Prediction of preeclampsia by biomarkers: A review of literature

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Abstract:

Preeclampsia is a leading cause of maternal and perinatal mortality and morbidity internationally. The aetiology of this disease is unknown, though widespread endothelial dysfunction is considered to be the major reason. Early identification of this disease would be helpful in early identification of the high risk patients, diagnosis and better prenatal care. Several biomarkers either individually or in combination have been identified which either increase or decrease in PE and may be of utility either as predictors or diagnostic tools. This review focuses on various available biomarkers and their utility from the already existing literature.

Keywords: Preeclampsia, Angiogenic factors, Laboratory investigations.

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Introduction:

Preeclampsia (PE) is a pregnancy-specific condition characterized by hypertension and proteinuria that remits after delivery. PE with a high prevalence in the first pregnancy is associated with the highest maternal and foetal morbidity and mortality, preterm birth, perinatal death, and intrauterine growth restriction and affects between 0.4% and 2.8% of all pregnancies in developed countries (1). The criteria for PE have not changed over the past decade (systolic blood pressure >140 mmHg or diastolic blood pressure ≥90 mmHg and 24-hour proteinuria ≥0.3 g). Clinical features and laboratory abnormalities define and determine the severity of PE.

Unfortunately, the pathophysiology of this multisystem disorder, characterized by abnormal vascular response to placentation, is still unclear. Considering the impact of PE in obstetrics, screening women at high risk, preventing recurrences and to offer specific preventive measures are key issues in the management of PE. Accurate prediction of PE would enable early and optimal management of women at high risk. Several predictive tests are being assessed currently. Though numerous tests have been described either in alone or combination, the sensitivity and specificity of the tests needs to be evaluated. This article focuses on the biochemical markers which may be used in the prediction of PE.

Pathophysiology:

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. It is postulated that circulating factors are produced by the placenta as a result of oxidative stress resulting in excessive systemic inflammatory response (2) and generalized maternal endothelial dysfunction, contributing to the maternal clinical features of PE (3). Shallow placentation is associated with abnormal invasion of cytotrophoblasts, leading to incomplete remodelling of maternal uterine spiral arterioles, which supply blood to the developing placenta (4). Hypoxic stress in the placenta causes the release of endothelial damaging factors into the maternal circulation (5). The severity of hypertension in PE may be related to the degree of trophoblastic invasion. It may also said to be associated with immunological responses.

Prediction is basically based on clinical tests, such as blood pressure measurement during the second trimester or 24-hour ambulatory blood pressure monitoring, but these lack sensitivity and specificity (6). Many biomarkers have been evaluated which could help in the accurate prediction of the PE in the first trimester itself. This review thus focuses on the available biomarkers and their utility.

Angiogenic factors:

Angiogenic factors are thought to be important in the regulation of placental vascular development. Their receptors, fms- like tyrosine kinase or Flt1 (also known as vascular endothelial growth factor receptor 1 (VEFGR-1), VEGFR-2, Tie-1, and Tie-2, are essential for normal placental vascular development. Since the placenta is a rich source of these factors, during the first trimester in pregnancy, in humans,

VEGF ligands and receptors are highly expressed by the placental tissue. Invasive cytotrophoblasts express VEGF, placental growth factor (PlGF), and VEGFR-1; and these are altered in PE (7). Evidence suggest higher expression of placental sFlt-1 along with decreased VEFGR and PIGF signalling during the first trimester are associated with a significantly increased risk of PE (8).

Circulating sFlt1 levels stay relatively low early in pregnancy (9), gene-expression studies from chorionic villous biopsies at 11 weeks of gestation in women who subsequently developed PE showed marked alterations in angiogenic factors, including upregulation of sFlt1 message (10) and begin to rise in the third trimester.

Other studies have also demonstrated that compared to normotensive controls, in patients with severe PE, free PlGF and VEGF levels are significantly decreased (11), and sFlt1 levels are significantly elevated (12-13).

VEGF is a central requirement for endothelial stability, and its blockade is an important part of the pathophysiology of PE.VEGF is necessary for glomerular capillary repair and may be particularly important in maintaining the health of the endothelium. VEGF is highly expressed by glomerular podocytes, and VEGF receptors are present on glomerular endothelial cells (14). As with sFlt1, circulating sEng levels are elevated weeks prior to PE onset (15). The levels of sflt-1 and PIGF in some studies (16) have also been found to be altered in the second trimester in cases with subsequent IUGR. Hence this biomarker may not be specific for PE.

Inhibin A and Activin A:

These glycoproteins are produced by the fetoplacental unit. Though the levels of these glycoproteins are increased (17) in the maternal blood in the first trimester of patients who subsequently developed PE, no association was found between the impaired trophoblast invasion and endothelial dysfunction.

Pregnancy associated plasma protein-A (PAPP-A):

It is 1628 amino acid peptide linked by disulphide bonds mainly produced by the trophoblastic cells. It is said to have a role in regulating foetal growth due to its action of cleavage of insulin like growth factor binding proteins. Studies have indicated a decrease in the plasma levels of PAPP-A in all the trimesters of pregnancy suggesting the requirement of larger trials to confirm its utility as a biomarker in PE (18).

