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Ana Catarina Pinho Freitas de Carvalho Pedrosa

Screening for pre-eclampsia: a systematic review of tests combining uterine artery Doppler with other markers

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Professora Doutora Alexandra Matias Pereira da Cunha Coelho de Macedo

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ABSTRACT

Aims

To perform a systematic review of screening for pre-eclampsia (PE) with the combination of uterine artery Doppler (UAD), maternal history, mean arterial pressure and/or maternal serum markers.

Methods

We identified eligible studies through a search of Medline, and, for each included study, we assessed the risk of bias and extracted relevant data. We reported the performance of screening tests according to the target population (low or high-risk), the trimester of screening (first and/or second) and the subset of PE screened for (early and late).

Results

Several tests provided moderate or convincing prediction of early PE, but screening for late PE was poor. Although UAD is more accurate in the second-trimester, we found encouraging results for first-trimester screening when it was combined with other markers. Performance of screening was consistently lower in populations with risk factors for PE in the maternal history.

Conclusions

We present encouraging results for the prediction of early PE, even in the first-trimester of pregnancy. The different performance of tests in screening for early versus late PE, and of low versus high-risk populations, supports the concept that PE is a heterogeneous disease.

KEYWORDS

Biochemical serum markers

Blood pressure

Doppler

First trimester

Maternal history

Pre-eclampsia

Screening

Second trimester

Systematic review

INTRODUCTION

Pre-eclampsia (PE) affects 2-8% of pregnancies and is a major cause of maternal and perinatal morbidity and mortality [45]. In mothers, PE may lead to disseminated coagulopathy, pulmonary edema, renal or liver failure, eclampsia, stroke and placental abruption [38]. In fetuses, it may cause intrauterine growth restriction (IUGR), hypoxia-neurologic injury and preterm delivery [38]. Ultimately, PE may lead to death of the mother and/or the fetus [38].

Considering the impact of PE in obstetrics, the development of an accurate screening method would be of great value. Although, at present, there is no effective preventive intervention for PE [38,45], screening would allow us to select a group of pregnant women who would receive increased maternal and fetal monitoring [12]. From a research point of view, it would be essential for future development of effective prophylactic measures, as it would enable the recruitment of high-risk women in which the effect of those measures could be evaluated [12].

Classically, PE has been associated with inadequate trophoblast invasion of the spiral arteries and consequent failure of development of a low-resistance uteroplacental circulation that characterizes normal pregnancies [10,13]. Therefore, uterine artery Doppler (UAD) has been extensively studied as a screening test for PE. A recent meta-analysis [11] reported that a high second-trimester pulsatility index (PI) detects 42% of PE cases with a specificity of 91%. In the first-trimester, the accuracy is lower, with a sensitivity of 25% and a specificity of 95%.

The National Institute for Health and Clinical Excellence [24] currently recommends the assessment of each woman's risk for PE on the basis of maternal history. Age $\geq$ 40 years, body mass index $\geq$ 30 Kg/m^2, pre-existing vascular or renal disease, nulliparity or pregnancy interval of > 10 years, prior or family history of PE and multiple pregnancy increase the probability of developing PE. However, accuracy of screening with maternal history alone is low [32].

In addition to UAD and maternal history, a large number of maternal serum markers have been investigated for the prediction of PE, but their use as single screening tests has also been disappointing [6]. Finally, early measurement of mean arterial pressure (MAP) is another screening test that should not be forgotten because it is simple and inexpensive and appears to be an important predictor of subsequent PE [6].

Despite great research efforts, in 2004, the World Health Organization [12] concluded that no single test was yet available to provide accurate screening for PE. Since then, there has been growing interest in the combination of markers for PE screening. Recently, this was reviewed by Giguère et al. [17], who concluded that the combination of biochemical and ultrasonographic markers improves prediction of PE. However, the authors did not systematically evaluate the contribution of maternal history and MAP to combined screening.

In this context, we performed the current systematic review to evaluate first and second-trimester screening for PE with tests that combine UAD with maternal history, MAP and/or maternal serum markers.

METHODS

A search was conducted in the Medline database using the following MeSH terms or keywords, with no limits:

preeclampsia, *pre-eclampsia*, *diagnosis*, *screening*, *prediction*, *uterine artery*, *Doppler*, *clinical*, *maternal*, *characteristics*, *factors*, *history*, *blood pressure*, *pregnancy-associated plasma protein-A, PAPP-A, chorionic gonadotropin, hCG, alpha-fetoprotein, inhibin A, activin A, placental protein 13, placental growth factor, soluble fms-like tyrosine kinase 1, soluble vascular endothelial growth factor receptor-1*.

Additional keywords were tested but were not included in the final query because they did not improve the sensitivity of the search.

Table 1 presents the selection criteria used to determine the eligibility of the studies identified by the search, and, when appropriate, the rationale for using those criteria. They were applied in two stages: first, to the titles and abstracts of the articles yielded by the query; second, to the full texts of the articles selected in the first stage.

The reference list of the selected articles was also searched to identify additional potential articles of interest, which were then retrieved and submitted to the selection criteria.

The search was updated periodically and was last run on 10 December 2010.

Relevant data were extracted from each article using a standardized form. Risk of bias was assessed according to criteria that had been previously used [12] and that we adapted to our own review (*Table 2*). In nested case-control studies, we considered selection adequate when cases included "all (or a representative sample of) individuals with the outcome of interest occurring in the defined cohort" and controls were "a random sample of the individuals remaining in the cohort" [47]. This way, investigators ensured that cases were representative of individuals with the outcome in the population studied and that controls were representative of individuals without the outcome in the same population.

When available, we reported the following measures of accuracy: area under the ROC curve (AUC), specificity (Sp), sensitivity (Sn), and likelihood ratios of the positive (LR+) and negative (LR-) results. The LR+ is defined as Sn/(1-Sp) and the LR- as (1-Sn)/Sp [12]. Convincing prediction is provided by tests with LR+ > 10 and LR- < 0.1 [11,12]. On the other

hand, tests with LR+ < 5 or LR- > 0.2 achieve only minimal prediction and the other tests achieve moderate prediction [12].

We followed the PRISMA guidelines [22] in order to maximize the quality of the report of our systematic review.

RESULTS

Figure 1 depicts the results of each stage of the selection process. According to the selection criteria previously described, 35 articles were eligible and, of those, three [34,36,37] reported results of the same cohort. Therefore, 33 studies were reviewed, which are described in *Table 3*.

Twenty-one cohort and 12 nested case-control studies were included. Seven were conducted in high-risk populations, defined by the presence of risk factors for PE in the maternal history, an abnormal second-trimester UAD or high second-trimester levels of human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP).

Studies of low-risk populations reported a prevalence of PE that varied between 1.2% and 10.5%, although it was ≤3.0% in the majority. Those which evaluated screening for early PE reported a prevalence of this outcome of 0.3%-0.8%, with the exception of one study which reported a prevalence of 2.3%.

The conclusions of some studies are limited by the size of their samples, which is partly related to the low frequency of PE and especially early PE in the general population. For example, six studies included only ≤10 participants with early PE.

Screening tests were performed in the first-trimester in 12 studies, in the second-trimester in 15 and in both trimesters in six.

Maternal history was evaluated in 16 studies, pregnancy-associated plasma protein-A (PAPP-A) in 11, inhibin A in nine, placental growth factor (PlGF) in eight, hCG, activin A and placental protein 13 (PP13) in six each, soluble fms-like tyrosine kinase 1 (sFlt1) in four, MAP and AFP in three each.

It should be noted that some studies are related. Seven of them [1-3,30,33-35] were conducted as part of the same research program and had overlapping study groups. This also happened in two additional studies [27,49]. To avoid data duplication, whenever a screening test was evaluated in more than one of these studies, we only reported its performance in the study with the largest sample. Other studies [40 and 44, 42 and 43] also had common participants but we considered them separately because they evaluated different screening tests.

Figure 2 presents the results of the assessment of the risk of bias. Selection of the study participants was generally adequate but occasionally inadequate or unreported. The study population was adequately described in nearly all studies whereas description of the screening tests was frequently inadequate because the selected cut-off points were not specified. Blinding of the readers of the screening tests was usually adequate, but sometimes unreported. On the other hand, complete blinding of the readers of the reference standard was accomplished in only two studies and was inadequate or unreported in the remaining. Follow-up and verification was adequate in most studies but in several it was unreported.

Tables 4, 5, 6 and *7* summarize the results of each study. The performance of screening tests is reported quantitatively, through AUC, Sp, Sn, LR+ and LR-, and qualitatively, through a citation of the article.

Figures 3 and *4* show the screening tests that provided moderate or convincing prediction, according to the LR values. None of the screening tests for late PE qualified. A few screening tests for total PE were moderately predictive, all of which involved second-trimester testing. On the other hand, screening for early PE was accomplished with moderate accuracy by several first and second-trimester tests. Additionally, four tests were on the verge of providing convincing prediction, and one first-trimester test was highly predictive.

