ejpmr, 2019,6(2), 311-318

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

NEW BIOCHEMICAL MARKERS FOR PREECLAMPSIA-A MINI REVIEW

Dr. Neeru Bhaskar*

Professor and Head, Dept of Biochemistry, Adesh Medical College, Shahbad (Mohri) Haryana, India.

***Corresponding Author: Prof. Dr. Neeru Bhaskar**

Professor and Head, Dept of Biochemistry, Adesh Medical College, Shahbad (Mohri) Haryana, India.

Article Received on 03/12/2018 **Article Revised on 24/12/2018** **Article Accepted on 15/01/2019**

ABSTRACT

Pre-eclampsia (PE) is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mmHg or more with proteinuria after 20 weeks of pregnancy in a previously normotensive and non-proteinuric patients. It is one of the most common complications in obstetrics and is one of the primary cause of maternal and perinatal mortality and morbidity worldwide. A large number of biochemical markers have been investigated for the prophecy of PE which include molecules from trophoblast, angiogenic/anti-angiogenic factors, inflammatory markers, free fetal hemoglobin (HbF), and renal markers. The particular biochemical markers discussed in this review are: VEGF, PAPP-A, s-Flt-1/PlGF, s-Endoglin, PP13, cystatin-C, HbF, and α_1-microglobulin (A1M) , Cell free fetal DNA, Inhibin and Activin A, Pentraxin3, cystatin C and B- microglobin. Screening pregnant women with biochemical markers for PE can reduce needless suffering and health care costs by early recognition of mothers at increased risk for PE, thus avoiding unnecessary hospitalization of pregnant women with suspect or mild PE and enabling monitoring of the progression of the disease thereby optimizing time for delivery and expectantly reducing the number of premature births. Our review presents an overview of the new methods and techniques used for early screening for preeclampsia and pregnancy-induced hypertension. Various studies have been conducted worldwide for identifying the population at high risk of pregnancy-induced hypertension and preeclampsia and more need to be done in order to tender appropriate antenatal care to these women.

KEYWORDS: Preeclampsia, VEGF, PAPP-A, S-Endoglin, PP13, Cystatin-C, HbF, Cell free Fetal DNA, Pentraxin 3.

INTRODUCTION

Pre-eclampsia is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mmHg or more with proteinuria after 20 weeks of pregnancy in a previously normotensive and non-proteinuric patients. Pre-eclampsia is one of the most common complications in obstetrics. The occurrence of preeclampsia has continued to increase worldwide, and it is associated with significant maternal morbidity and mortality, accounting for about 50,000 deaths worldwide annually. The incidence of pre-eclampsia in primigravidae is about 4 - 5%. Reducing maternal mortality by 75% between 1990 and 2015 has been measured as part of the millennium development goals of the World Health Organization (WHO) Nations.[1] The exact etiology is unidentified, but it is associated with a failure of the trophoblastic invasion of the spiral arteries.[2] Altered renal function is an essential component of the patho-physiology of pre-eclampsia, which could lead to acute renal failure - an important cause for maternal morbidity and mortality.[3] The majority of deaths due to pre-eclampsia and eclampsia are preventable through the provision of appropriate and effective care to the women presenting with these complications. An early recognition of this complication may pave the way to an improvement in pregnancy outcome by increasing the patient's surveillance or allowing an early initiation of suitable therapeutic interventions.[4]

Preclampsia: Preeclampsia (PE) is a multisystem disorder specific to human pregnancy. It is defined as the association of pregnancy-induced hypertension with proteinuria that occurs after 20 weeks of gestation. Even though the cause of preeclampsia remains hard to pin down, the origin of the condition is recognized as lying in the placenta. This is because preeclampsia occurs only in the presence of pregnancy and it resolves after delivery of the placenta. The initiating episode in PE appears to be reduced uteroplacental perfusion as a result of abnormal cytotrophoblast invasion of spiral arterioles. Recent hypothesis is that pre-eclampsia is a two stage disorder, stage 1 caused by faulty endovascular trophoblastic remodeling that downstream causes the stage 2 clinical syndrome.[4]

It has been hypothesized that placental ischemia is an early event, leading to the placental production of a

soluble factor or factors that cause maternal endothelial dysfunction resulting in the clinical findings of hypertension and proteinuria. The main target organ is the kidney (glomerular endotheliosis). An altered renal function is an critical component of the pathophysiology of the disorder. So, proteinuria and hypertension dominate the clinical picture. Implantation of the placenta and vascular changes are completed by 20–22 weeks of gestation. Although PE is usually diagnosed in the second half of pregnancy, damage has already occurred at an earlier stage of pregnancy.[5]

