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REVIEW ARTICLE

Prediction of Pre-eclampsia

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Abstract Pre-eclampsia (PE) is a disease of high maternal, fetal, and neonatal mortality and morbidity. Early recognition, ideally in the first trimester of women at risk for PE will enable prophylaxis and help reduce associated adverse outcomes. No single test is supported by robust evidence to predict PE and no single test has emerged as a front runner. Screening based on risk factors has low sensitivity. Uterine artery Doppler is the primary screening modality for prediction of PE. Individually, no biomarker has shown to have sufficient clinical value in prediction of PE. However, sFlt-1/PlGF ratio performs better than others. A combination of uterine artery Doppler, maternal serum biomarkers, and maternal characteristics offers best predictive power at the moment.

Keywords Pre-eclampsia · Prediction of pre-eclampsia · Screening of pre-eclampsia

Introduction

The incidence of pre-eclampsia (PE) and eclampsia is 4.6 and 1.6 %, respectively with an overall incidence of 10 % for all hypertensive disorders of pregnancy [1, 2]. Pre-eclampsia is subdivided into early onset and late onset type, the former diagnosed and needing delivery before 34 weeks and the later after 34 weeks. Overall, 10–15 % of direct maternal deaths are associated with PE and eclampsia [2]. PE is also a major cause of fetal, neonatal mortality, and morbidity worldwide. It is, therefore, not surprising that intense research is on to predict and thus prevent PE.

Pathophysiology

The disease is illusive. Whatsoever the trigger may be genetic, immunological, or environmental, the basic pathophysiology, as understood today, is a 'defective placentation', which means failure of trophoblasts to migrate, invade the spiral arterioles, and convert them into wide flaccid channels from narrow contractile ones. When this remodeling is incomplete, there is an increase in resistance to blood flow in the uterine arteries as reflected by measurement of uterine artery Doppler. Because of reduced uteroplacental perfusion and resultant ischemia, there is release of various biochemical analytes, which can be measured in the maternal serum. These resulting ischemic products cause multiorgan dysfunction. Early onset PE is due to defective placentation, whereas late onset PE is because of aging of normal placenta or/and increased maternal predisposition.

Prediction

World Health Organization (WHO) in 2004, while reviewing all existing tests for prediction of PE, laid down the criteria for a good prediction test that the test should be simple, rapid, noninvasive, inexpensive, easy to carry out, early in gestation, impose minimal discomfort or risk, widely available, valid, reliable, and reproducible with high likelihood ratio (LR) for a positive result (>10), and low likelihood ratio for a negative result (<0.1). WHO further concluded that none of the existing tests meet these criteria [3]. The various screening modalities are discussed below.

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Screening Based on Risk Factors

Traditionally, screening or prediction of PE has been based on risk factors (Table 1) [4].

Table 1 Risk factors for prediction of PE and relative risk

Risk factors for PE	Relative risk
Nulliparity	3
Prior PE	7
Advanced maternal age	2
Chronic hypertension	–
Chronic renal disease	–
Diabetes	3.5
Obesity	–
Multiple gestation	3
Vascular/Connective tissue disorder(e.g., lupus)	–
Antiphospholipid antibody syndrome/Thrombophilia	9
Family history of PE	2–4
Patient born SGA	–
Prior adverse pregnancy outcomes	–

PE pre-eclamsia *SGA* small for gestational age

Poon et al. [5] showed that screening tool based on risk factors carries a detection rate of 37 % for early PE, 28.9 % for late PE, and 20.7 % for gestational hypertension (GH) at a false positive rate of 5 %.

Uterine Artery Doppler during First Trimester and Prediction of PE

The first prospective study correlating abnormal uterine artery Doppler waveforms and PE was published by Harrington et al. in 1997 [6]. Following this landmark study, many studies have been published with a wide range of prediction and use of different criteria (Table 2).

