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Review Article

Preeclampsia: Where do we stand for an Early Diagnosis?

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Abstract

Preeclampsia represents a danger to nearly 10 million pregnant women worldwide. This gestational pathology has very important consequences for preeclamptic (PE) women but also for newborns. To date, no early diagnostic tools are available for PE, resulting from the difficulties to identify the originating cause of this disease. However, researchers and clinicians are actively working on the identification of a biomarker acceptable to all. This is a challenging work as this biomarker must be able to identify pregnant women at risk of developing PE as early as possible during their pregnancy, in a non-invasive way and at low costs. The identification of early PE biomarkers will allow a better management of pregnant women at risk for PE or suspected for PE, and reduce maternal and child morbidity and mortality associated with this disease. Several molecules and genes have been identified as potential candidates over the years. However, not one of these has been unanimously accepted. This review will present the current state of research regarding the potentially best PE markers or combination of markers identified as of now.

ABBREVIATIONS

PE: Preeclampsia; CTLA4: Cytotoxic T-Lymphocyte-Associated protein 4; F2: the coagulation factor II; FV: the coagulation factor V; SERPINE: Serine Peptidase Inhibitor 1; LEPR: Leptin Receptor Gene; NAD(P)H: Methylenetetrahydrofolate Reductase; WG: Weeks of Gestation; hCG: human Chorionic Gonadotropin; hPL: human Placental Lactogen; PlGF: Placental Growth Factor; VEGF: Endothelial Growth Factor; sFLT1: Soluble fms-Like Tyrosine Kinase 1; LXRα: Liver X Receptor Alpha; PAPP-A: Pregnant-Associated Plasma Protein A; PP13: Placenta Protein 13; sTWEAK: soluble TNF-Like Weak Inducer of Apoptosis; SDE: Serum Derived-Exosomes; CD: Cluster of Differentiation; NGAL: Neutrophil Gelatinase-Associated Lipocalin; MAP: Mean Arterial Pressure

INTRODUCTION

Preeclampsia (PE) is a serious placental disorder characterized by the onset of hypertension and the presence of either proteinuria or other severe features during pregnancy in previously normotensive woman [1-3]. In the absence of medical care, this obstetric disorder can lead to multiorgan dysfunction, eclamptic crisis and maternal death [4-6] and is thereby one of the important causes of maternal and perinatal mobidity and mortality. PE affects 2 to 10% of pregnancies and occurs more frequently in low-income countries [7-9]. The clinical symptoms appear after 20 weeks of gestation and can in fact be detected as late as 4-12 weeks postpartum [10-13]. Risks are also important for the fetus and newborn. These include increased morbidity and mortality, associated with uterine growth retardation and iatrogenic premature childbirth [4,14]. Each year, 10 million pregnant women develop PE around the world. Worldwide, about 100,000 pregnant women and 500,000 babies die each year from preeclampsia. 99% of these mortalities occur in low and middle income countries [15]. Management of PE is limited to treatment of symptoms and in severe cases, require early childbirth to prevent deterioration of the condition of the mother and the fetus. Early diagnosis of PE would be helpful for careful monitoring of pregnant women and preventive strategies. Research efforts in the last ten years have improved our understanding of the pathophysiology of PE. Indeed, it is now accepted that this obstetrical disorder is the consequence of poor placentation [16-23]. Therefore, important efforts have been made for the identification of biomarkers or risk factors associated to PE. This has further led to the development of new algorithms combining clinical risk factors with biomarkers for a good prediction of PE [24-29].

Since PE is a multifactorial pathology, a single marker is likely not to be sufficient in terms of diagnostic value [30]. To improve early PE diagnosis, researchers are thus seeking to develop multiparametric models including biochemical, molecular and genetic markers, body-mass index, mean arterial blood pressure, presence of nulliparity or previous preeclampsia and Doppler parameters [31-36]. Markers of fetal, placental or renal origin and specific markers of oxidative stress have been included in these studies [37].

MOLECULAR AND GENETIC MARKERS

Although important discoveries have been made with

respect to PE and its origins, the pathogenesis of this disorder still remains mostly obscure. Meta-analysis has been used to identify specific genes that are associated to preeclampsia or severe preeclampsia. Among these, the Angiotensin-Converting Enzyme, Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA4), the coagulation factor II (F2, also known as prothrombin), the coagulation factor V (FV), Lipoprotein lipase and SERPINE Serine Peptidase Inhibitor 1 genes have been shown to be associated with preeclampsia [38]. Furthermore, Fong et al., showed that coagulation factor V gene (proaccelerin) polymorphism, leptin receptor gene (LEPR) polymorphism, mutated coagulation factor II (thrombin) and the thrombophilic gene group polymorphism (including F2, FV and Methylenetetrahydrofolate reductase (NAD(P)H genes were associated to severe preeclampsia [39].

