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The Role of Factor Angiogenic (VEGF) in The Development of Preeclampsia: A Literature Review

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ABSTRACT

Preeclampsia is a multiorgan disorder of pregnancy that affects about 2-8% of all pregnancies and is one of the leading causes of maternal morbidity and mortality. Preeclampsia occurs in 4.6% of the total 39 million pregnancies. The prevalence of preeclampsia varies in different countries, ranging from 0.4% in Vietnam, 0.015% in Finland, to about 2.9% in some parts of Africa. The pathogenesis of preeclampsia begins with the failure of the physiological transformation of the spiral artery, which causes the placenta to secrete antiangiogenic factors into the maternal blood circulation. Angiogenic factors, such as Vascular Endothelial Growth Factor (VEGF), play an important role in the process of blood vessel formation in the placenta. Angiogenic factors play a role in the pathophysiology of preeclampsia, one of which is VEGF. The literature regarding the association of VEGF with preeclampsia is still limited, so this study was conducted.

Keywords: preeclampsia; angiogenic; VEGF.

INTRODUCTION

Preeclampsia occurs in 4.6% of a total of 39 million pregnancies. The prevalence of this condition varies across countries, with rates of 0.4% in Vietnam, 0.015% in Finland, and around 2.9% in some parts of Africa [1]. Preeclampsia is one of the leading causes of maternal and foetal morbidity and mortality, with a prevalence of approximately 4-5% of all pregnancies. It is a typical multisystem condition of pregnancy, characterised by the onset of hypertension and proteinuria after 20 weeks of pregnancy. Preeclampsia can develop into severe complications, such as eclampsia (seizures), stroke, renal failure, pulmonary oedema, liver dysfunction, and coagulation disorders [2].

The pathogenesis of preeclampsia begins with the failure of the physiological transformation of the spiral artery, resulting in suboptimal placentation and reduced blood flow to the placenta. Subsequently, the placenta releases antiangiogenic factors into the maternal blood circulation, which triggers systemic dysfunction in endothelial cells, metabolic disturbances, pro-thrombotic tendencies, activation of balancing factors, intravascular inflammation, as well as damage to various organs [3].

Angiogenicity is the process of formation and maintenance of blood vessel structures from existing blood vessels, which is essential for the physiological function of tissues. Failures in the regulation and imbalance between placental proangiogenic and antiangiogenic vasoactive agents, such as placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1), play an important role in the pathogenesis of preeclampsia. Oxidative stress inhibits the production of VEGF and PlGF proteins, thereby increasing sFlt-1 protein levels in patients with preeclampsia compared with normal pregnancies [4].

REVIEW CONTENT

1. Preeclampsia

Preeclampsia is one of the leading causes of maternal and foetal morbidity and mortality, with a prevalence of approximately 4-5% of all pregnancies. It is a typical multisystem condition of pregnancy, characterised by the onset of hypertension and proteinuria after 20 weeks of pregnancy. Preeclampsia can develop into severe complications, such as eclampsia (seizures), stroke, renal failure, pulmonary oedema, liver dysfunction, and coagulation disorders [2].

Risk factors that can increase the occurrence of preeclampsia include nulliparity (never having given birth), multiple pregnancies (delivering more than one foetus), and a history of preeclampsia in a previous pregnancy. Medical conditions that are also risk factors include chronic hypertension, diabetes

before pregnancy, and gestational diabetes. In addition, conditions such as thrombophilia, systemic lupus erythematosus, and antiphospholipid antibody syndrome also contribute. The risk of pre-eclampsia is also higher in women with a pre-pregnancy body mass index (BMI) of more than 30, maternal age of 35 years or older, and those with kidney disease. The use of assisted reproductive technology and the presence of obstructive sleep disorders such as sleep apnoea are also associated with an increased risk of preeclampsia (sitasi). The etiology of preeclampsia is still not fully understood, but there are four main hypotheses, including placental ischaemia, very low-density lipoprotein (VLDL) toxicity, immune maladaptation, and genetic imprinting [5].