Neutrophil gelatinase-associated lipocalin (NGAL):

NGAL is a protein belonging to the lipocalin superfamily. It is encoded by the LCN2 gene. It is basically expressed in neutrophils. Low levels are found in the kidney, prostate, and epithelia of the respiratory and alimentary tracts (19). NGAL has been used as a biomarker of kidney injury (20).

It is responsible for the decrease in GFR primarily through reduction in ultra-filtration as opposed to diminished plasma flow (21). The circulating increase of serum NGAL may be a result of a leukocyte-derived inflammatory activity and endothelial activation (22) and the serum level of NGAL are closely related to endothelial injury. It has been demonstrated that positive correlation between serum NGAL level and covariate such as systolic and diastolic blood pressure and proteinuria might be a consequence of endothelial dysfunction on which hypertension and proteinuria probably depend (23).

Placental protein 13:

Galactoside-binding soluble lectin 13 or placental protein 13(PP13) is a protein encoded by the *LGALS13* gene in humans (24). Females having PP13 levels low in the first trimester of pregnancy have a risk for developing PE later in pregnancy (25). Although the in vivo functions of PP13 are still unknown, a meta-analysis study has shown that low serum levels of PP13 in the first trimester of pregnancy can predict the development of PE later in pregnancy. A recent pilot study conducted by Huppertz (26) has shown that in gravid rats PP13 causes significant vasodilatation, reduced blood pressure and increased maternal uterine artery remodelling. However, according to Akolekar R(17) measurement of serum PP13 at 11–13 weeks does not improve the performance of screening for early-PE achieved by a combination of maternal factors, uterine artery PI and serum PAPP-A.

Soluble endoglin (sEng):

Endoglin is a type I membrane glycoprotein located on cell surfaces is an auxiliary receptor for the TGF-beta receptor complex (27). Hence, it is involved in modulating a response to the binding of TGF-beta1, TGF-beta3, activin-A, BMP-2, and BMP-7. Beside TGF-beta signalling endoglin may have other functions. In vitro, sEng is a negative regulator of angiogenesis and hence to be elevated in PE. The levels of sEng are also increased in pregnancies with IUGR without maternal syndrome (28), gestational hypertension or chronic hypertension (29). Preliminary results have suggested that the patterns of changes in the levels of sEng alone are not specific.

Large scale studies are required to clarify the role of sEng in the prediction of PE.

PTX3:

Pentraxin-related protein PTX3 (TNF-inducible gene 14 protein (TSG-14)) is a protein encoded by the *PTX3* gene in humans (30). Since an excessive maternal inflammatory response to pregnancy is one of the etiology of PE, elevated maternal plasma levels of PTX3 has been found in preeclamptic versus normal pregnancies (31)**.**

ADAM 12:

The soluble form of the disintegrin metalloprotease ADAM 12 (a disintegrin and metalloproteinase 12; meltrin-alpha) represented the most upregulated transcript. ADAM 12 could serve as an early biomarker for PE that may be of predictive and/or functional significance (32). The maternal serum levels of ADAM12 are significantly lower during the first trimester in women who later develop PE during pregnancy when compared with levels in women with normal pregnancies (33) and are significantly decreased in correlation with C reactive protein (34).

P selectin:

P-selectin is a protein is encoded by the SELP gene in humans (35). Platelet activation in PE is reflected by elevated levels of platelets exposing P-selectin. In plasma, a non-cell bound (soluble) form of P-selectin is present. Elevated levels of this soluble form have been reported in PE. Plasma P-selectin may consist of two fractions: microparticle (MP)--associated P-selectin and non-MP--associated P-selectin. MP associated P-selectin exclusively originates from platelets, this fraction indicates platelet activation. Platelet activation is prominent in PE and this study proves that at least a part of the plasma P-selectin originates from platelets (36). In an inflammatory model for PE it is thought that endothelial cell activation may be secondary to a primary inflammatory response. Thus plasma P-selectin has significant potential as a first trimester clinical marker of PE (37).

Adiponectin:

The reports of the role of adiponectin in PE are conflicting. It is proposed that adiponectin might be part of a feedback mechanism improving insulin sensitivity and cardiovascular health in pre-eclamptic patients (38) and thus PE is characterized by alterations in adiponectin multimers (39).

Resistin:

Resistin, along with human placental lactogen, prolactin, steroid hormones and other hormones, decreases insulin sensitivity, whereas leptin increases insulin sensitivity (40). The increase in serum resistin in the third trimester of pregnancy is in accordance with insulin resistance in normal pregnancy (41-42). PE has been proposed to be an exaggeration of insulin resistance although differing opinions exist (43).

Also an increase in serum resistin was found in the third trimester of normal pregnancy, but this increase was not present in PE (44).

Other tests:

Laboratory tests for oxidative response i.e malondialdehyde along with antioxidants have been assessed, including assays for uric acid, urinary kallikrein, and fibronectin, cytokines but no evidence of their relevance has so far been found (45).

Thus in clinical practice, because no single marker effectively predicts the risk of PE, the current trend is to test a combination of markers. Studies involving a larger population are the need of the hour to determine the specificity and sensitivity of the individual parameters or a combination before any molecule is labelled as a biomarker for the early prediction of PE.

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