Several studies have demonstrated that cell-free DNA could also potentially be used as PE markers [40-44]. But these studies are very heterogeneous and it is difficult to make a precise conclusion about the statistical and clinical relevance of these findings. Recently, the search for PE biomarkers and therapeutic molecules led to the identification of several microRNAs (miRNAs), which expression are dysregulated during PE [45-51]. miRNA are noncoding RNAs that modulate the expression of various target genes through complementary annealing to targeted mRNA. Interestingly, these miRNAs are detected in maternal serum. In 2015, using qRT-PCR, Murphy et al., have shown an increase in levels of miR-98, miR-222, miR-210, miR-155, miR-296, miR-181a, and miR-29b in the blood of severe PE pregnant women [51]. More recently, Zhang et al., showed a decrease of miR-942 prior to 20 weeks of gestation (WG) in the plasma of PE women [52]. This recent result is interesting as this reduction in miRNA abundance was observed before 20 WG unlike other identified miRNAs, where the variation in levels were detected at childbirth. Combined together, these studies on miRNAs show promising advances in the identification of plasma PE biomarkers but more studies are needed to confirm that miRNAs can be used as early PE marker.

PLACENTAL RELATED BIOMARKERS

Preeclampsia is characterized by the onset of hypertension and proteinuria during pregnancy [53] but the factor or combination of factors responsible for these disturbances is unknown. However, a relevant marker of PE should be linked to these symptoms. It is undeniable that this marker, once identified and validated, will allow better surveillance and pharmacological intervention involving a low-dose of aspirin or calcium supplementation to improve PE outcome [54-56]. Since PE is intrinsically related to the placenta [16-23,57], a good marker could be directly related to its structure and/or function. This indispensable organ is composed of various cell types, which include extravillous and villous cytotrophoblasts. Villous cytotrophoblasts have the ability to differentiate into a multinucleated cellular barrier called the syncytiotrophoblast that covers the chorionic villi. The resulting overlaying structure is in direct contact with maternal blood and plays a crucial role for nutrient and hormone exchanges between the mother and the fetus as well as producing important soluble factors, such as human chorionic gonadotropin (hCG) and human placental lactogen (hPL) [58] and pro- and anti-angiogenic factors [59-61]. Thus, a defect in the formation of the placenta would result in a defect in the production of these soluble factors.

Ideally, this placenta-associated biomarker must be detectable before 20 weeks of gestation (WG) in order for clinicians to act early in pregnancy. Several biomarkers associated with the placenta have been identified and are considered promising. Among them is the Placental Growth Factor (PlGF), a member of the vascular endothelial growth factor (VEGF) family that plays a role in angiogenesis and trophoblastic invasion [60,62]. Indeed, the studies of Tsiakkas et al. (2015), have shown low PlGF plasma levels in PE pregnancies before 13 weeks of gestation [63,64]. Another promising marker is the soluble fms-Like Tyrosine Kinase 1 (sFLT1), a soluble VEGF receptor and antiangiogenic protein involved in inhibition of VEGF and PlGF signaling. It is known that plasma levels of sFLT1 are significantly higher in PE compared to normal pregnancies [65] and several studies suggest the use of sFLT1 levels as a biomarker of PE and severe PE [66-68].

Decrease in plasma PlGF levels during PE is thought to be due to higher release of sFLT1 from the placenta [66] which binds to circulating PlGF [69,70]. Combining both sFLT1 and PlGF plasma levels could also help predict the occurrence of PE in pregnant women. Indeed, several studies showed that the sFLT1/PlGF ratio was significantly higher in women that were diagnosed with PE or that later developed PE compared to normal pregnancies [69,71,72]. The use of sFLT1 and PlGF as PE markers is interesting as both proteins are placental-derived, and their expression levels in maternal serum presumably reflect impaired placentation [25,31,63,66].

As PE is associated with several maternal factors, including obesity, it is important to evaluate the accuracy of PE biomarkers in different populations of pregnant women. A thorough analysis of the use of PlGF as a biomarker in obese pregnant women showed lower plasma PlGF levels in early pregnancy associated with the later development of PE in obese women but not in women with normal body-mass index [73] This study shows that obesity influences PlGF plasma levels and consequently that this biomarker might rather be specific to certain populations of pregnant women. PlGF has further been associated to PE and severe PE in pregnant women with established hypertension and chronic kidney disease. In several studies, the authors have shown that PlGF decreased several weeks before the onset of PE symptoms [66,74-76]. PlGF appears to be an early biomarkers but might be more related to maternal risk factors-associated PE and its single use as biomarker might not identify all PE cases [25,76-78].

