressure gauges. MAP has been shown to be significantly elevated as early as the end of first trimester in patients who subsequently develop PE and therefore, incorporated into many prediction algorithms in order to increase the prediction rate [43]. The increased MAP in patients who subsequently develop PE is probably caused by reduced elasticity of the maternal arteries combined with increased vasoconstriction [43].

Table 1 Prediction algorithms shown with prediction rates and false positive rates

Author/journal/ year	Cohort	Markers	Prediction rate /FPR
Kenny L et al.	Low risk cohort	PlGF	All PE, 17–22 %*
Hypertension	5,690 patients	MAP	ePE, 44–67 %**
2014 [19]	278 PE	Maternal characteristics	tPE, 6–19 %**
	14–16 weeks	UtAD RI	FPR, 5 %
Skråstad RB et al.	Nulliparous	FMF model:	All PE, 40 %
BJOG	women		Preterm PE, 80 %
2014 [40]	541 patients		
		Predictor model:	All PE, 30 %
	11 + 0–13 + 6 weeks		FPR, 10 %
Crovetto et al.	Low-risk cohort	Maternal characteristics	ePE, 87.7 %
Prenatal diagnosis	9,462 patients		
2015 [41]	303 PE	MAP	lPE, 68.3 %
		UtAD PI	
	Plasma sampling 8–11 weeks	PlGF	FPR, 5 %
	UtAD 11–13 + 6 weeks	sFlt-1	
Akolekar et al.	Low-risk cohort	Maternal characteristics	All PE, 38 %
Fetal diagnosis and Therapy	58,884 patients		
2013 [18]	1,426 PE	MAP	ePE, 93 %
		UtAD PI	
	11 + 0–13 + 6 weeks	PlGF	ptPE, 61 %
	weeks	PAPP-A	
			FPR, 5 %
Parra-Cordero et al.	Not normal cohort	Maternal characteristics	ePE, 47 %
Ultrasound in Obstetrics and Gynecology	359 patients	UtAD PI	lPE, 29 %
	70 PE	PlGF	
2013 [42]			FPR, 10 %
	11+0–13+6 weeks weeks		
Anderson et al.	Not normal cohort	HbF	All PE, 69 %
American Journal of Obstetrics and Gynecology	96 patients	A1M	
2011 [16]	60 PE		FPR, 5 %

ePE = early onset PE (≤34 + 0 weeks), l*PE* = late onset PE (>34 + 0 weeks), *ptPE* = preterm PE (<37 + 0 weeks), *tPE* = term PE (≥37 + 0 weeks

*Training cohort and validation cohort

**Slightly different prediction models than for all PE

Doppler Ultrasound

Almost all first and second trimester prediction algorithms include uterine artery Doppler ultrasound (UtAD) measured as either pulsatility index (PI) or resistive index (RI). Furthermore, diastolic notching is used as a sign of increased vascular resistance and reduced vascular elasticity. A high first trimester PI is however, reversible and can appear at the end of first trimester in pregnant women with a normal placentation [44]. Therefore, first and early second trimester UtAD have relatively low positive

predictive value (approximately 21 % of PE cases) [44]. In contrast, a normal PI by the end of first trimester is highly predictive for a normal placentation as these women have less than 1 % risk of subsequent development of PE and therefore, a high negative predictive value [44]. Several studies have been published listing reference values for PI by the end of first and second trimester [45, 46]. Based on these publications, it has been concluded that Doppler ultrasound should not be used alone as a first trimester prediction method for PE but may be valuable as part of other predictive algorithms that also include plasma biomarkers.

Prediction Algorithms

During the last 4 years, research on biomarkers has been predominately focused on prediction algorithms that combine maternal characteristics with one or more biophysical markers (mainly Doppler ultrasound and MAP) and several plasma/serum-biochemical markers. The best performing algorithms are listed in Table 1 and described in detail below.

Although the algorithms are similar with regards to included parameters, the prediction rates differ between the studies [18, 19, 40, 41, 47]. Kenny et al. evaluated several serum markers in a low risk cohort containing 5,690 patients, part of the SCOPE study [19]. A prediction model was suggested containing maternal characteristics, MAP, UtAD-RI, and PlGF, with small variations in maternal characteristics for subgroups like ePE and term PE (PE that leads to delivery after 37+0 weeks of gestation). The results showed 44 % PR in the validation cohort and 67 % in the test cohort for ePE at a fixed FPR of 5 %.

