AUCTORES
Globalize your Research

Journal of Obstetrics Gynecology and Reproductive Sciences
Ruiman Li *

Open Access

Research Progress on Angiogenesis Imbalance and Pathogenesis of Preeclampsia and Predictive Treatment

Jingyun Wang [1], Jinju Yang[2] , Chenyang Dai[1,3], Ruiman Li[1*]

[1]Department of Obstetrics and Gynecology, the First Affiliated Hospital of Jinan University, Guangzhou, China

[2]Jiangmen Maternity and Child Health Care Hospital, Jiangmen, China.

[3]Department of Obstetrics and Gynecology, The First People's Hospital of Foshan, Foshan, China

***Corresponding Author:** Ruiman Li. Department of Obstetrics and Gynecology, the First Affiliated Hospital of Jinan University, Guangzhou, China.

Received date: May 15, 2022; Accepted date: May 20, 2022; Published date: June 03, 2022.

Citation: Jingyun Wang, Jinju Yang, Chenyang Dai, Ruiman Li. (2022). Research progress on angiogenesis imbalance and pathogenesis of preeclampsia and predictive treatment, *J. Obstetrics Gynecology and Reproductive Sciences*, 6(4) DOI: 10.31579/2578-8965/124

Abstract:

Preeclampsia, one of the unique diseases of pregnancy, is a systemic vascular disease induced by various factors. Its main feature is that new-onset hypertension and proteinuria will appear after 20 weeks of pregnancy. Preeclampsia is the main cause of morbidity and mortality in pregnant women and perinatal babies. Many clinical and experimental studies have shown that the pathological basis of preeclampsia is maternal endothelial dysfunction caused by placental factors. Moreover, it has been determined that the increase in placental anti-angiogenic factors is the main cause of vascular endothelial dysfunction and systemic vascular dysfunction in pregnant women. This review summarizes the latest advances in the molecular mechanisms of endothelial dysfunction caused by placental anti-angiogenic factors and new clinical strategies based on these findings.

Keywords: preeclampsia; pregnancy; placental anti-angiogenic factors; endothelial dysfunction

Introduction:

Preeclampsia is a systemic vascular disease characterized by hypertension and proteinuria, which accounts for 2% to 8% of all pregnancies [1]. Preeclampsia can affect almost every organ and system and can cause undesirable complications, such as eclampsia, hemolysis elevated liver enzymes low platelets (HELLP) syndrome, placental abruption, and fetal growth restriction [2]. The only existing treatment for preeclampsia is early delivery, which leads to increases in the birth rate of premature babies and the incidence of low-birth-weight babies. Although the clinical symptoms of preeclampsia completely disappear after delivery, recent evidence suggests a significant association between preeclampsia and the future risk of cardiovascular disease [3]. It is currently believed that the extensive maternal endothelial dysfunction caused by placental factors plays a vital role in the pathogenesis of preeclampsia. Serum markers in many patients with preeclampsia indicate increased endothelial activation. Some studies have confirmed that excessive placental anti-angiogenic factors, such as soluble fms-like tyrosine kinase 1 (sFLT1), can antagonize vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) and induce general maternal endothelial dysfunction [4]. In this review, we summarize the latest advances in endothelial dysfunction caused by placental anti-angiogenic factors and the association between preeclampsia and future cardiovascular risk.

Risk factors:

Genetic factors:

Preeclampsia has a familial tendency, and the incidence of immediate family members can be increased by 2- to 5-fold [3]. A large clinical genome-wide association study indicated that a single-nucleotide polymorphism near the FLT1 locus (rs4769613) on chromosome 13 of the fetal genome is significantly associated with the development of preeclampsia. Furthermore, women with trisomy 13 fetuses are more likely to develop preeclampsia. Trisomy 13 is associated with increased maternal sFLT1 levels and a high risk of preeclampsia [5].

Nongenetic factors:

Certain maternal diseases, such as obesity, diabetes, chronic hypertension, antiphospholipid syndrome (APS), chronic kidney disease (CKD), and systemic lupus erythematosus (SLE), are associated with an increased risk of preeclampsia. In addition, the sFLT1 level of pregnant women with chronic hypertension and diabetes was significantly increased, while the PlGF level of obese pregnant women was significantly reduced. These factors are all risk factors leading to the onset of preeclampsia. All these risk factors have been previously mentioned in risk factors for endothelial dysfunction and atheroma development [6, 7].