Inference from these studies is that prediction accuracy is greater for early onset PE than for late onset PE and accuracy increases when maternal history and risk factors are included.

A very recent large meta-analysis by Velauthar on 55,974 women firmly established that uterine artery Doppler during first trimester is a useful tool for prediction of PE (sensitivity 47.8 %, specificity 92.1 % for early onset PE; sensitivity 26.4 %, specificity 93.4 % for any PE). The numbers needed to treat (NNT) with aspirin to prevent one case of early onset PE fell from 1000 to 173 and from 2500

Table 2 Uterine artery Doppler velocimetry during first trimester and the prediction of PE

Author, year	Prevalence of PE	Doppler criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Martin, 2001 [7]	63/3045 (2.1 %)	Mean PI>2.35	27	95.4	11	98.4
Martin, 2001 [7] Early PE	14/3045 (0.46 %)	Mean PI>2.35	50	95.1	4.5	99.8
Gomez, 2005 [8]	22/999 (2.2 %)	Mean PI>95th centile	24	95.1	11.3	97.9
Melchiorre, 2008 [9]	90/3058 (2.9 %)	Mean UtA-RI>90th centile	48.5	91.8	6.2	99.4
Plasencia, 2008 [10] Early PE	22/3107 (0.71 %)	Mean PI>95th centile + history	90.9	90	6	99.9
Plasencia, 2008 [10] Late PE	71/3107 (2.3 %)	Mean PI>95th centile + history	40.8	90	8.7	98.4
Poon, 2009 [11] Early PE	37/8366 (0.44 %)	Lowest UtA-PI MOM+ history	81.1	90	3.1	99.9
Poon, 2009 [11] Late PE	128/8366 (1.5 %)	Lowest UtA-PI MOM + history	45.3	90	10.1	99

MOM multiples of the median, *NPV* negative predictive value, *PI* pulsatility index, *PPV* positive predictive value, *UtA* uterine artery

Table 3 Uterine artery Doppler velocimetry during second trimester and the prediction of PE

Author, Year	Doppler criteria	Sensitivity
Steele, 1990 [13]	RI > 0.58	63 % all PE
North, 1994 [14]	RI > 90th percentile Notch 27%	27 % all PE
Albaiges, 2000 [15]	Bilateral notching PI > 95th percentile	35 % all PE 80 % early onset PE
Yu, 2008 [16]	PI > 95th percentile	77 % early onset PE 21.9 % late onset PE
Onwudiwe, 2008 [17]	MAP Maternal history PI > 95th percentile	100 % early onset PE 56.4 % late onset PE
Cnossen, 2008 [18]	Review of 74 studies 80,000 women ↑ PI, notch	*Low-risk women* Sens. 23 %, Sp. 99 % over all Sens. 78 % Sp. 95 % severe PE *High-risk women* Sens. 19 %, Sp. 99 % over all Sens. 80 %, Sp. 78 % severe PE

MAP mean arterial pressure, *PE* pre-eclampsia, *PI* pulsatility index, *RI* resistance index

to 421 for a background risk varying between 1 and 0.4 %, respectively. The authors conclude that based on NNT, abnormal uterine artery Doppler in low-risk women achieves a sufficiently high performance to justify aspirin prophylaxis in those who test positive [12].

Uterine Artery Doppler during Second Trimester and Prediction of PE

Studies on the performance of uterine artery Doppler for prediction of PE during second trimester are set in Table 3.

Inference from this data is that uterine artery Doppler during second trimester has the benefit of improved detection rates as compared to first trimester Doppler, but may be identifying pregnancies at a point when intervention is no longer effective or possible.

A sequential use of uterine artery Doppler during first and second trimester suggests that women who have a relative worsening of mean pulsatility index (PI) from first to second trimester and those who have persistence of abnormal PI in second trimester are more likely to develop PE [19, 20].

