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Review

Angiogenic and antiangiogenic factors in preeclampsia

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ABSTRACT

Background: Pre-eclampsia is a multifactorial hypertensive disorder that is triggered by placental insufficiency and that accounts for up to 15% of maternal deaths. In normal pregnancies, this process depends on the balance between the expression of angiogenic factors and antiangiogenic factors, which are responsible for remodeling the spiral arteries, as well as for neoangiogenesis and fetal development.
Purpose: The aim of this review is to discuss the main scientific findings regarding the role of angiogenic and antiangiogenic factors in the etiopathogenesis of preeclampsia.
Methods: An extensive research was conducted in the Pubmed database in search of scientific manuscripts discussing potential associations between angiogenic and antiangiogenic factors and preeclampsia. Ninety-one papers were included in this review.
Results: There is an increased expression of soluble fms-like tyrosine kinase receptor and soluble endoglin in pre-eclampsia, as well as reduced placental expression of vascular endothelial growth factor and placental growth factor. Systemic hypertension, proteinuria and kidney injury – such as enlargement and glomerular fibrin deposit, capillary occlusion due to edema, and hypertrophy of endocapillary cells – are some of these changes. The complex etiopathogenesis of preeclampsia instigates research of different biomarkers that allow for the early diagnosis of this entity, such as vascular endothelial growth factor, placental growth factor, soluble fms-like tyrosine kinase receptor, soluble endoglin, placental glycoprotein pregnancy-associated plasma protein-A and protein 13.
Conclusion: Even though it is possible to establish an efficient and effective diagnostic tool, three key principles must be observed in the management of preeclampsia: prevention, early screening and treatment.

1. Introduction

Preeclampsia (PE) is a complex hypertensive pregnancy syndrome that affects between 2 and 7% of pregnant women after the 20th week, and which may appear superimposed on chronic hypertension (CH), for instance. It is characterized by systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg in hypertensive women, followed by proteinuria ≥ 300 mg/L in urine/24 h [1–3]. Moreover, the presence of thrombocytopenia (platelets < 100,000/mμl), renal failure (creatinine ≥ 1.1 mg/dl) or impairment of liver function (doubled normal concentration of oxaloacetic transaminase and pyruvate transaminase), pulmonary edema, as well as cerebral and visual

Abbreviations: AT1-AA, angiotensin II type 1 receptor agonistic autoantibodies; ATF, activating transcription factor; CH, chronic hypertension; dNK, decidual NK cell; ECM, extracellular matrix; eIF2a, eukaryotic initiation factor 2 subunit a; ER, endoplasmatic reticulum Flk-1 kinase insert domain receptor; Flt-1, fms-like tyrosine kinase receptor; GRP78, glucose-regulated protein 78; ICAM, intercellular adhesion molecule; IL, interleukin; NOTCH, notch transmembrane receptors; PAPP-A, placental glycoprotein pregnancy-associated plasma protein-A; PE, preeclampsia; PERK, PKR-like endoplasmic reticulum kinase; PlGF, placental growth factor; PP13, protein 13; sEng, soluble endoglina; sFlt-1, soluble form of Flt-1; sTNF-R, soluble tumor necrosis factor receptors; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor

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disturbances, accompanied by hypertension [4] in the absence of proteinuria, are other criteria for the diagnosis of PE [3,5].

Eclampsia, from the Greek *eklampsis* (lightning), refers to the sudden onset of persistent headache, photophobia, scotomas, epigastric pain or pain in the right upper quadrant, as well as seizures [3,6]. It is noteworthy that the impairment of hepatic and renal function may lead to hemolysis, which is characterized by increased plasma level of lactate dehydrogenase, persistent increase in the level of liver enzymes and in thrombocytopenia, which is called HELLP (hemolysis, elevated liver enzymes and low platelets) [7]; and which may lead to intense inflammatory response, endothelial injury, generalized vascular resistance [8], disseminated intravascular coagulation, hepatic infarction, cerebral vascular disease, premature placental abruption and oliguria [2,3], for instance.

Different risk factors for PE have been discussed in the literature, and predisposing factors may include the following: African descent, obesity, short stature, nutritional deficiencies, previous CH (prevalent in up to 35% of the cases) or gestational hypertension [9] in previous pregnancies, heredity, urinary tract infections, diabetes mellitus, autoimmune diseases, hydatidiform mole, multiple pregnancy, and fetal macrosomia [10–13]. According to Chaiworapongsa et al. [15], other factors include primiparity in young women, which is associated with intolerance of the maternal immune system to paternal alloantigens present in the seminal fluid and in the sperm; heredity, represented by the presence of genetic variations in collagen α1-chain (I), interleukin-1α (IL-1α), urokinase-type plasminogen activator receptor; maternal-fetal incompatibility of lymphotoxin-α, von Willebrand factor, and α2 chain of collagen [14]; mutations in factor V Leiden, in human leukocyte antigen, in endothelial nitric oxide synthases, and in angiotensin converting enzyme [15].

Although little is known about the etiopathogenesis of preeclampsia, this syndrome has a major impact on maternal and fetal health worldwide, since it is responsible for 10–15% of maternal deaths [16,17], preterm births, intrauterine growth restriction (IUGR), and fetal deaths [2]. In developing countries, there are high rates of maternal morbidity and mortality from PE, mainly due to poor prenatal care [16]. In Brazil, according to data by the National Health System (*SUS*, in Portuguese) [18], approximately 76,000 maternal deaths and 500,000 perinatal deaths are estimated to be associated with PE every year, with an average of three maternal deaths/day due to complications arising from the disease [19].

