10.5005/jp-journals-10006-1456

REVIEW ARTICLE

Prediction of Preeclampsia: Role of Antiangiogenic and Proangiogenic Biomarkers

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ABSTRACT

The pathogenesis of preeclampsia (PE) is unknown, but recent studies have revealed that placenta is the place of origin of this disorder, and widespread maternal endothelial dysfunction is the charactertstic feature of the disease. Some biochemical molecules that are involved in the pathogenesis of the disease have recently been identified, which may help in early identification of patients at risk and help in providing proper prenatal care. Several promising biomarkers have been proposed, alone or in combination. Maternal serum concentrations of these biomarkers either increase or decrease in PE during gestation. This review focuses on the various biomarkers available and their utility in prediction and diagnosis of PE.

Keywords: Antiangiogenic, Endothelial, Placenta.

How to cite this article: Garg R, Roy P, Agrawal P, Shanthakumari S. Prediction of Preeclampsia: Role of Antiangiogenic and Proangiogenic Biomarkers. J South Asian Feder Obst Gynae 2017;9(1): 47-52.

Source of support: Nil

Conflict of interest: None

Date of received: 25 October 2016

Date of acceptance: 10 December 2016

Date of publication: January 2017

INTRODUCTION

Preeclampsia (PE) is an important cause of maternal and perinatal morbidity and mortality. About 2 to 8% of pregnancies are affected by PE.[1] More than 50,000 maternal deaths annually happen due to PE worldwide.[2,3]

Preeclampsia can be classified as early-onset PE occurring before 34 weeks of gestational age and late-onset PE that develops after 34 weeks of gestational age. Early-onset PE is commonly associated with fetal growth restriction, abnormal uterine and umbilical artery Doppler waveforms, and adverse maternal and perinatal outcomes, whereas a mild form of maternal and fetal involvement with usually a favorable perinatal outcome is seen in late-onset PE.[4-6] About one-third of maternal mortality is caused by PE in developing countries due to poor health care facilities.[7] In India, the incidence of PE and eclampsia is around 4.6%,[8] and the neonatal mortality rate is around 43 per 1,000 live births.[9]

For prediction of PE, numerous tests have been described either singly or in combination; the sensitivity and specificity of these tests need evaluation.

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PATHOGENESIS

The etiology of PE is unknown. Evidence suggests that the presence of a placenta but not necessarily a fetus is required for the development of this disorder.[10] Several mechanisms have been implicated in the pathogenesis of PE, including endothelial dysfunction,[11] inflammatory pathway,[12] oxidative stress,[13] and the renin–angiotensin system.[14]

Preeclampsia has been considered as a two-stage disease in which abnormal placentation precedes endothelial dysfunction.[15,16] In normal placental development, the cytotrophoblasts invade the maternal spiral arterioles and transform them from small-caliber resistance vessels to high-caliber conduit vessels. The beginning of this initial event has occurred around 10 to 12 weeks and is completed by 18 to 20 weeks of gestation. During this vascular invasion, the cytotrophoblasts differentiate from epithelial phenotype to an endothelial phenotype, a process known as pseudovasculogenesis. During this process, these make a direct contact with maternal blood. This process involves a considerable number of transcription factors, growth factors, and cytokines like VE-cadherin and alpha(v)beta-3 integrins.[17] During PE, the invasive cytotrophoblasts fail to transform epithelial phenotype into endothelial phenotype along with shallow invasion of the spiral arteriole, which leads to defective uteroplacental circulation and worsening placental perfusion causing placental ischemia and hypoxia.[18] All

these directly or indirectly damage endothelial cell function.[19] Generalized endothelial dysfunction with systemic inflammatory response is thought to be the final common pathway that leads to the maternal signs of PE with *de novo* hypertension and proteinuria in the second half of pregnancy.[20]

As PE is very common in pregnancy and carries a high maternal and perinatal morbidity and mortality, a number of methods are tried to predict the development of PE so that we can identify these women early and appropriate measures can be taken for safe pregnancy outcomes.

Prediction is basically dependent on clinical tests, such as blood pressure measurement during the second trimester or 24-hour ambulatory blood pressure monitoring, angiotensin infusion test, roll-over test, and some more, but these lack sensitivity and specificity.[21]

ANGIOGENIC FACTORS

Circulating factors that regulate blood vessel formation and health are referred to as angiogenic factors. Some novel soluble angiogenic factors are identified that are related to the pathogenesis of the disease.[22] Angiogenic factors are thought to be important in the regulation of placental vascular development. These factors include circulating antiangiogenic proteins, such as soluble fms-like tyrosine kinase-1 (sflt-1) and soluble endoglin (sEng) and proangiogenic protein, such as placental growth factor (PlGF) and vascular endothelial growth factor (VEGF). Their receptors, fms-like tyrosine kinase or Flt-1, also known as vascular endothelial growth factor receptor-1 (VEGFR-1), VEGFR-2, Tie-1, and Tie-2, are essential for normal placental vascular development. A strong association between altered circulating angiogenic factors and PE has been demonstrated by several studies. The higher relative concentration of antiangiogenic factors is believed to trigger vascular endothelial cell injury in the liver, kidney, brain as well as in the placenta.[5,15,23] Some of the factors are described here.