The pathophysiology of preeclampsia involves two stages, namely incomplete remodelling of the spiral arteries in the uterus contributing to placental ischaemia (stage 1) and the release of antiangiogenic factors from the ischaemic placenta into the maternal circulation contributing to endothelial damage (stage 2). [6].

In the early stages of normal placental development, extravillous cytotrophoblasts invade the spiral arteries found in the decidua and uterine myometrium. These invasive fetal cells replace the endothelial lining of the uterine blood vessels, transforming the spiral artery from a high-resistance blood vessel to a large-calibre, elastic vessel. This transformation allows for increased blood flow to the uterus, which is necessary to support the growing foetus during pregnancy. However, in the condition of preeclampsia, the transformation does not take place completely. Cytotrophoblast invasion is limited to the superficial decidual layer, so arterial segments in the myometrium remain narrow and do not dilate [7].

During the process of placental vasculogenesis, invasive cytotrophoblasts downregulate the expression of adhesion molecules typical of their native epithelial cells and switch to adopt an endothelial cell surface adhesion phenotype, a process known as pseudovasculogenesis. However, in preeclampsia, cytotrophoblasts fail to undergo this phenotype transition, including changes in integrins and cell surface adhesion molecules. As a result, cytotrophoblasts are unable to invade the spiral artery in the myometrium at optimal [8].

Abnormal placentation occurs due to the failure of cytotrophoblast remodelling of the uterine spiral artery, which can lead to the release of several antiangiogenic factors that enter the maternal circulation and culminate in clinical signs and symptoms of preeclampsia called a maternal syndrome. Clinical manifestations of preeclampsia include glomerular endotheliosis, increased vascular permeability, and a systemic inflammatory response resulting in organ damage or hypoperfusion. These clinical manifestations usually occur after the 20th week of pregnancy [9].

2. Angiogenic Signal in Placental

Angiogenic factors have an important role in the regulation of placental vasculogenesis. Molecules such as VEGF, PlGF, and Flt1 are significantly expressed by invasive cytotrophoblasts, with altered expression patterns in preeclamptic conditions. The sFlt1 protein is known to inhibit cytotrophoblast invasion. In early pregnancy, circulating levels of sFlt1 and sEng are relatively low, but both increase gradually in the third trimester. This suggests the hypothesis that placental blood vessel development is regulated by proangiogenic and antiangiogenic factors. Changes in this balance in the early stages of pregnancy may affect the cytotrophoblast invasion process, which plays a role in the pathogenesis of preeclampsia. In the third trimester, increased production of sFlt1 from the placenta is detected in the maternal circulation, causing impaired organ function. In this context, placental ischaemia may not be the primary cause, but rather a manifestation of angiogenic imbalance [10].

3. VEGF

The VEGF-VEGFR system is known to play a crucial role in the process of angiogenesis, regulating two important mechanisms: vasculogenesis, which is the formation of blood vessels from precursor cells during early embryogenesis, and angiogenesis, which is the formation of new blood vessels from existing blood vessels at later stages of development [11]. VEGF plays an important role in maintaining endothelial cell stability in adult blood vessels, especially in the fenestrated and sinusoidal endothelium found in organs such as the kidney, brain, and liver [12].

The VEGF family in humans consists of five related glycoproteins: VEGFA, VEGFB, VEGFC, VEGFD, and PlGF (placental growth factor). These proteins are secreted in the form of homodimers and interact with three types of receptor tyrosine kinases: VEGFR1 (VEGF receptor 1), VEGFR2, and VEGFR3. VEGFA and VEGFB bind to VEGFR1, while VEGFA binds to VEGFR2. VEGFC and VEGFD can bind to both VEGFR2 and VEGFR3, while PlGF mainly interacts with VEGFR1[13].

