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UNDERSTANDING PREECLAMPSIA: ANGIOGENESIS BIOMARKERS IN FOCUS

Resume

This article delves into preeclampsia, a significant pregnancy complication marked by high maternal mortality. It highlights the central role of angiogenesis biomarkers, particularly PlGF and sFlt-1, in understanding the disease's pathogenesis and aiding early diagnosis. The study examines the predictive value of the sFlt-1/PlGF ratio for risk stratification, emphasizing the potential for timely intervention to improve maternal and fetal outcomes. Further research is encouraged to enhance clinical applications and explore preeclampsia's underlying mechanisms.

Introduction

Preeclampsia is a distinctive condition exclusive to humans, characterized by a comprehensive hypertensive disorder affecting women in the later stages of pregnancy. The condition, as delineated by the International Society for the Study of Hypertension in Pregnancy (ISSHP), manifests itself post the 20th pregnancy week, marked by elevated blood pressure readings (exceeding 140/90 mmHg) coupled with substantial protein presence in urine (in excess of 300 mg per day) [1, 2, 3]. Being one of the gravest complications during pregnancy, it has a global prevalence rate up to 8%, according to WHO, positioning it as a leading cause of maternal mortality, contributing to approximately 14% of such cases annually. Over 50,000 women lose their lives each year globally due to complications arising from hypertensive disorders [4, 5, 6, 7]. The International Federation of Gynecology and Obstetrics (FIGO) stresses that many deaths from hypertensive conditions during pregnancy, preeclampsia included, can be averted with prompt and effective medical intervention, highlighting the critical need for accurate and effective diagnostic and prognostic tools in contemporary obstetrics [8, 9, 10].

Presentation of the Main Material

Insufficient trophoblast invasion is considered one of the leading mechanisms in the pathogenesis of preeclampsia, leading to disturbed angiogenesis, endothelial dysfunction, changes in immunoreactivity, development of hypoxia, placental dysfunction, and ultimately the manifestation of the preeclampsia syndrome itself. Persistent hypoxia in the environment under preeclampsia creates a vicious cycle with high levels of factors that inhibit trophoblast invasion and lead to insufficient placentation with impaired remodeling of spiral arteries and the development of hypercoagulation [11].

Angiogenesis plays a crucial role in developing the placental blood vessels, with vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) being central to this process. Their activity is balanced by inhibitors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng). [12].

Placental growth factor (PlGF) is a protein belonging to the endothelial growth factor family, playing a crucial role in angiogenesis. Its normal dynamics during pregnancy involve a gradual increase during the first and second trimesters, with peak levels at 29–32 weeks followed by a decrease. In pregnancies complicated by preeclampsia, PlGF levels significantly decrease compared to normal levels for the gestational age [13]. According to a study by the Royal College of London, a decrease in PlGF concentration with high sensitivity allows for identifying women at risk of developing preeclampsia before 35 weeks of gestation, who, in case of disease development, will require urgent delivery within 14 days [14]. Changes in PlGF concentration logically reflect the development of endothelial disorders, but in terms of preeclampsia development, it was found to have limited prognostic value when used in isolation [15].

sFlt-1, a soluble form of fms-like tyrosine kinase-1, is a short fragment of a membrane protein that circulates in serum and inactivates VEGF and PlGF by binding to them, acting as an anti-angiogenic factor. It has been found that serum levels of sFlt-1 begin to increase 5 weeks before the manifestation of the first symptoms of preeclampsia and continue to rise progressively with the disease's development [16]. The level of sFlt-1 directly correlates with the severity of the disease, the development of proteinuria, and hypertension, but differences in its concentration in the serum of women with a physiological course of pregnancy and those with preeclampsia are only detectable after the 20th week of pregnancy. ACOG limits the reliability of using this test in isolation for predicting the development of preeclampsia at 5 weeks [17].

A more promising approach seems to be the combined analysis of PGF and sFlt-1 concentration changes. In the blood of pregnant women, there is a significant increase in sFlt-1 concentration simultaneously with a decrease in PlGF level. Evaluating this ratio allows stratification of the risk of developing complications in women with presumed preeclampsia: those with a ratio higher than 85 will more likely face complications such as multi-organ damage, premature labor, small for gestational age fetus, and the need for neonatal intensive care within two weeks of manifestation. Conversely, with a ratio below 85, the development of these complications is less likely, even with a preeclampsia diagnosis. Additionally, this ratio can be useful for predicting the manifestation of preeclampsia within four weeks from the analysis, thus enabling the screening of patients with clinical signs that are not sufficient for preeclampsia verification [18]. Roche conducted the PROGNOSIS study from December 2010 to January 2014 among pregnant women suspected of preeclampsia, which provided evidence that the sFlt-1/PlGF ratio could be used for predicting the development of preeclampsia in conjunction with other diagnostic and clinical data. Doubling the sFlt-1/PlGF index in a short term indicates the disease's severity and underscores the correctness of the decision to terminate the pregnancy via cesarean section. The PROGNOSIS study among patients with presumed preeclampsia found that a ratio of sFlt-1/PlGF $\leq$38 had significant prognostic value for excluding the development of preeclampsia within the next week after analysis (NPV 99.3%). At the same time, an sFlt-1/PlGF ratio >38 had enough prognostic value to indicate the development of preeclampsia within the next 4 weeks after analysis (PPV=36.7%) [19]. Later studies confirmed these data: a ratio below 38 excludes the development of preeclampsia for at least the next week with a high sensitivity and specificity. Similarly, for a ratio above 38 within the next four weeks, the development of preeclampsia could be predicted with a sensitivity of 66.2% and a specificity of 83.1% [20, 21].

Another biomarker under prolonged discussion for its role in the pathogenesis of preeclampsia is vascular endothelial growth factor (VEGF). It is noteworthy that it belongs to a family of proteins that regulate the balance between angiogenic and anti-angiogenic signals during placentation. VEGF is essential for the physiological growth of stromal vessels and placenta through regulation of the invasive properties of cytotrophoblasts. One of the primary functions of VEGF in the placenta at late gestation terms is to ensure increased endothelial cell viability and vascular stability. It should be noted that VEGF stimulates the production of sFlt-1 in the human placenta through its action on VEGF-2 receptors. The level of VEGF depends on the level of sFlt-

1 and is regulated by feedback. Dysregulation of this feedback mechanism may play a role in the pathogenesis of preeclampsia [22].

Conclusion

In conclusion, preeclampsia emerges as a critical pregnancy complication with notable implications for maternal health, highlighted by its high prevalence and mortality rates. Central to its pathogenesis are insufficient trophoblast invasion and impaired angiogenesis, leading to significant endothelial dysfunction and placental abnormalities. Biomarkers such as PlGF and sFlt-1, and particularly their ratio, have been identified as promising tools for early diagnosis and risk stratification, offering potential for timely and targeted interventions. These findings underscore the urgency of integrating these biomarkers into clinical practice to enhance the prediction, diagnosis, and management of preeclampsia, ultimately aiming to improve maternal and fetal outcomes. Further research is warranted to refine these strategies and to explore the underlying mechanisms of preeclampsia, reinforcing the need for a multidisciplinary approach to tackle this complex condition.

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