Pathophysiology

The precise origin of preeclampsia remains mysterious, but it is believed to be likely multifactorial. A certainty is the central role played by the placenta in its pathology.[6,7] It is typically described as a two-stage syndrome(Fig. 1).[8] The first stage is characterized by shallow invasion of fetal trophoblast cells into the decidua and derisory modification of the spiral arteries.[9] This leads to uneven blood flow to the placenta, thus leading to placental stress. The inadequate placentation, followed by discontinuous perfusion of the intervillous space and fluctuating levels of oxygen result in chronic hypoxia or alternate periods of hypoxia/re-oxygenation within the intervillous space which produces tissue oxidative stress and increase placental apoptosis and necrosis.[10,11] The hemodynamic changes in placenta releases a number of factors and placental debris. Among these, fragments of syncytiotrophoblast microparticles (STMP), basal membrane, microparticles, microRNA, and fetal DNA have been detected in the maternal circulation where they cause inflammation and endothelial injuries.[12-15]

The second stage of PE is characterized by the maternal disease, presenting with elevated blood pressure and proteinuria (Fig.1).[8] It is characterized by a general systemic inflammatory response of which endothelial dysfunction is a well-known part. A number of circulating factors that contribute to maternal endothelial dysfunction, increased vascular permeability and oxidative stress are identified; such factors are STMP, cytokines, apoptotic factors and anti-angiogenic factors.[16] An activation of the coagulation cascade with formation of occlusive microthrombi is also a consequence of the endothelial dysfunction. The ability of the maternal system to handle the deficits in placentation and ensuing challenge to the maternal cardiovascular system partly depend on the immune system, as systemic inflammatory stress plays a key role in endothelial cell activation.[16] When the maternal vascular and immune systems cannot handle any longer the increased shedding of placental-produced debris and the aberrant expression of pro-inflammatory, anti-angiogenic and angiogenic factors, leading to a systemic endothelial cell dysfunction and an exaggerated inflammatory response.[17] But recently, this hypothesis has been challenged.[18]

The origin of preeclampsia is not only restricted to an alteration of trophoblast differentiation, but also in some cases depend on an underlying maternal constitutional factors such as genetic, obesity, dysfunctional maternal clearance or inflammatory systems. Women with a pre-gestational endothelial dysfunction, such as pre-existing hypertension, obesity and dyslipidemia, also have an increased risk of pre-eclampsia.[19]

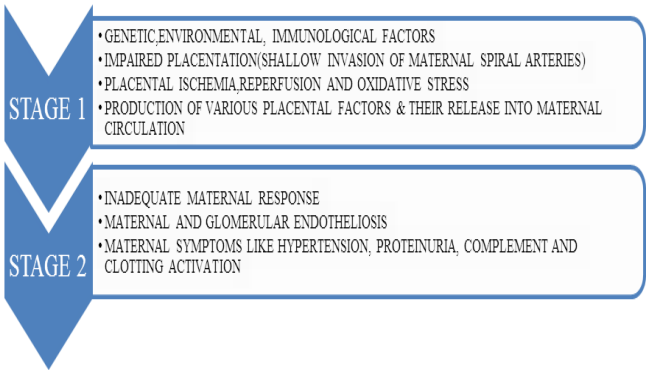

Figure. 1: Showing Two Stages of Preeclampsia.

Prevention and prediction of pre-eclampsia

To prevent pre-eclampsia would be a very significant contribution for maternal health. Prevention may be categorized into primary, secondary or tertiary. Secondary prevention demands knowledge of the pathophysiological mechanism of disease. Furthermore, the accessibility of techniques for early detection and intervention in the pathophysiological process are necessary. The major value of secondary prevention would be to recognize women at high risk of pre-eclampsia and make a medical intervention so that the disorder never occurs or is postponed. The eventual predictor of preeclampsia should presumably identify women with an increased risk of the disorder as early as in the first trimester. The test should also be simple, rapid, non-invasive, inexpensive and the technology generally available. Furthermore it should be valid, reliable and reproducible with a high positive and a low negative likelihood ratio.[20]

Screening by biochemical markers

PE is the major cause of fetal and maternal death and yet no specific treatment is available. Reliable biochemical markers for prediction and diagnosis of PE would have an enormous impact on maternal health. They help in developing an finest protocol to initiate treatment in early pregnancy and to reduce the rate of complications.[21] A large number of biochemical markers have been investigated for the prediction of PE (Table 1). Many of the described biochemical factors are measurable in maternal blood and have therefore been evaluated as biomarkers for the prediction and diagnosis of PE. Many such markers represent measurable manifestations of impaired placentation due to inadequate trophoblastic invasion of the maternal spiral arteries and reduced placental perfusion leading to placental ischaemia-related damage with the release of

inflammatory factors, platelet activation, endothelial dysfunction, maternal renal dysfunction or abnormal oxidative stress.[22]

At the moment only a few markers seem to be strong predictors of hypertensive disorders during pregnancy. Various studies have been done worldwide to recognize the population at high risk of preeclampsia in order to tender appropriate and timely antenatal care to these women so as to reduce maternal fetal morbidity and mortality. Our review presents an outline of the various markers used for early screening for preeclampsia and pregnancy-induced hypertension.[21]

Table. 1: showing biochemical markers of preeclampsia.