On the other hand, many authors do not recommend routine screening of all women for prediction of PE because of high false positive rates, health care costs, besides adding anxiety to patients [3, 21–23].

Table 4 Accuracy of seven markers for prediction of PE

Marker	No. of studies	Detection rates
PP13	5	36 – 80 % for early PE
PAPP A	8	22 – 43 % for early PE
PlGF	4	41 – 59 % for early PE, 33 % for late PE
ADAM 12	5	37 % unspecified PE
Inhibin A	2	35 % unspecified PE
Activin	1	20 % unspecified PE
fβHCG	1	22 % unspecified PE

Maternal Serum Biochemical Markers for Prediction of PE

A host of biomarkers have been linked to the development of PE

↓ PAPP –A, ↓ PP13, ↓ PlGF, ↓ VEGF, ↓ ADAM12, ↓ AFP
↑ Inhibin A, ↑ Activin A, ↑ fβHCG, ↑ sFlt, ↑ IMA, ↑ NGAL, ↑ Cystatin C, ↑ PTX3
↑ urinary kallikerin, altered PlGF sFlt ratio, and ↑ cell free fetal DNA

Sylwia Kuc et al. [24] undertook a systematic review of published literature to assess the accuracy of seven common biomarkers for prediction of PE. Table 4 depicts their observations on the studies for each biomarker with detection rates at a fixed false positive rate (FPR) of 10 %.

Recently, a lot of work has been done on angiogenic markers (PlGF) which are decreased and antiangiogenic markers (SFlt and SEng), which are increased in women who are destined to develop PE. Also, there is a plausible hypothesis that an imbalance between the two that is, an altered ratio can predict PE with greater accuracy. Findings of a large systematic review of 22 case control and 12 cohort studies—on PlGF, sEng, and sFlt-1 are presented below [25]:

- PlGF ⇩ Diag OR 9.0 (95 % CI 5.6–14.5) FPR 5 % Sensitivity 32 %
- sFlt-1 ⇧ Diag OR 6.6 (95 % CI 3.1–13.7) FPR 5 % Sensitivity 26 %
- sEng ⇧ Diag OR 4.2 (95 % CI 2.4–7.2) FPR 5 % Sensitivity 18 %

The authors conclude that although concentrations of these markers before 30 weeks were predictive of PE, most of these markers did not perform well in the first half of pregnancy.

Verlohren et al. have listed the studies on the performance of sFlt-1/PlGF ratio in the diagnosis and prediction of PE (Table 5) [26].

The above mentioned data demonstrate that the sFlt-1/PlGF ratio has the best detection rate for prediction of PE amongst all biomarkers, but how to utilize it in clinical practice, what are the alert cut-offs, and how often to repeat remain the core issues.

Stephan et al. in their opinion statement in 2015 have suggested that sFlt-1/PlGF ratio has become an additional tool for predicting as well as managing PE in the following manner [27].

Women with Suspicion of PE or PE Already Confirmed

- <38—rules out PE irrespective of GA for one week
- >85 (early onset PE 20–33.6 weeks), >110 (late onset PE ≥ 34 weeks)—likely to have PE, re-measure after 2–4 days
- 38–85 (early onset PE), 38–110 (late onset PE)—moderate or high risk for developing PE in four weeks, follow in 1–2 weeks early onset PE, lower threshold for induction of labor (IOL) for late onset PE
- Already confirmed PE

> 655 at $< 34 + 0$ weeks Need to deliver
> 201 at $\geq 34 + 0$ weeks

Asymptomatic Women at High Risk of PE

- History or abnormal UtA Doppler
- Normal ratio (<38)—rules out PE for at least one week
- Serial measurements can be considered
- Optimal time to start is 24–26 weeks because at this time, the difference in values between women with normal outcome and those destined to develop early PE are usually already significant.

However, the authors caution that as of today, Sflt, PlGF, or Sflt/PlGF ratio has not been incorporated into any official guideline.

