EDITORIAL

The clinical utility of newly approved angiogenic markers for identifying patients at risk for adverse outcomes due to preeclampsia

Preeclampsia is one of the biggest clinical challenges in obstetric practice. A normal ratio of soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) identifies patients with a hypertensive disorder in pregnancy who are unlikely to progress to preeclampsia with severe features. An elevated sFlt-1/PlGF ratio identifies patients with a hypertensive disorder in pregnancy who are most likely to have adverse maternal and fetal outcomes.

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In the United States there is an epidemic of hypertensive disorders in pregnancy, with 16% of pregnant people being diagnosed with preeclampsia, gestational hypertension, chronic hypertension, preeclampsia superimposed on chronic hypertension, HELLP, or eclampsia.[1] Preeclampsia with severe features increases the maternal risk for stroke, pulmonary edema, kidney injury, abruption, and fetal and maternal death. Preeclampsia also increases the fetal risk for growth restriction, oligohydramnios, and preterm birth.

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Angiogenic factors and the pathophysiology of preeclampsia—From bench to bedside

The pathophysiology of preeclampsia is not fully characterized, but a leading theory is that placental ischemia causes increased placental production of anti-angiogenesis factors and a decrease in placental production of pro-angiogenesis factors.[2-4] Clinical studies support the theory that preeclampsia is associated with an increase in placental production of anti-angiogenesis factors, including soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin, and a decrease in the placental production of pro-angiogenesis factors, including placental growth factor (PlGF).[5-15]

The US Food and Drug Administration (FDA) has recently approved an assay for the measurement of sFlt-1 (Brahms sFlt-1 Kryptor) and PlGF (Brahms sFlt-1 Kryptor) (Thermo Fisher Scientific; Waltham, Massachusetts).[16] This editorial focuses on the current and evolving indications for the measurement of sFlt-1 and PlGF in obstetric practice.

FDA approval of a preeclampsia blood test

The FDA approval of the tests to measure sFlt-1 and PlGF is narrowly tailored and focused on using the sFlt-1/PlGF ratio to assess the risk of progression to preeclampsia with severe features within 2 weeks

among hospitalized patients with a hypertensive disorder in pregnancy with a singleton pregnancy between 23 weeks 0 days (23w0d) and 34w6d gestation.[16] The test is meant to be used in conjunction with other laboratory tests and clinical assessment. The FDA advises that the test results should not be used to diagnose preeclampsia, nor should they be used to determine the timing of delivery or timing of patient discharge.[16] The sFlt-1 and PlGF measurements are both reported as pg/mL, and the sFlt-1/PlGF ratio has no units.

The FDA approval is based on clinical studies that demonstrate the effectiveness of the test in predicting the progression of a hypertensive disorder in pregnancy to preeclampsia with severe features within 2 weeks of testing. In one study, the sFlt-1/PlGF ratio was measured in 556 pregnant patients with a singleton pregnancy who were between 23w0d and 34w6d gestation and hospitalized with a hypertensive disorder in pregnancy without severe features at study enrollment.[15] Those patients receiving intravenous heparin were excluded because of the effect of heparin on sFlt-1 levels. Participants' mean age was 31.7 years, and their mean gestational age was 30w3d. The patients' mean body mass index (BMI) was 34.2 kg/m^2, with mean maximal blood pressure (BP) at enrollment of 159 mm Hg systolic and 95 mm Hg diastolic.