ADAM12	Insulin-like growth factor binding protein	PAPP-A	Activin A
Endothelin	Alpha fetoprotein	Leptin	Pentraxin
L-arginine	Vitamin D	Placental protein 13	P-selectin
Isoprostanes	Vascular endothelial growth factor	Placenta growth factor	Microalbuminuria
Resistin	Calcium, Magnesium	Circulating trophoblast	Ang-2 angiopoietin-2
Free foetal haemoglobin	Human placental growth hormone	Beta2-microglobulin	Antiphospholipid antibodies,
Uric acid	Inhibin A	Alpha-1-microglobulin	Haptoglobin
Foetal DNA/RNA	Genetic markers	Soluble endoglin	Soluble fms

***(i)*Molecules from the trophoblasts**

An improper formation of trophoblasts may produce a reduced amount of placenta derived proteins such as pregnancy-associated protein A (PAPP-A), placental protein (PP 13), in women later developing pre-eclampsia.[23] The failure of trophoblast invasion may contribute to the alteration of the surface layer of the syncytiotrophoblasts and result in leakage of alfa fetoprotein (AFP) into the maternal circulation resulting in an increased level of these proteins in women with pre-eclampsia.[24] Inhibin A and Activin A are both prominent before the onset of pre-eclampsia. In women who develop early-onset pre-eclampsia the levels are increased at an earlier gestational week than for women with late-onset pre-eclampsia.[25] Foetal cells cross the placenta during pregnancy. In pregnancies where pre-eclampsia develops the amount of foetal cells and cell-free foetal DNA and RNA have been demonstrated to be higher than in normal pregnancies. This may be explained by placental necrosis and apoptosis and an impaired DNA elimination.[26]

PP-13: Placental protein 13 (PP-13, galectin-13) is a small protein with 139 amino acids which is highly homologous (69%) to the human eosinophil Charcot-Leyden Crystal protein, a phospholipase that belongs to the beta-galactoside binding S-type animal lectin super family. The homodimer which is linked by disulfide bonds possibly has special haemostatic and immunobiological functions at the feto-maternal crossing point or a developmental role in the placenta.[10] The serum levels of PP-13 slowly increase during a normal pregnancy but abnormally low levels of PP-13 were detected in first trimester serum samples of women subsequently developing fetal growth restriction and preeclampsia, in particular cases with early onset.[27] Elevated serum concentrations of PP-13 have been found in the second and third trimester in women with preeclampsia, IUGR and in preterm delivery.[10] Romero R et al in his study concluded that first-trimester serum levels of PP-13 may dole out as a suitable marker for preterm preeclampsia but are weak for the prediction of severe preeclampsia and unsuccessful for mild preeclampsia at term.[28] Combination of several diagnostic tools results in improved predictive power as was shown by combined measuring of first trimester serum PP-13 levels and median uterine artery pulsatility index by ultrasound. This combination achieved a detection rate for preeclampsia of 90% with a false positive rate of 6%.[29]

PAPP-A: PAPP-A (pregnancy-associated plasma protein A, pappalysin 1, insulin-like growth factor binding protein-4 protease) is a disulfide bond linked homodimeric peptidase of 1628 amino acids . It can be detected during pregnancy in maternal circulation mainly as a complex with the proform of the eosinophil major basic protein, an inhibitor of PAPP-A. Insulin-like growth factor binding proteins are substrates for the hydrolytic activity of PAPP-A.[10] PAPP-A is a glycoprotein formed in the placenta which has been evaluated as a biochemical marker to be measured in pregnancy for the last three decades . During normal pregnancy its concentration in plasma gradually increases. PAPP-A's function is not completely clear, but it has been suggested that PAPP-A is associated with placental development. PAPP-A is extensively used in combination with HCG and the ultrasound parameter nuchal translucency thickness to assess the risk of Down's syndrome.[30] Besides being used in aneuploidy screening, low levels of PAPP-A are associated with the development of all placental syndromes: PE, IUGR, placental abruption and stillbirth.[31] Recently, decreased plasma levels of PAPP-A have been reported in all trimesters in women with preeclampsia.[32]

Cell-free fetal DNA

Many approaches have been used to detect cell free fetal DNA in maternal plasma for non-invasive diagnostic approaches.[10] Lo et al and Zhong et al in a small scale

study in the plasma of preeclamptic women and controls in the third trimester,and second trimester, observed that cffDNA was increased roughly 5-fold in women with preeclampsia. Levine et al in his study with 120 preeclamptic women and 120 controls observed two- to five-fold increase of cffDNA levels starting from week 17 until three weeks before the onset of preeclampsia. An increase of total cell free DNA was observed in women with preeclampsia at term and before the onset of preeclampsia. cffDNA has shown some predictive value for the prediction of preeclampsia between 20–25 weeks of gestation, however, higher sensitivities and specificities can be attained by combining several markers as has been shown in a nested case-control study for cell free DNA combined with Inhibin A in the second and third trimester.[10,33] Currently, several multicenter studies are being performed to confirm the predictive value of cffDNA to predict and monitor preeclampsia in combination with other potential markers, e.g. P-selectin, PAPP-A, PP-13, sflt-1, sEng, PlGF).

