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# THOROUGH INVESTIGATION OF BIOMARKERS FOR THE PREDICTION OF PREECLAMPSIA

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**Abstract:** Preeclampsia (PE) is one of the common serious complications during pregnancy, with an incidence rate of about 5% to 8%. It is the main cause of maternal death and poor fetal prognosis. The main manifestations of PE are systolic blood pressure = 140 mmHg or diastolic blood pressure = 90 mmHg after 20 weeks of pregnancy, accompanied by proteinuria, or involvement of organs or systems such as the heart, lungs, liver, kidneys, and coagulation system. Clinical practice shows that PE not only endangers maternal health, but is also closely related to fetal intrauterine growth restriction, premature birth, and low birth weight infants. It is estimated that 76,000 pregnant women and 500,000 fetuses die from this disease every year worldwide [1]. In addition, pregnant women who develop PE are at increased risk of future cardiovascular disease and end-stage renal disease. Children born to mothers with preeclampsia are also more likely to develop hypertension, stroke, cognitive decline and depression as adults [2]. Therefore, early prediction, diagnosis and timely intervention of PE are crucial to improving patient prognosis and pregnancy outcomes.
Relying solely on high-risk factors such as patient race, age, previous history of eclampsia, and obesity to predict PE is limited, so more research has focused on the identification of high-risk predictors. Current relevant biological research is mainly based on the pathophysiological changes of PE. The basic pathophysiological changes of PE are systemic small vessel spasm, endothelial damage and local ischemia. Its pathogenesis is related to many factors such as genetics, immunity, placental ischemia and hypoxia, endothelial dysfunction and so on. It is currently believed that the disease progression of PE includes two stages: (1) During the formation of the placenta, the invasion of the extravillous trophoblast into the muscular layer of the uterine spiral artery is insufficient, the remodeling of the uterine spiral artery is obstructed, and the fetal blood flow supply is limited; oxidative stress The stimulation reaction further aggravates placental ischemia, causing hypoperfusion, inflammation, cell apoptosis and structural damage. (2) The stage of organ damage, leading to the occurrence of various clinical signs. In recent years, with the widespread application of genomics, proteomics, and metabolomics in clinical research on PE, a series of PE-related markers for vascular endothelial cells, metabolism, oxidative stress, placenta, hemolysis, and inflammation have been discovered. It can be used as a candidate biomarker for predicting and diagnosing PE. There are currently more than a hundred types of biological markers used to predict or elucidate the pathological mechanisms of PE. The author briefly reviews the latest markers with clinical application potential in research in the past 10 years.
**Keywords:** Preeclampsia; Pregnancy; Complications; Biomarkers

## 1 BIOLOGICAL MARKERS FROM BLOOD

### 1.1 Studies on vascular

Endothelial growth factor (VEGF), placental growth factor (PLGF) and soluble vascular endothelial growth factor receptor-1 have shown that the VEGF family has a strong effect on inducing angiogenesis and vascular endothelial cell proliferation. VEGF and its receptor tyrosine kinase are involved in the process of placental angiogenesis. During the process of uterine artery vascular remodeling, an imbalance in the expression of angiogenic factors will lead to placental blood vessel formation disorders and may lead to PE. The predictive value of VEGF for early-onset PE is better than that on late-onset PE (PE occurring at 34 weeks or 32 weeks of gestation) [3]. In-depth research on the expression mechanism of VEGF may become a new diagnostic and therapeutic target for PE.
PLGF is one of many angiogenic factors secreted by the placenta. In one study, serum PLGF expression levels in 150 primigravida were analyzed and found to be highest at 26-28 weeks of gestation and decreased at 28-32 weeks of gestation. In patients with severe PE, the serum PLGF expression level is significantly lower than that of the normal control group. Therefore, it is believed that monitoring the serum PLGF expression level of pregnant women at 26 weeks of pregnancy can more sensitively predict the occurrence of PE [4]. In another prospective cohort study of pregnant women with singleton pregnancies, researchers evaluated PLGF in pregnant women at 11-14 weeks of gestation (1244 patients) and 22-24 weeks (1206 patients) (from the same cohort), and the receiver operating curve (ROC) was used to predict early-onset PE, and the serum PLGF cutoff values were 228 pg/mL and 144 pg/mL respectively. The results show that for predicting early-onset PE, the serum PLGF value in the second trimester (22-24 weeks of pregnancy) is more effective [5].
Soluble fms-like tyrosine kinase-1 (sFlt1) produced by the placenta can compete with Flt-1 for binding to VEGF and PLGF, thus inhibiting the biological functions of the latter two and leading to endothelial dysfunction [6]. In patients with preeclampsia, the ratio of sFlt1 to PLGF can be used as a biomarker to predict PE. Stubert et al [7] conducted a prospective cohort study on 50 women with high risk of preeclampsia who had abnormal uterine artery ultrasound results and found that 12 cases developed preeclampsia, of which 9 cases were early-onset preeclampsia (<34 week).

