Thrombosis Research 136 (2015) 189–195

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Promising prognostic markers of Preeclampsia: New avenues in waiting

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ARTICLE INFO

Article history:
Received 6 May 2015
Received in revised form 12 May 2015
Accepted 12 May 2015
Available online 20 May 2015

Keywords:
Preeclampsia
Biomarkers
Corin
Copeptin
Microparticles
MicroRNA

ABSTRACT

Preeclampsia is a pregnancy related condition identified by hypertension and either proteinuria or end-organ dysfunction after 20th week of gestation and complicates 2-8% pregnancies worldwide. Enigmatic pathophysiology and multi-system involvement hinder accurate identification and clinical management of patients. Inadequate trophoblast invasion and subsequent inflammatory response have been implicated in the onset of PE. In absence of effective treatment of preeclampsia except delivery, recent research has been focused on identification of specific and sensitive biomarkers for early prediction of PE. Several angiogenic, anti-angiogenic, inflammatory, biophysical (mean arterial pressure and uterine artery Doppler) biomarkers, alone and in combination, have been proposed for prediction but limited predictive values have hindered their use in clinical settings. Current review summarizes some of relatively new biomarkers such as corin, copeptin, microparticles and miRNA, the prognostic efficiency of which are either analyzed in associated disorders or recently discovered.

Contents

Introduction

Preeclampsia (PE), known as "disease of theories", is a human specific heterogeneous disease characterized by sudden onset of hypertension and associated end organ dysfunction after 20 weeks of gestation in previously normotensive women [1]. The disease is complicated by cerebral hemorrhage, renal failure, epilepsy, stroke, respiratory insufficiency and kidney damage. It affects 2-8% of pregnancies worldwide, with higher prevalence of 2-16% in developing countries due to poor management of PE. With annually ~ 63,000 maternal deaths worldwide, PE is one of the leading causes of maternal mortality and morbidity [2].

According to the latest guidelines of ACOG preeclampsia can be classified into mild and severe PE. Blood pressure of ≥140/90 mmHg or mean arterial pressure ≥105 mmHg is termed as mild PE. Severe PE is defined as blood pressure of ≥160/110 mmHg and/or new onset of thrombocytopenia (platelet count < 100000/ml), severe unresponsive

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http://dx.doi.org/10.1016/j.thromres.2015.05.011
0049-3848/

epigastric pain, impaired liver function, cerebral or visual disturbances, renal insufficiency, pulmonary edema [3].

Even after extensive research worldwide, the pathophysiology of PE remains elusive [4]. Hence for the management of patients, diagnosis and identification of potential biomarkers for early prediction of PE is important.

Risk Factors and Pathogenesis

High incidence of PE in nulliparous women reflects inexperienced maternal immune response to pregnancy. The conventional risk factors for development of PE include chronic hypertension, diabetes, maternal age, obesity, previous PE, thrombophilia, autoimmune disorder, vascular disease, ethnicity and multiple births [5,6]. Pre-existing risk factors play a vital role in altering the sensitivity towards adaptive changes involved in pregnancy and thus increase susceptibility to PE.

The pathogenesis of PE remains poorly understood due to its heterogeneous, multi-systemic nature. Various theories have been put forward to explain the pathogenesis of PE which involves genetic predisposition, immune system dysregulation, placental ischemia, inflammation and so on. But failure of adequate trophoblast invasion in maternal spiral artery during pregnancy remains the most promising explanation for the pathogenesis [7].

During normal pregnancy, developing fetus receives nutrition and oxygen supply via maternal spiral arteries. In order to match the increasing demand of oxygen and nutrition, arteries undergo vascular remodelling. The process of vascular remodelling begins at first trimester and ends at 18-20 weeks of gestation [8]. The purpose of remodelling is to convert maternal spiral arteries from high resistance, low capacity blood vessels to low resistance, high capacity vessels. The vascular remodelling occurs at 8-12 weeks of gestation during which extravillous trophoblast cells invade the decidual part of spiral arteries [9]. Trophoblast cells transform from high resistance epithelial to low resistance endothelial phenotype facilitating the establishment of viable pregnancy.

Development of PE is hypothesized to take place in two distinct stages; in the first stage, the trophoblast invasion is restricted to decidual segment of maternal spiral arteries leaving myometrial segment, thus leading to unchanged musculoelastic phenotype [10]. The inadequate trophoblast invasion results in decrease of feto-maternal surface area and high uteroplacental flow resistance. It leads to hypoperfusion and hypoxia in placenta [11]. The second stage is characterized by hypoxia and hypoperfusion mediated systemic inflammatory response releasing various inflammatory, antiangiogenic and vasoactive factors into circulation. These factors lead to maternal systemic endothelial dysfunction i.e. activation of coagulation system, vasoconstriction, hemolysis, resulting in proteinuria and hypertension, which are the clinical hallmarks of PE [12].