DISCUSSION

Best first-trimester screening tests for early PE

Our results suggest that, in the first-trimester, accurate screening for early PE probably requires the combination of several markers. Two tests that combined UAD with four other markers had a very good performance.

The combination of mean-PI (M-PI), maternal history, MAP, PAPP-A and PlGF was highly predictive of early PE, in a nested case-control study with almost 30 cases of early PE [33]. Of the 33 studies reviewed, one included the same number of early PE cases and only six included a higher number. Unfortunately, there were additional cases of early PE in the original cohort who did not have available serum for the measurement of PlGF and thus were not included in the case-control study. Although selection of cases was simply based on serum availability, we cannot be certain that the sample is representative of the original population. We conclude that these results are very encouraging but require confirmation by future studies.

The other test combined lowest-PI (L-PI), maternal history, PAPP-A, inhibin A and PlGF and was applied to a cohort of nulliparous women [8]. However, it should be considered with caution because the cohort included only four participants who subsequently developed early PE. Furthermore, the authors reported that L-PI was not significantly different between the PE and normal outcome groups and that it did not improve screening by maternal history combined with the three serum markers.

Several other tests had a good performance in the first-trimester, virtually all of them with a LR+ > 8.6 and a LR- ≤ 0.18. The majority took into account the maternal history. Other markers frequently considered were MAP, PAPP-A, inhibin A and PlGF. In particular, we'd like to highlight that screening with L-PI, maternal history, MAP and PAPP-A achieved a LR+ of 9.46 and a LR- of 0.06, in a cohort of over 8300 women, including 37 with early PE [34,36,37].

One study [25] also achieved promising results with the combination of M-PI and PP13, albeit in a sample that included only ten early PE cases. These results are supported by other studies, which demonstrated that first-trimester PP13 is a significant predictor of early PE [2] and that it improves screening with first [21] and second-trimester UAD [41]. However, one study did not confirm the predictive accuracy of PP13 [8].

Best second-trimester screening tests for early PE

Screening for early PE in the second-trimester probably requires the combination of fewer markers, as UAD alone is substantially more accurate when performed in this trimester [11].

The association of M-PI, maternal history and MAP almost provided convincing prediction in a cohort of over 3000 women, including 23 with early PE [26]. The same promising results were obtained when maternal history and first-trimester UAD were combined with the assessment of the ratio between M-PI in the second and first trimesters, in a cohort of similar dimensions [31]. Therefore, measurement of maternal serum markers may not be necessary to provide accurate screening for PE in the second-trimester, because the combination of UAD with the simple and inexpensive evaluation of maternal history and MAP may be sufficient.

In women with abnormal second-trimester UAD, sFlt1 appeared to be useful in early PE screening. In one study [14], sFlt1 provided moderate prediction and the sFlt1/PlGF ratio almost provided convincing prediction. A similar study [46] demonstrated a good performance of the two serum markers when they were concurrently measured but not combined in a ratio. However, both studies were limited by the size of their samples, which included only 8 and 9 women with early PE, respectively. Moreover, their results were challenged by a larger study, which found that sFlt1 was not able to predict early PE in a group of women with abnormal UAD [15].

In one second-trimester study [40], combination of UAD and PP13, with or without other serum markers, achieved moderate prediction of early PE (LR+=5, LR-=0). However, this was a case-control study which included only five cases of early PE that were selected from a cohort on the basis of serum availability. Furthermore, the authors reported that the addition of PP13 to UAD did not improve screening.

Best screening tests for late and total PE

In contrast with early PE, none of the tests were even moderately predictive of late PE. On the other hand, prediction of total PE was accomplished with moderate accuracy by some tests, all of which involved second-trimester screening and combined UAD with inhibin A, activin A, PlGF and/or sFlt1.

What to screen? Early versus late PE

The performance of screening tests was consistently and substantially better in the prediction of early PE, comparing to late PE. Our results support the concept that these are distinct disease entities [20,48], with impaired placentation and defective angiogenesis being related especially to early PE [13,14,45], and cardiovascular and metabolic risk factors probably leading to late PE [45]. Although much less frequent than the late form of the condition [20], early PE is the main contributor to the maternal and perinatal morbidity and mortality seen in PE [1,31], as it is associated with premature delivery, a higher risk of IUGR, more severe maternal disease and a higher rate of pregnancy-related maternal death [20,48]. Considering its impact, the low incidence of early PE should not prevent routine screening. Moreover, trisomy 21, for which screening is currently performed, is even less frequent, affecting only 0.14% of newborns in the absence of any intervention [24].

When to screen? First versus second-trimester screening

Even though UAD is more accurate in the second-trimester [11], we found encouraging results for first-trimester screening when it was combined with other markers. We believe that screening for PE is most relevant in the first-trimester because, as suggested by a recent meta-analysis [10], preventive interventions are more likely to be effective if initiated early in pregnancy, when pathogenic mechanisms can still be modified.

Who to screen? Low versus high-risk populations

Three studies evaluated the performance of screening tests in high-risk populations characterized by the presence of certain risk factors in the maternal history.

Screening a preselected high-risk population is of particular interest when the condition screened is infrequent, as is the case of early PE. Assuming that the sensitivity and specificity of the screening test remain constant, the positive predictive value increases when it is applied to a population with higher disease prevalence.

Interestingly, however, the accuracy of screening tests was consistently lower in the previously mentioned studies than in studies of low-risk populations. In nulliparous women [8], the performance of screening with L-PI and maternal history was poorer than in unselected pregnancies [34,36,37]. In women with risk factors such as chronic hypertension, pregestational diabetes mellitus and obesity, screening with M-PI and maternal history [19] or with M-PI and PP13 [21] was also less predictive than in low-risk populations [31,25].

In the meta-analysis performed by Cnossen et al. [11], screening with the pulsatility index was less accurate in high-risk populations. Thus, our results may be explained by the lower performance of UAD in women with historical risk factors. They further support the concept of PE as a heterogeneous disease [13,38,48] and suggest that, in these women, impaired placentation may play a less important role in the development of PE [19].

Limitations of the reviewed studies

Several studies that we reviewed were limited by the size of their samples and by the risk of bias in certain methodological areas.

Selection of study participants was occasionally inadequate. Some nested case-control studies included only a subset of PE cases of the original cohort because only those had available blood samples for the measurement of specific markers. Additionally, some cohort studies did not apply the screening tests to all eligible participants.

Outcome assessors were not completely blinded to the results of the screening tests in several studies. In some cases, blinding was inadequate because the results of UAD influenced the subsequent management of pregnancies. In other cases, investigators evaluated screening for PE with first-trimester PAPP-A or hCG, or with second-trimester hCG or AFP, and had to communicate the results of the screening tests to pregnant women and their managing clinicians because they were necessary for routine assessment of trisomy 21 risk. This shows that, at times, although the methodology of the study may lead to bias, it is the best that researchers are able to do, and for that reason the PRISMA statement [22] recommends that the term "quality" be replaced by "risk of bias".

The comparison of individual studies is limited by differences observed among them, concerning, for example, the definitions of PE and early PE and the UAD technique.

Although, in the studies reviewed, the definitions of PE always included the concurrent presence of hypertension and proteinuria, we identified among them several differences. Concerning hypertension, some studies considered it to be present when either the systolic (SBP) or diastolic (DBP) blood pressure (BP) was elevated, while others did so only in the presence of high DBP. Generally, the diagnosis of hypertension required at least two recordings of elevated BP with a minimal 4-6 hour interval, and cutoffs of 140 mmHg and 90 mmHg were considered for high SBP and DBP, respectively. Occasionally, however, studies reported the presence of hypertension when DBP was $\geq$ 110 mmHg on any occasion or $\geq$ 90 mmHg on at least two occasions. Proteinuria was usually defined as protein excretion of

≥ 300 mg in a 24-hour urine collection, but two dipstick readings of ≥ 2+, or occasionally ≥ 1+, were also frequently considered diagnostic if no 24-hour collection was available.

The definition of early PE was also not uniform and almost one third of the studies did not report screening for this outcome.

The technical performance of UAD was usually but not always clearly reported. Investigators used color Doppler to identify the uterine arteries (UA) and pulsed wave Doppler to obtain the flow velocity waveforms. In the first-trimester, UAD was generally performed using a transabdominal approach. In the second-trimester, transabdominal UAD was also used, but the transvaginal approach was more frequent, often because investigators concurrently measured the cervical length for the assessment of the risk of premature delivery. In the majority of studies, waveforms were obtained from the UA at the level of the internal cervical os but in several others they were obtained at or one centimeter distal to the crossover point with the external iliac artery. Investigators variably required an angle of insonation below 30º, 50º or 60º, and several did not describe it. Although PI was most frequently reported, some studies evaluated other Doppler parameters, such as the resistance index or the presence of early diastolic notches.