In this cohort, 31% of enrolled patients progressed to preeclampsia with severe features within 2 weeks. At enrollment, the median sFlt-1/PlGF ratio was greater among the patients who progressed to preeclampsia with severe features than among those who did not have progression to preeclampsia with severe features (291 vs 7). An elevated sFlt-1/PlGF ratio (determined to be a ratio ≥ 40) predicted that patients would progress to severe preeclampsia with severe features—with positive and negative predictive values of 65% and 96%, respectively. Among the subgroup of patients with a history of chronic hypertension, an sFlt-1/PlGF ratio ≥ 40 had positive and negative predictive values of 59% and 94%, respectively. Focusing the analysis on patients who self-reported their race as Black, representing 30% of the cohort, the positive and negative predictive values for a sFlt-1/PlGF ratio ≥ 40 were 66% and 99%, respectively.[15]

Receiver-operating curve analyses were used to compare the predictive performance of sFlt-1/PlGF measurement versus standard clinical factors and standard laboratory results, including systolic and diastolic BP; levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine; and platelet count.[15] The area under the curve for predicting progression to preeclampsia with severe features was much greater for the sFlt-1/PlGF test (0.92) than for

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systolic (0.67) and diastolic BP (0.70), AST level (0.66), ALT level (0.61), creatinine level (0.65), and platelet count (0.57).[15] These results demonstrate that measuring sFlt-1/PlGF ratios is a much better way to predict the progression of preeclampsia to severe disease than measuring standard clinical and laboratory results.

Patients with a sFlt-1/PlGF ratio ≥ 40 had higher rates of adverse maternal outcomes including severe hypertension, abruption, stroke, eclampsia, pulmonary edema, thrombocytopenia, low platelets, and/or coagulation disorder, than those patients with a ratio < 40, (16.1% vs 2.8%, respectively; relative risk [RR], 5.8; 95% confidence interval [CI], 2.8 to 12.2).[15] Adverse fetal and neonatal outcomes (including fetal death, small for gestational age and early delivery due to progression of disease) were more common among patients with a sFlt-1/PlGF ratio of ≥ 40 (80% vs 26%; RR, 3.1; 95% CI, 2.5–3.8).[15] Many other studies support the hypothesis that the sFlt-1/PlGF ratio is predictive of adverse outcomes among patients with hypertensive disorders in pregnancy.[6-15]

Applying the bottom-line study findings. Patients with a hypertensive disorder in pregnancy and a sFlt-1/PlGF ratio < 40 have a low risk of progressing to preeclampsia with severe features over the following 2 weeks, with a negative predictive value of 96%. The remarkably high negative predictive value of a sFlt-1/PlGF ratio < 40 will help obstetricians generate a care plan that optimizes the use of limited health care resources. Conversely, about two-thirds of patients with a hypertensive disorder in pregnancy and a sFlt-1/PlGF test ≥ 40 will progress to preeclampsia with severe features and may need to prepare for a preterm delivery.

Clinical utility of the sFlt-1/PlGF ratio in obstetric triage

Measurement of the sFlt-1/PlGF ratio may help guide clinical care among patients referred to obstetric triage or admitted to the hospital for the evaluation of suspected preeclampsia. In one study, 402 patients with a singleton pregnancy referred to the hospital for evaluation of suspected preeclampsia, had a standard evaluation plus measurement of an sFlt-1/PlGF ratio.[13] The clinicians caring for the patients did not have access to the sFlt-1/PlGF test results. In this cohort, 16% of the patients developed preeclampsia with severe features in the 2 weeks following the initial assessment in triage. In this cohort, a normal sFlt-1/PlGF ratio reliably predicted which patients were not going to develop preeclampsia with severe features over the following 2 weeks, with a negative predictive value of 98%. Among the patients with an elevated sFlt-1/PlGF ratio, however, the positive predictive value of the test was 47% for developing preeclampsia with severe features within the 2 weeks following initial evaluation. Among patients < 34 weeks' gestation, an elevated sFlt-1/PlGF ratio had a positive predictive value of 65%, and a negative predictive value of 98%. Other studies also have reported that the sFlt-1/PlGF ratio is of value for assessing the risk for progression to preeclampsia with severe features in patients being evaluated for suspected preeclampsia.[6,17,18]

In obstetric triage, it is difficult to predict the clinical course of patients referred for the evaluation of suspected preeclampsia based on BP measurements or standard laboratory tests. The sFlt-1/PlGF test will help clinicians identify patients at low and high risk of progressing to preeclampsia with severe features.[19] Patients with a normal sFlt-1/PlGF test are at low risk of developing preeclampsia with severe features over the following 2 weeks. Patients with an elevated sFlt-1/PlGF test are at higher risk of progressing to preeclampsia with severe features and may warrant more intensive obstetric care. An enhanced care program might include:

- patient education
- remote monitoring of BP or hospitalization
- more frequent assessment of fetal well-being and growth
- administration of glucocorticoids to advance fetal maturity, if indicated by the gestational age.