Elusive pathophysiology, lack of effective diagnostic and therapeutic interventions makes PE, a major challenge for clinicians. Delivery of placenta remains the only effective treatment for subsidence of symptoms of PE. Hence identification of novel, clinically effective biomarkers for early prediction of PE is a key area of research. Single or combination of biomarkers will allow surveillance of high risk patients for PE as well as proper monitoring of patients which will reduce misdiagnosed or undiagnosed cases [13]. The biomarkers may also be used as therapeutic targets for development of effective intervention against PE.

Existing Prognostic Biomarkers and Need for New Biomarkers

In the absence of an effective method for prevention of PE, early prediction will be beneficial for appropriate antenatal surveillance and for the use of prophylactic treatment such as low dose aspirin. The prophylactic use of low dose aspirin will be beneficial if started early in pregnancy i.e. on or before 16 weeks of gestation [14].

Spiral artery remodelling, which begins in the first trimester of pregnancy, ensures increase in blood supply by decreasing maternal blood flow resistance and high uteroplacental perfusion [15]. The process of remodelling is a crucial adaptive change in the pregnant uterus mediated by diverse molecules such as angiogenic factors, hormones, adhesion molecules, vasodilators and so on [16,17]. As defects in signalling mediated by these effector molecules are hypothesized in impairment of spiral artery remodelling and hence in pathogenesis of PE, large number of studies have analyzed these markers as potential early predictors of PE [18–24]. Elevated levels of anti-angiogenic factors such as placental soluble fms-like tyrosine kinase (sFlt-1) and soluble endoglin (sEng) reported in PE cases as early as 12 weeks of gestation, but poor predictive value of these markers in the follow up studies encumbered its clinical application as predictive markers [21,22].

Additional studies have examined circulating levels of pregnancy-associated plasma protein-A (PAPP-A), C-Reactive protein (CRP) and interleukin-1β (IL-1β) in the first trimester of pregnancy as predictive markers, but these molecules showed poor to moderate predictive value for PE [25]. Moore Simas et al, in a prospective longitudinal analysis of serum samples of women with risk factors for PE demonstrated high predictive value of ratio of sFlt1 and placental growth factor (PlGF) for early onset PE at 22-26 weeks of gestation, but did not find significant association in women who developed late onset PE [18]. Similarly, in other cross sectional analysis of healthy nulliparous women, Levine et al demonstrated poor predictive value of elevated serum levels of sFlt1:PlGF ratio and sEng at 21-32 weeks of gestation in prediction of late onset PE [19].

The multifactorial nature of PE has promoted use of combination of biochemical and biophysical markers for early prediction. Biophysical markers such as uterine artery Doppler (UAD) and mean arterial pressure in combination of angiogenic/anti-angiogenic factors have been analyzed for prediction of PE [21,26]. In a large prospective screening study involving 9149 singleton pregnancies, Poon et al demonstrated high predictive potential of uterine artery Doppler pulsatility index (UAD-PI) in first trimester with AUC of 0.91. In conjunction with maternal history and aneuploidy markers, UAD-PI showed better predictive for PI in the first trimester (AUC = 0.96) [26]. Although predictive value of angiogenic/anti-angiogenic factors enhanced when combined with first trimester UAD-PI (AUC = 0.74), yet limitations of performing UAD analyses by experienced sonologists, standard methodology to minimize inter-study result variability, constraint use of UAD as a predictive marker, particularly in developing countries [21].

Kusanovic et al, in a large longitudinal cohort study, analyzed plasma samples at 6-15 and 20-25 weeks of gestation and found low predictive value for sFlt-1, PlGF and PlGF/sFlt-1in early gestation. Consistently, with early gestational results, these markers showed poor predictive value in mid-trimester (20-25 weeks) analysis too [27]. In one of the largest prospective cohort studies, the angiogenic factors alone and in conjunction with UAD velocimetry was evaluated for early prediction of PE at 22-26 weeks of gestation. While maternal plasma levels of PlGF showed high predictive values for identification of early onset (AUC = 0.80) and severe PE cases (AUC = 0.789), sFlt-1 levels demonstrated low predictive value [28]. Similarly, another prospective case-control study found low discriminatory potential of PlGF, sFlt-1 and sENG in discriminating cases from controls [35].

New Prognostic Markers for PE

Numerous studies investigated and proposed biomarkers including sENG, sFlt-1, PlGF for prediction of PE (Table 1); however different studies reported contradictory results regarding effectiveness of these markers in prediction of PE. Identification of novel potential markers for prediction of PE is of clinical importance due to limited sensitivity and specificity of identified biomarkers.