International Journal on Obstetrics and Gynecology

Usefulness of Angiogenic Factors in Diagnosis and Prognosis of Preeclampsia in High Risk Pregnancies

Mini Review

Volume 3 Issue 1- 2023

Author Details

Carlos José Molina Pérez[1], María Guadalupe Berumen Lechuga[2] and Alfredo Leaños Miranda[3]*

[1]MSc, DSc., Instituto Mexicano del Seguro Social (IMSS), México

[2]MSc, DSc., Órgano de Operación Administrativa Desconcentrada Regional México Poniente, México

[3]MSc, DSc., Unidad Médica de Alta Especialidad Hospital de Ginecología y Obstetricia Luis Castelazo Ayala, México

*Corresponding author

Carlos José Molina Pérez, MSc, DSc., Clinical Coordinator,General Hospital 252, Instituto Mexicano del Seguro Social (IMSS), México

Article History

Received: July 24, 2023 Accepted: July 27, 2023 Published: July 27, 2023

Abstract

Pregnant women with chronic diseases are at a high risk of developing adverse outcomes, including superimposed preeclampsia. Prediction and diagnoses of superimposed preeclampsia in women with high-risk pregnancies is often challenging. Pro-angiogenic factors: placental growth factor (PlGF), as well as the anti-angiogenic factors: soluble Fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) have gained increasing attention for their role in the pathogenesis of preeclampsia. Changes in serum concentrations of pro and anti-angiogenic factors are associated with the occurrence of superimposed preeclampsia in high-risk pregnancies. These changes are present up to four weeks before the final clinical manifestations of the disease. Pro and antiangiogenic factors might be useful for risk stratification of superimposed preeclampsia and other adverse outcomes in high-risk pregnancies. The aim of opinion is to describe the clinical usefulness of serum concentrations of pro and anti-angiogenic factors as biomarkers in progression and diagnoses to superimposed preeclampsia in women with high-risk pregnancies.

Keywords: High-risk pregnancies, Angiogenic factors, superimposed preeclampsia, Biomarkers, Pathogenesis of preeclampsia

Mini Review

Any unexpected or unanticipated medical or obstetric condition associated with a pregnancy with an actual or potential hazard to the health or well-being of the mother or fetus is considered a high-risk pregnancy. Worldwide, 20 million women have high-risk pregnancies and more than 800 die daily from perinatal conditions [1]. Pregnant women with chronic diseases are at a high risk of developing adverse outcomes, including superimposed preeclampsia, fetal growth restriction, admission to intensive care units, maternal and perinatal deaths, among other adverse outcomes [2-4]. Although women with chronic diseases are associated with reduced fertility and increased risk of adverse pregnancy outcomes, women at reproductive age with diseases like chronic hypertension, systemic lupus erythematosus, chronic kidney disease, antiphospholipid syndrome among a great variety of maladies will become pregnant or will be detected for first time during pregnancy. Superimposed preeclampsia is the most common complication in this group of women, along with other related events such as preterm delivery, infants with low birth weight, or perinatal death [5,6].

Pathophysiology of preeclampsia involves maternal, fetal, and placental factors. Abnormalities in the formation of the placenta during pregnancy may result in under perfusion and ischemia, which then leads to release of anti-angiogenic factors into the maternal circulation that cause a maternal systemic endothelial disfunction,

clinically manifested by hypertension and other end organ damage (hematologic, neurologic, cardiac, pulmonary, renal, and hepatic dysfunction) [7]. However, the trigger for abnormal placental development and the subsequent cascade of events remains unknown. Nonetheless, hypoxia is likely an important regulator. Other factors such as alterations in the renin-angiotensin-aldosterone axis, immune maladaptation, excessive shedding of trophoblast debris, oxidative stress, and genetic factors likely contribute to the pathogenesis of the abnormal placentation [8].