Inhibin and activin

Inhibin, is a glycoprotein hormone that belongs to the transforming growth factor - superfamily, consisting of αβ A (inhibin A) and αβ B (inhibin B). Corpus luteum was considered to be a source of inhibin A in pregnant women. Recent studies expose the origin of inhibin A to be the feto-placental unit. There is also indication for altered levels of these hormones in the blood of women affected by chromosomal abnormality, miscarriage and foetal growth restriction in pregnancy. Women with pre-eclampsia have distinctively high levels of activin A, inhibin A, and pro α. Serum inhibin A and activin A concentrations increase before the onset of pre-eclampsia at gestational ages that depend on when pre-eclampsia develops.[4] Muttukrishna S et al observed increase in serum inhibin A and activin A prior to pre-eclampsia, before 20 weeks in those with early onset pre-eclampsia. Screening efficacy was determined at 15-19 and 21-25 weeks in all women who developed pre-eclampsia (n = 70) and randomly selected controls (n = 240). Predictive sensitivities were low (16-59%) but much better for early onset pre-eclampsia: 67 and 44% at 15-19 weeks and 89 and 89% at 21-25 weeks for inhibin A and activin A respectively.[25]

(ii). **Angiogenic and anti-angiogenic factors**

Pre-eclampsia is characterized by an inequity between different factors that regulate vasculogenesis and angiogenesis. Vasculogenesis occurs mainly during foetal development when the formation of the vasculature derived from endothelial progenitor cells, angioblasts, form a primitive vascular network. Angiogenesis, development of new blood vessels from pre-existing ones, occurs during embryo implantation and placentation. In pre-eclampsia there is an inequality in the angiogenic state where antiangiogenesis dominates. A disturbed balance of these factors are projected as one cause of the deterioration of the endothelial cell dysfunction and increased vascular permeability seen in pre-eclampsia.[34] A variety of pro-angiogenic factors such as Vascular Endothelial Growth Factor (VEGF) and PlGF and anti-angiogenic factors i.e. soluble fms-like tyrosine kinase-1(sFlt-1) and Endoglin have been studied as budding markers of pre-eclampsia. In pregnancies subsequently developing pre-eclampsia, especially early onset, lower levels of PlGF and higher levels of sFlt-1 and Endoglin have been demonstrated weeks before diagnosis. A combination of these factors has been shown to potentially improve the predictive value.[35] To achieve higher predictive power not only combination of markers are of interest, also new potential predictors are of importance.

Angiogenic factors: Angiogenesis requires the complex interaction between the pro-angiogenic factors vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) with their cognate receptors VEGF receptor-1 (VEGFR-1, which is alternatively called fms-like tyrosine kinase (flt)-1) and VEGFR-2. Placenta is a rich source of these factors.[10] In addition to regulating blood vessel homeostasis, VEGF, PlGF and the flt-1 receptor have been shown to be key components in regulating trophoblast cell survival and function**.** Placental cells also secrete a soluble isoform of flt-1, which is generated through alternative splicing of the messenger RNA and acts as an anti-angiogenic factor by neutralizing, PlGF and VEGF.[10]

There is burly evidence for the occurrence of higher placental expression of sflt-1 and elevated circulating levels of sflt-1 and reduced free bioactive PlGF and VEGF in preeclamptic patients.[36] Studies suggested that a part of this excess of circulatory sflt- 1 may stem from the placenta. Maternal blood levels of sflt-1 were shown to correlate with the severity of preeclampsia, whereas, in an opposite manner, the quantities of bioactive VEGF and PlGF were further decreased in patients with severe symptoms compared to normal pregnant women or preeclamptic patients with mild symptoms. Nevertheless, owing to the evolving unbalance of angiogenic factors after 25 weeks of gestation in women with subsequent preeclampsia, the ratio sflt-1/PlGF has been advocated to be a unswerving marker of overall preeclampsia risk. It has recently been reported that patients with preeclampsia have lower plasma concentrations of soluble VEGF-R2.[37] However, this biomarker may not be specific for preeclampsia as an equivalent decrease was observed in patients with SGA babies in the absence of preeclampsia.

Soluble endoglin: Endoglin (Eng) is a co-receptor for transforming growth factor (TGF)-β1 and TGF-β3 that is highly expressed on cellular membranes of the vascular endothelium and on the syncytiotrophoblast. It functions as a modulator of TGF-β signaling and is implicated in angiogenesis and the regulation of the vascular tone. In vitro, sEng acts as a negative regulator of angiogenesis by competitive interaction with TGF-β, thereby impairing capillary formation by endothelial cells. A

circulatory form of endoglin, which consists of the extra cellular part of the molecule that may be produced through the proteocleavage of the placental membrane bound form, has been identified in normal pregnancy and in preeclampsia. It is there in excess in preeclamptic patients as compared to normotensive controls, and its concentrations appear to increase with the severity of the symptoms and are the highest in complicated cases of preeclampsia. Pregnancies with IUGR may also be characterized by elevated levels of sEng, suggesting that this factor is not specific for preeclampsia, but may be a marker for clinical conditions associated with an underlying placental pathology.[38] However, others demonstrated no association between IUGR and the sEng levels.