Endoglin

Endoglin, an antiangiogenic protein, has been implicated in the pathogenesis of PE. It is a 180-kDa, homodimeric, type I membrane glycoprotein located on cell surfaces. It is also commonly referred to as CD105, END, FLJ41744, HHT1, ORW, and ORW1. It is a part of the transforming growth factor (TGF) beta receptor complex expressed at high levels on vascular endothelial cells and functions as an antiangiogenic factor by binding TGFb-1 and TGFb-3 proteins that are important for angiogenesis.[24] Several studies have demonstrated that endoglin is expressed in human first trimester decidua cells and is highly upregulated in the syncytiotrophoblast of women with PE,[25,26] and concentration of its soluble form is increased in the circulation of preeclamptic women. This soluble form of endoglin (sEng) is produced by the proteolytic cleaving action of matrix metalloproteinase (MMP)-14 in extracellular domain.[24,27] It acts by antagonizing an angiogenic and vasodilator molecule known as TGFb-1, which is important in angiogenesis and also maintains the health of the blood vessels. Due to this, cells lining the blood vessels begin to sicken and die, blood pressure increases, and blood vessels leak protein into the tissues and urine.[28] It is an important protein for tumor growth, survival, and metastasis of cancer cells to other locations in the body.

In human pregnancy, alterations in serum sEng antedate clinical symptoms of PE by several months before the onset of disease.[29] Because high levels of serum sEng are released into the human circulation prior to the clinical manifestations of PE, this glycoprotein has been proposed recently as a serum diagnostic biomarker for PE.[30] Levine et al[29] evaluated the potential of sEng in combination with other pro- and antiangiogenic factors like PlGF, sFlt1 for the prediction of PE. The study implied that the sFlt-1:PlGF ratio and more specifically (sFlt-1+sEng):PlGF is a stronger predictor of PE in comparison to individual markers.[31]

Vascular Endothelial Growth Factor and Placental Growth Factor

Among the various angiogenic factors expressed by the placenta, VEGF and PlGF play a very important role.[32] The VEGFs are a family of structurally related dimeric proteins whose members include VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PlGF. The VEGF plays an important role to promote sustenance, migration, and differentiation of endothelial cells and also maintain the vascular permeability; VEGF interacts with VEGFR-2 and VEGFR-1 on the placental endothelial cells.[33] Several studies have reported that serum concentration of VEGF is reduced in preeclamptic patients. That is why the activity of sFlt-1 (a soluble form of VEGF receptor-1 or sVEGFR-1) is upregulated in preeclamptic conditions.[34] Increased levels of free serum sFlt1 bind with both VEGF and PlGF, thereby neutralizing them, and subsequently their levels in circulation are reduced.[34] There is also decreased production of VEGF by circulating T and natural killer cells in PE; it also plays a role in endothelial dysfunction, which is characteristic of the maternal syndrome of the disease.[35] Although VEGF has been studied as a promising marker for the prediction of PE,[36] it could not be detected by many available enzyme-linked immunosorbent assay (ELISA) kits because its circulatory levels are very low.[37] To overcome this limitation, highly sensitive ELISA kits can be used.[37]

One of the most important members of VEGF family is PlGF. It also has an important role in angiogenesis and placental vasculature.[38] Placental trophoblasts are the major source of PlGF; PlGF-1, PlGF-2, PlGF-3, and PlGF-4 are the different isoforms of PlGF; PlGF binds only to VEGFR-1.[39] In women who are destined to develop PE, the splice variant of VEGFR-1, the sFlt-1, readily neutralizes the PlGF, hence, its level in the serum reduces.[32,36,38] Various studies have demonstrated that maternal serum levels of PlGF are lower in both early- and late-onset PE.[38,40] Various studies suggest that the best method for prediction of PE is PlGF:sFlt-1 ratio.[38]

Soluble FMS-like Tyrosine Kinase 1

It is an antiangiogenic soluble form of type 1 VEGF receptor. It results from alternative splicing of Flt-1 receptor messenger ribonucleic acid, which is an endothelial receptor for VEGF and PlGF; sFlt-1 consists of an extracellular ligand binding domain of Flt-1, but lacks the transmembrane and intracellular signaling domain. This secretory form circulates freely in the serum where it binds and neutralizes the VEGF and PlGF.[41] When compared with control subjects, in the women who developed PE, a significant rise in serum levels of sFlt-1 was shown by several studies.[34] The sFlt-1-specific ELISA kits are used for estimation of its serum levels.[34] Baumann et al[42] reported the predictive role of sFlt1 and sEng in PE. Levine et al[29] also found that higher levels of serum sFlt-1 are predictive of PE. However, some studies showed the lower specificity and poor predictive value of sFlt-1 in the early stages of pregnancy.[38]

Inhibin A and Activin A

These glycoproteins are produced by the fetoplacental unit. In patients who subsequently developed PE, higher serum levels of these glycoproteins are found in their first trimester.[43] Hence, these can be used in prediction of PE.