Diagnosis of superimposed preeclampsia is difficult to stablish because these diseases often share clinical manifestations like hypertension, significant proteinuria, edema, impaired renal function among others. These facts represent a problem because treatment represents an intervention like the use of steroids, antihypertensives, admission to intensive care units or inclusive termination of pregnancy. The fact that misdiagnoses are often stablished, represents an adverse perinatal outcome like prematurity for the newborn, admission to neonatal intensive care unit, perinatal death with other long-term consequences [9]. The timely and accurate recognition and management of superimposed preeclampsia are often challenging because diagnostic criteria are still based on nonspecific signs and symptoms and because common severity criteria correlate poorly with adverse maternal and fetal outcomes [10].

Pathogenesis of preeclampsia is enigmatic; nonetheless, it has been proposed that originates in the placenta, starting with inadequate cytotrophoblast invasion and ending with widespread maternal endothelial dysfunction [11]. Production of placental anti-angiogenic factors, specifically sFlt-1 and sEng, have been shown to be upregulated in preeclampsia. These placental anti-angiogenic factors are released into the maternal circulation; their actions disrupt the maternal endothelium and result in hypertension, proteinuria, and the other systemic manifestations of preeclampsia [12].

The role of angiogenic factors in the onset of clinical manifestations of preeclampsia was demonstrated in 2003 by the implication of sFlt-1, PlGF and VEGF, and in 2006 by the implication of sEng [13-16]. Several angiogenic factors have been fully purified, their amino acid sequences determined, and their genes cloned. When evaluated according to their putative targets, they appear to fall into two groups: those that act directly on vascular endothelial cells to stimulate locomotion or mitosis, and those that act indirectly by mobilizing host cells (for example, macrophages) to release endothelial growth factors [17]. These placental anti-angiogenic factors are released into the maternal circulation; their actions disrupt the maternal endothelium and result in hypertension, proteinuria, and the other systemic manifestations of preeclampsia [9]. Numerous studies have shown the key role of angiogenic factors in the malformation of the placenta in the pathogenesis of preeclampsia [18].

In women with High-risk pregnancies, serum sFlt-1 and sEng concentrations and low PlGF serum concentrations are associated with the risk of superimposed preeclampsia and other adverse outcomes. The sFlt-1/PlGF ratio <38 rules out the short-term onset and diagnosis of superimposed preeclampsia, values between 39 and 85 are associated with superimposed preeclampsia in the next 4 weeks and sFlt-1/PlGF ratio ≥85 between 20 and 34 weeks of pregnancy and ≥110 beyond 34 weeks of pregnancy confirms a diagnosis of superimposed preeclampsia in most cases. It has been reported that sEng serum concentration increases with gestation weeks in women with high-risk pregnancies who eventually develop superimposed preeclampsia, thus, the risk of superimposed preeclampsia and other adverse outcomes increases too. Thus, sFlt-1, PlGF and sEng serum levels appear to be reliable biomarkers to predict and diagnose superimposed preeclampsia throughout pregnancy in women with high-risk pregnancies [19].

Other biomarkers have been reported to be useful tools to predict adverse outcomes in high-risk pregnancies. Protodiastolic Notch in combination with uterine artery doppler – pulsatility index (UtAD-PI) have been reported as a good tool for prediction of preeclampsia in high-risk pregnancies. UtAD is associated with an increased risk of presenting adverse fetal maternal events. UtAD ultrasonography predicts preeclampsia and FGR as a maternal consequence of placental disease. There is evidence that an increased PI with notching in the second trimester best predicts overall preeclampsia in low-risk and high-risk patients and that an increased PI alone or in combination with notching best predicts severe fetal growth restriction [20], It has been reported that urinary IgM excretion, proteinuria and the severity of renal function impairment are associated with the risk of subsequently develop adverse perinatal outcomes in pregnant women with chronic kidney disease. The preexisting atherosclerotic vascular disease induce placental ischemia or even aggravate already existing placental dysfunction as assessed by Doppler velocimetry of the uterine artery, which in turn causes or accelerates the occurrence of these adverse perinatal outcomes [2].