Limitations and strengths of our review

The strength of our conclusions is limited by the multiplicity of combinations evaluated, the variability of the gestational age at which tests were performed (even within the same trimester) and the diversity of populations studied. Additionally, as in any review, it is limited by the shortcomings of the original studies, which we have previously discussed.

On the other hand, our review has several strengths: we used explicit and reproducible methodology; we minimized the risk of bias using rigorously predefined selection criteria and a standardized data extraction form; we assessed the risk of bias of the included studies with objective criteria; we reported the findings of each study and summarized those findings in a systematic way.

Our review does not provide definitive conclusions but rather highlights important advances that have been made in PE screening and offers guidance and optimism for future research. To our knowledge, it is the first review that systematically evaluates the combination of UAD, maternal history, MAP and serum markers in the prediction of PE.

While screening for total and especially late PE remains disappointing, we have demonstrated encouraging results in the prediction of early PE. In addition to the eight serum

markers we reviewed, others, such as soluble endoglin and homocysteine, might be useful when combined with UAD.

We believe that future research should focus on first-trimester screening for early PE, with a combination of UAD, maternal history, MAP, and serum markers such as PAPP-A, inhibin A and PlGF. Large cohort studies are needed in order to accurately study this relatively infrequent outcome of pregnancy.

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APPENDICES

LIST OF CAPTIONS

Figures

Tables

Table 1 – Selection criteria used to determine eligibility of the studies for the systematic review.

Inclusion criteria	
1. Study design	Prospective studies, in which screening tests were applied before outcomes were developed, including cohort and nested case-control studies.
Rationale	A case-control design may represent a valid alternative to a cohort analysis if cases and controls belong to a common reference population; otherwise, selection bias may ensue. This is assured when participants are selected from a well defined cohort, as in nested case-control studies, which take advantage of "both the methodologic soundness of the cohort design (i.e., limiting selection bias) and the efficiency of the case-control approach" (limiting costs). [47]
2. Study aim	To evaluate the performance of screening tests.
3. Screening test	Combination of UAD and one or more of the following: maternal history, MAP, PAPP-A, hCG, AFP, inhibin A, activin A, PP13, PlGF, sFlt1.
4. Trimester of screening	First (0 to 13+6 weeks' gestation) and/or second (14+0 to 27+6 weeks' gestation).
5. Condition screened	Early and late PE, ideally. Total PE, in alternative. Other subtypes of PE (e.g., severe PE), if none of the previously referred outcomes were considered.
Rationale	According to von Dadelszen et al. [48], gestational age at onset of PE "is the most important clinical variable in predicting both maternal and perinatal outcomes".
6. Population screened	Low-risk population: recruitment of participants from an unselected obstetric population; *or* High-risk population: recruitment of (1) women with risk factors for PE in their clinical history (e.g. chronic hypertension) or (2) women with a positive result in a previous screening test (e.g. women with abnormal UAD).
7. Reference standard	Several definitions of PE were accepted, as long as they included the concurrent presence of hypertension and proteinuria. Several definitions of early PE were accepted, but the preferred one was: PE requiring delivery before 34 weeks' gestation. When other definitions were considered, they were specified.
Rationale	The selection of the preferred definition of early PE was based on the following facts: (1) the administration of glucocorticoids is recommended for fetal lung maturity when there is risk of preterm delivery in pregnant women with less than 34 weeks' gestation [18]; (2) preterm birth occurring after 34 weeks' gestation is rarely associated with mortality or major morbidity [18].
Exclusion criteria	
	The definition of PE considered in the study was not reported.
	PE was combined with other pregnancy complications in the outcome.

PE: pre-eclampsia; UAD: uterine artery Doppler; MAP: mean arterial pressure; PAPP-A: pregnancy-associated plasma protein-A, hCG: human chorionic gonadotropin; AFP: alpha-fetoprotein; PP13: placental protein 13; PlGF: placental growth factor; sFlt1: soluble fms-like tyrosine kinase 1.

Table 2 – Criteria for assessment of risk of bias.

1. Selection of study participants	
Adequate	• Cohort studies in which all eligible women were included consecutively or randomly into the study. • Nested case-control studies in which all eligible women were included consecutively or randomly into the original cohort, all or a random selection of the participants that developed PE in the original cohort were included as cases, and a random selection of the unaffected participants of the original cohort were included as controls.
Inadequate	• Studies which did not meet at least one of the above-mentioned criteria.
Unreported	• It was not possible to draw a conclusion based on the information reported in the article.
2. Description of the study population	
Adequate	• Two or more of the following characteristics were described: women's age, parity, underlying diseases or the risk status of the population (low or high).
Inadequate	• Only one or none of the above-mentioned characteristics was reported.
3. Description of the screening tests	
Adequate	• Cut-off levels, clear definitions of positive and negative test results, and gestational age at which the screening tests were performed were mentioned in the text.
Inadequate	• Absence of any of the above-mentioned information in the report.
4. Blinding of the readers of the screening tests	
Adequate	• Readers of all the screening tests were masked to the results of the reference standard.
Inadequate	• Readers of at least one of the screening tests were not masked to the results of the reference standard.
Unreported	• It was not possible to draw a conclusion based on the information reported in the article.
5. Blinding of the readers of the reference standard	
Adequate	• The results of the screening tests were not communicated to the managing clinicians and readers of the reference standard were masked to the results of the screening tests.
Inadequate	• The results of at least one of the screening tests were communicated to the managing clinicians or readers of the reference standard were not masked to the results of the screening tests.
Unreported	• It was not possible to draw a conclusion based on the information reported in the article.
6. Follow-up and verification	
Adequate	• At least 90% of the participants originally subjected to the screening tests were followed up and had verification by the reference standard. • Miscarriage, fetal abnormalities and multiple pregnancies were regarded as legitimate exclusions.
Inadequate	• Less than 90% of the participants originally subjected to the screening tests were followed up.
Unreported	• It was not possible to draw a conclusion based on the information reported in the article.

Adapted from Conde-Agudelo A. et al., 2004 [12].

PE: pre-eclampsia.

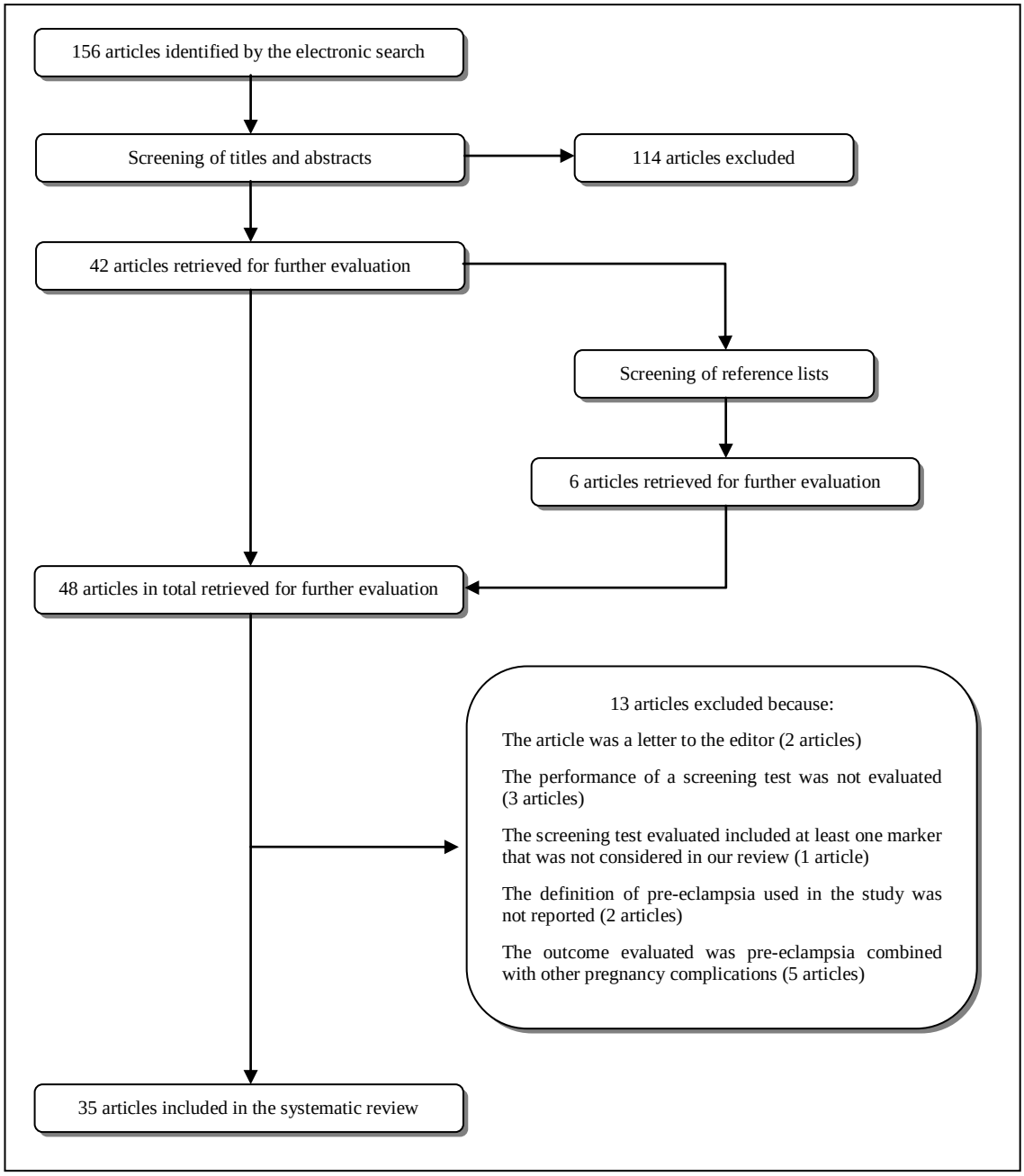


Figure 1 – Selection process of the articles for the systematic review.

