Recent years have seen considerable advances in the identification of biomarkers related to the development of preeclampsia.1–4 Elegant translational studies reported by Maynard et al3 and Venkatesha et al4 from the Karumanchi laboratory clearly demonstrated that the antiangiogenic factors soluble Fms-like tyrosine kinase 1 (sFlt-1; a vascular endothelial growth factor antagonist) and soluble endoglin (a transforming growth factor-β antagonist) play important roles in the pathophysiology of preeclampsia. In the following years, additional progress has been made with respect to our understanding of the mechanisms underlying the role of antiangiogenic factors in the pathophysiology of preeclampsia.2–6 Viewed in concert, these studies have clearly established the importance of angiogenic balance in the maintenance of cardiovascular function in normal pregnancy.

Despite marked progress toward these ends, the translation of these findings into clinically useful paradigms has moved at a much slower pace. In lieu of the development of novel treatments for preeclampsia, much current attention has been paid to determining the usefulness of these biomarkers for identification of patients who will go on to develop preeclampsia. Indeed, this is an important endeavor for several reasons, not the least of which is that early identification of preeclamptic patients is a high yield objective for enhancing the management and treatment of this devastating disorder. Moreover, the use of angiogenic markers may be helpful in discriminating patients with preeclampsia from those with other types of gestational hypertension. The study by Ohkuchi et al7 in the present issue of Hypertension represents another step in the quest to develop highly specific procedures to identify the “preeclamptic profile” as early as possible and identify patients who will go on to develop preeclampsia.

Recent studies have taken multiple approaches toward identifying robust methods for determining subsequent onset of preeclampsia. In addition to the more traditional tactics used by earlier studies that evaluated specific markers (sFlt-1, placental growth factor [PIGF], etc) and maternal characteristics (endothelial dysfunction and patient history) associated with preeclampsia,8,9 several recent studies have used cutting edge metabolomic and proteomic techniques to evaluate circulating and urinary biomarkers that are associated with the preeclamptic syndrome.10,11 Although there has been interest and effort focused on biomarkers that might predict the development of preeclampsia, identification of the most specific factor(s) that presage the onset of preeclampsia has remained elusive. To that end, the study by Ohkuchi et al7 brings forth an alternate approach by identifying plasma concentration thresholds of biomarkers such as sFlt-1, PIGF, and soluble endoglin that have come to be synonymous with preeclampsia in recent years.1–4

In contrast to determining odds ratios for the development or presence of preeclampsia in relation to maternal variables, Ohkuchi et al7 set out to determine whether thresholds for plasma concentrations of circulating angiogenic (ie, PIGF) and antiangiogenic (sFlt-1 and soluble endoglin) factors at the onset of preeclampsia could be determined. Indeed, the authors report that these thresholds exist for sFlt-1 and sFlt-1/PIGF ratio, and the threshold for sFlt-1/PIGF ratio measured between 26 to 31 weeks of age may hold the most promise for presaging the development of preeclampsia with onset before 36 weeks of gestation. Moreover, the authors report that consideration of other maternal characteristics such as prepregnancy body mass index, maternal age, uterine artery resistance, and family history of hypertension in their algorithm significantly increased the likelihood ratios of their prediction model. Although these other features have long been recognized as risk factors for preeclampsia, the present data suggest that there may be important relationships among metabolic factors, sFlt-1, and hypertension during pregnancy. Alternatively, one common feature of preeclampsia that was not incorporated into the present analysis was endothelial function. With previous studies demonstrating that endothelial function is markedly altered before the onset of preeclampsia,12 inclusion of noninvasive measures of vascular function13 could provide additional strength to the prediction equations.

In addition to maternal phenotypic characteristics, ethnicity has also been associated with alterations in the incidence of preeclampsia. The study by Ohkuchi et al7 substantiates and adds to previous work in largely white cohorts by showing robust associations between angiogenic balance and later development of preeclampsia in a cohort of nearly all Japanese descent. One noticeable difference between this work and previous studies is the inability to identify pregnancies with small for gestational age and gestational hypertension with the prediction equations.14 This is an interesting observation and suggests that this or a similar method could...
be useful in discriminating preeclamptic patients from those with gestational hypertension, thus allowing more specific treatment and monitoring. Moreover, further work is needed to determine whether this is a cohort-specific observation or broadly applicable to other patient populations.

Similar to previous work, the authors found that transformation of the raw data yielded the strongest results by minimizing the effects of outliers, which are reasonably common in endocrine data. In contrast to previous work that used the multiple of the median to account for large variation, the authors in the present study used SD scores of log-transformed data by using previously established reference values for their population.

A common theme that has emerged among studies seeking to develop predictive algorithms from concentrations of circulating antiangiogenic factors is that the ability to predict the subsequent development of preeclampsia deteriorates as sample collection time points move earlier in gestation. Recent studies have identified the angiotensin type 1 receptor autoantibody as a molecule that may play an important role in the pathological dysregulation of sFlt-1 in preeclampsia.\(^1,5\)

Indeed, it has been proposed recently that angiotensin type 1 receptor autoantibody may be an important molecule linking placental ischemia to angiogenic imbalance and the subsequent development of hypertension during preeclampsia.\(^16\)

Although relationships linking angiotensin type 1 receptor autoantibody to sFlt-1 and preeclampsia have been established, it remains to be determined whether these connections are present at earlier time points in gestation. Nevertheless, inclusion of these or other unresolved factors that may be responsible for the initial rise in sFlt-1 or decrease in PIGF into prediction models could generate advances in the sensitivity and specificity of future diagnostic algorithms.

Although the work of Ohkuchi et al.\(^7\) reveals a significant step toward identification of a combination of markers for the prediction of preeclampsia, there are additional possibilities that remain unexplored. Foremost, is there an unidentified circulating molecule marker that will herald the onset of angiogenic imbalance? Or is it a matter of determining the exact combination of already identified factors? Are there other early gestation screening tools that can be used to identify patients most at risk and in need of further testing?

With the large number of studies advancing our understanding of preeclampsia and other hypertensive disorders of pregnancy, it appears we are moving closer to the time we can call preeclampsia a curable disease rather than “the disease of many theories.”

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Approaching the Threshold for Predicting Preeclampsia: Monitoring Angiogenic Balance During Pregnancy
Christopher T. Banek and Jeffrey S. Gilbert

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