WHO global program to conquer PE has undertaken a large prospective observational study with the aim to measure sFlt1, sEng, VEGF, and PlGF levels longitudinally in blood and urine in about 8000 high- and low-risk women. Result of this study will perhaps establish the role of biochemical markers for prediction of PE.

Combination of Maternal Characteristics, Uterine Artery Doppler, and Serum Biomarkers

In order to improve upon detection rates, several investigators have combined different biomarkers along with maternal characteristics and uterine artery Doppler

Table 5 Studies on the performance of sFlt-1/PlGF ratio in the diagnosis and prediction of PE [26]

Study	Number of patients with PE (control)	Patients	Sensitivity (%)	Specificity (%)
I *Before onset of PE*				
Stepan et al. (2007)	12 (38)	All patients	62	51
	9 (38)	Early-onset PE	67	51
Kim et al. (2007)	46 (100)	All patients	80.4	78
Crispi et al. (2008)	38 (76)	Early-onset PE	84.2	90
Diab et al. (2008)	33 (108)	All PEs	100	85
	8 (108)	Early-onset PE	90	90
De Vivo et al. (2008)	52 (52)	All patients	88.5	88.5
Kusanovic et al. (2009)	62 (1560)	All patients	40.3	78.5
II *During PE*				
Verlohren et al. (2010)	37 (268)	Early-onset PE	89	97
	34 (268)	Late-onset PE	74	89
	71 (268)	All patients	82	95
Ohkuchi et al. (2010)	15 (144)	Early-onset PE	100	95
	19 (144)	Late-onset PE	95	95
	34 (144)	All patients	97	95
Sunderji et al. (2010)	39 (388)	All patients	96	97
	9 (1613)	Early-onset PE	100	89.1

in first trimester [24, 28–32] as well as in second trimester [32–34].

Giguere et al. while assessing 37 studies utilizing 71 different combinations have highlighted that in low-risk population PP13, PAPP-A, ADAM 12, activin A, or inhibin A in first or early second trimester and uterine artery Doppler in second trimester has a sensitivity of 60–80 % and specificity of >80 %, whereas in high-risk population PP13, uterine artery PI in first trimester has a sensitivity of 90 % and specificity of 90 % (result of a single study) [35].

A model for prediction of PE was developed by Poon et al. in 2009. The model incorporated maternal characteristics (BMI, nulliparity, previous h/o PE, ethnic origin), uterine artery Doppler, maternal MAP, PAPP-A, and PlGF. It was tested on 7797 women with singleton pregnancies in their first trimester. The results were impressive—for early PE, the sensitivity was 94.1 %, and specificity was 94.3 % at a FPR of 5 %. The positive likelihood ratio (LR) was 16.5 and negative LR was 0.06, easily meeting the WHO criteria [3]. Predictive result for late PE and GH were 35.7 % and 18.3 %, respectively. Overall, one in five women who were screen positive, developed hypertensive disease of pregnancy [36]. This model so far has the best predictive power but has not been replicated in any other study.

In nutshell, predictive efficacy of multiple markers for prediction of PE has been evaluated on a large scale as discussed in the article, but utilization in clinical practice for an individual patient and offering preventive strategies, like aspirin, metformin, anticoagulation, etc. is the key to overcome PE related maternal and fetal morbidities and mortality. The model of personalized risk prediction and prevention given by Baschat et al. [37] is perhaps the answer (Fig. 1). The model incorporates maternal risk factors (personal, placental, cardiovascular, metabolic, and prothrombotic) along with first trimester screening, and offering preventive modalities accordingly. The logic behind this is that women with these risk factors are more prone to develop PE. These findings are echoed in a study by Scholten et al. [38] where they evaluated 1297 formerly pre-eclamptic women 6–12 months postpartum for these risk profiles. Cardiovascular risk factors were seen in 66.1 % hyperhomocysteinemia in 18.7 %, metabolic syndrome in 15.5 %, and thrombophilia in 12.8 %. Overall, 77 % of women had at least one risk factor.