Therefore, the identification of risk factors and the establishment of criteria for the diagnosis of PE are essential for the effective treatment and prevention of complications during pregnancy. Platelet count, measurement of hepatic enzymes, evaluation of proteinuria and blood pressure levels, weight gain monitoring, analysis of kidney and lung function, and assessment of previous pregnancy history (*e.g.* premature birth, children born small for gestational age, *etc.*) must be recorded during prenatal care. However, it is interesting to note that this entity may have atypical manifestations as those observed in the HELLP syndrome, yet in the absence of proteinuria and hypertension; thereby, careful research and analysis of signs and symptoms of pregnant women are required [2,3].

According to the literature, several mechanisms are associated with the development of this multifactorial syndrome, including changes during placentation [20], oxidative stress [21,22], exacerbated inflammatory response [23–25], thrombosis, activation of the renin-angiotensin-aldosterone system [25,26], and endothelial dysfunction caused by changes in the angiogenic profile [27]; the latter is associated with the pathophysiological changes described in PE.

2. Etiopathogenesis of preeclampsia

The pathophysiology of PE remains largely unknown. Nonetheless, this hypertensive disorder is thought to be triggered by placental dysfunction, which favors the synthesis of specific factors in the maternal circulation that are responsible for causing clinical changes in PE [2,28].

In normal pregnancies, cytotrophoblasts (cells outside the blastocyst layer) invade the uterine wall between the 6th and 8th week, destroy the muscular middle layer, acquire endothelial cell phenotype, and transform spiral arteries into large vessels of low vascular resistance in order to increase blood flow to the intervillous space and thence to the fetus during embryonic development [2,14,28,29]. However, there are failures in this process in PE, and the absence of arterial remodeling promotes lipid deposition in the vessel wall, as well as blood flow turbulence, platelet aggregation, fibrinoid necrosis, and intense activation of the inflammatory response [2,14,17].

Even though the mechanisms of this disorder are not fully known [2,14], it is believed that poor cytotrophoblast invasion concomitant with uteroplacental hypoperfusion may contribute to PE, since multiple areas of infarction, sclerotic arterioles, increasing vascular resistance, and reduced placental perfusion are observed in the placenta [28,30,31], thus oxidative stress and IUGR are favored [30,32]. Furthermore, there is a reduction in the area and volume of the intervillous space, in the intermediate and terminal villi, both in cases with PE alone and in cases with PE accompanied by IUGR. Remodeling of blood vessels in both villi is also significantly reduced [32].

Therefore, placental hypoxia is considered as a triggering factor for the increase in the synthesis of vasoconstrictors such as endothelin and superoxide, as well as the increase in von Willebrand factor antigen, cellular fibronectin, soluble tissue factor, soluble E-selectin, platelet-derived growth factor, susceptibility to the effects of angiotensin II and norepinephrine; placental hypoxia is also a triggering factor for the reduction in nitric oxide synthesis by the maternal vascular endothelium. This endothelial dysfunction has systemic effects, since these factors affect the blood vessels in the liver, brain and kidneys, for example; in the latter, there is a reduction in the glomerular filtration rate as well as impairment of blood pressure regulation [17,28,29].

Abnormalities in placentation in patients with PE appear to be associated with changes in different components of the signaling pathway that mediates cytotrophoblast migration/invasion. Studies have showed that the activation of the Notch signaling pathway is associated with the differentiation and modulation of functions of trophoblast cells through the interaction of the Notch transmembrane receptors (NOTCH1-4) and their respective ligands, DLL1,3,4 and JAG1,2 [29,33]. An experimental study showed a correlation between the non-expression of the NOTCH-2 receptor and the reduction in the diameter of maternal uterine vessels during placentation, with significant impairment of perfusion [33]. Mutations in the gene encoding STOX1 transcription factor may also be associated with the pathogenesis of PE, since the overexpression of this factor in choriocarcinoma cells mimics the same transcriptional profile observed in PE [29,34].

Endoplasmatic reticulum (ER) stress, characterized by the accumulation of unfolded proteins and misfolded proteins within the organelle, interfering with functions of synthesis, post-translational folding and assembly of all secreted and membrane-bound proteins, including hormones, growth factors, and receptors [35–37]. Loss of homeostasis activates unfolded proteins response, consisting of three main signaling routes: PKR-like endoplasmic reticulum kinase (PERK), activating transcription factor 6 (ATF6) and inositol-requiring 1 (Ire1). Under normal conditions, these transmembrane proteins become inactive by binding glucose-regulated protein 78 (GRP78 or BiP) to its N terminal. However, consumption of GRP78 (Ca^{2+}–dependent chaperone protein) triggered by accumulation of misfolded proteins promotes dimerization, autophosphorylation and activation of PERK and Ire1. Consequently, activation of PERK favors the phosphorylation of eukaryotic initiation factor 2 subunit a (eIF2a) and translation of activating transcription factor-4 (ATF4), which results in blocking protein translation and reducing accumulation in ER. In Golgi complex, ATF6 is cleaved by the transcription factor responsible for the expression of ER chaperone genes. Splices Xbp1 mRNA (originated from activation of Ire

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