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Invited critical review

Is the imbalance between pro-angiogenic and anti-angiogenic factors associated with preeclampsia?

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ABSTRACT

Background: Preeclampsia (PE) is a multisystem disease characterized by the development of hypertension and proteinuria. Although PE etiology is not fully known, the placenta seems to play a central role in the development of disease. The inadequate placentation process results in a change in angiogenic factors levels, such as vascular endothelial growth factor (VEGF), placental growth factor (PlGF), soluble form of endoglin (s-Eng) and soluble form of vascular endothelial growth factor receptor type 1 (sFlt-1).
Objective: The aim of this review was to clarify if the imbalance between pro-angiogenic and anti-angiogenic factors is associated with PE.
Conclusion: It is known that inadequate placentation process is the primary mechanism suggested for PE occurrence and angiogenic factors are involved in this process. The state-of-the-art suggests that progress in grasp the imbalance of pro-angiogenic and anti-angiogenic factors is essential for the improvement of knowledge about PE. The development of prospective, longitudinal studies with serial determinations of these factors throughout pregnancy is needed to better assess the relevance of these markers for understanding the etiology, prevention, diagnosis, prognosis and treatment of this challenging disease.

Contents

1. Preeclampsia

Pure preeclampsia (PE) is a multisystem disease characterized by the development of hypertension and proteinuria after the twentieth week of pregnancy in previously normotensive women. PE can also affect hypertensive women, characterizing the superimposed PE [1,2]. According to gestational age (GA) at the onset of the disease, PE has been classified as early (GA 34 weeks) and late (GA ≥ 34 weeks) [3]. Another classification is based on blood pressure and proteinuria and distinguishes mild and severe forms. In the severe form, blood

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pressure is higher than 160 × 110 mm Hg and proteinuria is greater or equal to 2 mg/24 h. It has been suggested that the different forms of PE have distinct etiology [1,2].

Several genetic, clinical and epidemiological factors have been associated with the occurrence of PE as the first pregnancy, multiple pregnancy, maternal age at the extremes of the fertile range, personal and family history of PE, obesity, chronic hypertension, renal disease, systemic lupus erythematosus and diabetes. However, despite advances in research involving PE, its etiology and treatment remain unknown [1,2].

It is known that the placenta plays a central role in the development of PE. This disease has been diagnosed in cases of hydatidiform mole (placenta without the presence of the fetus), as well as after delivery in cases where the removal of the placenta was not performed properly and fragments were kept in uterus. Strong evidence comes from observation of significant improvement in symptoms after the end of pregnancy and complete placenta withdrawal [2].

During pregnancy, a particular vascular network to ensure proper blood flow between mother and fetus is built. This process involves the sequential mechanisms of vasculogenesis, angiogenesis and pseudovasculogenesis [4]. A fault in the vascularization process results in anti-angiogenic factor secretion in maternal circulation, and consequently endothelial dysfunction [5].

The imbalance between pro-angiogenic and anti-angiogenic factors has been thought to be key for PE development [6–8]. Thus, in recent years, several studies have aimed to clarify the relationship of angiogenic factors and PE occurrence for a better understanding of its etiology, prevention, diagnosis, prognosis and treatment.

2. Characterization of angiogenic factors

The vascular endothelial growth factor (VEGF) is a pro-angiogenic cytokine produced by macrophages, T cells, tumor cells and cytotrophoblast and it is involved in angiogenesis and vasculogenesis. Free VEGF plays an important role in the regulation of nitric oxide synthesis. VEGF gene is located on chromosome 6 (6p21.3), which consists of 8 exons that result in a family of proteins with major subtypes, PlGF (placenta growth factor), VEGF-A, VEGF-B, VEGF-C and VEGF-D, having VEGF-A as the predominant form [8,9]. Other subtypes such as VEGF-E and VEGF-F were described, but they are not expressed in mammals [10].

VEGF-A is a potent multifunctional cytokine that exerts its role in endothelial cells, by mediating the increased vascular permeability, which induces angiogenesis, vasculogenesis and the growth of endothelial cells [11,12]. Alternative splicing of mRNA generates isoforms of VEGF-A with different properties, the main ones being VEGF121, VEGF165, VEGF189 and VEGF206 that contain a sequence of 121, 165, 189 and 206 amino acids, respectively [13].

Studies have shown that VEGF inactivation in animal models results in significant embryo lethality and vascular defects in the placenta. Furthermore, symptoms such as hypertension and proteinuria were observed in patients under cancer treatment using VEGF inhibitors [14].

