REVIEW ARTICLE

Current preeclampsia prediction model and biomarker

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ABSTRACT

Preeclampsia (PE) is a serious hypertensive disorder that occurs during pregnancy and is often accompanied by proteinuria (excessive protein in the urine), posing significant risks to both maternal and neonatal health worldwide. PE is a leading cause of maternal and neonatal morbidity and mortality and is notably challenging to predict due to its unpredictable nature and steadily rising incidence rates globally. As a result, substantial efforts have been directed toward developing predictive models and identifying biomarkers to assess the risk and progression of PE. However, existing models vary widely in their design, methodologies, and efficacy. Current prediction models recommended by notable organizations, including the National Institute for Health and Care Excellence (NICE), the American College of Obstetricians and Gynecologists (ACOG), the Fetal Medicine Foundation (FMF), and the World Health Organization (WHO), generally involve screening based on maternal characteristics and known risk factors. These include parameters such as maternal age, body mass index (BMI), number of pregnancies and births, blood pressure, and uterine arterial pulse index (UtA-PI). Additionally, biomarkers like mean arterial pressure (MAP), UtA-PI, and the ratio of soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1/PlGF) are employed to improve predictive accuracy. Despite the diversity of predictive models and biomarkers, there is no consensus on the optimal model for PE prediction, largely due to the limitations in comparative studies and the challenges involved in cross-study comparisons. However, literature suggests that the FMF model demonstrates superior detection capacity compared to other predictive models.

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Highlights:

1. Most studies report that FMF predictive models involving a combination of maternal factor screening and biomarkers have significantly better detection capacity than risk factor screening alone.
2. All predictive models generally use maternal factors as the basis for calculations and algorithms.
3. Several biomarkers that have been reported in studies to act as elements of prediction models include MAP, UtA-PI, and the ratio of sFlt-1/PlGF level.

INTRODUCTION

The mortality and morbidity among pregnant are mostly caused by hypertension worldwide. It affects 1 in 10 women worldwide, with 20% pre-existing (chronic) and 80% de novo defined as gestational hypertension or preeclampsia.[1] Almost 15% of mortality among pregnant women is caused by preeclampsia or eclampsia. It has also ranked second or third in global rankings of maternal causes of morbidity and mortality, particularly in low to middle-income countries.[2–4] Hypertension in pregnancy includes gestational hypertension, preeclampsia, and eclampsia, characterized by enhanced blood pressure and multiorgan dysfunction. The World Health Organization (WHO) also reported that hypertension is a major leading for maternal death, which accounted for 14% of cases.[3]

During pregnancy, PE could be one of the complications among pregnant women that can impact the condition of the mother and the baby. It even leads to morbidity and mortality globally each year.[1] Preeclampsia happens when there is new-onset hypertension with positive proteinuria in ≥20 weeks of pregnancy, along with any of the following characteristics: defective placentation, the occurrence of placental ischemia, abnormal spiral artery remodeling conditions, increased oxidative stress at the maternal-fetal interface, and an imbalance between angiogenic in the maternal circulation against subsequent endothelial and end-organ damage. This condition can also lead to maternal complications such as placental abruption, kidney disease, eclamptic seizures, and HELLP syndrome. Moreover, fetal growth disturbance and respiratory distress syndrome in neonates could be complications in a fetus with a history of preeclampsia during pregnancy.[5]

Over the past 50 years, there has been a trend toward an increase in the incidence of these exacerbations in low and middle-income countries.[6,7] Previous studies found that most PE-related deaths were due to inadequate treatment. Hence, the maternal and fetal condition in PE cases was associated with broad access to services, quality care, and management of complications, which leads to improved perinatal outcomes. Moreover, better outcomes for both the mother and the baby could arise by precising and early identification and treatment of preeclampsia patients.[8]

Unfortunately, the onset and disease severity are still unpredictable despite the high quality of hospital equipment.[9] Preeclampsia remains one of the major pathological manifestations of preterm birth, approximately 15% of all preterm births10–12, and increases the length of stay of the mother or newborn in the ICU. This condition leads to the enhancement of health care costs.[13] To date, several predictive models have been developed to investigate the risk and development of PE and even the development of biomarkers that can be evaluated in early pregnancy. However, these predictive models have different characteristics and capacities. Some recent studies have shown different findings regarding the ability and capacity of existing predictive models. Therefore, this review aims to identify and assess the current prediction models for PE.

