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PREDICTING THE DEVELOPMENT OF THROMBOTIC MICROANGIOPATHY IN PREGNANCY BASED ON CLINICAL AND GENETIC FACTORS: A CRITICAL REVIEW AND FUTURE PERSPECTIVES

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Abstract
Thrombotic microangiopathies (TMAs) of pregnancy, including severe preeclampsia (PE) and its critical form, HELLP syndrome, remain leading causes of maternal and perinatal mortality, as well as long-term cardiovascular complications. Their fulminant course necessitates the development of highly accurate predictive methods. This review systematizes current scientific data on the clinical and genetic predictors of severe forms of PE. Key pathogenetic mechanisms are examined, including the imbalance of angiogenic factors (sFlt-1/PlGF), oxidative stress, immune maladaptation, and microangiopathic hemolysis. The predictive value of clinical factors, biochemical markers, and genetic polymorphisms is analyzed. Special attention is given to genes controlling vascular tone (AGTR1, eNOS), angiogenesis (FLT1), and the hemostatic system (F5, SERPINE1). The principles of constructing and the limitations of existing integrative models are discussed. It is emphasized that a personalized approach is key to the timely initiation of preventive measures, intensification of monitoring, and selection of the optimal timing for delivery.

Keywords: Thrombotic microangiopathy, severe preeclampsia, HELLP syndrome, prediction, clinical factors, genetic predictors, sFlt-1/PlGF, endothelial dysfunction, microangiopathic hemolysis, polygenic risk, personalized medicine.

Introduction

Thrombotic microangiopathies (TMAs) of pregnancy represent a heterogeneous group of life-threatening conditions united by a common pathomorphological feature: generalized endothelial damage and the formation of microthrombi in small-caliber vessels [George J.N., Nester C.M., 2014]. In obstetric practice, this term primarily encompasses severe forms of preeclampsia (PE) and its most formidable manifestation, HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome. Despite decades of research since HELLP syndrome was first described by Weinstein L. in 1982, predicting its development remains one of the "holy grails" of modern obstetrics.

Severe PE and HELLP syndrome are not merely obstetric complications but conditions with lifelong consequences. Studies by Harskamp-van Ginkel A.D. and Kajantie E. convincingly show that women who have experienced severe PE have a 2-4 fold higher risk of developing chronic hypertension and ischemic heart disease later in life, and their children have an

increased risk of metabolic syndrome [Harskamp-van Ginkel A.D. et al., 2019; Kajantie E. et al., 2010]. This shifts the problem from a purely obstetric issue to one of public health. The heterogeneity of these conditions, as pointed out by von Dadelszen P. (2003), remains the main challenge for prediction. He proposed that early-onset (<34 weeks) and late-onset (>34 weeks) preeclampsia might be different diseases from a pathogenetic standpoint: the former being predominantly of placental origin, the latter of maternal origin. This concept is gaining increasing support and explains why predictors effective for one form may be useless for the other.

The contemporary scientific dialogue, led by researchers such as Poon L.C., Nicolaides K.H., and Karumanchi S.A., is focused on creating multifactorial models that allow a shift from a "one-size-fits-all" approach to individual risk stratification. The paradigm of pregnancy management is changing from reactive to proactive, with the focus on preventing severe forms of the complication rather than treating it once it has developed.

The aim of this review is to critically analyze current scientific data on the predictors of severe PE and HELLP syndrome, compare the results of key studies, and discuss unresolved questions and the prospects for their integration into clinical practice.

1. Pathogenesis: A Complex Dialogue Between Mother, Placenta, and Genes

The fundamental "two-stage model" by Redman and Sargent (2005), where placental ischemia triggers the maternal syndrome, remains a cornerstone, but it has been significantly detailed and complicated in recent years.

1.1. The Placental Stage: More Than Just Hypoxia

It was initially thought that simple hypoxia due to insufficient blood supply was the underlying cause. However, studies by G.J. Burton et al. (2009), using histological analysis of placentas, showed that a more accurate model involves alternating periods of ischemia and reperfusion. Unstable uteroplacental blood flow leads to sharp fluctuations in oxygen partial pressure in the intervillous space. It is these reperfusion injuries, rather than stable hypoxia, that cause massive "oxidative stress"—an explosive production of free radicals that damage syncytiotrophoblast cells.