Several longitudinal case-control studies have evaluated the potential of sEng in combination with the pro-and anti-angiogenic factors PlGF and sflt-1 for the prophecy of preeclampsia. The studies reported that the pattern of changes in the ratio of different combinations of these factors collected at 13 weeks and around 20 weeks, was more enlightening than the individual biomarkers at single time-point screening. One study suggested that a scrupulous monitoring of the sequential changes in the profile of these three biomarkers between the first and the second trimesters permits sensitive and specific risk assessment.[10]

(iii). Inflammatory markers

Women who later develop pre-eclampsia have higher levels of Pentraxin 3, an inflammatory molecule, articulated in response to inflammatory stimuli by a variety of cells including endothelial cells.[39] Soluble tumour necrosis factor receptor 2 is another factor that reflects intravascular inflammation and has been shown to be increased in preeclampsia.[40]

PTX3

Pentraxin 3 [PTX3] belongs to the same family as C-reactive protein (CRP) or serum amyloid P component (SAP) and consists of 381 amino acids. The C terminus is highly homologous to SAP and CRP whereas the N-terminus doesn't show any homology to other proteins. Responding to proinflammatory stimuli CRP, SAP and PTX3 are produced by various tissues. It is also articulated in tissues undergoing cell death. PTX3 then interacts with several growth factors, extra cellular matrix components and certain pathogens but is also involved in the activation of the complement system and facilitates pathogen recognition by phagocytes. During pregnancy, PTX3 is more and more expressed in amniotic epithelium, chorionic mesoderm, trophoblast terminal villi, and perivascular stroma of placentae.[10] Cetin et al. showed that in case of a future preeclampsia and IUGR the PTX3 plasma levels are even more increased in all three trimesters .So far no studies that combine PTX3 with other potential markers have been performed.[41]

P-SELECTIN

P-selectin is a member of the selectin family of cell surface adhesion molecules expressed by platelets and endothelial cells upon activation and plays important role in inflammatory reactions by supporting the recruitment and activation of circulating leucocytes, and in coagulation through the generation of leukocyte-derived "blood borne" tissue factor. P-selectin is quickly shed from the cellular membrane of activated platelets and this release is recommended to contribute to most of the soluble isoform of the molecule that is found in the plasma. Preeclampsia is associated with extensive platelet activation.[10] P-selectin-released from activated platelets, have been found in the peripheral blood of preeclamptic women.[42] Captivatingly, it has newly been shown that alterations in the levels of soluble P-selectin before 20 weeks of gestation antedate the symptoms . In one of the studies, P-selectin was recognized as the marker with the highest discriminatory ability among three biomolecules evaluated between gestational weeks 11 to 15.[43] However, the combination of P-selectin with the two other markers, namely Activin A and VEGFR, showed a detection rate of only 59% (with a false-positive rate of 5%), which is not adequate for a possible routine clinical implementation as a screening test.

ADAM12

ADAM12 (a disintegrin and metalloprotease 12) is a membrane bound zinc dependant protease and belongs to the ADAM protein family, a group of proteins involved in cell-cell and cell-matrix interactions in fertilization, muscle development and neurogenesis.[10] The plasma concentration of ADAM12 has been found to be changed in several pregnancy related disorders. Several studies have demonstrated that the plasma level of ADAM12 is decreased in women carrying a fetus with trisomy 21 and trisomy 18.[44] It has also been shown that the ADAM12 concentration is decreased in women with other aneuploidies and in women with low for gestational age birth weights.

The first connection of ADAM12 serum levels to preeclampsia was verified by Laigaard et al in a study on 160 preeclampsic women and 324 healthy controls in the first trimester.[45] The serum concentration of ADAM12 was appreciably decreased in women that later developed preeclampsia. These results were confirmed by Spencer et al.[46] however, another study failed to confirm these promising results but concluded that measurement of ADAM12 does not provide useful prediction of SGA, preeclampsia, or spontaneous preterm delivery.

iv. Renal Markers

Cystatin C and B-Microglobulin

β2 Microglobulin also known as B2M is a component of MHC class I molecules . Possessing an Ig-like domain, B2M is non-covalently associated with a heavy chain of HLA antigens.[5]

Cystatin C is a low molecular weight non glycosylated basic protein made of 120 amino acid residues articulated in all nucleated cells. Cystatin C is produced at constant rate and is freely filtered by kidney glomeruli, completely reabsorbed but degraded in the tubules thus making it an superb GFR marker.[1] It is found in almost all tissues and body fluids and is a potent inhibitor of lysosomal proteinases. B2 microglobulin and cystatin C are freely filtered by the glomerulus and reabsorbed and catabolised by proximal tubular cells. Therefore, their serum values could be a superior marker of glomerular filtration rate (GFR) than serum creatinine level . Cystatin C values will be abnormally high when GFR decreases to 88–95 ml/min per 1.73 m^2.[5] The blood levels of cystatin are not dependent on age, sex, diet, muscle mass or inflammatory processes. It is sensitive to changes in the Creatinine blind area of GFR (40-70ml/min/1.73 m2). Since there is no tubular secretion of Cystatin C, it is particularly sensitive to minor changes in GFR in the earliest stages of kidney diseases. There are no known extra renal routes of elimination, with clearance from the circulation is only by glomerular filtration. Some studies found B2M to be less adequate than cystatin C as a GFR marker , but another did not show any differences. A previous study carried out by Kristensen and colleagues has reported that the plasma levels of cystatin C and beta-2-microglobulin are considerably elevated in preeclampsia and that these low molecular mass proteins are valuable markers of renal impairment in preeclampsia. High levels of cystatin C in PE might reveal placental ischemia.[5,47]