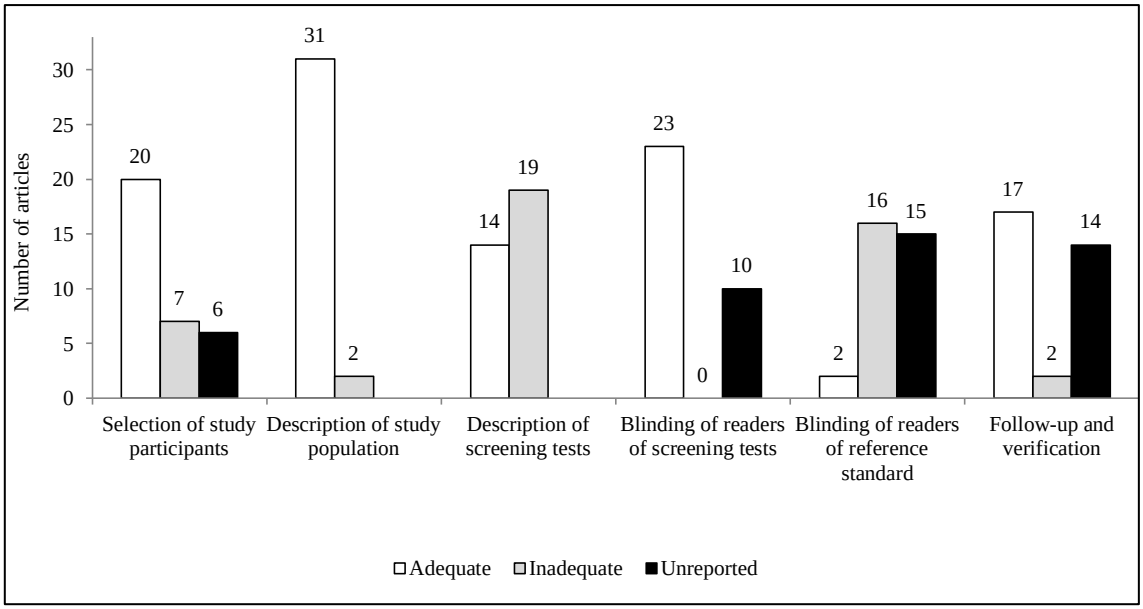


Figure 2 – Assessment of the risk of bias.

Table 3 – Description of the studies included in the systematic review.

Reference, study design and sample characteristics *We report the total number of participants of the cohort (N), the number of participants with each outcome and, in parentheses, the prevalence of each outcome in the cohort.*	**Tests performed**	**Time of testing (weeks)**
Akolekar R et al., 2009 [1] Nested case-control Cohort: N=8234, 147 (1.8%) PE, unreported early PE Cases and controls: 121 PE, 26 early PE, 208 controls	UAD, maternal history, PAPP-A, inhibin A	11-14
Akolekar R et al., 2009 [2] Nested case-control Cohort: N=15759, 298 (1.9%) PE, unreported early PE Cases and controls: 208 PE, 48 early PE, 416 controls	UAD, maternal history, PAPP-A, PP13	11-14
Akolekar R et al., 2008 [3] Nested case-control Cohort: 1.8% PE, other characteristics were not described Cases and controls: 127 PE, 29 early PE, 609 controls	UAD, maternal history, PAPP-A, PlGF	11-14
Alkazaleh F et al., 2006 [4] High-risk cohort (high 2nd trimester hCG and AFP) N=50, 13 (26.0%) severe PE¶	hCG, AFP UAD	15-18 19-23
Aquilina J et al., 2001 [5] Cohort N=640, 35 (5.5%) PE, 15 (2.3%) early PE§	Inhibin A UAD	15-19 18-22
Audibert F et al., 2005 [7] Cohort N=2615, 51 (2.0%) PE	hCG, AFP UAD	14-18 18-26
Audibert F et al., 2010 [8] High-risk cohort (risk factors in maternal history) Total cohort** N=893, 40 (4.5%) PE, 9 (1.0%) early PE* Cohort with PlGF measurement** N=531, 22 PE (4.1%), 4 (0.8%) early PE*	UAD, maternal history, PAPP-A, hCG, inhibin A, PP13, PlGF	11-13
Ay E et al., 2005 [9] Cohort N=178, 14 (7.9%) PE	hCG, AFP, inhibin A, activin A UAD	15-18 23-26
Diab AE et al., 2008 [14] High-risk cohort (abnormal 2nd trimester UAD) N=108, 33 (30.6%) PE, 8 (7.4%) early PE	UAD, PlGF, sFlt1	23
Espinoza J et al., 2007 [15] Cohort N=3296, 113 (3.4%) PE, 15 (0.5%) early PE	UAD, PlGF, sFlt1	22-26
Florio P et al., 2003 [16] High-risk cohort (abnormal 2nd trimester UAD) N=58, 18 (31.0%) PE	UAD, inhibin A, activin A	24
Herraiz I et al., 2009 [19] High-risk cohort (risk factors in maternal history) N=152, 20 (13.2%) PE, 7 (4.6%) early PE	UAD, maternal history	11-14
Khalil A et al., 2010 [21] Nested case-control (in high-risk cohort with risk factors in maternal history) Cohort: N=395, 42 (10.6%) PE, 14 (3.5%) early PE Cases and controls: 42 PE, 14 early PE, 210 controls	UAD, PP13	11-14
Llurba E et al., 2009 [23] Cohort N=6035, 75 (1.2%) PE, 20 (0.3%) early PE†	UAD, maternal history	19-22
Nicolaides KH et al., 2006 [25] Nested case-control Cohort: Not described Cases and controls: 10 early PE, 423 controls	UAD, PP13	11-14
Onwudiwe N et al., 2008 [26] Cohort N=3347, 101 (3.0%) PE, 23 (0.7%) early PE	UAD, maternal history, MAP	22-24
Papageorghiou AT et al., 2005 [27] Cohort N=16806, 369 (2.2%) PE	UAD, maternal history	22-24
Parra M et al., 2005 [28] Nested case-control Cohort: N=743, 33 (4.4%) PE Cases and controls: 33 PE, 137 controls (8 PE and 37 controls with 1st trimester screening; 26 PE and 100 controls with 2nd trimester screening)	UAD, PlGF, sFlt1 UAD, PlGF, sFlt1	11-14 22-25
Pilalis A et al., 2007 [29] Cohort N=878, 13 (1.5%) PE	UAD, maternal history, PAPP-A	11-14

Plasencia W et al., 2007 [30] Cohort N=6015, 107 (1.8%) PE	UAD, maternal history	11-14
Plasencia W et al., 2008 [31] Cohort N=3107, 93 (3.0%) PE, 22 (0.7%) early PE	UAD, maternal history UAD	11-14 21-25
Poon LC et al., 2009 [33] Nested case-control Cohort: N=7797, 157 (2.0%) PE, 34 (0.4%) early PE Cases and controls: 127 PE, 29 early PE, 418 controls	UAD, maternal history, MAP, PAPP-A, PlGF	11-13
Poon LC et al., 2009/2010 [34,36,37] Cohort N=8366, 165 (2.0%) PE, 37 (0.4%) early PE	UAD, maternal history, MAP, PAPP-A	11-14
Poon LC et al., 2009 [35] Cohort N=8051, 156 (1.9%) PE, 32 (0.4%) early PE	UAD, maternal history, PAPP-A	11-14
Simonazzi G et al., 2007 [39] Cohort N=152, 16 (10.5%) PE	UAD, maternal history	18-24
Spencer K et al., 2007 [40] Nested case-control Cohort: Not described Cases and controls: 12 PE, 5 early PE‡, 73 controls	UAD, PAPP-A, hCG, inhibin A, activin A, PP13	22-24
Spencer K et al., 2007 [41] Nested case-control Cohort: N=5867, 88 (1.5%) PE, 44 (0.8%) early PE‡ Cases and controls: 88 PE, 44 early PE‡, 446 controls	PAPP-A, PP13 UAD	11-14 22-24
Spencer K et al., 2008 [42] Nested case-control Cohort: N=4390, 64 (1.5%) PE, 34 (0.8%) early PE‡ Cases and controls: 64 PE, 34 early PE‡, 240 controls	Inhibin A, activin A UAD	11-14 22-24
Spencer K et al., 2005 [43] Cohort N=4390, 64 (1.5%) PE	PAPP-A, hCG UAD	11-14 22-24
Spencer K et al., 2006 [44] Nested case-control Cohort: Not described Cases and controls: 24 PE, 144 controls	UAD, inhibin A, activin A	22-25
Stepan H et al., 2007 [46] High-risk cohort (abnormal 2nd trimester UAD) N=63, 12 (19.0%) PE, 9 (14.3%) early PE	UAD, PlGF, sFlt1	19-24
Yu CK et al., 2005 [49] Cohort Total cohort†† N=30784, 612 (2.0%) PE, 144 (0.5%) early PE "Model validation group" †† N=15392, 297 (1.9%) PE, 72 (0.5%) early PE	UAD, maternal history	22-24
Yu J et al., 2010 [50] Nested case-control Cohort: N=613, 31 (5.1%) PE Cases and controls: 31 PE, 93 controls	Inhibin A, activin A, PlGF UAD	12-16 22-24