VEGFRs are found in various cell types. VEGFR1, also known as Flt-1 (fms-like tyrosine kinase 1), is present in vascular endothelial cells, haematopoietic stem cells, monocytes, and macrophages. VEGFR2, also called KDR (kinase insert domain) or Flk-1 (fetal liver kinase 1), is expressed on vascular and lymphatic endothelial cells. Meanwhile, VEGFR3, known as Flt-4, is restricted to lymphatic endothelial cells [14].

When ligands bind to VEGFRs, intracellular signals are transduced through various mediators. VEGFR2, the most studied, uses pathways such as phosphatidylinositol-3 kinase (PI3K)/Akt, mitogen-activated kinase, Src non-receptor tyrosine kinase, as well as PLCγ (phospholipase C gamma)/PKC (protein kinase C). These pathways support angiogenesis, lymphangiogenesis, vascular permeability, and vascular homeostasis [15].

VEGF-A together with its receptors, VEGFR-1 and VEGFR-2, play a major role in angiogenesis, both under physiological and pathological conditions. On the other hand, VEGF-C/D and its receptor, VEGFR-3, play a role in regulating angiogenesis in the early stages of embryogenesis but mainly serve as master regulators of lymphangiogenesis. VEGF-A has various functions, including a role as a pro-angiogenic factor, increasing vascular permeability, and stimulating cell migration in macrophage and endothelial cell lines [16].

4. VEGF in Preeclampsia

There are striking clinical and pathophysiological similarities between hypertension and renal injury resulting from VEGF signalling pathway inhibitors (VSP inhibitors) therapy and those occurring in preeclampsia. During pregnancy, PlGF and VEGF expression play an important role in normal placental development and vascularisation. However, in preeclampsia, this process is impaired by the increased production of soluble receptor Flt-1 by the placenta, which binds to and decreases the levels of VEGF and PlGF in the circulation. This imbalance between angiogenic and antiangiogenic factors eventually leads to systemic endothelial dysfunction, which triggers hypertension, renovascular disease, and coagulopathy as its clinical manifestations [17].

Proteinuria in preeclampsia is caused by increased renal tubular permeability to various large molecular weight proteins, such as albumin, globulin, transferrin, and hemoglobin. High levels of circulating sFlt-1 as well as decreased nitric oxide contribute to renal tubular injury in preeclampsia. VEGF inhibition by sFlt-1 also leads to glomerular endothelial damage, known as glomerular endotheliosis or pathognomonic lesions in preeclampsia [6].

Glomerular endotheliosis is characterized by swelling and vacuolization of endothelial cells accompanied by fibrils, swelling of mesangial cells, deposition of subendothelial proteins derived from glomerular filtrate, and formation of tubular casts. In addition, an enlarged glomerulus with a closed capillary lumen without capillary thrombus typical of thrombotic microangiopathy is also frequently found. High levels of sFlt-1 inhibit podocyte-specific VEGF function, thereby disrupting the glomerular filtration barrier and causing fenestra damage that exacerbates proteinuria [18].

Damage to podocytes is a major factor leading to proteinuria. Slit diaphragm proteins such as nephrin, podocin, synaptopodin, and podocalyxin play an important role in maintaining the integrity of the glomerular barrier. Loss of these proteins, which can be detected in the urine before the appearance of clinical symptoms of preeclampsia, suggests that damage to these structures precedes and contributes to the further development of proteinuria [19].

CONCLUSIONS

Angiogenic factors play an important role in the pathophysiology of preeclampsia. It is emphasized that an imbalance between proangiogenic and antiangiogenic factors, especially the decreased expression of VEGF may disrupt normal placental vascularization and cause systemic endothelial dysfunction. This dysfunction manifests as clinical features such as hypertension, proteinuria, and renal injury, which are hallmarks of preeclampsia. Moreover, these findings highlight that damage to renal structures, such as podocytes and the glomerular filtration barrier, play an important role in the development of proteinuria observed in preeclampsia. These insights reinforce the centrality of the angiogenic pathway in understanding and potentially managing this complication of pregnancy.

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