Using the ratio of sFlt-1/PLGF >95th percentile as the criterion to predict early-onset preeclampsia, the sensitivity, specificity, positive predictive value and negative predictive value were 85.7% and 86. 1%, 50.1% and 97.4%.

### 1.2 Pregnancy-Associated Protein A (PAPP-A)

PAPP-A is mainly produced by placental tissue. Studies have confirmed that patients with preeclampsia have reduced PAPP-A production in early pregnancy. Low levels of PAPP-A are closely related to the onset of preeclampsia. Odibo et al [8] tested the PAPP-A levels of 410 normal pregnant women and 42 cases of preeclampsia. When the false positive rate was 20%, the predictive sensitivity of PAPP-A for preeclampsia was 58%. When combined with other serological indicators, ultrasound examination, etc., the prediction effect of PE can be significantly improved [9]. By screening high -risk factors such as maternal mean arterial pressure, uterine artery Doppler examination, maternal serum PLGF and PAPP-A, about 95% of early-onset PE can be identified (the false-positive rate is about 10%) [10].

### 1.3 Placental Protein-13 (PP-13)

Produced by trophoblast cells, PP-13 is a member of the lectin family and its precise biological function remains to be defined. During normal pregnancy, serum PP-13 concentration increases with gestational age. Research has found [11] that compared with healthy pregnant women, the decrease in PP-13 concentration in early pregnancy is related to the occurrence of PE. PP-13 is often used in combination with other biochemical markers to improve its prediction rate for PE. In a retrospective cohort study, 4453 pregnant women were evaluated for prediction models using receiver operating characteristic curves for serum PAPP-A, PLGF, PP-13 and sEng combined with mean arterial pressure from 11 to 13 weeks of pregnancy. the value of. For the diagnosis of early-onset PE by the joint prediction model, when the false positive rate is set to 5%, the diagnostic rate is 67.4%; when the false positive rate is 10%, the diagnostic rate is 73.2% [12].

### 1.4 Disintegrin Metalloproteinase 12 (ADAM12)

Recent studies have found that ADAM12 is closely related to adverse pregnancy outcomes. ADAM12 is abundantly expressed in the cytoplasm and cell membrane of human placental trophoblasts and syncytiotrophoblasts, which can reduce the level of free insulin-like growth factor 1 in the blood, leading to a decrease in the infiltration ability of trophoblast cells, which in turn causes obstacles in the remodeling process of spiral arterioles. Domestic research results by Yan Jianying et al [13] showed that the serum ADAM12 level in pregnant women who developed PE was significantly higher than that in the normal pregnancy group in the second trimester. At the same time, it was found that there was no statistically significant difference in the serum ADAM12 levels of normal pregnant women between the second and third trimesters of pregnancy, but the serum ADAM12 levels of patients who developed PE further increased in the second trimester; this suggests that there is a correlation between the abnormal increase in ADAM12 and the occurrence of PE.. Kasimis et al. [14] found in a case-control study that ADAM-12 in maternal serum was detected at 11-13 weeks of pregnancy. Pregnant women who later developed PE had significantly lower ADAM-12 values than normal pregnant women. There was a significant difference between the two. ADAM12 alone has limited predictive value for PE, and it may be more meaningful to use it in combination with other markers.

### 1.5 Fetal Hemoglobin (HbF) and α-1 Microglobulin

HbF is mainly composed of 2 α chains and 2 γ chains, and is the main form of hemoglobin in the fetus. Research has found [15] that at 10 weeks of pregnancy, HbF begins to express until birth. In patients with preeclampsia, its elevated levels correlate with blood pressure levels in patients with preeclampsia. Olsson et al [16] found that in patients with preeclampsia, HbF mRNA gene expression was up-regulated and HbF secretion increased in placental tissue; the oxidative stress response caused the placental barrier to be destroyed, and HbF leaked into maternal peripheral blood; while the concentration of free HbF in peripheral blood Increased systemic oxidative stress damage in the mother. In a case-control study of 433 patients in early pregnancy, 86 developed preeclampsia. The serum HbF, α-1 microglobulin (AIM), total free hemoglobin, etc. of the subject population were jointly measured, and uterine artery Doppler ultrasound screening was performed at the same time. The results showed that when multiple indicators jointly predicted preeclampsia, the sensitivity was 60% when the specificity was 95%. In vitro experiments and animal experiments show [17-18] that AIM is an antioxidant protective protein that can prevent placental damage caused by free hemoglobin and participate in repairing the placental barrier. Research on HbF and A1M is expected to provide new targets for the diagnosis and drug treatment of preeclampsia in the future.

