Review Article

Indian Journal of Maternal-Fetal and Neonatal Medicine
Volume 11 Number 2, July - December 2024
DOI: http://dx.doi.org/10.21088/ijmfnm.2347.999X.11224.3

Predictors of Pre-Eclampsia

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How to cite this article:
Alka Patil, Priyanka Agrawal, Aakruti Ganla. Predictors of Pre-Eclampsia. Ind J of Matern-Fetal & Neonatal Med 2024;11(2):53–57.

Abstract

A major cause of maternal and perinatal morbidity and mortality, Preeclampsia (PE) is predominantly thought to be a consequence of impaired placentation. PE can be subdivided into early onset PE and late-onset PE. Early identification of pregnancies at high risk of early onset PE is a major challenge in modern obstetrics and undertaking measures to improve placentation and reduce the prevalence of the disease is the need of the hour. Large number of potential biochemical and biophysical markers have been identified which may help in predicting the risk of developing pre-eclampsia. Numerous clinical tests have been done to establish a reliable method to predict pre-eclampsia.

Keywords: Pre-eclampsia, Predictors, Biochemical markers, Biophysical markers, Doppler.

INTRODUCTION

A major cause of maternal and perinatal morbidity and mortality, Preeclampsia (PE) is predominantly thought to be a consequence of impaired placentation. Evidence suggests that PE can be subdivided into early onset PE, requiring delivery before 34 weeks' gestation and late onset PE, with delivery at or after 34 weeks, because the former is associated with a higher incidence of adverse outcome. A major challenge in modern obstetrics is early identification of pregnancies at high-risk of early onset PE and undertaking the necessary measures to improve placentation and reduce the prevalence of the disease.[1]

Predictive Tests for Preeclampsia

Early prediction of development of pre-eclampsia is important as it could lead to early and appropriate surveillance of women in the high-risk category, at the same time avoiding unnecessary intervention in those at low risk. Most obstetric units presently rely on clinical history, BP examination and urinary protein testing for prediction of preeclampsia. However, a large number of potential biophysical and biochemical markers have also been identified which may help in accurately predicting the risk of developing preeclampsia (Table 1). of these various markers, biochemical markers such as fetal nucleic acids, angiogenic vascular markers and placental proteins, either alone or in combination with uterine artery Doppler appear as promising agents for prediction of preeclampsia in future. However, research also needs to continue into developing preventive strategies and their benefit needs to be demonstrated, before screening of women using one of the predictive tests can be universally recommended in future.

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Received on: 27.08.2024

Accepted on: 05.10.2024

Table 1: Screening Tests for Pre-eclampsia

Biophysical parameters
Clinical factors (history and examination)
Doppler ultrasound of uteroplacental circulation
Microcirculation (capillary) changes in preeclampsia
Biochemical parameters
Free fetal nucleic acids (fetal DNA and mRNA) Pregnancy associated protein A (PAPP-4)
Placental protein 13 (PP13)
Cystatin C
Fetal hemoglobin (HbF) and alpha1-microglobulin(A1M)
Pentraxin 3 (PTX3)
Markers related to angiogenesis
Other markers

Some of the biochemical predictors of pre-eclampsia are products of the trophoblast or adjacent decidua and reflect the placental dysfunction, while others represent the maternal systemic inflammatory response and widespread endothelial dysfunction. In cases of preeclampsia, there is an increase in the levels of biochemical markers such as cystatin C. fetal hemoglobin (HbF), free HbF protein, Pentraxin 3, soluble endoglin (sEng), etc. Also, there is a reduction in the levels of biochemical markers produced by trophoblastic tissue or decidua such as pregnancy associated protein A (PAPP-A), placental protein 13 (PP13), etc. Furthermore, there is an increase in antiangiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt-1) and reduction in the level of angiogenic factors such as vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 (sFlt-1), placental growth factor (PIGF), etc. in cases of preeclampsia.[2]