PE: pre-eclampsia; UAD: uterine artery Doppler; MAP: mean arterial pressure; PAPP-A: pregnancy-associated plasma protein-A; hCG: human chorionic gonadotropin; AFP: alpha-fetoprotein; PP13: placental protein 13; PlGF: placental growth factor; sFlt1: soluble fms-like tyrosine kinase 1.

Unless otherwise specified, early PE refers to PE requiring delivery before 34 weeks' gestation and late PE refers to PE requiring delivery at or after 34 weeks' gestation. *PE diagnosed before 34 weeks' gestation. †PE requiring delivery before 32 weeks' gestation. ‡PE requiring delivery before 35 weeks' gestation. §PE requiring delivery before 37 weeks' gestation. ¶ Severe PE refers to PE with end-organ involvement or fetal growth restriction.

***"PlGF could only be measured in 531 women, because this test was initially not scheduled and additional serum was not available for women included in the first year of the study."* [8]

††*"The cohort was divided into a model development group and a model validation group using a pseudo-random number for allocation"*. [49] The results of this study presented in our review were estimated in the *"model validation group"*.

Table 4 – Screening for PE with UAD and one other marker.

Test	Type of PE	AUC	Sp %	Sn %	LR+	LR-
1st Trimester						
Poon LC et al, 2009/2010 [34,36,37] | *"significant contributions from a combination of (…) maternal risk factors with either the lowest, mean or highest (…) PI"	"Although there was no significant difference (…) screening appeared to be best with the lowest PI"*					
L-PI + Maternal history	Early	0.912	90.0	81.1	8.11	0.21
	Late	0.812	90.0	45.3	4.53	0.61
**Audibert F et al, 2010 [8]	** *"addition of Doppler did not improve (…) accuracy of screening by clinical characteristics alone"*					
L-PI + Maternal history	Early*	0.738	90.0	50.0	5.00	0.56
	Total	0.746	90.0	35.1	3.51	0.72
**Pilalis A et al, 2007 [29]	** *"although the difference was not statistically significant (…) the combination of (…) PI and maternal history (…) was better compared with (…) Doppler alone"*					
M-PI + Maternal history	Total	0.753	95.0	42.0	8.40	0.61
**Plasencia W et al, 2008 [31]	** *"effective screening (…) can be achieved by a combination of maternal variables and (…) Doppler"*					
M-PI + Maternal history	Early	0.931	90.0	77.3	7.73	0.25
	Late	0.779	90.0	42.3	4.23	0.64
**Poon LC et al, 2009/2010 [34,36,37]	** *See above.*					
M-PI + Maternal history	Early	0.902	90.0	78.4	7.84	0.24
	Late	0.813	90.0	46.9	4.69	0.59
**Herraiz I 2009 [19]	** *"detection rates of the combination of (…) Doppler and maternal history (…) were considerably lower than in the original study with low-risk pregnancies" [30]*					
M-PI + Maternal history	Early	0.779	90.0	42.9	4.29	0.63
	Late	0.641	90.0	23.1	2.31	0.85
**Poon LC et al, 2009/2010 [34,36,37]	** *See above.*					
H-PI + Maternal history	Early	0.884	90.0	64.9	6.49	0.39
	Late	0.810	90.0	46.1	4.61	0.60
**Poon LC et al, 2009 [35]	** *"significant contributions from serum PAPP-A (…) PI (…) in the prediction of early PE"*					
M-PI + PAPP-A	Early	0.852	90.0	59.4	5.94	0.45
**Audibert F et al, 2010 [8]	** *"we did not confirm the predictive accuracy of (…) free ß-hCG"*					
L-PI + hCG	Not available					
**Audibert F et al, 2010 [8]	** *"we did not confirm the predictive accuracy of (…) PP13"*					
L-PI + PP13	Not available					
**Nicolaides KH et al, 2006 [25]	** *"Effective screening (…) can potentially be provided by (…) PP-13 and (…) Doppler"*					
M-PI + PP13	Early	-----	90.0	90.0	9.00	0.11
M-PI followed by PP13 in 32% with highest risk	Early	-----	84.0	90.0	5.63	0.12
PP13 followed by M-PI in 14% with highest risk	Early	-----	94.0	90.0	15.00	0.11
**Khalil A et al, 2010 [21]	** *"any pair combination provided better prediction than any individual marker"*					
M-PI + PP13	Early	0.900	90.0	78.6	7.86	0.24
	Total	0.880	90.0	71.4	7.14	0.32
**Parra M et al, 2005 [28]	** *"none of the parameters assessed during the first trimester was significantly associated with PE"*					
M-PI + PlGF	Not available					
M-PI + sFlt1	Not available					
2nd Trimester						
**Llurba E et al, 2009 [23]	** *"combination of both methods did not significantly improve the sensitivity"*					
M-PI + Maternal history	Not available					
Yu CK et al, 2005 [49] | *Early PE: "Ultrasound had an extremely high predictive value (…) which was not significantly different from the combination of maternal and ultrasound prediction"	Late PE: "the combination of ultrasound and maternal characteristics provided the best (…) model"*					
M-PI + Bilateral diastolic notches + Maternal history	Early	0.945	90.0	81.9	8.19	0.20
	Late	0.798	89.8	47.6	4.67	0.58

Simonazzi G et al, 2007 [39] | *"lower detection rate compared with the values stated by Yu et al." [49]*						
M-PI + Bilateral diastolic notches + Maternal history	Total	0.760	90.0	50.0	5.00	0.56
Spencer K et al, 2007 [40] | *"combining (...) Doppler with (...) PAPP-A (...) did not improve detection"*						
M-PI + PAPP-A	Early‡	0.800	80.0	60.0	3.00	0.50
	Late	0.520	80.0	43.0	2.15	0.71
Audibert F et al, 2005 [7] | *"[UAD combined with hCG or AFP] despite a poor sensitivity, offers a very high PPV [positive predictive value] in a low-risk population, multiplying the risk by 2-3 compared to Doppler alone"*						
Diastolic notch + hCG	Total	-----	99.53	7.84	16.68	0.93
Ay E et al, 2005 [9] | *"addition of these hormonal measurements [AFP, hCG, inhibin A, activin A] to (...) Doppler (...) does not cause a clinically significant improvement (...) over the use of Doppler (...) alone"*						
Doppler + hCG	Not available					
Audibert F et al, 2005 [7] | *See above.*						
Diastolic notch + AFP	Total	-----	99.02	7.84	8.00	0.93
Bilateral diastolic notches + AFP	Total	-----	99.57	5.88	13.67	0.95
Ay E et al, 2005 [9] | *See above.*						
Doppler + AFP	Not available					
Spencer K et al, 2006 [44] | *"screening can be improved by combining (...) Doppler scan with (...) biochemical analysis"*						
M-PI + Inhibin A	Total	0.913	90.0	75.0	7.50	0.28
M-PI + Activin A	Total	0.935	90.0	75.0	7.50	0.28
Aquilina J et al, 2001 [5] | *"statistically significant improvement in the screening efficacy (...) when (...) Doppler studies (...) are combined with inhibin-A"*						
M-RI + Diastolic notch + Inhibin A	Early§	-----	97.0	60.0	20.00	0.41
	Total	-----	93.4	71.4	10.82	0.31
Inhibin A followed by Doppler in 53% with highest risk	Early§	-----	93.0	73.0	10.43	0.29
	Total	-----	93.0	70.0	10.00	0.32
Ay E et al, 2005 [9] | *See above.*						
Diastolic notch + Inhibin A	Total	-----	100.0	71.4	∞	0.29
RI + Inhibin A	Total	-----	100.0	71.4	∞	0.29
Diastolic notch or high inhibin A	Total	-----	93.9	85.7	14.05	0.15
High RI or high inhibin A	Total	-----	82.9	78.6	4.60	0.26
Florio P et al, 2003 [16] | *"activin A and inhibin A (...) may add significant prognostic information for predicting pre-eclampsia among women with specific Doppler alterations"*						
Inhibin A, in women with diastolic notches	Total	0.555	92.0	39.0	4.88	0.66
Ay E et al, 2005 [9] | *See above.*						
Diastolic notch + Activin A	Total	-----	100.0	78.6	∞	0.21
Diastolic notch or high activin A	Total	-----	86.0	100.0	7.14	0.00
Florio P et al, 2003 [16] | *See above.*						
Activin A, in women with diastolic notches	Total	0.678	89.0	61.0	5.55	0.44
Spencer K et al, 2007 [40] | *"combining (...) Doppler with (...) PP13 (...) did not improve detection"*						
M-PI + PP13	Early‡	0.930	80.0	100.0	5.00	0.00
	Late	0.620	80.0	29.0	1.45	0.89
Parra M et al, 2005 [28] | *"Doppler is the best predictor of PE and none of biochemical markers significantly improved its capacity to screen"*						
M-PI + PlGF	Not available					
Espinoza J et al, 2007 [15] | *"[the addition of PlGF to UAD] improved the positive predictive value (...) without a significant reduction in the sensitivity"*						
M-PI + Bilateral diastolic notches + PlGF	Early	-----	96.4	73.3	20.36	0.28
	Total	-----	96.4	27.3	7.58	0.75
Stepan H et al, 2007 [46] | *"measurement of angiogenic factors has a useful predictive power when used in a risk group and focused to severe and early presenting forms of preeclampsia"*						
PlGF	Early	-----	62.0	83.0	2.18	0.27
in women with M-PI>1.45 and/or bilateral diastolic notches	Total	-----	62.0	77.0	2.03	0.37