1.2. The Maternal Stage: From Anti-Angiogenesis to Systemic Inflammation

The damaged placenta releases a "cocktail" of pathological factors into the maternal circulation.

The Anti-Angiogenic Theory. Experimental work by S.A. Karumanchi and his group was a turning point, proving that the administration of sFlt-1 (soluble fms-like tyrosine kinase-1) to laboratory animals could fully replicate the preeclampsia phenotype, including hypertension, proteinuria, and glomerular endotheliosis [Maynard S.E. et al., 2003]. sFlt-1 acts as a "trap" for the pro-angiogenic factors VEGF and PlGF, which are essential for maintaining endothelial health. Thus, sFlt-1 was moved from being a simple marker to a key pathogenetic agent. Later, Levine R.J. et al. (2006) added soluble endoglin (sEng) to this picture, which blocks the signaling pathways of another important factor, TGF-β, exacerbating endothelial dysfunction.

The Immunological Theory and Systemic Inflammation. Parallel to the anti-angiogenic theory, an immunological one has been developing. I.L. Sargent and C.W. Redman (2009) proposed that the excessive shedding of syncytiotrophoblast microparticles (products of placental cell apoptosis and necrosis) causes an excessive systemic inflammatory response (SIRS) in the mother. These microparticles carry procoagulant and pro-inflammatory molecules, activating neutrophils, monocytes, and the complement system. Studies by S. Saito et al. (2010) have shown that in PE, the balance between T-helper 1 and 2 cells (Th1/Th2) is shifted in favor of pro-inflammatory Th1 cytokines (TNF-α, IFN-γ).

Discussion: How are these theories connected? These theories are not contradictory but complementary. Anti-angiogenic factors like sFlt-1 can themselves activate inflammatory cells. At the same time, pro-inflammatory cytokines like TNF-α can stimulate sFlt-1 production in the placenta. Thus, a vicious circle is formed. The unresolved question: What is the trigger? Is inflammation a reaction to the anti-angiogenic stimulus, or does the mother's initial immune maladaptation (e.g., an inadequate reaction to paternal antigens of the fetus) itself contribute to placental damage and the initiation of the entire cascade? The answer to this question will determine future therapeutic strategies.

2. Clinical Predictors and Biomarkers: The Evolution of Approaches

The prediction of TMA has evolved from the assessment of anamnestic data to the use of complex biophysical and biochemical markers.

2.1. From Anamnesis to Biophysics: Limitations and Achievements

The traditional approach, based on risk factor assessment (e.g., according to ACOG recommendations), is criticized for its low efficacy. A meta-analysis by Duckitt K. and Harrington D. (2005) showed that most anamnestic factors have a low likelihood ratio. For example, a maternal history of PE increases the risk, but only a small fraction of daughters will develop the complication. This makes such screening insufficiently accurate for individual prediction.

A breakthrough was the inclusion of objective biophysical markers in first-trimester screening. Measurement of mean arterial pressure (MAP) and uterine artery Doppler velocimetry with calculation of the pulsatility index (PI), standardized by the group of Nicolaides K.H., significantly increased predictive value. An elevated PI in the uterine arteries at 11-13 weeks reflects inadequate spiral artery transformation and high peripheral resistance, thus being a direct marker of placentation defects.

2.2. Biochemical Markers: A Comparison of Strategies and Tools

First-Trimester Screening (PlGF, PAPP-A). The work of Akolekar R. et al. (2013) and statistical models developed by D.G. O'Gorman formed the basis of the combined Fetal Medicine Foundation (FMF) algorithm. Low levels of placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A) in the first trimester reflect general placental dysfunction.

Discussion

It is important to understand that the efficacy of this approach for predicting late-onset PE (>34 weeks) is significantly lower than for early-onset PE (detection rate of about 90% for early vs. only 40-50% for late). This is a strong argument for von Dadelszen's theory of different pathogenetic mechanisms for these two conditions. Late-onset PE may be more related to maternal inability to adapt to the metabolic and hemodynamic demands of advancing pregnancy, especially against a background of pre-existing risk factors (obesity, age), rather than a profound placentation defect.