References

1. Holness N (2018) High-Risk Pregnancy. Nurs Clin North Am 53(2): 241-251.
2. Leanos Miranda A, Campos Galicia I, Ramirez Valenzuela KL, Berumen Lechuga MG, Isordia Salas I, et al. (2019) Urinary IgM excretion: a reliable marker for adverse pregnancy outcomes in women with chronic kidney disease. J Nephrol 32(2): 241-251.
3. Masuyama H, Nobumoto E, Okimoto N, Inoue S, Segawa T, et al. (2012) Superimposed preeclampsia in women with chronic kidney disease. Gynecol Obstet Invest 74(4): 274-281.
4. Piccoli GB, Cabiddu G, Attini R, Vigotti FN, Maxia S, et al. (2015) Risk of Adverse Pregnancy Outcomes in Women with CKD. J Am Soc Nephrol 26(8): 2011-2022.
5. Zhang JJ, Ma XX, Hao L, Liu LJ, Lv JC, et al. (2015) A Systematic Review and Meta-Analysis of Outcomes of Pregnancy in CKD and CKD Outcomes in Pregnancy. Clin J Am Soc Nephrol 10(11): 1964-9178.
6. Leanos Miranda A, Campos Galicia I, Berumen Lechuga MG, Molina Perez CJ, Garcia Paleta Y, et al. (2015) Circulating Angiogenic Factors and the Risk of Preeclampsia in Systemic Lupus Erythematosus Pregnancies. J Rheumatol 42(7): 1141-1149.
7. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, et al. (2004) Circulating Angiogenic Factors and the Risk of Preeclampsia. New England Journal of Medicine 350(7): 672-683.
8. Lam C, Lim KH, Karumanchi SA (2005) Circulating angiogenic factors in the pathogenesis and prediction of preeclampsia. Hypertension 46(5): 1077-1085.
9. Leaños Miranda A, Graciela Nolasco Leaños A, Ismael Carrillo Juárez R, José Molina Pérez C, Janet Sillas Pardo L, et al. (2020) Usefulness of the sFlt-1/PlGF (Soluble fms-Like Tyrosine Kinase-1/Placental Growth Factor) Ratio in Diagnosis or Misdiagnosis in Women With Clinical Diagnosis of Preeclampsia. Hypertension 76(3): 892-900.
10. Herraiz I, Llurba E, Verlohren S, Galindo A (2018) Update on the Diagnosis and Prognosis of Preeclampsia with the Aid of the sFlt-1/PlGF Ratio in Singleton Pregnancies. Fetal Diagn Ther 43(2): 81-89.
11. Karumanchi SA, Maynard SE, Stillman IE, Epstein FH, Sukhatme VP (2005) Preeclampsia: a renal perspective. Kidney Int 67(6): 2101-2113.
12. Bardin N, Murthi P, Alfaidy N (2015) Normal and pathological placental angiogenesis. Biomed Res Int 2015: 354359.
13. Luttun A, Tjwa M, Carmeliet P (2002) Placental growth factor (PlGF) and its receptor Flt-1 (VEGFR-1): novel therapeutic targets for angiogenic disorders. Ann N Y Acad Sci 979: 80-93.

14. Maynard S, Epstein FH, Karumanchi SA (2008) Preeclampsia and angiogenic imbalance. Annu Rev Med 59: 61-78.

15. Maynard SE, Min JY, Merchan J, Lim KH, Li J, et al. (2003) Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 111(5): 649-658.

16. Maynard SE, Venkatesha S, Thadhani R, Karumanchi SA (2005) Soluble Fms-like tyrosine kinase 1 and endothelial dysfunction in the pathogenesis of preeclampsia. Pediatr Res 57(5 Pt 2): 1r-7r.

17. Folkman J, Klagsbrun M (1987) Angiogenic factors. Science 235(4787): 442-447.

18. Verlohren S, Stepan H, Dechend R (2012) Angiogenic growth factors in the diagnosis and prediction of pre-eclampsia. Clin Sci (Lond) 122(2): 43-52.

19. Risau W (1990) Angiogenic growth factors. Prog Growth Factor Res 2(1): 71-79.

20. Molina Pérez CJ, Nolasco Leaños AG, Carrillo Juárez RI, Berumen Lechuga MG, Isordia Salas I, et al. (2021) Soluble Endoglin and Uterine Artery Flow Doppler Ultrasonography as Markers of Progression to Preeclampsia in Women with Gestational Hypertension. Gynecol Obstet Invest 86(5): 445-453.