### 1.6 Decorin

Studies have reported [19] that PE has both poor trophoblast invasion and poor intravascular differentiation, and this situation is closely related to decorin. Decorin is produced by decidual cells and is rich in leucine proteoglycans. Decorin can bind to a variety of tyrosine kinase receptors (especially vascular endothelial growth factor receptor 2) in the early stages of placenta formation, limiting Invasion and differentiation of extravillous trophoblast cells into the vascular endothelium. The researchers selected a healthy control group and a PE group (14 in each group)

For example, 23 to 40 weeks of gestation) placenta, quantitative polymerase chain reaction and 35S-labeled in situ hybridization antisense complementary RNA probe were used to measure decorin messenger RNA expression, and the same placental tissue was immunostained.. The results confirmed that in the placental basal plate decidual cells, the PE group showed significantly higher expression of decorin messenger RNA compared with the control group; while there was no significant difference in the villous interstitial cells. Furthermore, the researchers knocked out the decorin gene that is overexpressed in endometrial cell lines. It was found that the inhibitory effect of decorin on the invasion of trophoblast cells disappeared. The researchers retrospectively compared the plasma decorin expression levels in the normal control group and the PE group (mid-trimester, 28 cases each). The results showed that decorin levels were significantly increased in all patients in the PE group. ROC curve analysis also confirmed that decorin has good predictive value for the occurrence of PE. In the second trimester, decorin levels were not significantly correlated with gestational age, whereas their levels were significantly inversely correlated with body mass index or body weight.

### 1.7 Copeptin

Copeptin is a glycopeptide at the carboxyl end of proarginine vasopressin (pro-AVP), and the two are secreted in a 1:1 molar ratio. However, compared with arginine vasopressin (AVP), copeptin has a longer biological half-life and has become a clinically useful biomarker. Studies have confirmed [20] that the plasma copeptin levels of pregnant women with PE were significantly higher than those of the control group throughout pregnancy. Multiple regression analysis showed that increased copeptin concentration was significantly related to the development of PE. In addition, using receiver operating characteristic curve (ROC) curve analysis, it was found that the plasma copeptin concentration of pregnant women increased as early as the 6th week of pregnancy. In addition, long-term infusion of AVP (24 ng/h) in C57BL/6J mice can produce a mouse PE model (pregnancy-specific hypertension, glomerular endothelial hyperplasia, proteinuria, intrauterine growth restriction in fetal mice). The above studies indicate that the release of copeptin in early pregnancy is expected to be a candidate marker for predicting PE.

### 1.8 Inhibin A and Related Combined Biochemical Screening

Inhibin A belongs to the TGF-β superfamily. It is synthesized and secreted by syncytiotrophoblast cells in the placenta during pregnancy and can regulate the differentiation and infiltration functions of placental trophoblast cells. Compared with normal pregnancy, the expression is increased in the serum of patients with preeclampsia. In a prenatal screening program in California, USA [21], 136,139 pregnant women with live births from 2006 to 2008 were screened, and the logistic binary regression method was used to analyze abnormal mid-trimester maternal serum. Relationship between biomarkers and severe PE. It was found that approximately 0.9% of women (n = 1208) experienced severe PE, of which 329 women were <34 weeks gestation and 879 women =34 weeks gestation. Studies have shown that higher levels of inhibin, alpha-fetoprotein (AFP), human chorionic gonadotropin, and lower levels of unconjugated estriol are closely related to severe PE; when abnormal biomarkers appear together, the risk of PE increases. will be greatly increased.

### 1.9 Transthyretin (TTR)

The main function of TTR is to participate in the transport of thyroxine and retinol and maintain normal levels of retinol and thyroxine in the body. During pregnancy, TTR can be secreted in the uterus, placenta and other parts of the body, and may be involved in the transport of maternal thyroxine to the fetus and the recasting of the placental spiral arteries [22]. Zhu et al. [23] used Western blot analysis and ELISA to detect TTR concentrations in pregnant women with severe PE (43 cases) and healthy controls (37 cases) at different gestational months. The results showed that TTR levels gradually increased with increasing gestational age, but the average concentration in the severe PE group was significantly lower than that in the normal pregnancy group. As a new candidate molecular marker for PE, TTR requires more in-depth research.