Anti-angiogenesis status of pregnant women and preeclampsia:

The pathogenesis of preeclampsia is not clear, but it is generally believed that the placenta plays a central role in the pathogenesis of preeclampsia. Regarding the pathophysiology of preeclampsia, maternal endothelial dysfunction caused by placental factors and the two-stage theory have long been recognized. In addition, susceptible immunity, genetics, and pre-existing maternal risk factors may also affect the disease. In preeclampsia, the failure of the physiological remodeling of the decidual blood vessels leads to a decrease in placental perfusion, which leads to the release of a series of inflammatory factors in the placenta, which in turn leads to vascular endothelial damage, vasoconstriction, and increased blood pressure, a condition that eventually develops into preeclampsia [2, 6]. Many studies have shown that the level of sFLT1 in the serum of women with preeclampsia is elevated. Subsequently, Levine et al. [5] showed that the serum sFLT1 level is correlated with the disease severity and decreases after it subsides. Studies have shown that placental sFLT1 is one of the most important placental factors causing maternal endothelial dysfunction.

Pathogenesis:

Mechanism of endothelial dysfunction caused by inhibition of the VEGF signaling pathway

The mechanism of endothelial dysfunction in women with preeclampsia due to increased levels of sFLT1 in the circulation is still unclear. Direct administration of VEGF will increase the release of nitric oxide (NO) in the vascular endothelium and cause nitric oxide-dependent hypotension in the body. Vascular endothelial growth factors can stimulate the production of NO by upregulating the expression of nitric oxide synthase (NOS) in epithelial cells. Studies have shown that VEGF can also induce the synthesis of prostacyclin (PGI2) [8]. NO activates soluble guanylate cyclase (sGC), leading to cGMP synthesis. PGI2 activates adenylate cyclase (AC) and increases cAMP synthesis. Both cGMP and cAMP can reduce the intracellular Ca2+ concentration, which can cause smooth muscle relaxation and vasodilation [9]. There is evidence that VEGF inhibitory therapy has a dose-dependent activation effect on endothelin 1 (ET-1) [10]. ET-1 is the most effective vasoconstrictor, and the level of ET-1 in women with preeclampsia is significantly higher than that in normal pregnant women; thus, ET-1 may be involved in the onset of preeclampsia.

The mechanism of upregulation of sFLT1 produced by trophoblasts:

The mechanism of upregulation of sFLT1 in the placenta is currently unclear. Some studies have reported that the hypoxic environment caused by abnormal placenta stimulates the production of sFLT1. According to this view, in both in vivo and in vitro models of human placenta, elevated hypoxia-inducible factor 1α (HIF1α) resulted in the upregulation of sFLT1[11]. Mitochondrial dysfunction leads to reactive oxygen generation and oxidative stress, which may contribute to the production of sFLT1[12].

Complement system and angiogenesis imbalance

The immune complement system can resist pathogens, but excessive activation can lead to diseases such as hemolytic uremic syndrome. There is a large amount of evidence that complement activation is related to the pathogenesis of preeclampsia. Some research findings have further confirmed the role of complement activation in the pathogenesis of preeclampsia. Elevated levels of C5b-9 in the urine of women with preeclampsia serve as a useful biomarker to distinguish preeclampsia from other hypertensive diseases [13]. In recent years, many reports have shown the mechanism that may link the complement system to the imbalance of angiogenesis. Among them, placental complement activation and damage are increased in preeclampsia and are related to the expression of sFLT1[14]. Another study reported that HTR-8/Svneo human extravillous trophoblast cells treated with C5a significantly increased the expression of sFLT1 at the mRNA level while reducing the mRNA level of PlGF [15], indicating that complement activation can affect angiogenesis and lead to the onset of preeclampsia.