Akolekar et al. published a large prediction algorithm in which they studied 58,884 low risk patients at 11+0–13+6 weeks of gestation [18]. The model included maternal characteristics, MAP, UtAD PI, PAPP-A and PlGF. The PR was 93 % for ePE and 38 % for all PE at a fixed FPR of 5 %. This model showed the strongest predictive capacity for ePE, i.e. PE with strong placenta pathology, but less efficient in predicting term PE, confirming their previous results [17, 33, 48].

Crovetto et al. used the antiangiogenic protein sFlt-1 instead of PAPP-A in an otherwise identical model to the one presented by Akolekar et al. [40]. In a cohort of 9,462 patients, plasma was collected at 8–11 weeks of gestation and UtAD measured at 11+0–13+6 weeks of gestation, the PR was 88 % for ePE and 68 % for late PE at FPR 5 %. The model has similar PR as the one described by Akolekar et al. described, regarding ePE.

In most cases, sFlt-1 is not used in early pregnancy since several studies have shown that sFlt-1 levels do not rise until later in the second trimester in the patients who subsequently develop PE [39]. This is, however, a matter of debate as other studies have shown increased levels of sFlt-1 as early as the beginning of the second trimester of pregnancy [40].

Parra-Cordero et al. presented a prediction model with PlGF as the only biomarker combined with maternal characteristics and UtAD PI [41]. In general, they found lower prediction rates compared to the other models, 47 % for ePE and 29 % for lPE, at a fixed FPR of 10 %.

Our own data suggests an alternative model based on a different set of biomarkers [16]. By only using free HbF and the heme scavenger A1M, a prediction rate of 69 % at an FPR of 5 % was described [16]. Interestingly, the hemoglobin model performs well without UtAD PI, which is an advantage particularly if the screening method were to be implemented in developing countries.

Randomized Clinical Trials

Only one randomized clinical trial has been published that combines biomarker-screening for PE with prophylactic interventions using low-dose aspirin [49•]. The aim of the study was to analyze the benefit of low-dose aspirin treatment in patients with singleton pregnancies identified as high risk for PE. The prediction model was based on the Fetal Medicine Foundation (FMF) prediction algorithm, including maternal characteristics, MAP, Uterine Artery Doppler (UtAD) and PAPP-A [48, 50]. In total, 5,783 patients were included in the study, of which 3,066 were used to validate the prediction model in an observational cohort [50]. The remaining 2,717 patients were included in the intervention cohort. Women identified as high risk by the prediction model were treated with 150 mg aspirin daily starting directly after screening until 34+0 weeks of gestation. The results from the observational cohort showed a PR of 92 % of ePE with 8 % FPR. This was in full concordance with previously published cohorts [48]. The study also revealed a significant risk-reducing effect of low-dose aspirin in the intervention group, both for ePE and preterm PE (PE before 37+0 weeks of gestation). They were able to significantly reduce the risk of ePE from 0.4 % in the observational cohort to 0.04 % in the intervention cohort. The number-needed-to-treat (NNT) to prevent one case of ePE in the intervention group was 29 [49•]. The intervention strategy also statistically significant reduced the overall need to deliver before 37+0 weeks of gestation, from 0.83 % in the observational cohort, to 0.37 in the intervention cohort (p=0.03)[49•].

Discussion

Several of the studied prediction algorithms contained similar components, biochemical markers, maternal characteristics and biophysical markers (UtAD and MAP). Generally, most of the models predict ePE very well (up to 93 %) and lPE or term PE at a much lower rate. Currently, none of the described models are implemented into general clinical practice due to their low sensitivity and specificity. The World Health Organization (WHO) has defined a set of criteria that should be fulfilled for an ideal screening using biomarkers in a clinical setting [51]. These criteria can be condensed as follows: The biomarker should (1) represent the pathogenesis behind the condition and be specific

for the disorder, (2) appear before the onset of clinical disease, (3) be easy and cheap to measure in blood or urine, (4) display a high sensitivity and specificity for the condition, (5) correlate with severity of the disease, and (6) not be detectable or measured at very low levels in the normal condition. Ideally, an effective intervention should also be available for those at risk.