The literature search was carried out from January 2022 to January 2023 through three online scientific journal databases, namely ScienceDirect, PubMed and Google Scholar. The keywords used in the search were "preeclampsia", "biomarker", "prediction", "model", and "diagnosis" accompanied by the use of boolean operators such as "AND" and "OR". The inclusion criteria used in this literature review are (1) publications in the last 10 years; (2) studies use English or Indonesian. After a literature study was carried out, a study screening was then carried out so that all articles that were suitable as the main reference and had been reviewed in terms of validity. importance, and applicability.

PREECLAMPSIA

Definition

Preeclampsia is a condition that only affects pregnant women with hallmarks, including hypertension (high blood pressure) and endothelial dysfunction, which cause extensive end-organ damage. This end-organ damage usually can be evaluated in the liver, blood, brain, placenta, and especially kidneys, represented in proteinuria. Preeclampsia is a systolic blood pressure ≥140 mmHg and/or ≥90 mmHg with positive protein in the urine.[14–16]

Preeclampsia after twenty weeks of pregnancy is diagnosed by the occurrence of new hypertension that is accompanied by one of the following conditions1, 1proteinuria (24-hour proteinuria above 300 mg/24 hours, a urine dipstick test with a result of ≥1+, or enhancement of the proteinuria/creatinine ratio (>0.3 mg/mg); 2), there is maternal organ dysfunction, such as renal impairment (creatinine level > 1.02 mg/dL), liver impairment (transaminases levels arise twice above normal or there is a pain in the right hypochondrium), and persistent neurological symptoms such as scotoma or cephalgia which is followed by hyperreflexia or mental state disturbance);3) dysfunction of utero-

placental which can be assessed from the existence of fetal growth limitation.[16,17]

Risk Factors

Preeclampsia in prior pregnancies, nulliparity, extreme pregnancy age (<20 years old or >40 years old), and African American descent are major risk factors for PE. Body mass index (BMI) of more than 35 kg/m2 and use of contraceptives,[18,19] pre-existing chronic medical history such as chronic hypertension, diabetes mellitus, renal disease, antiphospholipid antibody syndrome, and chronic hypertension[17,19] were also identified as risk factors for PE. Furthermore, previous studies showed that PE rates are also influenced by multiple pregnancy rates and the mean age of women at first pregnancy.[20–22]

The National Institute for Health and Clinical Excellence (NICE) also identified risk factors for PE, which are divided into two categories, namely "moderate risk" and "high risk." This classification aims to provide a tool that can be used to determine which group needs to adopt preventive actions immediately. The conditions are considered "high risk," including any history of hypertensive disorders during prior pregnancies, autoimmune (antiphospholipid antibody syndrome or SLE), diabetes, chronic kidney disease, and persistently high blood pressure. The following conditions are deemed to be "moderate risk," including age above 40 years old, 10 years or more duration between pregnancies, BMI above 35 kg/m2, family history, multiple pregnancies, and primiparous women.[8]

Classification

The classification of PE also affects the timing of applying the appropriate condition. There are several classifications for the disease severity by measuring blood pressure, such as mild PE and severe PE. Mild PE occurs when the blood pressure is 140/90 or more in two inspection times; each inspection is at least 6 hours apart and without organ damage. Severe PE occurs when the blood pressure is 160/110 or more with target organ damage that is represented by proteinuria, pulmonary edema, oliguria, headache, epigastric pain, or oligohydramnios. In addition, there is a classification based on the onset of events, namely early onset (<34 weeks of gestation) and late onset (>34 weeks of gestation).[23]

The classification based on the onset of events is generally based on the differences in etiology and pathogenesis. In early onset, the development of PE commonly involves abnormal placentation under hypoxic conditions. One of the initial examinations that can be performed is Uterine Doppler. Several studies have reported high accuracy in analyzing patients who will subsequently develop early-onset PE. On uterine doppler examination, there will be signs of abnormally high impedance in uterine blood flow, which causes failure of the spiral arteries to form. Early-onset PE generally has a poorer prognosis due to early developmental delay than late-onset PE.[16] In late-onset (also called maternal PE), the development of PE is generally involved in interactions between placental tissue and abnormal maternal factors, such as endothelial dysfunction and oxidative stress. However, the two types of PE are generally indistinguishable clinically because of similar manifestations, especially in the presence of abnormal placentation in both types of PE.[16]