M-PI + PlGF in women with M-PI>1.45 and/or bilateral diastolic notches	Early	-----	76.0	83.0	3.46	0.22
	Total	-----	68.0	77.0	2.41	0.34
Diab AE et al, 2008 [14] | *"We found (…) angiogenic factors to be highly predictive in (…) women with high-risk pregnancies"*						
PlGF in women with M-PI>1.45 and/or bilateral diastolic notches	Early	0.904	76.0	100.0	4.17	0.00
	Total	0.897	81.0	88.0	4.63	0.15
Parra M et al, 2005 [28] | *See above.*						
M-PI + sFlt-1	Not available					
Espinoza J et al, 2007 [15] | *"[sFlt1] did not improve the diagnostic indices of an abnormal [UAD]"*						
M-PI + Bilateral diastolic notches + sFlt1	Not available					
Stepan H et al, 2007 [46] | *See above.*						
sFlt1 in women with M-PI>1.45 and/or bilateral diastolic notches	Early	-----	89.0	67.0	6.09	0.37
	Total	-----	70.0	62.0	2.07	0.54
M-PI + sFlt1 in women with M-PI>1.45 and/or bilateral diastolic notches	Early	-----	89.0	83.0	7.55	0.19
	Total	-----	73.0	77.0	2.85	0.32
Diab AE et al, 2008 [14] | *See above.*						
sFlt1 in women with M-PI>1.45 and/or bilateral diastolic notches	Early	0.956	87.0	100.0	7.69	0.00
	Total	0.935	87.0	96.0	7.38	0.05
1st and 2nd Trimesters						
Plasencia W et al, 2008 [31] | *"the ratio of uterine artery PI (…) improved significantly the prediction of pre-eclampsia"*						
M-PI (T1) + Ratio M-PI (T2/T1) + Maternal history	Early	0.983	90.0	100.0	10.00	0.00
	Late	0.783	90.0	46.5	4.65	0.59
M-PI (T1) + Maternal history followed by Ratio M-PI (T2/T1) in 20% with highest risk	Early	-----	90.0	95.5	9.55	0.05
	Late	-----	90.0	43.7	4.37	0.63
Spencer K et al, 2005 [43] | *"The detection rate (…) in screening by (…) Doppler is improved by the inclusion of (…) PAPP-A"*						
M-PI (T2) + PAPP-A (T1)	Total	0.853	95.0	62.1	12.42	0.40
Spencer K et al, 2007 [41] | *"both PP-13 and PAPP-A when coupled with (…) PI (…) improve prediction over (…) Doppler (…) alone"*						
M-PI (T2) + PAPP-A (T1)	Early‡	0.860	80.0	76.0	3.80	0.30
	Late	0.810	80.0	70.0	3.50	0.38
Spencer K et al, 2005 [43] | *"levels of free β-hCG were not significantly altered in pregnancies that developed complications"*						
M-PI (T2) + hCG (T1)	Not available					
Spencer K et al, 2008 [42] | *"When combined [inhibin-A and activin-A] with (…) PI some improvement (…) could be observed"* | *"the predictive model was no better at identifying early- from late-onset pre-eclampsia"*						
M-PI (T2) + Inhibin A (T1)	Total	-----	95.0	67.5	13.50	0.34
Yu J et al, 2010 [50] | *"inhibin A, activin A, PIGF and (…) PI may add further information for prediction of pre-eclampsia"*						
M-PI (T2) + Inhibin A (T1-T2)	Total	0.813	90.0	47.0	4.70	0.59
Spencer K et al, 2008 [42] | *See above.*						
M-PI (T2) + Activin A (T1)	Total	-----	95.0	63.2	12.64	0.39
Yu J et al, 2010 [50] | *See above.*						
M-PI (T2) + Activin A (T1-T2)	Total	0.852	90.0	57.0	5.70	0.48
Spencer K et al, 2007 [41] | *See above.*						
M-PI (T2) + PP13 (T1)	Early‡	0.900	80.0	79.0	3.95	0.26
	Late	0.790	80.0	70.0	3.50	0.38
Yu J et al, 2010 [50] | *See above.*						
M-PI (T2) + PlGF (T1-T2)	Total	0.880	90.0	73.0	7.30	0.30

PE: pre-eclampsia; UAD: uterine artery Doppler; AUC: area under the ROC curve; Sp: specificity; Sn: sensitivity; LR+: likelihood ratio of the positive result; LR-: likelihood ratio of the negative result; PI: pulsatility index; L-PI: lowest PI; M-PI: mean PI; H-PI: highest PI; RI: resistance index; M-RI: mean RI; PAPP-A: pregnancy-associated plasma protein-A; hCG: human chorionic gonadotropin; AFP: alpha-fetoprotein; PP13: placental protein 13; PlGF: placental growth factor; sFlt1: soluble fms-like tyrosine kinase 1; T1: first trimester; T2: second trimester.

Unless otherwise specified, early PE refers to PE requiring delivery before 34 weeks' gestation and late PE refers to PE requiring delivery at or after 34 weeks' gestation. *PE diagnosed before 34 weeks' gestation. †PE requiring delivery before 32 weeks' gestation. ‡PE requiring delivery before 35 weeks' gestation. §PE requiring delivery before 37 weeks' gestation.

Table 5 – Screening for PE with UAD and two other markers.