Short-Term Prediction in the Second Half of Pregnancy (sFlt-1/PlGF). This is a fundamentally different tool. The PROGNOSIS study, led by H. Zeisler (2016), was the first major prospective study to establish clear cutoff values for the sFlt-1/PlGF ratio for clinical use. Its unique strength lies in its high negative predictive value: a value <38 allows for the exclusion of PE development within a week with 99.3% certainty, thus avoiding unnecessary hospitalization.

Comparison: The FMF model and the sFlt-1/PlGF ratio are not competing but complementary strategies. The FMF model is a *screening* test for an asymptomatic population in the first trimester, aimed at identifying a high-risk group for aspirin prophylaxis. The sFlt-1/PlGF ratio is a *diagnostic/prognostic* test for women with suspected PE in the second half of pregnancy, aimed at aiding in tactical decisions (hospitalization, monitoring, delivery).

HELLP Syndrome and Classification. The work of A.L. Tranquilli within the ISSHP (International Society for the Study of Hypertension in Pregnancy) consistently emphasizes the importance of a clear classification of hypertensive disorders. This is critically important for research, as lumping women with different forms of PE into one group can "dilute" results and hinder the search for specific predictors for HELLP syndrome. Extensive research by Martin J.N. Jr. has revealed significant heterogeneity in HELLP syndrome, including atypical forms without severe hypertension or with a partial set of features (e.g., ELLP syndrome). This underscores that relying solely on blood pressure levels to predict HELLP is dangerous. Dynamic monitoring of LDH, platelets, and ALT/AST becomes critically important.

3. Genetic Predictors: From Single Genes to Genomic Profiles

The genetic contribution to the development of PE is estimated to be 50-60%, with maternal genes having a predominant effect over paternal/fetal genes [Salonen Ros H. et al., 2000]. Approaches to studying the genetics of PE have evolved significantly.

3.1. The Era of Candidate Genes: Achievements and Disappointments

Early research focused on genes whose function is logically linked to the pathogenesis of PE. The Renin-Angiotensin System (RAS). F. Broughton Pipkin studied the role of the RAS in adaptation to pregnancy and its dysfunction in PE for decades. Her work laid the foundation for studying polymorphisms in RAS genes. The most studied was the A1166C polymorphism in the *AGTR1* gene. A meta-analysis by Zhou S.L. et al. (2015) confirmed a statistically significant, though modest, association of this polymorphism with the risk of PE. Hereditary Thrombophilias. The work of B. Dekker et al. systematized data on the association

of hereditary thrombophilias with the risk of severe PE. The Factor V Leiden mutation (*F5*) and the prothrombin gene mutation (*F2*) are the strongest genetic predictors of thrombosis. Their role in PE is more complex. A meta-analysis by Lindqvist P.G. and Dahlbäck B. (2005) showed that these mutations are associated more with severe complications (severe PE, placental abruption, FGR) than with PE in general. This supports the hypothesis that a prothrombotic state is not a cause of PE but a factor that exacerbates its course.

Limitations of the Approach

The main problem with candidate gene studies was poor reproducibility of results. Associations found in one population often were not confirmed in another. This was due to small sample sizes, ethnic differences, and the complexity of the disease itself.

3.2. The Modern View: Genome-Wide Association Studies and Polygenic Risk

The breakthrough came with the advent of microarray technology and genome-wide association studies (GWAS). This approach does not require a priori hypotheses and allows for scanning the entire genome for regions associated with the disease. The work of the international InterPregGen consortium, in which H. Laivuori played an active role, identified new, previously unknown genetic loci associated with PE. The most significant signal was found near the *FLT1* gene, which encodes the VEGF-A receptor and its soluble form, sFlt-1 [McGinnis R. et al., 2017]. This finding was a brilliant confirmation of the central role of the anti-angiogenic pathway in the genetics of PE, linking biochemical and genetic data.