v. Markers of Oxidative Stress-CELL-Free Fetal Hemoglobin

Techniques such as proteomics and genomics were used, revealing fetal Hb to be a budding factor linking two stages in PE. Gene microarrays and proteomic techniques were used to try to identify placental genes related to PE. The results showed the up-regulated expression of genes coding for α2 and γ-chains of fetal hemoglobin in the PE placentas. The proteomics and in situ hybridization analyses publicized an accumulation of free HbF in the placental vascular lumen.[48] Cell-free hemoglobin and its metabolites, free heme and ferrous iron (Fe++), are toxic to tissue in general because they induce oxidative stress.[49] In PE, oxidative stress has been described both in the placenta and in the maternal circulation. In addition, the concentrations of circulating antioxidants are reduced in women with PE. The strong oxidative properties of cell-free Hb are mainly attributed to the redox activity of the iron atom. The cell Hb binds strongly to the vasodilator nitric oxide (NO), which leads to vasoconstriction and thus to increased blood pressure.[50] Free heme also has direct effects on inflammatory pathways and is able to induce both neutrophils and cytokine synthesis.[51] Through these mechanisms, cell-free Hb and its metabolites induce oxidative stress, vasoconstriction, hemolysis, and endothelial damage in both the maternal vascular bed and the kidneys.

A1-Microglobulin

α1-microglobulin (A1M) is a plasma- and extravascular protein that provides protection through its ability to bind and neutralize free heme and radicals. Several in vitro and in vivo studies have shown that A1M protects cells and tissues in conditions with increased concentrations of extracellular Hb, heme, and reactive oxidative species (ROS). In PE, A1M expression in liver and placenta cells has been shown to be up-regulated following exposure to Hb, heme, and ROS. Furthermore, the serum concentration of A1M has also been shown to be appreciably elevated in maternal blood in the first trimester for patients who consequently develop PE and in term pregnancies with manifest PE.[52]

CONCLUSION AND FUTURE PERSPECTIVES

Even though there exists many different potential markers for preeclampsia, the reliability of these markers in predicting preeclampsia has been contradictory between different studies. Furthermore, preeclampsia is a complicated disorder, certain say it is not one but several diseases. Some of the biochemical markers shows potential predictive performance, but so far there is no clinically validated screening procedure. Screening pregnant women with biochemical markers for PE can reduce redundant suffering and health care costs by early detection of mothers at increased risk for PE, thus avoiding preventable hospitalization of pregnant women with suspect or mild PE and enabling monitoring of the development of the disease thereby optimizing time for delivery and optimistically reducing the number of premature births. Therefore, there is a need for high quality, large scale multicenter trials which enrol patients with different risks of developing the syndrome and throughout multiethnic background, in order to assess the predictive value of different markers and finally offer the best marker combination for a routine use in clinical settings.

REFRENCES

1. Sumithra K, Vibha C, Vishwanath HL. Study of serum cystatin C in pre-eclampsia. International Journal of Current Research, 2013; 5(10): 2994-96.
2. Redman CWG, Sargent IL, Roberts JM. In:Lindheimer MD, Cunningham FG, Roberts JM. Chesley's Hypertensive Disorders in Pregnancy, 3rd Ed, Elsevier, Amsterdam, The Netherlands, 2009; 129–144.
3. Vikse BE, Irgens LM, Leivestad T, Skjærven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. New Engld J Med., 2008; 359(8): 800–9.
4. Harshini Vana, Suchitra Thunga. A comparison between serum inhibin A levels in pre-eclampsia and normotensive pregnancy. Int J Pharm Biomed Res., 2012; 3(3): 147-151.
5. Farag MK, Maksoud NA, Ragab HM. Predictive value of cystatin C and beta-2 microglobulin in preeclampsia. Journal of Genetic Engineering and Biotechnology, 2011; 9(2): 133–6.

