Of Risks and Ratios
The Usefulness of Angiogenic Balance for Diagnosing Preeclampsia at Different Gestational Ages
Jeffrey S. Gilbert, Sara A. Babcock, Ronald R. Regal, Jean F. Regal

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Preeclampsia is a devastating pregnancy-specific condition that can result in adverse maternal or fetal outcomes, including preterm delivery, very low birth weight, or maternal–fetal demise. In addition, preeclampsia is a heterogeneous multisystem disorder, with simple defining symptoms that do not adequately represent the complex nature of the syndrome. The clinical presentation of preeclampsia is often secondary to one or more maternal risk factors, such as obesity, advanced maternal age, or history of hypertension at the onset of pregnancy. Given the increasing prevalence of these risk factors in the general population, the rates of preeclampsia are likely to continue rising in the coming years.

Preeclampsia is often considered in 2 discrete phases: (1) a silent stage of abnormal placental development and function with no overt symptoms and (2) a symptomatic stage of endothelial dysfunction, hypertension, and abnormal cardiovascular function likely because of excess production of circulating inflammatory and vasoactive factors, largely of placental origin. To this end, there has been a significant interest in identifying factor(s) that presage clinical onset of the disease and prove useful as biomarkers or therapeutic targets. Molecules that have captured the attention of basic and clinical researchers in recent years are the angiogenic factor soluble fms-like tyrosine kinase-1 (sFlt-1) and the proangiogenic placental growth factor (PlGF) and vascular endothelial growth factor. The hypothesis that an imbalance in pro- and antiangiogenic factors plays an important role in the pathophysiology of preeclampsia was initially championed by the Karumanchi laboratory with their elegantly designed seminal studies that used in vitro experiments and the development of an animal model of preeclampsia to substantiate findings from a clinical cohort. The work put forth by Verlohren et al in the current issue of Hypertension builds on the previous studies by Ohkuchi et al using cutoffs at 2 different gestational phases in an effort to provide improved diagnostic accuracy of data obtained from the sFlt-1 and PlGF assays.

In uncomplicated pregnancies, the sFlt-1/PlGF ratio remains fairly constant in midpregnancy and then begins to increase in the last trimester. The present study by Verlohren et al demonstrates that an increase in this ratio before 34 weeks of gestation has high sensitivity and specificity to predict the occurrence of preeclampsia in their European cohort, 95% and 94% respectively, for a cutoff of 33. However, sFlt-1/PlGF ratios after 34 weeks in preeclamptic pregnancies are not as informative because of the increase in these ratios during uncomplicated pregnancy. Moreover, the similarities of values in late-onset preeclampsia to those in uncomplicated pregnancies may contribute to hypertension in late-onset preeclampsia. As the authors acknowledge in their present work for combined late gestational phase, the predictive power of sFlt-1/PlGF is limited, with sensitivity only 58% for a diagnostic test achieving 95% specificity even with a cutoff of 110. Repositioning the sFlt-1/PlGF cutoff for late gestational phase to 110 improves sensitivity but does not achieve a sensitive diagnostic test.

In contrast to the approach of Verlohren et al in the present study that determines cutoffs for grouped mid- and grouped late gestational phases, modeling continuous trends will give more accurate age-specific predictions. Ohkuchi et al modeled the continuous change in relationships across gestational ages in developing their onset and abnormal thresholds (ie, lower bounds from preeclampsia and upper bounds from non–preeclamptic cases, respectively). In addition, predictions could be improved by including other risk factors in the calculations as in Ohkuchi et al. Studies of Verlohren et al could also be

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used to estimate chances of preeclampsia. The availability of easily calculated risks would be a useful clinical tool beyond comparing the sFlt-1/PIGF ratio with a threshold. Although a much higher value of sFlt-1/PIGF indicates higher risk, the question remains: how great is the chance of preeclampsia? In their discussion of limitations, Verlohren et al\(^6\) note that they did not calculate positive or negative predictive values directly from their data set because of the study design. However, one can combine an overall preeclampsia rate of 2% to 5% and the distributions of sFlt-1/PIGF for preeclampsia and non–preeclamptic pregnancies to derive risks of preeclampsia for given gestational ages, as well as positive or negative predictive values.\(^7\) In addition, other risk factors or recently identified biomarkers in blood or urine, such as complement products C3a, C5a, C5b-9, angiotensin type 1 receptor auto-antibodies, or the insulin-like growth factor acid labile subunit, should also be tested in models to refine this approach.\(^3\)\(^,\)\(^8\)\(^,\)\(^9\)

The present study from Verlohren et al\(^6\) demonstrates that the predictive ability of sFlt-1/PIGF in early gestation is much better than in late gestation. Monitoring sFlt-1/PIGF longitudinally may be useful to identify women with early onset preeclampsia, but trying to make that one marker fit all things for a heterogeneous disorder with multiple mechanisms may be asking too much. Moreover, the decreasing sensitivity and specificity of the sFlt-1/PIGF assay for predicting late-onset preeclampsia may suggest the presence of additional pathways contributing to hypertension in this setting. Of course, further studies are needed to thoroughly explore this possibility.

For prediction of early gestational preeclampsia, the sFlt-1/PIGF ratio cutoff can provide both a high specificity and high sensitivity marker. High specificity is very important for predicting events with low prevalence and will certainly minimize the number of false alarms for pregnant women. Including information on adverse maternal and fetal outcomes in these algorithms may provide important information. Accumulating evidence suggests that preeclampsia and increases in antiangiogenic factors elevate risk for later development of chronic diseases, such as bronchopulmonary dysplasia.\(^10\) Extending the studies of Verlohren et al\(^6\) to calculate risk is also clearly needed to translate these important findings into a useful clinical tool to guide the decision-making process and to improve maternal and fetal outcomes for the balance of gestation. Although the present study provides important information to move our ability to diagnose preeclampsia forward, further studies investigating different biomarkers and end points are needed to expand the clinical tool kit and optimize management and treatment of preeclampsia and to minimize the long-term effects on both mothers and children.

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**Disclosures**

None.

**References**


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