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Prediction of pre-eclampsia

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Abstract

Pre-eclampsia is a leading cause of neonatal and maternal mortality and morbidity that complicates approximately 2–8% of all pregnancies worldwide. The precise cause of pre-eclampsia is not completely understood, with several environmental, genetic, and maternal factors involved in its pathogenesis and pathophysiology. An accurate predictor of pre-eclampsia will facilitate early recognition, close surveillance according to the individual risk and early intervention, and reduce the negative consequences of the disorder. Current evidence shows that no single test predicts pre-eclampsia with sufficient accuracy to be clinically useful. A combination of markers into multiparametric models may provide a more useful and feasible predictive tool for pre-eclampsia screening in the routine care setting than a test of either component alone. This review presents a summary of the current advances on prediction of pre-eclampsia, highlighting their performance and applicability. Key priorities when conducting research on predicting pre-eclampsia are also analyzed.

Keywords

Biological markers, pre-eclampsia, prediction, screening, pregnancy complications

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Introduction

Pre-eclampsia (PE), a complex, multisystem, pregnancy-associated hypertensive disorder, typically developing after the 20th week of gestation, that complicates 2–8% of pregnancies, is a leading cause of neonatal and maternal mortality and morbidity.[1–4] PE is considered to be the most prevalent hypertensive disorder of pregnancy, associated with an increased risk of both short- and long-term complications for both the mother and the neonate, contributing to more than 60,000 maternal deaths per year.[3,5–7] There is growing evidence highlighting that in addition to the immediate risk, PE is also considered a cardiovascular risk factor for both mother and child in later life.[8–10] Despite an intensive research effort to elucidate the origin of PE, the exact underlying pathophysiological mechanisms still remain complex and unclear with several environmental, genetic and maternal factors contributing.[11] An accurate prediction of PE and early identification of women at increased risk is a clinical priority to minimize complications by both careful monitoring and early treatment (i.e. low-dose aspirin started prior to 16 weeks of gestation).[12–16] Several studies have evaluated the predictive ability of different tests to predict PE using individual or a combination of clinical characteristics, biomarkers, and ultrasound markers. Despite this, no consensus on the optimal screening strategy has been reached, mostly because of the lack of adequate performance.[17] The aim of this review is to provide an overview of the current knowledge regarding PE prediction.

Screening for pre-eclampsia

Considering pre-eclampsia's prevalence and clinical importance, an effective screening test would be most useful in its ability to detect women who require close monitoring. To assess a screening tool's predictive ability, sensitivity, specificity, positive predictive value, and negative predictive value should be evaluated. A perfect screening test would be 100% sensitive and 100% specific, henceforth would be positive for all those with the disease and negative for all those who did not.[18] In clinical terms, with a high sensitivity test, most patients with PE will correctly be identified as having the condition. While with a high specificity test, most healthy women (without PE) will correctly be identified as not having the condition. The test should also be simple, rapid, non-invasive, inexpensive as well as valid, reliable, and reproducible with a high positive and a low negative likelihood ratio.[19] The cost-effective test should ideally identify women with an increased risk early in pregnancy, who could be offered potential treatment to prevent the disorder and thereby minimize its negative impact. However, the optimal timing for PE screening is controversial. While the conventional approach to PE diagnosis is based on the incidence of clinical symptoms, usually discovered during routine obstetric visits in the second or third trimester of pregnancy, an alternative screening method has been proposed in 2011 by Dr. Nicolaides, which involves a comprehensive screening in the first trimester for stratification for all major obstetric complications, and then contingent screening based on the risk reassessment at each visit.[20,21] By following this proposed inverted pyramid of pregnancy care, low-risk pregnancies would attend a standard care program with fewer visits, while a more accurate monitoring of high-risk groups and possible prophylactic pharmacological interventions (e.g. low-dose aspirin) would possibly lead to a reduction of

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complicated pregnancies, but also could lead to fewer long-term complications for both mother and child.[20–23]