Pathophysiology of PIH

During normal pregnancy, the spiral arteries of the uterus undergo a series of morphological changes. Trophoblast cells invade the spiral arteries which then become incorporated into the vessel wall and replace the endothelium and muscular layer resulting in the conversion of the small spiral arteries into vessels of greater diameter with low resistance and high compliance, in absence of maternal vasomotor control. Impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide non-muscular channels is thought to be the underlying mechanism for the development of PE.[3]

Doppler ultrasound is a noninvasive method for the assessment of the uteroplacental circulation. Impaired placental perfusion, is the consequence of impaired placentation which is reflected in increased uterine artery PI and is associated with the development of PE which is congruent with the hypothesis and is supported by the results of previous first and second-trimester Doppler studies as well as histological studies of the maternal spiral arteries.[4]

Numerous other clinical tests have been done to establish a reliable method to predict pre-eclampsia but none of them have been accepted as useful. Some important tests are:

- Gantt's Rollover test at 28-32 weeks. This test was designed to detect disorder of vascular responsiveness, which occurs in pre-eclampsia. In this test blood pressure is measured in the left lateral position and then again in the supine position. A 20 mmHg or more rise in diastolic pressure, when the patient is placed in the supine position, is thought to predict pre-eclampsia .
- Doppler velocimetry of uterine vessels at 24 weeks. Detection of diastolic notch at 24 weeks of pregnancy predicts future development of pre-eclampsia
- Maternal serum uric acid level (higher level at 12 weeks in cases who develop pre-eclampsia)
- Maternal serum alpha fetoprotein and β-human chorionic gonadotropin (β-hCG) level increased in second trimester
- Plasma fibronectin level increased

- Urinary calcium excretion decreased
- Sex hormone binding globulin (SHBG) decreased
- Increased level of lipid peroxidases. Homocysteine level (elevated)
- Serum level of placental peptide placental [PIGF (Phos-phatidylinositol-glycan biosynthesis class F protein) and SFLT1] in first trimester.[5]
- MAP-2: Mean arterial pressure in the second trimester >/= 90 mm Hg. MAP = (2 DBP + SBP)/3).
- Angiotensin infusion test (invasive): women destined to develop pre-eclampsia lose their refractoriness on infusion of angiotensin between 28 and 32 weeks of pregnancy. Women who exhibit a pressor response with less than 8 ng/kg/minute, 90% of them were seen to develop the disease.[6]
- Isometric hand grip exercise test: Resting BP is taken; the woman is then asked to press an inflated BP cuff for 30 seconds. She then presses the cuff at 50% of maximal contraction for three minutes. If the rise in DBP is >20 mm Hg, the test is positive. The test takes longer but is more reliable than the roll-over test.
- Calcium/creatinine ratio: Since in pre-eclampsia urinary calcium excretion is reduced, a calcium/ creatinine ratio of <0.04 is considered significant This has a sensitivity of 70%.
- Fetal DNA: The presence of fetal DNA in maternal serum at the time of endothelial activation has been shown to predict the disease earlier in pregnancy. Elevated fetal fibronectin at about 12 weeks. Elevated inhibin A, and corticotropin releasing hormone have not been found to be reliable predictors.[7]

Serious maternal and fetal complications are associated with pre-eclampsia particularly when it is severe and early in onset. The focus of screening for pre-eclampsia has therefore shifted from second to first trimester so that preventive interventions can be instituted in women found to be at high risk of developing early and late pre-eclampsia. Maternal risk factors. The approach for prediction of pre-eclampsia has been essentially based on maternal risk factors derived from demo- graphic characteristics, past medical and obstetric history. The ACOG recommends treatment with low-dose aspirin when one or more high-risk factors or two or more moderate risk factors are identified in the first trimester. However, this model lacks sufficient predictive value. The FIGO (International Federation of Gynecology and Obstetrics) now recommends universal screening for pre-eclampsia in early pregnancy by combining maternal risk factors and biomarkers as a one-step procedure in the first trimester.

Universal screening - The best combined test includes maternal risk factors, measurements of mean arterial pressure (MAP), serum PLGF and uterine artery pulsatility index (UTPI). A woman is considered high risk when the risk is 1 in 100 or more based on the first-trimester combined test with maternal risk factors, MAP, PLGF and UTPI.