Preeclampsia prevention

Low-dose aspirin

The role of aspirin in the primary or secondary prevention of preeclampsia has long been an important clinical concern [16]. In preeclampsia, platelet production of TXA2 (thromboxane A2: platelet activator and vasoconstrictor) increases, while endothelium production of PGI2 (prostacyclin) decreases. Both TXA2 and PGI2 are synthesized from arachidonic acid by cyclooxygenase (COX). Although low-dose acetylsalicylic acid (aspirin) irreversibly blocks COX, the endothelium can restore PGI2 production by synthesizing COX de novo. Aspirin has angiogenic properties by preventing the production of sFLT1 in human trophoblasts and increasing the production of PlGF in trophoblasts [17]. Recent studies have shown that aspirin enhances cell invasiveness and inhibits the production of sFlt-1 in trophoblasts [16]. In addition, sFlt-1 itself can also inhibit the invasion of trophoblasts, indicating that the preventive effect of aspirin on pre-eclampsia may be exerted through these two mechanisms.

Low-dose aspirin plus heparin:

Antiphospholipid syndrome (APS) is an autoimmune disease that causes patients with persistent antiphospholipid antibodies to have an increased risk of thrombosis or adverse obstetric events [18]. Among pregnant women with APS, one-third are women with preeclampsia. For a long time, low-dose aspirin plus heparin therapy has been the most effective regimen. Using this regimen can significantly improve maternal and perinatal outcomes [18]. To prevent preeclampsia with or without APS, a previous meta-analysis reported that heparin can improve the efficacy of low-dose aspirin [19]. However, subsequent trials have shown that heparin has no potential efficacy in preventing preeclampsia in high-risk patients without APS, indicating that heparin may only benefit some patients [20].

Clinical prediction and treatment strategy

Disease prediction

Currently, screening women at risk of preeclampsia during the first trimester has become an important area of clinical research. Although a large number of studies have shown that the level of sFLT1 in preeclampsia is not significantly related to the development of preeclampsia, in the prediction of preeclampsia, the level of PlGF in early pregnancy can provide the predictive value of preeclampsia [21]. In addition, it has been reported that the mean arterial pressure (MAP) and uterine artery pulsatility index (UtA-PI) are more convincing for the screening performance of preeclampsia. It has recently been reported in the literature that the sFLT-1/PlGF ratio can be used as an indicator for the development and evaluation of preeclampsia severity, providing objective evidence for the treatment of patients with preeclampsia and for the prediction of preeclampsia at low cost [22].

Prediction of adverse complications in pregnant women and the perinatal period

Clinically, it is not uncommon for pregnant women without clinical manifestations of hypertension or proteinuria to have adverse complications related to preeclampsia. In contrast, a considerable number of women who meet the diagnostic criteria for preeclampsia do not have any adverse complications and can have a nearly full-term pregnancy. Therefore, a large amount of literature has studied the relationship

between the imbalance of maternal angiogenesis and the adverse complications related to preeclampsia. Among pregnant women suspected of having preeclampsia, the severity of the mother's anti-angiogenic state more accurately predicts the adverse complications associated with preeclampsia. Another randomized controlled trial confirmed that the detection of PlGF levels can significantly improve the prognosis of pregnant women [23].

Regulation of the therapeutic potential of angiogenic factors

A large number of basic studies have shown that regulating angiogenesis factors has therapeutic potential [24]. Studies have suggested that administering recombinant VEGF or PlGF and reducing the level of sFLT1 through RNA interference may have clinical therapeutic significance [25]. However, only one human trial has reported its clinical benefit by directly regulating the imbalance of maternal angiogenesis; that is, the use of dextran sulfate hemodialysis to remove sFLT1 can stabilize blood pressure and prolong pregnancy [26].