Patient identification: Risk factors

Due to lack of knowledge of possible underlying pathophysiological mechanisms responsible for PE, there are not yet any reliable and validated predictors to identify most women who will develop the disease. The diagnosis of PE is usually made by detection of signs including hypertension and proteinuria during antenatal monitoring that could indicate development of the disease. However, this method is not appropriate for early prediction or identification of high-risk women that are likely to develop the disease.[24,25] The uncertainty of clinical diagnosis, with a fraction of pregnant women developing subjective symptoms and signs of PE (e.g. headache, abdominal pain, visual disturbances) and only 20% of these are diagnosed, indicates that there is a clear need for improved testing methods.[26] Even though the precise etiology of PE remains complex and unclear, distinguishing between women of moderate- and high-risk is possible. It was proposed by the National Institute for Health and Clinical Excellence (NICE) that there is a classification for moderate risk and high risk factors, which could be used to identify the women most likely to benefit from aspirin prophylaxis.[27] Women viewed as high risk include those with chronic hypertension, history of any hypertensive disorder or PE in previous pregnancies, diabetes (type 1 or type 2), chronic kidney disease and autoimmune disorders, including systemic lupus erythematosus or antiphospholipid antibody syndrome.[22,28,29] Factors considered to be of moderate risk are primiparity or pregnancy interval greater than 10 years, extreme age (below 20 years old or above 40), BMI of 35 kg/m^2 or more, a family history of PE, polycystic ovarian syndrome, and multiple pregnancies.[22,30] According to this classification, aspirin is advised, if two moderate-risk or a single high-risk factor are present.[15] The American College of Obstetricians and Gynecologists (ACOG) considers the same risk factors, with the exception of a value higher than 30 kg/m^2 for the BMI at the beginning of the pregnancy and makes no distinction between their severity but rather considers them all as 'high-risk' factors.[31] The main advantage of using such risk factors is to allow the identification of those women that should be offered subspecialty referral very early in their pregnancy. However, despite the fact that organizations such as ACOG and NICE endorse evaluation of clinical and demographic factors as the best and only recommended screening approach for PE, yet, they are neither sensitive or specific enough to be used alone and therefore, they cannot be used reliably for PE prediction. Likewise, this screening approach is likely to identify many women as requiring additional monitoring, and increase the resources required with potentially limited diagnostic utility.[25,32]

Maternal hemodynamic and vascular markers

No early and reliable first trimester marker is available for early prediction of pre-eclampsia development. Blood pressure remains an important clinical predictor used as part of routine antenatal assessment. However, in an evaluation of a heterogenous population, mean arterial pressure (MAP) has shown prediction rates of 58% for early PE and 44% for late PE, and a 5% of false positives.[33,34] An additional non-invasive screening tool that is used for the evaluation of the uteroplacental circulation is the study of uterine arteries using Doppler velocimetry. The use of it on a large scale is restricted by the cost, availability of the ultrasound device and the expertise of the professional performing the examination.[33] Pulse wave analysis has been found to be a promising noninvasive technique when applied in a sample of 210 intermediate-risk women at 11–14 weeks as an 88% detection rate for a 10% false positive for the detection of early onset PE was found.[35] These findings indicate that this pulse wave analysis may offer a more accurate evaluation of central vascular pressure than conventional blood pressure. Despite several years of research in the field, a single test, accurate enough to predict PE sufficiently well, has not yet been found.[17,19,36,37] In actual practice, the use of clinical and lifestyle factors in the prediction of PE has shown an overall predictive potential of 30% to 37% for early-onset PE and 29% for late-onset PE and had a 5% of false-positive results.[33,38]

Biochemical, biophysical, or ultrasound markers

Amongst other alternatives of potential predictors is the use of biochemical markers. Extensive research has identified a range of potential biophysical and biochemical predictors of PE.[39–42] Several of these markers are measurable in maternal blood and have therefore been evaluated as biomarkers for PE prediction. These include serum and plasma markers of placental endocrine function, maternal endothelial dysfunction, renal dysfunction, general metabolic status, oxidative stress, and hemolysis and inflammatory markers.[43] Screening markers that have recently undergone investigation for PE include factors related to angiogenesis, coagulation, lipids, placental hormones, cell adhesion, fetal DNA, inflammation, and growth factors. Despite rigorous research efforts to identify potential biochemical markers, no factor established a sufficient degree of accuracy for the prediction of PE.[17] A recent review of different biochemical markers for PE before the 25th week of gestation did not reveal a single test with a sensitivity and specificity over 90%.[36] Likewise, another study that reviewed 27 different tests for PE prediction found only a few reached specificities above 90%. These were BMI of 34 kg/m^2 or higher, α-fetoprotein, and bilateral uterine artery Doppler notching.[44] As far as genetic markers are concerned, there were numerous suggestions of gene mutations playing a role in the development of PE, although no single polymorphism has shown any predictive value.[17] Amongst the genes being investigated are methylenetetrahydrofolate reductase and endothelial nitric oxide synthase, while PAI-1 4G/5G (recessive model) polymorphism showed evidence of contribution to PE.[11]