If measuring PLGF and/or UTPI is not feasible, the baseline screening should combine maternal risk factors with MAP, rather than relying solely on maternal risk factors. If PAPP-A is tested as part of routine first-trimester screening for fetal aneuploidies, its result can also be used to assess pre-eclampsia risk.

Contingent screening - Where resources are limited, all women can be screened with maternal risk factors and MAP and PLGF and UTPI measured in those found to have high-risk factors.

An abnormal UTPI in the first trimester is defined as being above the 90th percentile, which provides a 48% detection rate for early-onset pre-eclampsia, with an 8% false positive rate. The detection rate for predicting late-onset pre-eclampsia is lower, 26% at a 7% false positive rate.

PLGF is a glycosylated dimeric glycoprotein secreted by trophoblastic cells. It is synthesized in villous and extravillous cytotrophoblasts and has both vasculogenic and angiogenic functions. PGLF levels are significantly lower in the first trimester in women who subsequently develop pre-eclampsia. A systematic review and meta-analysis demonstrated that PLGF is superior to the other biomarkers for predicting pre-eclampsia. Maternal PLGF concentrations alone achieve a detection rate of 56% with 95% false positive rate for the prediction of early-onset pre-eclampsia.

PAPP-A is a metalloproteinase which acts on insulin-like growth factor binding protein secreted by the syncytiotrophoblast that plays an important role in placental growth and development.

It is a well-established biochemical marker in the screening of trisomies 21, 18 and 13. Low levels of PAPP-A are associated with a risk of developing pre-eclampsia. However, its predictive value is poor, and therefore, not useful in predicting pre-eclampsia when used alone.

In a multicentre trial, screening with the use of a combination of maternal risk factors, MAP, UTPI and serum PLGF detected 100% of pre-eclampsia developing before 32 weeks, 75% of pre-eclampsia at <37 weeks and 43% of pre-eclampsia at ≥37 weeks with a 10% false positive rate.[8]

Early onset PE can be effectively screened in the first-trimester of pregnancy but late onset PE requiring delivery after 34 weeks' gestation accounting for two-thirds of all PE remains a significant challenge for effective early screening. The initial phase, occurring at 11–13 weeks, should focus on accurately predicting early-onset preeclampsia (PE), as the incidence of this condition can be significantly lowered through preventive treatment with low-dose aspirin if begun before 16 weeks of gestation.[9]

The second stage, between 30 and 33 weeks, should focus on accurately predicting preeclampsia (PE) that necessitates delivery at or after 34 weeks. Close monitoring during this period can enhance perinatal outcomes by allowing for earlier diagnosis and intervention, such as administering antihypertensive medication and planning an early delivery.[10]

A competing risk model, using Bayes theorem, has been developed that combines maternal characteristics and history with biophysical and biochemical markers at 30–33 weeks' gestation which can be used to assess the risk of developing preeclampsia (PE) that may necessitate delivery within specified time frames from the screening. Prior risk for pre-eclampsia is increased with -

- Increasing maternal age and weight.
- Personal or family history of pre-eclampsia.
- Pre-existing chronic hypertension, diabetes mellitus, systemic lupus erythematosus, antiphospholipid syndrome.

In the third trimester, uterine artery pulsatility index (PI) and mean arterial pressure (MAP) are influenced by maternal characteristics and history. The adjusted measurements, expressed as multiples of the median (MoM), are inversely related to the severity of the disease, as indicated by the gestational age at delivery.[11]

CONCLUSION

Pre-eclampsia remains one of the most severe pregnancy complications with significant legacy of both maternal and perinatal morbidity. Early detection improves the outcome. Combining biomarkers derived from multiple organs and cellular sources may yield the best predictive performance. There is no one test which is truly predictive. Currently, women at increased risk of pre-eclampsia are identified on the basis of epidemiological factors. But these lack sensitivity and specificity. Most of the above tests have good negative predictive value; that is, if the test is negative, the woman may not develop hypertension. The only drug recommended for the prevention of pre-eclampsia is low-dose aspirin in women at high risk for developing the disease.

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