### 1.10 Applications of Genomics

As the scope and depth of research increase, genomics has also been applied to the study of preeclampsia. Anderson et al [24] recruited 55 nulliparous women for a prospective study. In the first 3 months of pregnancy, peripheral blood leukocytes and placental chorionic tissue were collected from pregnant women with normal blood pressure and pregnant women with PE. After quantitative analysis of whole-genome DNA methylation on the samples, it was found that 12.7% of women could eventually develop late-onset syndrome. PE. Others screened and compared the whole set of gene expression in placental villus tissue from PE patients and normal pregnant women. They extracted whole-group gene expression from placental villus tissue from patients after elective cesarean section (9 PE patients and 7 normotensive pregnant women). RNA and perform gene expression analysis on it. The results confirmed that a total of 896 genes had significant differences in expression, of which 9 were up-regulated and 5 were down-regulated. Through real-time quantitative PCR detection, it was found that the expression of β-hCG, HTRA4 and LHB1 were all up-regulated, while the expression of NOX4 was down-regulated. In addition, the expression levels of plasma LHB and β-hCG proteins in PE and normal pregnant women have also been confirmed to be significantly different [25].

## 2 BIOLOGICAL MARKERS FROM URINE

Proteomics is increasingly being used in the study of preeclampsia, and some studies have used urine proteomics for the diagnosis and screening of PE. Carty et al. [26] used urine proteomics methods and found that urine includes protein components such as collagen α chain, fibrinogen α chain, and uromodulin fragments. And it was found that the urine proteome model had good predictive value for PE at 28 weeks of gestation.

Preliminary research by Casarini et al. [27] showed that angiotensin converting enzyme (ACE) with a molecular weight of 90 kda can be used as a potential hypertension marker. Follow-up studies confirmed that pregnant women suffering from PE alone also had increased ACE enzyme activity in their urine. When postpartum blood pressure was normal, ACE levels also became normal. If postpartum ACE enzyme activity remains high for a long time, patients may develop chronic hypertension under the influence of environmental factors and/or other diseases.

In addition, increased levels of podocytes [28] and related proteins have been detected in the urine of PE patients, and are related to the degree of kidney damage and the severity of eclampsia. Different research results suggest that lower levels of urinary podocytes may occur during normal pregnancy. Therefore, whether urinary podocytes can be used as a marker to predict PE is still controversial.

## 3 BIOLOGICAL MARKERS FROM CEREBROSPINAL FLUID

Some researchers used cerebrospinal fluid proteomic analysis to determine the characteristics of PE protein biomarkers and their correlation with the severity of the disease. The study collected cerebrospinal fluid from patients with severe PE group (8 cases), moderate PE group (8 cases) and normal control group (8 cases), and used surface-enhanced laser defolding ionization time-of-flight mass spectrometry (SELDI-TOF-MS) technology to analyze the samples. Proteomic analysis was performed and PE-related markers were scored. The results showed that the scores of relevant markers in the severe PE group were significantly different from those of the other two groups, and this score was not affected by therapeutic magnesium, cerebrospinal fluid white blood cell count, and total protein count. The study also found that cerebrospinal fluid hemoglobin concentration was significantly higher in the severe PE group. It can be seen from this that free hemoglobin at the nanomolar level can be detected in the cerebrospinal fluid of patients with severe PE, and proteomic analysis of cerebrospinal fluid can accurately determine the severity of PE [29]. Since the collection of cerebrospinal fluid is an invasive operation, the research and application of biomarkers in cerebrospinal fluid are limited.

## 4 CONCLUSION

The development of genomics and proteomics have jointly promoted the diagnosis of PE and the study of its molecular mechanisms [30]. However, related work mainly relies on complex laboratory examinations and analytical techniques, and these methods are rarely used in resource-poor areas. Based on this, simple, low-cost, sensitive and relatively specific point-of-care testing is particularly necessary [31]. An ideal biological marker should be highly sensitive and specific, be able to not only predict the prognosis and progression of the disease, but also reflect the results of treatment, be easy to detect, and easily accepted by patients.

Currently, research on using systemic biomarkers to predict PE is still in its infancy, and neither of these factors alone or in combination can fully predict PE. The greatest prediction of PE comes from the combined application of maternal high-risk factors, clinical parameters, laboratory and uterine artery ultrasound examination.

The emerging relevant biomarkers for predicting PE have certain research prospects, and are of great significance for the diagnosis and pathogenesis of PE. However, it still needs to be verified through a large number of extensive and high-quality clinical studies before it can be used in clinical applications. It is expected that research on these biomarkers will provide a basis for developing an economical and efficient early screening program for PE, thereby reducing maternal and neonatal morbidity and mortality.

## COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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