Twin pregnancy complicated by preeclampsia

Twin pregnancy is associated with a high risk of developing preeclampsia and fetal growth restriction. For patients with a twin pregnancy and a hypertensive disorder in pregnancy, an elevated sFlt-1/PlGF ratio is associated with the need for delivery within 2 weeks and an increased rate of adverse maternal and neonatal outcomes. In a retrospective study involving 164 patients with twin pregnancy first evaluated for suspected preeclampsia at a median gestational age of 33w4d, the sFlt-1/PlGF ratio was positively correlated with progression of preeclampsia without severe features to severe features within 2 weeks.[20] In this cohort, at the initial evaluation for suspected preeclampsia, the sFlt-1/PlGF ratio was lower among patients who did not need delivery within 2 weeks compared with those who were delivered within 2 weeks, 24 versus 84 (P<.001). The mean sFlt-1/PlGF ratio was 99 among patients who needed delivery within 1 week

following the initial evaluation for suspected preeclampsia. Among patients who delivered within 1 week of presentation, the reasons for delivery were the development of severe hypertension, severe dyspnea, placental abruption, rising levels of serum liver function enzymes, and/or onset of the HELLP syndrome.

An important finding in this study is that a normal sFlt-1/PlGF ratio predicted that the patient would not need delivery within 2 weeks, with a negative predictive value of 96%. Other studies also have reported that an elevated sFlt-1/PlGF ratio in twin pregnancies is associated with an increased risk of adverse outcomes and early delivery.[21-23] An adequately powered multicenter study of twin pregnancies is needed to identify the sFlt-1/PlGF ratio associated with the greatest combined negative and positive predictive values.

The sFlt-1/PlGF test is a welcome addition to OB care

FDA approval of laboratory tests to measure circulating levels of sFlt-1 and PlGF will advance obstetric practice by identifying patients with a hypertensive disorder in pregnancy who are at low and high risk of developing preeclampsia with severe features within 2 weeks of the test. No laboratory test can replace the clinical judgment of obstetricians who are responsible for balancing the maternal and fetal risks that can occur in the management of a patient with a hypertensive disorder in pregnancy. The sFlt-1/PlGF ratio is highly dependable for identifying those patients with a hypertensive disorder in pregnancy who will not progress to severe disease within 2 weeks. The sFlt-1/PlGF ratio also identifies those patients with preeclampsia who are most likely to have adverse maternal and neonatal outcomes. The patients with an elevated sFlt-1/PlGF ratio may need more intensive antenatal care and consideration for transfer to a health system with a higher level of maternal and neonatal services. The sFlt-1/PlGF test is a welcome addition to obstetric care because it will improve the precision of our management of pregnant patients with hypertension. ●