Preeclampsia and the future risk of cardiovascular disease

Systemic vascular dysfunction is considered to be the outcome of the pathophysiology of preeclampsia. During normal pregnancy, maternal vascular resistance decreases, resulting in a slight decrease in blood pressure. However, in women with preeclampsia, due to systemic vascular dysfunction caused by systemic vascular disease, the vascular resistance of these pregnant women will not be reduced to the level of normal pregnant women [16]. Although the exact mechanism of systemic vascular disease caused by endothelial dysfunction is still unclear, studies have shown that abnormal matrix metalloproteinases (MMPs) and increased collagen deposition in the extracellular matrix (ECM) are thought to cause vascular remodeling. Insufficiency leads to an important role in systemic vascular dysfunction [27]. Bevacizumab's VEGF inhibitory therapy has also been proven to reduce endothelial-mediated vasodilation. In addition, these data indicate that even if the clinical symptoms of preeclampsia are relieved later, vascular dysfunction still exists, which suggests that it may be related to future cardiovascular disease risk. Additionally, studies have shown that through the use of several noninvasive vascular function tests and echocardiographic examinations, maternal endothelial and vascular dysfunction persists after delivery [28]. In addition, according to reports, less than 1% of the people whose sFLT1 level dropped to its pre-delivery value within 24 hours after delivery [29]. The sFLT1 level in women with preeclampsia is also elevated 5-8 years after delivery. Recent studies have shown that women with a history of preeclampsia/eclampsia have higher risks of subsequent diagnoses of diabetes, dyslipidemia, hypertension, congestive heart failure, and cerebrovascular disease [30]. Although the history of preeclampsia is now considered a risk factor for women suffering from cardiovascular disease later in life, how to improve the cardiovascular health of these women is still unclear. Further research is required to determine the monitoring and intervention strategies for these women.

Conclusions:

In the future, clinical treatment strategies to restore the imbalance of angiogenesis are expected to improve the complications of women with preeclampsia and extend the number of weeks of pregnancy. In addition, clarifying the pathophysiology and establishing effective screening and prevention strategies are expected to reduce the risk of cardiovascular disease in women with preeclampsia in the future.

Acknowledgments:

Jingyun Wang, Jinju Yang and Chenyang Dai contribute equally to the article. This article did not receive any financial support.

Conflict of Interest

The authors declare that they have no conflict of interests.

References:

1. Jaszczuk I., Koczkodaj D., Kondracka A., et al. (2022) The role of miRNA-210 in pre-eclampsia development. Ann Med. 54(1): 1350-1356.
2. Lin S., Leonard D., Co M. A., et al. (2015) Pre-eclampsia has an adverse impact on maternal and fetal health. Transl Res. 165(4): 449-463.
3. Diniz A. L. D., Paes M., Diniz A. D. (2020) Analyzing Preeclampsia as the Tip of the Iceberg Represented by Women with Long-Term Cardiovascular Disease, Atherosclerosis, and Inflammation. Curr Atheroscler Rep. 22(3): 13.
4. Cindrova-Davies T., Sanders D. A., Burton G. J., Charnock-Jones D. S. (2011) Soluble FLT1 sensitizes endothelial cells to inflammatory cytokines by antagonizing VEGF receptor-mediated signalling. Cardiovasc Res. 89(3): 671-679.
5. Levine R. J., Maynard S. E., Qian C., et al. (2004) Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 350(7): 672-683.
6. Ives C. W., Sinkey R., Rajapreyar I., Tita A. T. N., Oparil S. (2020) Preeclampsia-Pathophysiology and Clinical Presentations: JACC State-of-the-Art Review. J Am Coll Cardiol. 76(14): 1690-1702.
7. De Jager S. C. A., Meeuwsen J. A. L., van Pijpen F. M., et al. (2017) Preeclampsia and coronary plaque erosion: Manifestations of endothelial dysfunction resulting in cardiovascular events in women. Eur J Pharmacol. 816: 129-137.
8. Mirabito Colafella K. M., Dorst D., Neuman R., et al. (2022) Differential effects of cyclo-oxygenase 1 and 2 inhibition on angiogenesis inhibitor-induced hypertension and kidney damage. Clin Sci (Lond).
9. Robinson E. S., Khankin E. V., Karumanchi S. A., Humphreys B. D. (2010) Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: mechanisms and potential use as a biomarker. Semin Nephrol. 30(6): 591-601.
10. Lankhorst S., Danser A. H., van den Meiracker A. H. (2016) Endothelin-1 and antiangiogenesis. Am J Physiol Regul Integr Comp Physiol. 310(3): R230-234.
11. Nevo O., Soleymanlou N., Wu Y., et al. (2006) Increased expression of sFlt-1 in in vivo and in vitro models of human placental hypoxia is mediated by HIF-1. Am J Physiol Regul Integr Comp Physiol. 291(4): R1085-1093.
12. Vaka V. R., McMaster K. M., Cunningham M. W., Jr., et al. (2018) Role of Mitochondrial Dysfunction and Reactive Oxygen Species in Mediating Hypertension in the Reduced Uterine Perfusion Pressure Rat Model of Preeclampsia. Hypertension. 72(3): 703-711.
13. Burwick R. M., Velasquez J. A., Valencia C. M., et al. (2018) Terminal Complement Activation in Preeclampsia. Obstet Gynecol. 132(6): 1477-1485.
14. Yonekura Collier A. R., Zsengeller Z., Pernicone E., et al. (2019) Placental sFLT1 is associated with complement activation and syncytiotrophoblast damage in preeclampsia. Hypertens Pregnancy. 38(3): 193-199.
15. Ma Y., Kong L. R., Ge Q., et al. (2018) Complement 5a-mediated trophoblasts dysfunction is involved in the development of pre-eclampsia. J Cell Mol Med. 22(2): 1034-1046.
16. Malah N., Hofstaetter C., Raio L., Surbek D. (2022) Effects of early aspirin therapy on utero-placental hemodynamics in patients at risk of preeclampsia. J Matern Fetal Neonatal Med. 35(12): 2304-2310.