Combination of markers

The absence of a single robust, sensitive marker is not surprising since PE is characterized by a complex etiology with a range of heterogeneous clinical and laboratory findings. Hence, it is unlikely that a single marker could predict the mixed presentations and potential causes of the disorder.[40,41] It is established that combinations of markers that reflect different aspects of pathogenesis are needed to improve the possibility for predicting PE with a high degree of accuracy.[19] Potential components of such combinations could be anamnestic risk factors, angiogenic, inflammatory and other biochemical factors, uterine artery Doppler, and MAP. In the last decades, many studies have combined one or more biochemical markers with uterine Doppler to assess prediction rates for early and late PE separately. Yet, until now, there is no general acceptance of these combinations in clinical practice.[40,41] A previous large study that combined maternal characteristics, including MAP, uterine artery pulsatility index and several biochemical markers (PAPP-A, PlGF, PP13, sEndoglin, Inhibin-A, Activin-A, Pentraxin 3, and P-Selectin) has shown 95% specificity for early-onset 91% sensitivity, intermediate onset 79% sensitivity, and late onset PE 61% sensitivity.[45] Similarly, a study that examined a combination of different maternal characteristics and biochemical markers in the first trimester (MAP, uterine artery

pulsatility index, PAPP-A, and PlGF) has revealed predictive values with 95% specificity and 93% sensitivity for early-onset and 36% for late-onset PE.[46] Another example of such combination is the fetal hemoglobin (HbF)/hemoglobin ratio and α1-microglobulin, that has showed 90% sensitivity and 77% specificity for prediction of PE in early pregnancy.[47] Findings of systematic reviews and meta-analyses that evaluated the predictive capabilities of combinations of biochemical and ultrasonographic markers demonstrated that such combinations predicted PE in a better way than a single predictor would. This insight might improve the prediction of PE, especially in high-risk populations.[37,48–50] However, even though these multiparametric models have shown promising results, when applied to populations, other than the population from which they were derived, they have shown a poorer performance.[51] This finding is also supported by several studies which found that only a minority of these models were externally validated or calibrated.[52–57]

Priorities for future research

There is a need to broaden our understanding of PE and particularly its prediction and prevention. Optimising the early identification of women at high risk will increase the opportunities for earlier intervention which may alter the prognosis and reduce the chance of adverse pregnancy outcomes. Thus, establishing a reliable screening program will enable the improvement of clinical guidelines, better surveillance, and efficient prophylactic measures as well as support for high risk women and offspring.

The challenge of PE prediction requires additional research studies to define the best and most accurate models and methods of prediction that could be used in clinical practice. More emphasis should be targeted at predicting PE in the first trimester so that prophylactic interventions such as low-dose aspirin can be initiated. Also, when evaluating the prediction of a given test or combination of tests for PE, a clear distinction must be made between early-onset and late-onset phenotypes. Thus, standardization of definitions, methods, and statistical analyses will be useful for multi-national comparison and meta-analysis of results as well as development and evaluation of prediction models, which ultimately promote clinical health practice.[58] Furthermore, well-designed large prospective studies are needed to assess the accuracy of risk prediction models according to disease onset and population risk in comparison to the current single risk factor screening. Further research is necessary to determine whether predictive models can be further improved with the addition of novel biomarkers implicated in the pathophysiology of PE as well as identify additional combinations of markers that may predict the occurrence of PE. Finally, multiparametric models need to be validated externally to assure validity and reliability of their predictive performance before they can be used in clinical practice.

Conclusions

Clinical history remains important in the assessment of pregnant women, to identify features that put them at higher risk of developing pre-eclampsia. Considering the rising prevalence, as well as the great social and economic impact of PE, the early identification would mean plans for enhanced monitoring could be instituted in a subgroup of women. Overall, no reliable single predictor for PE exists and the clinical tools are restricted to subjective symptoms with poor specificity and sensitivity. A combination of maternal characteristics, biophysical, biochemical, and ultrasound markers may provide a more useful and feasible predictive tool for PE screening in the routine care setting than a test of either component alone. However, further validation and calibration of promising multivariable prediction models in required before can be clinically implemented universally.

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