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References

1. Ford ND, Cox S, Ko JY, et al. Hypertensive disorders in pregnancy and mortality at delivery hospitalization-United States 2017-2019. *Morb Mortal Week Report*. 2022;71:585-591.
2. Nagamatsu T, Fujii T, Kusumi M, et al. Cytotrophoblasts up-regulate soluble fms-like tyrosine kinase-1 expression under reduced oxygen: an implication for placental vascular development and the pathophysiology of preeclampsia. *Endocrinology*. 2004;145:4838-4445.
3. Rana S, Lemoine E, Granger JP, et al. Preeclampsia: pathophysiology, challenges and perspectives. *Circ Res*. 2019;124:1094-1112.
4. Rana S, Burke SD, Karumanchi SA. Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders. *Am J Obstet Gynecol*. 2022(2S):S1019-S1034.
5. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med*. 2004;350:672-683.
6. Chaiworapongsa T, Romero R, Savasan ZA, et al. Maternal plasma concentrations of angiogenic/anti-angiogenic factors are of prognostic value in patients presenting to the obstetrical triage area with the suspicion of preeclampsia. *J Matern Fetal Neonatal Med*. 2011;24:1187-1207.
7. Rana S, Powe CE, Salahuddin S, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. *Circulation*. 2012;125:911-919.
8. Moore AG, Young H, Keller JM, et al. Angiogenic biomarkers for prediction of maternal and neonatal complications in suspected preeclampsia. J *Matern Fetal Neonatal Med*. 2012;25:2651-2657.
9. Verlohren S, Herraiz I, Lapaire O, et al. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. *Am J Obstet Gynecol*. 2012;206:58.e1-e8.
10. Verlohren S, Herraiz I, Lapaire O, et al. New gestational phase-specific cutoff values for the use of soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia. *Hypertension*. 2014;63:346-352.
11. 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;374:13-22.
12. Duckworth S, Griffin M, Seed PT, et al. Diagnostic biomarkers in women with suspected preeclampsia in a prospective multicenter study. *Obstet Gynecol*. 2016;128:245-252.
13. Rana S, Salahuddin S, Mueller A, et al. Angiogenic biomarkers in triage and risk for preeclampsia with severe features. *Pregnancy Hyertens*. 2018;13:100-106.
14. Bian X, Biswas A, Huang X, et al. Short-term prediction of adverse outcomes using the sFlt-1/PlGF ratio in Asian women with suspected preeclampsia. *Hypertension*. 2019;74:164-172.
15. Thadhani R, Lemoine E, Rana S, et al. Circulating angiogenic factor levels in hypertensive disorders of pregnancy. *N Engl J Med Evidence*. 2022. doi 10.1056/EVIDoa2200161.
16. US Food and Drug Administration. FDA approval letter for an assay to measure sFlt-1 and PlGF. May 18, 2023. https://www.accessdata.fda.gov/cdrh_docs/pdf22/DEN220027.pdf
17. Chaiworapongsa T, Romero R, Korzeniewski SJ, et al. Plasma concentrations of angiogenic/anti-angiogenic factors have prognostic value in women presenting with suspected preeclampsia to the obstetrical triage area: a prospective study. *J Matern Fetal Neonatal Med*. 2014;27:132-144.
18. Palomaki GE, Haddow JE, Haddow HR, et al. Modeling risk for severe adverse outcomes using angiogenic factor measurements in women with suspected preterm preeclampsia. *Prenat Diagn*. 2015;35:386-393.
19. Verlohren S, Brennecke SP, Galindo A, et al. Clinical interpretation and implementation of the sFlt-1/PlGF ratio in the prediction, diagnosis and management of preeclampsia. *Pregnancy Hyper*. 2022;27:42-50.
20. Binder J, Palmrich P, Pateisky P, et al. The prognostic value of angiogenic markers in twin pregnancies to predict delivery due to maternal complications of preeclampsia. *Hypertension*. 2020;76:176-183.
21. Sapantzoglou I, Rouvali A, Koutras A, et al. sFlt-1, PlGF, the sFlt-1/PlGF ratio and their association with pre-eclampsia in twin pregnancies- a review of the literature. *Medicina*. 2023;59:1232.
22. Satorres E, Martinez-Varea A, Diago-Almela V. sFlt-1/PlGF ratio as a predictor of pregnancy outcomes in twin pregnancies: a systematic review. *J Matern Fetal Neonatal Med*. 2023;36:2230514.
23. Rana S, Hacker MR, Modest AM, et al. Circulating angiogenic factors and risk of adverse maternal and perinatal outcomes in twin pregnancies with suspected preeclampsia. *Hypertension*. 2012;60:451-458.