17. Panagodage S., Yong H. E., Da Silva Costa F., et al. (2016) Low-Dose Acetylsalicylic Acid Treatment Modulates the Production of Cytokines and Improves Trophoblast Function in an in Vitro Model of Early-Onset Preeclampsia. Am J Pathol. 186(12): 3217-3224.
18. Kemp M., Thomas W. (2018) Antiphospholipid syndrome in obstetrics. Lupus. 27(Suppl): 28-31.
19. Roberge S., Demers S., Nicolaides K. H., et al. (2016) Prevention of pre-eclampsia by low-molecular-weight heparin in addition to aspirin: a meta-analysis. Ultrasound Obstet Gynecol. 47(5): 548-553.
20. Haddad B., Winer N., Chitrit Y., et al. (2016) Enoxaparin and Aspirin Compared With Aspirin Alone to Prevent Placenta-Mediated Pregnancy Complications: A Randomized Controlled Trial. Obstet Gynecol. 128(5): 1053-1063.
21. Stepan H., Hund M., Andraczek T. (2020) Combining Biomarkers to Predict Pregnancy Complications and Redefine Preeclampsia: The Angiogenic-Placental Syndrome. Hypertension. 75(4): 918-926.
22. Rowson S., Reddy M., De Guingand D. L., et al. (2022) Comparison of circulating total sFLT-1 to placental-specific sFLT-1 e15a in women with suspected preeclampsia. Placenta. 120: 73-78.
23. Duhig K. E., Myers J., Seed P. T., et al. (2019) Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. Lancet. 393(10183): 1807-1818.
24. Phipps E. A., Thadhani R., Benzing T., Karumanchi S. A. (2019) Pre-eclampsia: pathogenesis, novel diagnostics and therapies. Nat Rev Nephrol. 15(5): 275-289.
25. Turanov A. A., Lo A., Hassler M. R., et al. (2018) RNAi modulation of placental sFLT1 for the treatment of preeclampsia. Nat Biotechnol. 36:1164-1173.
26. Thadhani R., Kisner T., Hagmann H., et al. (2011) Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. Circulation. 124(8): 940-950.
27. Yu W., Gao W., Rong D., Wu Z., Khalil R. A. (2018) Molecular determinants of microvascular dysfunction in hypertensive pregnancy and preeclampsia. Microcirculation. e12508.
28. Orabona R., Vizzardi E., Sciatti E., et al. (2017) Insights into cardiac alterations after pre-eclampsia: an echocardiographic study. Ultrasound Obstet Gynecol. 49(1): 124-133.
29. Saleh L., van den Meiracker A. H., Geensen R., et al. (2018) Soluble fms-like tyrosine kinase-1 and placental growth factor kinetics during and after pregnancy in women with suspected or confirmed pre-eclampsia. Ultrasound Obstet Gynecol. 51(6): 751-757.
30. Kuo Y. L., Chan T. F., Wu C. Y., Ker C. R., Tu H. P. (2018) Preeclampsia-eclampsia and future cardiovascular risk among women in Taiwan. Taiwan J Obstet Gynecol. 57(3): 364-369.

DOI: 10.31579/2578-8965/124