Discussion and Comparison:

GWAS has shown that the contribution of "classic" candidate genes (like *AGTR1*) to the overall risk of PE may be smaller than previously thought. The main contribution comes from hundreds of genetic variants with small effects. This shifts the focus from testing individual polymorphisms to creating Polygenic Risk Scores (PRS). A PRS sums the effects of multiple genetic variants into a single score reflecting an individual's genetic predisposition. Discussion: PRS is a powerful research tool, but its clinical application is still under question. First, most PRS have been developed in European populations and may not be accurate for other ethnicities. Second, as shown by Gray K.J. et al., adding a PRS to the already powerful FMF combined model provides only a modest improvement in predictive accuracy (an increase in the area under the ROC curve of 1-2%). It must be proven that this improvement is clinically and economically justified.

4. Integrative Predictive Models: Synergy and Challenges

No single approach is self-sufficient. The future lies in integrating data from various sources, which allows for accounting for the multifactorial nature of TMA.

4.1. The FMF Model as an Example of Successful Integration

The FMF model is a clear example of successful synergy. It combines:

- Maternal factors (medical history, age, weight, ethnicity).

- Biophysical markers (mean arterial pressure, uterine artery PI).
- Biochemical markers (PlGF, PAPP-A).

This approach allows for a detection rate of early-onset PE of 90% at a 10% false-positive rate, which is sufficient for effective screening and the prescription of aspirin prophylaxis, the efficacy of which was proven in the large ASPRE trial [Rolnik D.L. et al., 2017].

4.2. Discussion of the Future: Dynamic, Multilevel Models

What will the next-generation model look like? It will likely be a dynamic, multilevel algorithm that adapts to the patient's individual risk.

First Trimester: The Basic Stratification Level.

1. A baseline risk is calculated using the FMF model.
2. A PRS is added to refine the genetic predisposition.
3. Patients are divided into low, moderate, and high-risk groups.

Second and Third Trimesters: The Tactical Monitoring Level.

1. A specific monitoring trajectory is defined for each risk group.
2. Low-risk group: Routine care.
3. Moderate-risk group: Periodic monitoring of the sFlt-1/PlGF ratio (e.g., at 28 and 34 weeks).
4. High-risk group: Weekly or bi-weekly monitoring of the sFlt-1/PlGF ratio starting from 24-28 weeks, along with monitoring of markers of organ dysfunction (LDH, platelets, ALT/AST).

The Main Challenge: Such a complex system requires not only further clinical validation but also the resolution of organizational and economic issues. It is necessary to develop a convenient IT infrastructure integrated with electronic health records, create decision support systems for physicians, and provide staff training. The cost-effectiveness of this approach also requires careful evaluation.

Conclusion

Predicting severe PE and HELLP syndrome is a dynamic process, not a single action. A critical analysis of research shows that we are moving from a static assessment of anamnestic risks to a dynamic, multilevel assessment of individual predisposition and current pathophysiological state. The foundational work of Weinstein, Sibai, Redman, and Burton laid the groundwork. Modern research, led by groups like those of Nicolaides, Karumanchi, Zeisler, and consortia such as InterPregGen, is building the edifice of personalized medicine on this foundation.

The main challenge for the near future is not so much the search for new markers as the smart integration of existing ones. It is necessary to develop and validate adaptive algorithms that combine clinical, biochemical, and genomic data into a clinician-friendly decision support tool. Only in this way can we transform scientific achievements into real improvements in outcomes for mothers and their children, both during pregnancy and in the long term, reducing not only perinatal losses but also the burden of future cardiovascular diseases.