SCREENING AND PREDICTION MODEL

Clinical guidelines for PE prediction models generally involve screening for risk factors, including the number of pregnancies and births, BMI, blood pressure, maternal age, and uterine arterial pulse index (UtA-PI). A recent systematic review involving 70 studies with 425,125 participants also reported that the most commonly used predictive models were patient characteristics and risk factors.[24] Based on findings in literature searches, preeclampsia prediction models generally use clinical findings and maternal history in overall risk assessment. A number of studies also report the use of supporting examinations in the form of blood biomarker examinations to increase predictive value and make more appropriate treatment decisions, such as placental protein which will be discussed later. Four models have been developed by the most commonly used organizations, including guidelines by The National Institute for Health and Care Excellence (NICE), the American College of Obstetricians and Gynecologists (ACOG), and Fetal Medicine Foundation (FMF), and the World Health Organization (WHO) models. Based on previous studies, for gestational age <32 weeks, the ACOG model detected 94% of PE, NICE detected 41% of PE, and FMF detected 100% of PE.[25] Both NICE and ACOG have been reported for use in the entire population of pregnant women without the need for additional testing. However, the FMF model uses additional biomarker tests that aim to increase sensitivity compared to NICE or ACOG.[26,27] All prediction model discussed in this review is described in Table 1.

National Institute for Health and Care Excellence (NICE)

Following the NICE recommendation, a person is determined to have a high risk of experiencing PE if you

have more than one moderate risk factor such as nulliparity, age over 40, BMI more than 35 kg/m2, a family history of PE, or an interval between pregnancies that is more than 10 years) or one of the risk factors tall. The high-risk factors include hypertension in previous pregnancies, chronic kidney disease, diabetes mellitus, or autoimmune diseases. Thus, NICE guidelines also recommended taking an aspirin of 75 to 150 mg daily starting at 12 weeks of pregnancy and continuing until labor.[1,25,27]

American College of Obstetricians and Gynecologists (ACOG)

The ACOG guidelines are quite similar to the NICE guidelines. Still, additional factors, such as a history of small gestational age and sociodemographic characteristics, including African American race or low socioeconomic status, are classified as moderate risk factors.[28,29] Previous study that evaluated ACOG 2013 guidelines showed that only 5% (95%CI: 2%–14% and 2% (95%CI: 0.3%–5%) of preterm and term PE are detected in screenings, with a 0.2% false-positive rate (FPR). In contrast, screening based on the NICE recommendation achieves detection rates for preterm and term PE of 39% (95% CI: 27%-53%) and 34% (95% CI: 27%-41%), respectively, with 10% FPR.[25]

Fetal Medicine Foundation (FMF)

The FMF guideline uses a comprehensive combination of biomarkers and maternal history. Mean arterial pressure (MAP), uterine artery PI (UTPI), and serum PLGF are usually used as biomarkers at 11–14 weeks (or PAPP-A when PLGF is not available) of pregnancy. These combined maternal characteristics with MAP, UtA-PI, and PlGF levels have been shown to improve the prediction of PE in the first trimester of pregnancy. The screening program for preeclampsia (SPREE) study has found that this combined approach has a better detection rate than the NICE method (82.4% vs. 40.8%).[27] As a pooled analysis showed that the combined approach detected 90% of early PE in <32 weeks of gestational age. Therefore, this combined approach is generally recommended for early-onset PE. Furthermore, with a 10% FPR, the overall FMF combined test provides detection rates of 90% for early PE and 75% for preterm PE, respectively. Therefore, it can be concluded that a screening based on the FMF recommendation should be carried out whenever possible.[27,30]

Table 1. PE prediction models based on international organizations guidelines

Prediction model (years)	Country	Description	Evidence
NICE (2019)	United Kingdom	Utilized into two categories of risk factors, namely high risk with a history of pregnancy before with PE, persistent hypertension, autoimmune, diabetes mellitus, chronic kidney disease, antiphospholipid syndrome) and moderate-risk (nulliparous woman, advanced age more than 40 years old, gestational interval more than >10 years, BMI more than 35, family history, and multifetal gestation.	Applicable and feasible to access for all women and can be used to give prophylactic aspirin, but with modest detection capacity
ACOG (2018)	United States of America	Similar to NICE. However, multifetal gestation is categorized as a high-risk factor, and the addition of socio-demographics is moderate-risk.	Applicable and feasible to access for all women and can be used to give prophylactic aspirin, but with modest detection capacity
FMF (2021)	Global	Combination of maternal risk and several biomarkers such as MAP, UTPI, and serum PLGF. When the PLFG is not available, the PAPP-A could be used.	Archives have a higher detection capacity even in early pregnancy, but with additional cost, thus can not be applied in all screening settings.
WHO (2021)	Global	Traditional risk factors of PE, including a history of PE before, diabetes, persistent hypertension, renal disease, autoimmune disease, and multiple gestations	Applicable and feasible to access for all women and can be used to give prophylactic aspirin, but with the lowest detection capacity