It has also been suggested that abnormal liver X receptor alpha (LXRα) and endoglin might play significant roles in the development of PE [79-83]. Studies showed that LXRα inhibited cholesterol transport, human chorionic gonadotropin and trophoblast invasion [84], while endoglin, a trans-membrane glycoprotein expressed on syncytiotrophoblast and invasive cytotrophoblast, is involved in placental trophoblast differentiation and uterus invasion[85]. Endoglin is a co-receptor for transforming growth factor−β1 and 3 [82] and is a direct target of LXRα on human syncytiotrophoblast [79]. According to the role associated to LXRα and endoglin in placental trophoblast

differentiation, Wang et al., have tested the relationship between LXRα and endoglin levels and occurrence of preeclampsia. In their study, they showed that elevated levels of LXRα and endoglin was associated with PE pathogenesis and development and have suggested that LXRα and endoglin could be used as PE biomarker. However, it is important to note that the decrease in levels pf these markers was observed at 36 weeks of pregnancy [86].

Ongoing studies have shown that Pregnant-Associated Plasma Protein A (PAPP-A), a highly glycosylated protein produced by developing trophoblast cells [87], and Placenta Protein 13 (PP13), a member of the galectin super-family (known as galectin 13 and β-galactoside-specific lectins [88] could also be potential markers to predict PE [35,89-91]. Unfortunately, these preeclampsia biomarkers were shown to have extremely variable diagnostic value [35,92-97]. In a pilot clinical study, Kayaoglu et al. (2016), showed that soluble TNF-Like Weak Inducer of Apoptosis (sTWEAK) could represent a new potential marker for preeclampsia. Indeed, they have shown that sTWEAK levels decreased in patients with PE, although this decrease was detected at 20 WG compared to normal pregnant women [98]. Further work is needed to assess the diagnostic value of this potential PE biomarker at earlier points during pregnancy.

RETROVIRAL-DERIVED BIOMARKERS

As indicated above, several scientific studies have shown that preeclampsia is the consequence of a defect in placenta formation [16-18,20-23,57], followed by an exaggerated systemic inflammatory response [30,99-112]. Syncytin-2 is a protein derived from a human endogenous retrovirus sequence. We have recently demonstrated that syncytin-2 is an important player in the formation of the placenta [58,113]. It has also been strongly suggested that syncytin-2 could contribute in generating the immunosuppressive environment needed for proper fetal development [111,112]. In addition to its role in maternal-fetal exchange, the placenta produces microvesicles called exosomes that seem to be endowed with immunosuppressive properties [58,114]. We and others have recently shown that syncytin-2 is present on the surface of these exosomes and could contribute to maternal-fetal immune tolerance [112,115]. Our recently published results showed a lower incorporation of syncytin-2 on the surface of serum-derived exosomes of women with preeclampsia [115].

Based on these findinds, we have recently initiated a new study, in which 450 pregnant women were enrolled at Cotonou, Benin, and have monitored the incorporation of syncytin-2 in their serum derived-exosomes (SDE) until 25 weeks of gestation. This ongoing study shows that the mean ratio of Sync-2/CD63 (CD63 being an exosome marker) in women who developed preeclampsia was significantly lower compared to women without preeclampsia between 7 and 13 weeks of pregnancy (Lokossou et al., unpublished data). Recent results from our team and others thus concur to the possiblity that this protein could be a promising PE marker and could be ideal for early diagnosis.

OTHER BIOMARKERS

Other predictive models for estimating individualized risk for onset PE are currently being explored. Among these, Karampas et al., have shown that the combination of Neutrophil Gelatinase-associated Lipocalin (NGAL), maternal clinical characteristics and Doppler parameters in the first and/or second trimester can be used to identify an important number of PE pregnancies [116]. As an alternative, Chang et al. (2016), proposed a new predictive model for early-onset PE through quantification of maternal serum levels of PAPP-A, PlGF, PP13 and soluble endoglin, measurement of mean arterial pressure (MAP) and analyses of uterine artery Doppler [117]. It is hoped that the best algorithm will eventually detect a larger number of pregnant women at risk of developing PE and limit the number of false positives. Other biomarkers, such as syncytin-2, will thereby be interesting addition to these models to potentially improve their diagnostic value, especially at early time points of pregnancy.

CONCLUSION

Significant progress has been made in the understanding of the pathophysiology of preeclampsia and suggests that the best prediction for PE development during pregnancy may be a combination of specific parameters. Given the heterogeneous nature of this obstetric placenta-derived disorder, the chosen biomarkers should be related to the physiopathology of the placenta. It is also important to take into account the capacities of low-income countries to appropriately conduct early diagnosis of PE and consequently diagnostic tools will have to be easy-to-use and bear reasonable costs. Indeed, it would be very difficult to consider the use of molecular and genetic markers for the early diagnosis of preeclampsia in middle and low income countries. In addition, most of these genetic markers were tested in small samples. Their representativeness can therefore be questioned. For this, serum biomarkers derived from the placenta such as PlGF, sFLT1 and syncytine-2 may be good tools for early diagnosis of preeclampsia. However, PlGF and sFlt do not seem to allow a diagnosis before 20 which is not the case of syncytin-2 which could be used between 7 and 13 weeks for early diagnosis of PE.

Future studies should permit to assess new PE markers for early diagnosis and provide such a clinical tools, which will greatly improve care of pregnant women showing predisposition to PE development.

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