VEGF receptors are protein tyrosine kinases that stimulate cell response. They consist of a single extracellular component, a transmembrane segment, a just membrane segment, an intracellular tyrosine kinase domain and a carboxiterminal tail [11]. VEGF-A, VEGF-B and PlGF bind to receptors VEGFR-1 (or Flt-1) and only the VEGF-A binds to VEGFR-2 (or KDR-growth factor receptor or Flk1), inducing the development of placental vascular [15]. While VEGF has a greater affinity for Flt1, KDR has been described as the main mediator of angiogenesis and induces increase in vascular permeability due to VEGF [5].

The soluble form of the transmembrane type 1 receptor for VEGF, sFlt-1 (or sVEGFR1), also binds to PlGF [7]. The sFlt-1 is produced by the syncytiotrophoblast due to an alternative splicing of the RNA messenger of VEGRF-1 (or Flt-1) gene, resulting in a truncated protein without the capacity of binding to VEGF or PlGF inside the cells, which may capture such growth factors in their free forms in maternal circulation [4,8,16].

Significant amounts of sFlt-1 from monocytes and endothelial cells were observed in plasma of healthy and non-pregnant women, suggesting that sFlt-1 contributes to the physiological regulation of VEGF viability, regardless of pregnancy [8]. This regulation is important since continuous levels of VEGF are required for endothelial cell survival and proliferation. The sFlt-1 acts as antagonist of VEGF and PlGF, preventing interaction of these angiogenic factors with their endogenous receptors and resulting in endothelial cell dysfunction and vasoconstrictor effects in maternal circulation [4,14]. The regulation of sFlt-1 viability by VEGF occurs with heterodimer formation with their receptors on the cell surface, abolishing their transduction signals [8].

PlGF is an angiogenic factor that belongs to the VEGF family. It can be found in isoforms PlGF-1, PlGF-2, PlGF-3 and PlGF-4 [5]. These isoforms are of great importance for the whole period of embryo development, due to their participation in vasculogenesis [17].

PlGF expression occurs in trophoblast, starting with the syncytiotrophoblast layer that is in direct contact with maternal circulation. During the first 30 weeks of a normotensive pregnancy, there is an increase of PlGF levels followed by a decrease. Non-pregnant women have low levels of PlGF (mean 44 ± 4.7 pg/mL) [8].

Finally, endoglin (Eng) is a hemodimeric transmembrane glycoprotein, also known as CD105, which is part of the complex TFG-β (transforming growth factor beta). Eng has pro-angiogenic activity that prevents apoptosis in hypoxic endothelial cells and it is essential for endothelial nitric oxide (eNOS) activation. Eng is a co-receptor of TGF-β1 and TGF-β3, expressed on cell membrane of vascular endothelium and sinciciotrofoblast. TGF-β1 induces the migration and proliferation of endothelial cells by binding to these receptors [8]. However, the soluble form of Eng (sEng) has anti-angiogenic activity, since it prevents the binding of transforming growth factor (TGF-β1) to its receptors on endothelial cells, compromising the eNOS activation and consequently the NO production. sEng is induced by hypoxia and has an antagonistic action to endoglin. s-Eng has been identified as a possible marker for PE, once it inhibits endothelial function in vitro [18].

3. Angiogenic factors and PE pathophysiology

During placentation process under physiological conditions, vasculogenesis is followed by angiogenesis, which promotes endothelial proliferation and vascular remodeling [8]. From the twenty-first day of gestation, soluble angiogenic factors expressed in placenta trophoblasts, maternal decidua and macrophages mediate the formation of new capillaries in the chorionic villi of the placenta, which persists until the twenty-sixth week of pregnancy [5,19].

The first trimester of pregnancy is characterized by a progressive invasion of extravillous trophoblasts in the spiral arteries of the uterus, known as pseudovasculogenesis phenomenon. Trophoblasts have vasculogenic activity and replace the cells of the uterine spiral artery, resulting in the development of vessels responsible for making gas exchange between the mother and fetus assuring the supply of oxygen and nutrients. The trophoblast also increases the resistance of maternal vessels aiming to facilitate placenta blood circulation [19].

In PE vascular invasion is insufficient, which reduces placental perfusion, resulting in chronic hypoxia and intrauterine growth restriction [19]. Oxygen deficiency results in placental production of anti-angiogenic factors, such as sFlt-1, s-Eng, TGF-β1 and TGF-β3. These factors cross to maternal bloodstream, resulting in endothelial dysfunction, hypertension and proteinuria [20].

In normotensive pregnant women, sFlt-1 levels are stable around the thirty-third and thirty-sixth weeks of pregnancy. After this period, there is an increase in sFlt-1 and a decrease of PlGF levels. Throughout the third trimester, increased sFlt1 persists and there is a reduction of VEGF and PlGF. In PE, sFlt-1 increase and PlGF decrease are also