6. Saito S, Shiozaki A, Nakashima A, Sakai M, Sasaki Y. The role of the immune system in preeclampsia. Mol Aspects Med., 2007; 28: 192–209.
7. Wen SW, Chen XK, Rodger M, White RR, Yang Q, Smith GN, et al. Folic acid supplementation in early second trimester and the risk of preeclampsia. Am J Obstet Gynecol, 2008; 198: 45–7.
8. Olsson MG, Centlow M, Rutardóttir S, Stenfors I, Larsson J, Hosseini-Maaf B, et al. Increased levels of cell-free hemoglobin, oxidation markers, and the antioxidative heme scavenger 1-microglobulin in preeclampsia. Free Radic Biol Med., 2010; 48: 284-291.
9. Wester-Rosenlof L, Casslen V, Axelsson J, Edstrom-Hagerwall A, Gram M, Holmqvist M et al. A1M/alpha1-microglobulin protects from heme-induced placental and renal damage in a pregnant sheep model of preeclampsia. PloS One, 2014; 9: e86353.
10. Santo Monte. Biochemical markers for prediction of preclampsia: review of the literature J Prenat Med., 2011 Jul-Sep; 5(3): 69–77.
11. Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. Hypertension, 2008; 51(4):970-5.
12. James JL, Whitley GS, Cartwright JE. Pre-eclampsia: fitting together the placental, immune and cardiovascular pieces. J Pathol, 2010; 221(4): 363-78.
13. Naav A, Erlandsson L, Axelsson J, Larsson I, Johansson M, Wester-Rosenlof L et al. A1M Ameliorates Preeclampsia-Like Symptoms in Placenta and Kidney Induced by Cell-Free Fetal Hemoglobin in Rabbit. PloS One, 2015; 10: e0125499.
14. Son GH, Kwon JY, Lee S, Park J, Kim Y-J, Yun B, Park JH. Comparison of serum and urinary nephrin levels between normal pregnancies and severe preeclampsia. Eur J Obstet Gynecol Reprod Biol., 2013; 166: 139-144.
15. Salih M, Zietse R, Hoorn EJ: Urinary extracellular vesicles and the kidney: biomarkers and beyond. Am J Physiol Renal Physiol, 2014; 306: F1251-1259.
16. Redman CW, Sargent IL. Placental stress and pre-eclampsia: a revised view. Placenta, 2009; 30: A:S38-42.
17. Redman CW, Sargent IL.Latest advances in understanding preeclampsia. Science 2005; 308: 1592–4.
18. Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. Hypertension, 2008; 51: 970–5.
19. Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. Placenta, 2009; 30(Suppl A): S32–S37.
20. Conde-Agudelo A, Villar J, Lindheimer M. World Health Organization systematic review of screening tests for preeclampsia. Obstet Gynecol, 2004; 104(6): 1367-91.
21. Poprawski G, Wender-Ozegowska E, Zawiejska A, Brazert J. Modern methods of early screening for preeclampsia and pregnancy-induced hypertension--a review. Ginekol Pol., 2012 Sep; 83(9): 688-93.
22. Poon LC and Nicolaides KH. First-trimester maternal factors and biomarker screening for preeclampsia. Prenatal Diagnosis, 2014; 34: 618–627.
23. Romero R, Kusanovic JP, Than NG, Erez O, Gotsch F, Espinoza J, et al. Firsttrimester maternal serum PP13 in the risk assessment for preeclampsia. Am J Obstet Gynecol, 2008; 199(2): 122 e1-22 e11.
24. Audibert F, Benchimol Y, Benattar C, Champagne C, Frydman R. Prediction of preeclampsia or intrauterine growth restriction by second trimester serum screening and uterine Doppler velocimetry. Fetal Diagn Ther. 2005; 20(1): 48-53.
25. Muttukrishna S, North RA, Morris J, Schellenberg JC, Taylor RS, Asselin J, et al. Serum inhibin A and activin A are elevated prior to the onset of preeclampsia. Hum Reprod, 2000; 15(7): 1640-5.
26. Levine RJ, Qian C, Leshane ES, Yu KF, England LJ, Schisterman EF, et al. Two-stage elevation of cell-free fetal DNA in maternal sera before onset of preeclampsia. Am J Obstet Gynecol, 2004; 190(3): 707-13.
27. Huppertz B, Sammar M, Chefetz I, Neumaier-Wagner P, Bartz C, Meiri H. Longitudinal determination of serum placental protein 13 during development of preeclampsia. Fetal Diagn Ther., 2008; 24: 230–6.
28. Romero R, Kusanovic JP, Than NG, Erez O, Gotsch F, Espinoza J, et al. First-trimester maternal serum PP13 in the risk assessment for preeclampsia. Am J Obstet Gynecol, 2008; 199(2): 122.
29. Nicolaides KH, Bindra R, Turan OM, Chefetz I, Sammar M, Meiri H, et al. A novel approach to first-trimester screening for early pre-eclampsia combining serum PP-13 and Doppler ultrasound.Ultrasound Obstet Gynecol, 2006; 27: 13–17.
30. Kagan KO, Anderson JM, Anwandter G, Neksasova K, Nicolaides KH. Screening for triploidy by the risk algorithms for trisomies 21, 18 and 13 at 11 weeks to 13 weeks and 6 days of gestation. Prenat Diagn 2008;28(13):1209-13.
31. Conde-Agudelo A, Bird S, Kennedy SH, Villar J, Papageorghiou AT. First- and second-trimester tests to predict stillbirth in unselected pregnant women: a systematic review and meta-analysis. BJOG 2015; 122(1): 41-55.
32. Spencer K, Cowans NJ, Nicolaides KH. Low levels of maternal serum PAPP-A in the first trimester and the risk of preeclampsia. Prenat Diagn, 2008; 28: 7–10.
33. Diesch CH, Holzgreve W, Hahn S, Zhong XY. Comparison of activin A and cell-free fetal DNA levels in maternal plasma from patients at high risk for preeclampsia. Prenat Diagn, 2006; 26: 1267–1270.