Indian data on prediction of PE is scant. Studies from year 2000 onwards have linked low calcium, creatinine ratio [39, 40], low superoxide dismutase, catalase, RBC glutathione, vitamin E [41], high midtrimester β-hcg [42], positive microalbuminuria [43], and isometric handgrip test to the development of PE [44]. These new markers have not been studied in the Indian population, but the potential is enormous for a nation of 1.32 billion with a birth rate of 22.22/1000 population.

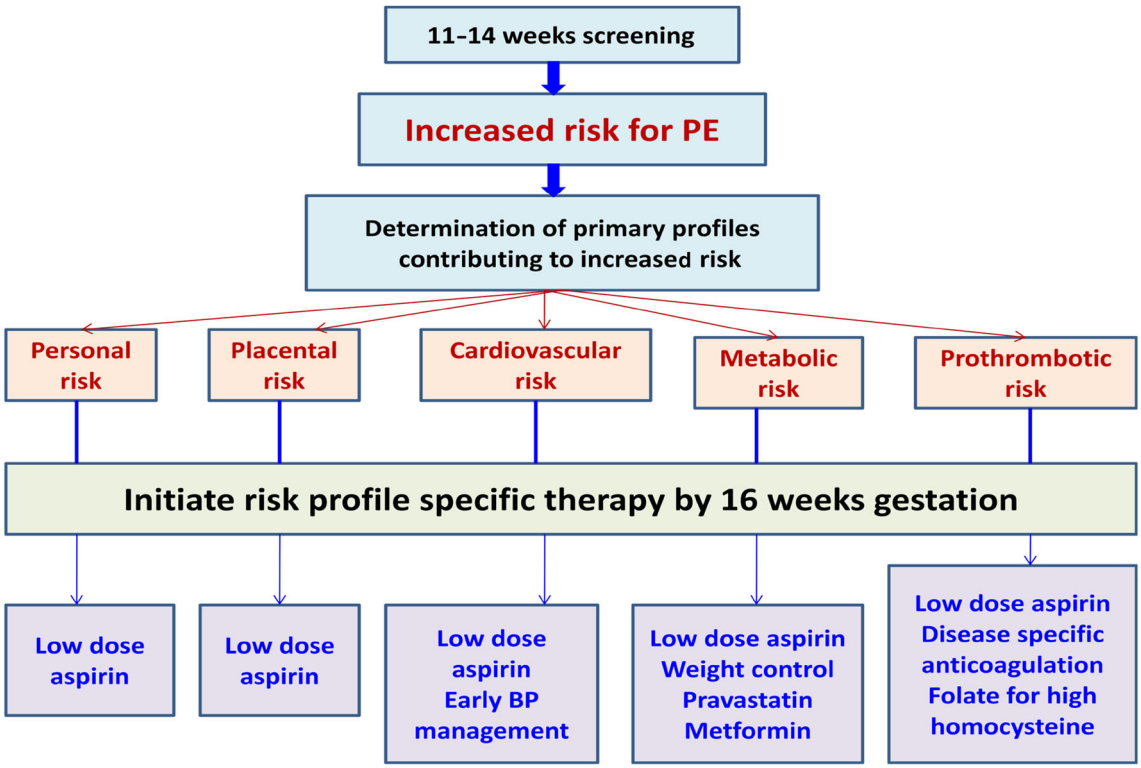

Fig. 1 Model of personalized risk prediction and prevention [37]

Conclusion

Pre-eclampsia remains an important cause of maternal/fetal mortality and morbidity. Prediction of PE is a challenging task. Individually, no test is supported by robust evidence to predict PE. A combination of uterine artery Doppler, maternal serum analytes, and maternal characteristics offers best predictive approach at the moment.

Compliance with Ethical Standards

Conflict of interest None.

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