World Health Organization (WHO)

In WHO guidelines, examination and assessment are only focused on assessing risk factors, including previous PE in earliest pregnancy, diabetes, chronic hypertension, renal disease, autoimmune disease, and multifetal pregnancy. However, WHO guidelines are more commonly used globally because the previous model used only a certain country's population base. In addition, WHO recently issued additional guidelines regarding drug management and preventive therapy for women at risk of PE, including calcium supplementation and antiplatelet therapy if needed, such as aspirin.[31,32]

In general, all prediction models use the evaluation of maternal risk factors as the main basis. However, each guideline or recommendation's systematic calculations and algorithms can cause very different detection rates. So far, the test, combined with other tests and biomarkers, such as FMF, is reported to have the best detection capacity.[33] In addition, the administration of aspirin with adjusted doses has also been reported to have good benefits in all types of prediction models.[33,34] However, the application of the prediction model is also strongly influenced by the target population. The detection capability and validity of the prediction model can vary widely in different countries. This is due to the different maternal characteristics between countries; for example, women of Asian race have a lower average BMI than Caucasian.[31,32] This causes the need to test the validity and adaptation of the model, such as the application of the Bayes-theorem in the FMF model in Asian populations.[35]

In addition, there is a new model that also requires attention, namely the Full Preeclampsia Integrated Estimate of Risk (FullPIERS) that utilizes and assesses not only the signs and symptoms of the mother but also so the laboratory finding. It can be used to predict maternal side effects and perinatal outcomes in patients with PE. The FullPIERS can also be used in planning delivery times and preventing complications for both mother and child. The factors or elements used are the age of the pregnancy, chest pain or dyspnea, oxygen saturation, platelets, creatinine, and AST/ALT.[1]

Apart from applying prediction models through a number of guidelines, weaknesses and limitations of prediction models can be resolved by applying biomarker examinations during pregnancy. Based on a number of recent studies, there are a number of biomarkers that can be used and are being developed in the diagnosis and treatment of preeclampsia. This group of biomarkers was developed based on the pathophysiology and mechanisms involved in the development of preeclampsia, namely damage to placental tissue, vasculature and organ involvement which can later be detected in the patient's body fluids, including urine and blood. The biomarker products that are currently being developed to complement currently available predictive models include RNA, DNA, protein and tissue metabolite products. The placenta is generally the main tissue involved in the pathophysiology of preeclampsia, especially during early pregnancy (gestational age >11 weeks), such as placenta-enriched RNAs, adrenomedullin (Adm) which decreases during the second trimester of pregnancy in preeclampsia patients. In addition, microRNA (miRNA) is also reported to be able to predict the occurrence of preeclampsia, such as miRNA on chromosome 19 and exosomal miRNA. Furthermore, RNA examination also supports the examination of placenta-related proteins, including placental protein 13 (PP13), Pregnancy-associated plasma protein A (PAPP-A), Growth Differentiation Factor 15 (GDF-15), and alpha fetoprotein (AFP) which have been reported to have significant predictive value. The inflammatory process found in preeclampsia also causes vascular involvement, which supports the examination of vascular-related biomarkers, such as endothelin and nitric oxide (NO) proteins and their related substrates which are significantly increased in preeclampsia patients.[36–40]

BIOMARKER TESTING IN PREDICTION MODEL

Another predictive factor that can be used in the PE prediction model is the biomarkers during pregnancy. In clinical practice, biomarker tests are commonly associated with other pregnancy conditions and can also monitor fetal development. In cases of PE, biomarker examination can be performed at the beginning of pregnancy (early first trimester) and late pregnancy (second and third trimesters). Screening tests are generally used when there is some risk of PE accompanied by other risks of pregnancy disease, such as persistently high blood pressure without signs of PE or non-specific general symptoms such as persistent nausea and dizziness.[36–40]

Several key biomarkers used in cases of PE include MAP, UtA-PI, and the ratio of sFlt-1/PIGF. Previous studies have shown that the combination of PE risk assessment with biomarkers produces a better detection capacity than maternal risk analysis alone. So far, only FMF recommendations have integrated analysis of biomarker results and underwent extensive internal and external validation.[37,38,40]