Pregnancy-associated Plasma Protein-A

It is a 1,628-amino-acid peptide. It is mainly produced by the trophoblastic cells. It has a role in cleavage of insulin-like growth factor-binding proteins. It has a role in regulation of fetal growth. Some studies have shown that plasma levels of pregnancy-associated plasma protein-A (PAPP-A) have decreased in all trimesters of pregnancy[44]; some other studies indicate that the levels of PAPP-A were significantly reduced in early-onset PE, while in cases of late-onset PE, the levels did not differ from the control group.[45] Hence, PAPP-A is not useful in predicting late-onset PE, and larger trials are required to confirm these preliminary predictions.[34]

Neutrophil Gelatinase-associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kDa protein and belongs to the lipocalin family.[46,47] It is also known as lipocalin-2, siderocalin, uterocalin, and 24p3.[46,47] It was first identified as a matrix protein of specific granules of human neutrophils. Its expression is highly upregulated in damaged epithelial cells, during inflammation, neoplastic conditions, cardiovascular diseases, infections, and renal disorders.[48] The NGAL can be detected in urine within 2 hours of kidney damage; hence, it is considered as the best and the earliest marker of acute kidney damage.[48,49] In some recent studies, serum level of NGAL was found to be increased at the end of the second trimester in women who subsequently developed PE compared with the control group.[45,47,50] A positive correlation of serum NGAL was found with the systolic and diastolic blood pressure and with proteinuria.[36,45,47] Hence, serum NGAL can be used as a reliable biomarker for early prediction of PE.

Placental Protein 13

Placental protein 13 (PP13) is a 32-kDa dimeric protein. It was first isolated in 1983 from the syncytiotrophoblast of the placenta[51] by Bohn et al.[52]. It was identified as a member of the galectin superfamily, which has an important role in placental implantation and remodeling of maternal arteries.[36,53] To perform this function, PP13 has a carbohydrate binding domain, to which two proteins annexin II and actin-beta bind. In normal pregnancy, PP13 levels are gradually increasing, while abnormally low levels of PP13 were found in the first trimester of women who subsequently developed PE, compared with controls.[53-55] Hence, it can be used as a serum biomarker for the prediction of PE.[54]

Nicolaides et al[53] demonstrated that the combination of serum PP13 levels and uterine artery pulsating index measured by Doppler ultrasonography has a good prediction rate to identify patients with the risk of developing PE in the first trimester. The PP13-specific ELISA kits are used to measure the serum PP13 levels with good sensitivity and specificity.[53,54] Hence, by using serum PP13 either alone or in combination with Doppler studies, early identification of high-risk patients can be done, and we have a good opportunity for implementation of treatment strategies.[53-56]

Pentraxin-related Protein 3

Pentraxin-related protein 3 (PTX3) is a TNF-inducible gene 14 protein. This protein is encoded by the *PTX3* gene in humans.[57] Maternal plasma levels of PTX3 was found to be elevated in preeclamptic women in comparison to

control group, supporting the excessive maternal inflammatory response to pregnancy as one of the etiologies of PE.[58]

P-Selectin

P-selectin is a protein encoded by the SELP gene in humans.[59] Platelet activation in PE is reflected by elevated levels of platelets exposing P-selectin. In plasma, a noncell bound (soluble) form of P-selectin is present. Elevated levels of this soluble form have been reported in PE.

Other Tests

Laboratory tests for oxidative response, i.e., malondialdehyde, along with antioxidants have been assessed, including assays for uric acid, urinary kallikrein, fibronectin, and cytokines, but till date no test was found relevant.[60] Because no single marker effectively predicts the risk of PE, in clinical practice, the current trend is to test a combination of markers. Larger studies are required to label a single molecule as a biomarker for the early prediction of PE.

CONCLUSION

Our understanding about the etiology and pathogenesis of PE has been improved a lot in the last decade. Several studies have been done, and a lot of biomarkers were studied for prediction and diagnosis of PE, such as antiangiogenic factors like serum soluble endoglin, sFlt-1, sEng, and proangiogenic factors like VEGF and PlGF. These biomarkers have certain drawbacks like lack of high-sensitive assay kits, inability to predict onset of the disease during initial stages of gestation, low specificity, lack of prognostic value, and many other issues. Hence, further studies are required with larger population and with more precise and advanced techniques.

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