References

1. Akolekar R., Syngelaki A., Poon L., Wright D., Nicolaides K.H. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. *Am J Obstet Gynecol*. 2013;208(1):82.e1-10.
2. Brosens I.A., Pijnenborg R., Vercruysse L., Romero R. The "Great Obstetrical Syndromes" are a consequence of maternal-fetal endothelial dysfunction. *Am J Obstet Gynecol*. 2011;204(3):193-201.
3. Burton G.J., Jauniaux E. Placental oxidative stress: from miscarriage to preeclampsia. *J Soc Gynecol Investig*. 2004;11(6):342-352.
4. Dekker G., de Vries J.I., Doelitzsch P.M., et al. Underlying disorders associated with severe early-onset preeclampsia. *Am J Obstet Gynecol*. 1995;173(4):1042-1048.
5. Duckitt K., Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ*. 2005;330(7491):565.
6. George J.N., Nester C.M. Syndromes of thrombotic microangiopathy. *N Engl J Med*. 2014;371(7):654-666.
7. Gray K.J., Kovacheva V.P., Mirzakhani H., et al. A Polygenic Risk Score for Preeclampsia Is Not Associated with Fetal Growth. *Am J Perinatol*. 2018;35(7):645-652.
8. Haram K., Svendsen E., Abildgaard U. The HELLP syndrome: clinical issues and management. A Review. *BMC Pregnancy Childbirth*. 2009;9:8.
9. Harskamp-van Ginkel A.D., I-Kyeun, L., Thangaratinam S., et al. Pre-eclampsia and risk of later-life cardiovascular disease: a prospective cohort study of 21.6 million pregnancies. *Lancet*. 2019;394(10213):2031-2039.
10. Kajantie E., Eriksson J.G., Osmond C., Thornburg K., Barker D.J. Pre-eclampsia is associated with increased risk of stroke in the adult offspring: the Helsinki Birth Cohort Study. *Stroke*. 2010;41(6):1176-1180.
11. Levine R.J., Lam C., Qian C., et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med*. 2006;355(10):992-1005.
12. Lindqvist P.G., Dahlbäck B. The relationship between pregnancy and venous thromboembolism. *Hematol Oncol Clin North Am*. 2005;19(5):857-868.
13. Martin J.N. Jr., Brewer J.M., Wallace K., Hondo E.A., Keiser S.D., May W.L. HELLP Syndrome: A Fetal Perspective. *Semin Perinatol*. 2013;37(2):129-133.
14. Maynard S.E., Min J.Y., Merchan J., et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest*. 2003;111(5):649-658.
15. McGinnis R., Steinthorsdottir V., Williams N.O., et al. Variants in the fetal genome near FLT1 are associated with risk of preeclampsia. *Nat Genet*. 2017;49(8):1255-1260.
16. Ness B., Roberts J.M. Heterogeneous causes for the syndrome of preeclampsia. *Carnforth, UK: Parthenon Publishing Group*. 2008.
17. Poon L.C., Shennan A., Hyett J.A., et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. *Int J Gynaecol Obstet*. 2019;145(Suppl 1):1-33.

18. Redman C.W., Sargent I.L. Placental stress and pre-eclampsia: a revised view. *Placenta*. 2009;30(Suppl A):S38-S42.
19. Rolnik D.L., Wright D., Poon L.C., et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *N Engl J Med*. 2017;377(7):613-622.
20. Saito S., Shima T., Nakashima A., Shiozaki A., Sasaki Y. What is the role of regulatory T cells in the success of implantation and placentation? *Semin Immunopathol*. 2010;32(2):101-108.
21. Salonen Ros H., Lichtenstein P., Lipworth L., Cnattingius S. Genetic effects on the liability of developing pre-eclampsia and eclampsia. *Am J Med Genet*. 2000;91(4):257-260.
22. Sibai B.M. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? *Am J Obstet Gynecol*. 1990;162(2):311-316.
23. Tranquilli A.L., Dekker G., Magee L., et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertens*. 2014;4(2):97-104.
24. von Dadelszen P., Magee L.A., Roberts J.M. Subclassification of preeclampsia. *Hypertens Pregnancy*. 2003;22(2):143-148.
25. Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. *Am J Obstet Gynecol*. 1982;142(2):159-167.
26. Zeisler H., Llurba E., Chantraine F., et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. *N Engl J Med*. 2016;374(1):13-22.
27. Zhou S.L., Li T., Ma D., Chen S. The angiotensin II type 1 receptor A1166C polymorphism and preeclampsia risk: a meta-analysis. *Hypertens Res*. 2015;38(11):773-779.