MAP and UtA-PI values have been integrated with FMF algorithms and other predictive models. However, the sFlt-1/PlGF ratio has yet to be further developed. Several factors expressed in the placenta such as sFlt-1, have a role as anti-angiogenic factors and PIGF as pro-angiogenic factors. Those factors are associated with placental dysfunction. In the 20– 34 weeks of pregnancy, the sFlt-1/PlGF ratio is useful and rules out PE risk based on NICE and the European Society of Cardiology assessment.[41,42] Moreover, the sFlt-1/PlGF ratio could be detected in >37 weeks of pregnancy. Previous studies have shown that the sFlt-1/PlGF ratio has a negative predictive value (NPV) of 99.3% with a cut-off ratio of <38. However, within the next four weeks, a lower positive predictive value (36.7%) was also reported with a cut-off ratio of ≥85. Therefore, the current recommendation states that women with a 38 – 85 sFlt1/PlGF ratio require enhanced monitoring followed by a retest after 1–2 weeks or immediately if there are changes in the clinical situation. Furthermore, with a value of less than 100 pg/ml, the measurement of PlGF alone can also be employed in pregnant women suspected of having PE. This method has a sensitivity and negative predictive value (NPV) of 96% and 98%, respectively. This accuracy was claimed to be higher than common clinical tests, including blood pressure, ALT, and proteinuria.[43]

Most of the blood biomarkers studied in preeclampsia studies show high predictive value and diagnostic capacity, such as sFlt1 and PlGF with sensitivity and specificity values reaching >90% at gestational age <35 weeks. However, there are limitations to its application, including the capacity to predict positive cases ("rule in") preeclampsia and limitations in predicting preeclampsia at a gestation period of >37 weeks. In direct clinical application, the results of biomarker examinations can be changed and adapted to the conditions and characteristics of patients in certain populations.[44] The conversion method can use multiples of the median (MoM) equivalent and Bayes-theorem. These conversions are influenced by characteristics such as age, weight, and ethnicity. The MoM value is determined by dividing the actual value by the predicted value of the biomarker. In the multivariate analysis, the predicted value is determined using a formula that integrates all parameters identified as independent predictors of the biomarker.[45,46] It is also necessary to standardize and routinely monitor biomarker inspection procedures because one of the biggest obstacles in biomarker examination is unstandardized protocols for biomarker measurements and low-quality assessment, which causes inaccurate measurement results.[40]

CHALLENGE AND BARRIER

The main obstacles to applying the prediction model for PE in clinical practice are limited examination facilities and delays in evaluation or screening at primary health centers. Most prediction models are carried out in the first trimester of pregnancy. However, some pregnant women generally find clinical changes related to PE in the second and third trimesters, so cases of PE often cannot be detected and treated properly. Examinations are also generally limited to screening maternal factors and many available examination parameters. In addition, the limitations of studies that comprehensively assess each model's internal and external validity in the global population need to be revised in choosing the most suitable predictive model. Patient characteristics between studies were considerable. Several studies have evaluated the external validation of PE prediction models. In addition, no prospective study has compared the accuracy of single risk factor screening with risk prediction by one or more specified algorithms.

Comparative studies similar to systematic reviews and meta-analyses also need help comparing several studies with different models due to the high heterogeneity of studies, so there is a high risk of bias during the analysis process, especially for models with multifactor algorithms. However, in several studies, high detection capability and more effective prevention through the application of models with additional examinations and multifactor algorithms, such as FMF, show good potential in clinical applications. Apart from this, only a few studies have reported evidence and clinical utility in specific populations, especially in Asia and Indonesia. Further evaluation can also be carried out to compare different models in specific populations, especially in Asian countries, so that the number of examinations can be fewer and more specific, especially by only relying on basic tools in primary health centers.[47]

CONCLUSION

In summary, several predictive models and biomarkers have been developed to investigate the risk and development of PE. Currently, all prediction models, such as NICE, ACOG, FMF, and WHO, generally involve maternal characteristics and risk factors screening. Several biomarkers are also used, including MAP, UtA-PI, and sFlt-1/PlGF ratio. However, there is yet to be a conclusion regarding the best predictive model due to the limitations of comparative studies and some barriers to comparing studies. Based on the current literature, FMF recommendation has the best detection capacity compared to other predictive models.

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