34. James JL, Whitley GS, Cartwright JE. Pre-eclampsia: fitting together the placental, immune and cardiovascular pieces. J Pathol, 2010; 221(4): 363-78.
35. De Vivo A, Baviera G, Giordano D, Todarello G, Corrado F, D'Anna R. Endoglin, PlGF and sFlt-1 as markers for predicting pre-eclampsia. Acta Obstet Gynecol Scand, 2008; 87(8): 837-42.
36. Levine RJ, Karumanchi SA. Circulating angiogenic factors in preeclampsia. C. lin Obstet Gynecol, 2005; 48: 372–386.
37. Chaiworapongsa T, Romero R, Gotsch F, Espinoza J, Nien JK, Goncalves L, et al. Low maternal concentrations of soluble vascular endothelial growth factor receptor-2 in preeclampsia and small for gestational age. J Matern Fetal Neonatal Med., 2008; 21: 41–52.
38. Jeyabalan A, McGonigal S, Gilmour C, Hubel CA, Rajakumar A. Circulating and placental endoglin concentrations in pregnancies complicated by intrauterine growth restriction and preeclampsia. Placenta, 2008; 29: 555–563.
39. Thilaganathan B, Wormald B, Zanardini C, Sheldon J, Ralph E, Papageorghiou AT. Early-pregnancy multiple serum markers and second-trimester uterine artery Doppler in predicting preeclampsia. Obstet Gynecol, 2010; 115(6): 1233-8.
40. Popovici RM, Krause MS, Jauckus J, Germeyer A, Brum IS, Garlanda C, et al. The long pentraxin PTX3 in human endometrium: regulation by steroids and trophoblast products. Endocrinology, 2008; 149: 1136–43.
41. Cetin I, Cozzi V, Papageorghiou AT, Maina V, Montanelli A, Garlanda C, et al. First trimester PTX3 levels in women who subsequently develop preeclampsia and fetal growth restriction. Acta Obstet Gynecol Scand, 2009; 88(7): 846-9.
42. Lok CA, Nieuwland R, Sturk A, Hau CM, Boer K, Vanbavel E, Vanderpost JA. Microparticle-associated P-selectin reflects platelet activation in preeclampsia. Platelets, 2007; 18: 68–72.
43. Banzola I, Farina A, Concu M, Sekizawa A, Purwosunu Y, Strada I, et al. Performance of a panel of maternal serum markers in predicting preeclampsia at 11–15 weeks' gestation. Prenat Diagn, 2007; 27: 1005–10.
44. Spencer K, Cowans NJ. ADAM12 as a marker of trisomy 18 in the first and second trimester of pregnancy. J Matern Fetal Neonatal Med., 2007; 20: 645–50.
45. Laigaard J, Sorensen T, Placing S, Holck P, Frohlich C, Wojdemann KR, et al. Reduction of the disintegrin and metalloprotease ADAM12 in preeclampsia. Obstet Gynecol, 2005; 106: 144–149.
46. Spencer K, Cowans NJ, Stamatopoulou A. ADAM12s in maternal serum as a potential marker of preeclampsia. Prenat Diagn, 2008; 28: 212–6.
47. Kristensen K,Wide-Swensson D, Schmidt C, Blirup-Jensen S,Lindstrom V, Strevens H, Grubb A. Acta Obstet Gynecol Scand, 2007; 86(8): 921–6.
48. Centlow M, Carninci P, Nemeth K, Mezey E, Brownstein M, Hansson SR. Placental expression profiling in preeclampsia: local overproduction of hemoglobin may drive pathological changes. Fertil Steril, 2008; 90(5): 1834-43.
49. Nääv A, Erlandsson L, Axelsson J, Larsson I, Johansson M, Wester-Rosenlöf L, et al. A1M Ameliorates Preeclampsia-Like Symptoms in Placenta and Kidney Induced by Cell-Free Fetal Hemoglobin in Rabbit. PLoS One., 2015; 10(5): e0125499.
50. Hansson SR, Naav A, Erlandsson L. Oxidative stress in preeclampsia and the role of free fetal hemoglobin. Frontiers in physiology, 2014; 5: 516.
51. May K, Rosenlof L, Olsson MG, Centlow M, Morgelin M, Larsson I, et al. Perfusion of human placenta with hemoglobin introduces preeclampsia-like injuries that are prevented by alpha1-microglobulin. Placenta, 2011; 32(4): 323-32.
52. Olsson MG, Allhorn M, Bulow L, Hansson SR, Ley D, Olsson ML, et al. Pathological conditions involving extracellular hemoglobin: molecular mechanisms, clinical significance, and novel therapeutic opportunities for alpha(1)-microglobulin. Antioxidants & redox signaling, 2012; 17(5): 813-46.