Test	Type of PE	AUC	Sp %	Sn %	LR+	LR-
1st Trimester						
**Poon LC et al, 2009/2010 [34,36,37]	** *Early PE: "significant contributions from PAPP-A (…) maternal factors, MAP and (…) L-PI" | Late PE: "prediction from the combination of maternal factors (…) L-PI and MAP (…) was not improved by addition of PAPP-A"*					
L-PI + Maternal history + MAP	Early	0.954	90.0	89.2	8.92	0.12
	Late	0.863	90.0	57.0	5.70	0.48
L-PI + Maternal history + PAPP-A	Early	0.925	90.0	81.1	8.11	0.21
**Pilalis A et al, 2007 [29]	** *"We found increased (…) PI and maternal history (…) but not PAPP-A (…) to be independent risk factors for pre-eclampsia"*					
M-PI + Maternal history + PAPP-A	Not available					
**Poon LC et al, 2009 [35]	** *Early PE: "[AUC] was significantly higher in screening by history with (…) PI than by history alone (…) but there was no further improvement in screening if (…) PAPP-A was included" | Late PE: "[AUC] was not significantly higher for screening by history with (…) PI than by history alone (…), or by history with serum PAPP-A than by history alone"*					
M-PI + Maternal history + PAPP-A	Early	0.905	90.0	71.9	7.19	0.31
**Akolekar R et al, 2009 [1]	** *"Maternal plasma inhibin A in combination with (…) the maternal history and (…) PI could provide effective first-trimester screening"*					
M-PI + Maternal history + Inhibin A	Early	0.938	90.0	88.5	8.85	0.13
	Late	0.823	90.0	42.1	4.21	0.64
**Akolekar R et al, 2009 [2]	** *Early PE: "PP13 (…) did provide significant contribution to prediction" but it "did not improve the detection achieved by the combination of maternal factors, (…) L-PI and (…) PAPP-A" | Late PE: "PP13 (…) was not significantly different from controls and therefore did not add value in screening"*					
L-PI + Maternal history + PP13	Early	0.924	90.0	77.1	7.71	0.25
**Akolekar R et al, 2008 [3]	** *Early PE: "significant contributions (…) from maternal factors, PlGF, PAPP-A and (…) PI" | Late PE: "significant contributions (…) from maternal factors, PlGF and (…) PI but not PAPP-A"*					
M-PI + Maternal history + PlGF	Early	0.941	90.0	89.7	8.97	0.11
	Late	0.817	90.0	49.0	4.90	0.57
2nd Trimester						
**Onwudiwe N et al, 2008 [26]	** *"maternal characteristics, (…) PI and (…) MAP provided significant independent contribution"*					
M-PI + Maternal history + MAP	Early	0.996	90.0	100.0	10.00	0.00
	Late	0.830	90.0	56.4	5.64	0.48
**Spencer K et al, 2007 [40]	** *"combining (…) Doppler with (…)PP13 or PAPP-A or all three together did not improve detection"*					
M-PI + PAPP-A + PP13	Early*	0.880	80.0	80.0	4.00	0.25
	Late	0.610	80.0	43.0	2.15	0.71
**Alkazaleh F et al, 2006 [4]	** *"these ultrasound tests [including UAD] did not identify women at greater (…) risk of severe preeclampsia"*					
M-PI, in women with hCG>2.5 MoM and AFP>2.0 MoM	Severe†	-----	49.0	69.0	1.35	0.63
**Spencer K et al, 2007 [40]	** *"combination [of PP13] with other biochemical or ultrasound markers did not improve the detection"*					
M-PI + hCG + PP13	Early*	0.930	80.0	100.0	5.00	0.00
	Late	0.580	80.0	14.0	0.70	1.08
**Spencer K et al, 2006 [44]	** *"screening can be improved by combining (…) Doppler scan with (…) biochemical analysis"*					
M-PI + Inhibin A + Activin A	Total	0.970	90.0	92.0	9.20	0.09
**Florio P et al, 2003 [16]	** *"combining both hormones may improve the predictive value of the test"*					
Inhibin A + Activin A, in women with diastolic notches	Total	-----	97.5	33.3	13.32	0.68
High inhibin A or activin A, in women with diastolic notches	Total	-----	72.5	66.7	2.43	0.46
**Spencer K et al, 2007 [40]	** *See above.*					
M-PI + Inhibin A + PP13	Early*	0.910	80.0	100.0	5.00	0.00
	Late	0.550	80.0	29.0	1.45	0.89
M-PI + Activin A + PP13	Early*	0.920	80.0	100.0	5.00	0.00
	Late	0.840	80.0	71.0	3.55	0.36

Stepan H et al, 2007 [46] | *"measurement of angiogenic factors has a useful predictive power when used in a risk group and focused to severe and early presenting forms of preeclampsia"*						
sFlt1/PlGF ratio in women with M-PI>1.45 and/or bilateral diastolic notches	Early	-----	51.0	67.0	1.37	0.65
	Total	-----	51.0	62.0	1.27	0.75
sFlt1 + PlGF in women with M-PI>1.45 and/or bilateral diastolic notches	Early	-----	95.0	83.0	16.60	0.18
	Total	-----	73.0	77.0	2.85	0.32
Diab AE et al, 2008 [14] | *"We found (…) angiogenic factors to be highly predictive in (…) women with high-risk pregnancies"*						
sFlt1/PlGF ratio in women with M-PI>1.45 and/or bilateral diastolic notches	Early	0.959	90.0	100.0	10.00	0.00
	Total	0.937	85.0	100.0	6.67	0.00
1st and 2nd Trimesters						
Spencer K et al, 2007 [41] | *"the use of all three markers had no advantage over using just two of them"*						
M-PI (T2) + PAPP-A (T1) + PP13 (T1)	Early*	0.850	80.0	70.0	3.50	0.38
	Late	0.820	80.0	73.0	3.65	0.34
Yu J et al, 2010 [50] | *"The combination of activin A, inhibin A and (…) PI or activin A, PIGF and (…) PI provided a test with high sensitivity and specificity"*						
M-PI (T2) + Inhibin A (T1-T2) + Activin A (T1-T2)	Total	0.907	90.0	83.0	8.30	0.19
M-PI (T2) + Inhibin A (T1-T2) + PlGF (T1-T2)	Total	0.840	90.0	66.0	6.60	0.38
M-PI (T2) + Activin A (T1-T2) + PlGF (T1-T2)	Total	0.925	90.0	84.0	8.40	0.18

PE: pre-eclampsia; UAD: uterine artery Doppler; AUC: area under the ROC curve; Sp: specificity; Sn: sensitivity; LR+: likelihood ratio of the positive result; LR-: likelihood ratio of the negative result; PI: pulsatility index; L-PI: lowest PI; M-PI: mean PI; MAP: mean arterial pressure; PAPP-A: pregnancy-associated plasma protein-A; hCG: human chorionic gonadotropin; AFP: alpha-fetoprotein; PP13: placental protein 13; PlGF: placental growth factor; soluble fms-like tyrosine kinase 1; T1: first trimester; T2: second trimester.

Unless otherwise specified, early PE refers to PE requiring delivery before 34 weeks' gestation and late PE refers to PE requiring delivery at or after 34 weeks' gestation. *PE requiring delivery before 35 weeks' gestation. †Severe PE refers to PE with end-organ involvement or fetal growth restriction.

Table 6 – Screening for PE with UAD and three other markers.

Test	Type of PE	AUC	Sp %	Sn %	LR+	LR-
1st Trimester						
Poon LC et al, 2009/2010 [34,36,37] | *Early PE: "significant contributions from PAPP-A (...) maternal factors, MAP and (...) L-PI" | Late PE: "prediction from the combination of maternal factors (...) L-PI and MAP (...) was not improved by addition of PAPP-A"*						
L-PI + Maternal history + MAP + PAPP-A	Early	0.960	90.0	94.6	9.46	0.06
Poon LC et al, 2009 [33] | *Early PE: "significant contributions from maternal factors, (...) PI, MAP, PAPP-A, and PlGF" | Late PE: "significant contributions from maternal factors, (...) PI, MAP, and PlGF but not PAPP-A"*						
M-PI + Maternal history + MAP + PlGF	Early	-----	95.0	82.8	16.56	0.18
	Late	-----	95.0	44.9	8.98	0.58
Akolekar R et al, 2009 [2] | *Early PE: "PP13 (...) did provide significant contribution to prediction" but it "did not improve the detection achieved by the combination of maternal factors, (...) L-PI and (...) PAPP-A" | Late PE: "PP13 (...) was not significantly different from controls and therefore did not add value in screening"*						
L-PI + Maternal history + PAPP-A + PP13	Not available					
Audibert F et al, 2010 [8] | *"the addition of Doppler did not improve the diagnostic accuracy of screening by clinical characteristics alone or combined with PAPP-A, PlGF and Inhibin A"*						
L-PI + Maternal history + PAPP-A + Inhibin A	Early*	0.834	90.0	37.5	3.75	0.69
	Total	0.745	90.0	32.4	3.24	0.75
Akolekar R et al, 2009 [1] | *Early PE: "significant contributions from (...) PI (...) PAPP-A (...) inhibin A (...)" and maternal history | Late PE: "significant contributions from (...) PI (...) inhibin A" and maternal history "but not from (...) PAPP-A"*						
M-PI + Maternal history + PAPP-A + Inhibin A	Early	0.938	90.0	88.5	8.85	0.13
Akolekar R et al, 2008 [3] | *Early PE: "significant contributions (...) from maternal factors, PlGF, PAPP-A and (...) PI" | Late PE: "significant contributions (...) from maternal factors, PlGF and (...) PI but not PAPP-A"*						
M-PI + Maternal history + PAPP-A + PlGF	Early	0.936	90.0	86.2	8.62	0.15
1st and 2nd Trimesters						
Yu J et al, 2010 [50] | *"Combination of the three serum markers [inhibin A, activin A, PIGF] and (...) PI has a higher prediction value"*						
M-PI (T2) + Inhibin A (T1-T2) + Activin A (T1-T2) + PlGF (T1-T2)	Total	0.941	90.0	90.0	9.00	0.11

PE: pre-eclampsia; UAD: uterine artery Doppler; AUC: area under the ROC curve; Sp: specificity; Sn: sensitivity; LR+: likelihood ratio of the positive result; LR-: likelihood ratio of the negative result; PI: pulsatility index; L-PI: lowest PI; M-PI: mean PI; MAP: mean arterial pressure; PAPP-A: pregnancy-associated plasma protein-A; PP13: placental protein 13; PlGF: placental growth factor; T1: first trimester; T2: second trimester.