Few of the described algorithms meet all the criteria stipulated by WHO. For example, none of the models are specific for PE as they also predict IUGR to a certain extent and PAPP-A is normally used for aneuploidy screening. All algorithms do, however, reflect the pathogenesis of placental insufficiency and therefore meet criterion 1. Furthermore, these are all first trimester screening algorithms and therefore appear before the clinical manifestations according to criterion 2. Most algorithms are based on biomarkers that are measured with standard laboratory methodology but are not always cheap and easy to measure. The Doppler Ultrasound scans require expensive equipment and trained personnel for adequate measurements. The models based on PAPP-A and PlGF display a high sensitivity for ePE (92 %) but much lower for lPE. The biomarker PlGF correlates with severity of the disease at the time of diagnosis fulfilling criteria 5. Neither PAPP-A nor PlGF meet criteria 6 since they both are present at high levels in the normal pregnancy.

The prediction model based on increased HbF production presents a potential alternative to the models based on PAPP-A and PlGF [16, 52•]. This model is based on free HbF and the heme-scavenger A1M measured in maternal plasma combined with maternal characteristics. Doppler ultrasound indices do not improve the algorithm, which makes the HbF model ideal for low and middle-income countries. The use of free HbF/A1M meet WHO criteria 1 as the biomarker family reflects a new etiology for the disease [9]. Secondly, the HbF/A1M levels increase as early as the first trimester, before the onset of clinical symptoms. The experimental ELISAs used are relatively cheap and do not require any advanced equipment. The model also displays a relatively high sensitivity and specificity for PE [16]. Furthermore, the maternal levels of circulating cell-free HbF correlate with the level of blood pressure and therefore the severity of the disease and in a normal pregnancy the circulating HbF levels are low or non-detectable.

Effective first trimester screening for PE would allow clinicians to reverse the order of the maternal care pyramid, allowing focus on high-risk pregnancies. Low-risk pregnancies may consequently attend a standard care program with fewer visits. This strategy would allow for more accurate intervention with prophylactic low-dose aspirin. According to Bujold et al., low-dose aspirin should be initiated before 16 weeks of gestation [53•] but a recent report from the US Preventive Services Task Force suggests prophylactic treatment with aspirin should be initiated as early as 12 weeks of gestation [54] emphasizing the need for first trimester screening.

In June 2015, the Fetal Medicine Foundation (London, UK) started the ASPRE project—a large randomized trial screening patients with a prediction model containing maternal characteristics, MAP, UtAD PI, PAPP-A, and PlGF (https://fetalmedicine.org/aspre-1). They plan to screen a large number of patients (33,680) during 2015–2016 and randomize the high-risk patients between low-dose aspirin (150 mg) and placebo. If the results of this randomized study will support the findings from the Australian randomized trial by Park et al. that PE-prediction at 11+0–13+6 and interventional treatment with aspirin highly reduce the incidence of PE, it may be a possible method for a more generalized screening for PE.

In conclusion, we present a range of potential algorithms for first- and early second trimester prediction of PE. The pathophysiology leading to PE is most likely multifactorial and, as demonstrated in this article, the models therefore need to include several biochemical (and biophysical) markers. The models based on PAPP-A and PlGF primarily predict early onset PE, which are often the most serious cases and the cases where prophylactic treatment with low-dose aspirin has the best effect. These models do not, however, predict the majority of the PE cases, lPE, very well. The model based on cell-free HbF and A1M predicts both ePE and lPE, and furthermore, it is not dependent on Doppler ultrasound. This method is, therefore in general, more useful particularly in developing countries. This model also offers an interesting potential new prophylactic strategy using heme- and/or hemoglobin-scavengers to suppress HbF-induced oxidative stress [55].

Compliance with Ethics Guidelines

Conflict of Interest Drs. Åkerström and Hansson declare grants from Swedish Medical Research Council and A1M Pharma; they are board members and stock holders of A1M Pharma, have a grant pending from Swedish Medical Research Council, and have a patent pending for diagnosis of preeclampsia. Drs. Anderson and Gram have no conflicts of interest.

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.

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