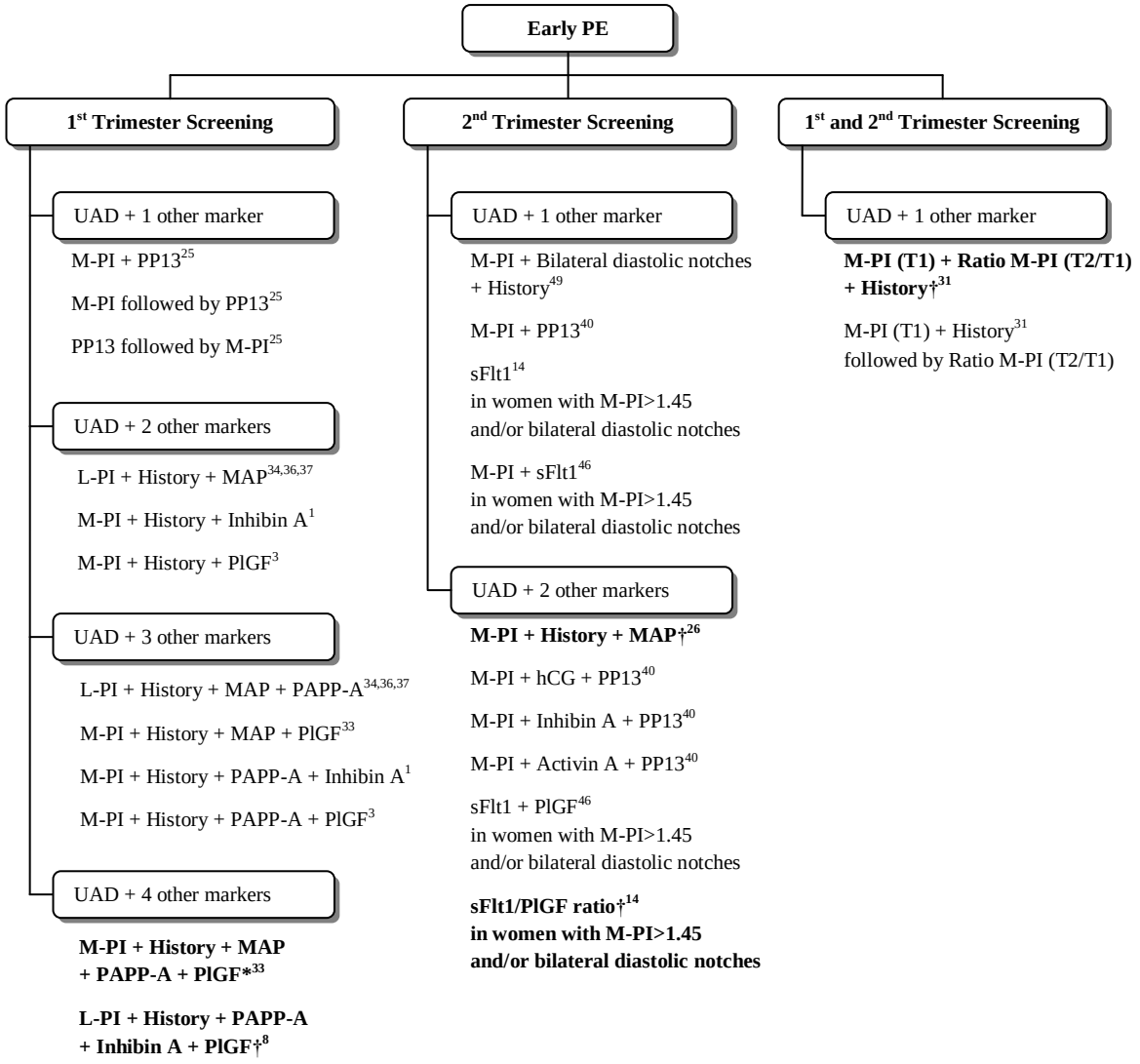
Unless otherwise specified, early PE refers to PE requiring delivery before 34 weeks' gestation and late PE refers to PE requiring delivery at or after 34 weeks' gestation. *PE diagnosed before 34 weeks' gestation.

Table 7 – Screening for PE with UAD and four other markers.

Test	Type of PE	AUC	Sp %	Sn %	LR+	LR-
1st Trimester						
Poon LC et al, 2009 [33] | *Early PE: "significant contributions from maternal factors, (...) PI, MAP, PAPP-A, and PlGF" | Late PE: "significant contributions from maternal factors, (...) PI, MAP, and PlGF but not PAPP-A"*						
M-PI + Maternal history + MAP + PAPP-A + PlGF	Early	-----	95.0	93.1	18.62	0.07
	Late	-----	95.0	35.7	7.14	0.68
Audibert F et al, 2010 [8] | *"the addition of Doppler did not improve the diagnostic accuracy of screening by clinical characteristics alone or combined with PAPP-A, PlGF, and Inhibin-A"*						
L-PI + Maternal history + PAPP-A + Inhibin A + PlGF	Early*	0.994	90.0	100.0	10.00	0.00
	Total	0.815	90.0	40.0	4.00	0.67

PE: pre-eclampsia; UAD: uterine artery Doppler; AUC: area under the ROC curve; Sp: specificity; Sn: sensitivity; LR+: likelihood ratio of the positive result; LR-: likelihood ratio of the negative result; PI: pulsatility index; L-PI: lowest PI; M-PI: mean PI; MAP: mean arterial pressure; PAPP-A: pregnancy-associated plasma protein-A; PlGF: placental growth factor.

Unless otherwise specified, early PE refers to PE requiring delivery before 34 weeks' gestation and late PE refers to PE requiring delivery at or after 34 weeks' gestation. *PE diagnosed before 34 weeks' gestation.

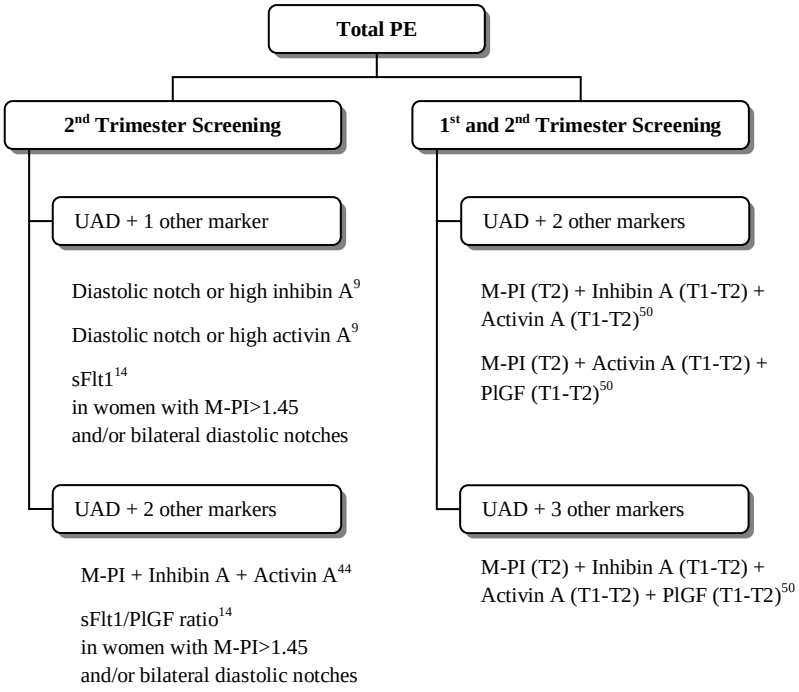


PE: pre-eclampsia; UAD: uterine artery Doppler; PI: pulsatility index; L-PI: lowest PI; M-PI: mean PI; MAP: mean arterial pressure; PAPP-A: pregnancy-associated plasma protein-A; hCG: human chorionic gonadotropin; PP13: placental protein 13; PlGF: placental growth factor; sFlt1: soluble fms-like tyrosine kinase 1; T1: first trimester; T2: second trimester.

*LR+ > 10 and LR- < 0.1.

†LR+ = 10 and LR- < 0.1.

Figure 3 – Screening tests which provided moderate or convincing prediction of early PE, according to the likelihood ratio (LR) values.



PE: pre-eclampsia; UAD: uterine artery Doppler; PI: pulsatility index; M-PI: mean PI; PlGF: placental growth factor; sFlt1: soluble fms-like tyrosine kinase 1; T1: first trimester; T2: second trimester.

Figure 4 – Screening tests which provided moderate or convincing prediction of total PE, according to the likelihood ratio (LR) values.

JOURNAL OF PERINATAL MEDICINE

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Brown AM, Stubbs DW, editors. Medical physiology. New York: Wiley; 1983.
5. *Chapter in a book:*
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5. *Chapter in a book:*
Meltzer PS., Kallioniemi A., Trent JM., Chromosome alterations in human solid tumors. In: Vogelstein B., Kinzler KW., editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93–113.

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