Angiogenic Factors in Diagnosis, Management, and Research in Preeclampsia

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Observational studies in humans and experimental studies in animals provide strong evidence that abnormalities in circulating angiogenic factors play a pathogenic role in preeclampsia.1 Numerous angiogenic factor abnormalities have been noted in preeclampsia, but the factors studied most extensively are the angiogenic protein, soluble fms-like protein kinase 1 (sFlt1), and the proangiogenic protein, placental growth factor (PIGF).2 Placental expression of sFlt1 is strikingly increased in preeclampsia, and this is associated with increased levels of maternal circulating sFlt1 and decreased levels of free bioactive PIGF;3 a finding confirmed by several groups.4 Alterations in these angiogenic factors occur before clinical signs and symptoms and correlate with the severity of the disease and adverse maternal/neonatal outcomes.4–7 In addition, basal sFlt1 levels are higher in women with multiple gestation, trisomy 13, and molar pregnancy conditions associated with higher preeclampsia rates.1 Other synergistic antiangiogenic proteins such as soluble endoglin have also been demonstrated to contribute to preeclampsia.1 It has therefore been hypothesized that excessive production of both angiogenic proteins sFlt1 (inhibiting vascular endothelial growth factor and PIGF signaling) and soluble endoglin (inhibiting transforming growth factor-β signaling) may lead to endothelial dysfunction, and the manifestations of human preeclampsia, and that phenotypic preeclampsia is attributable to an angiogenic state.9,10

During the last decade, several clinical studies were designed to determine potential of angiogenic factors as prediction tests in preeclampsia.5,7,11–16 However, their accuracy fell far short of sensitivities and likelihood ratios required for clinical use,17–19 although prediction was much more reliable for early-onset (<34 weeks) preeclampsia.12,13,16,20–23 The modest results were interpreted by some as evidence that preeclampsia is a heterogeneous disease with no single pathway to explain its spectrum24 and led to a decreased interest in the importance of these measurements. However, important new roles in diagnoses, and prognosis, plus their potential regarding developing novel treatments, and improving classification schema for more meaningful immediate and remote follow-up investigations have recently emerged.14–16 Here, we explore dilemmas that compromise many preeclampsia studies, discuss potentially new exciting uses of these biomarkers to guide clinical care, and postulate that analysis of angiogenic profiles by improving classification will lead to better studies, particularly those designed to clarify the natural history and remote prognosis of the disorder.

Problems With Clinical Studies to Predict Preeclampsia

Substantial resources have been allocated to preeclampsia prediction studies. In most of these studies, however, the diagnostic criteria are imprecise, few using adverse outcomes other than hypertension and proteinuria in their definitions. We have known for decades that many patients diagnosed preeclamptic by clinical criteria alone are misclassified.26 This is particularly relevant when risk factors such as diabetes mellitus, chronic hypertension, and obesity are present.27–29 In a clinical study of women diagnosed with preeclampsia, renal biopsies revealed that diagnosis was incorrect in 15% of the nulliparas and almost half the multiparas, glomerulonephritis being a frequent imposter.26 Such observations are not surprising given that de novo hypertension and proteinuria are non-specific in delineating disease. Perhaps other end points such as adverse outcomes might better define the disorder, but few studies use this approach. However, incorporating outcomes would not eliminate all errors because certain conditions that mimic preeclampsia may lead to adverse outcomes as well. Another conclusion to consider from the 1981 report26 is the lack of reliability of protocols that study multiparas.

Other problems arise when studying high-risk gestations. Chronic hypertensives and the very obese frequently harbor glomerulosclerosis,30,31 the latter also demonstrating glomerulomegaly.31,32 Daily protein excretion slightly increased but still normal in early gestation may become abnormal near term, as proteinuria increases in all gravid women as gestation progresses.33 In such instances, the appearance of frank proteinuria may have nothing to do with any new pathological process but lead to an erroneous diagnosis of superimposed preeclampsia.

Of interest, prediction accuracy seems far better for early than late preeclampsia because late disease often presents with mild features. With advancing gestation, production and circulating levels of sFlt1 increase in all pregnant women,
including those who remain normotensive. These factors combined with the above discussed physiological increments in protein excretion make it more difficult to discriminate preeclampsia from controls using angiogenic factor measurements when the disease presents near term. However, beyond gestational week 37, such testing seems unnecessary as then hypertension, whatever the cause, is considered by most as sufficient reason to deliver.46

One argument against pursuing biomarker research has been the absence of disease-modifying agents to make such pursuits useful. Critics argue that angiogenic profile use differs from those for biomarkers measured to predict aneuploidy or diabetes mellitus where pregnancy can be terminated or blood glucose controlled. It is therefore imperative that studies to predict preeclampsia focus not only on identifying the disease, but also demonstrate clinical usefulness, that is, what does the obstetrician do if disease is predicted early?

Finally, most studies using angiogenic factors were performed with manual ELISA kits, methodology often displaying high interassay coefficient of variation (10%–20%). Automated assays, now available, are much more reliable, (interassay coefficients of variation <5%), report the results rapidly, and produce more robust associations with altered factor levels and preeclampsia.35–37

An Improved Approach to Diagnosis and Prognosis

An emerging role for angiogenic factors is risk stratification that permits determination of the potential morbidity of the disease when women present with diagnosed or suspected preeclampsia.6,38–42 This approach resembles evaluation of suspected cardiac disease, in which use of highly sensitive cardiac troponin has revolutionized management of patients presenting with chest pain.43,44 Rather than focusing on diagnostic certainty, we have suggested that angiogenic biomarkers can predict serious imminent adverse outcomes far better than traditional laboratory and clinical criteria. For instance, our published data, although still preliminary, demonstrate that the plasma sFlt1/PlGF ratio on arrival for triage of suspected preeclampsia predicts those destined to have adverse outcomes within 2 weeks, versus those who do not, especially when women present preterm.6 The ratio alone outperformed currently relied on approaches, including blood pressure, proteinuria, uric acid, alanine aminotransferase, platelet count, and creatinine.6 Of further note is a report that measuring angiogenic proteins also permits accurate risk assessment of severe late preeclampsia, importantly identifying imminent stillbirths (the latter, if confirmed, a major breakthrough in prenatal care).45–46 Measurement of angiogenic proteins in the plasma may also serve as noninvasive surrogate of placental dysfunction.15 Circulating angiogenic factors are also useful to differentiate preeclampsia from diseases such as chronic and gestational hypertension, acute and chronic glomerulonephritis, lupus flares, and gestational thrombocytopenia.47–50

Our data further suggest that clinical tests, signs, and symptoms currently used for triage lead to significant misclassification and overtreatment/treating, substantial resources and costs erroneously allocated to low-risk patients.6 Thus increased specificity, using the sFlt1/PlGF ratio in triage, should by more accurately defining the population at risk, enable appropriate and reduced cost/resource expenditure.51 Most importantly this approach should permit temporization and prevent unnecessary early deliveries.25

Quantitative proteinuria and liver function tests used routinely to assess preeclampsia’s severity are neither sensitive nor specific in predicting maternal and fetal complications.52–54 Similarly, headache and epigastric pain lack specificity.55 Recently, a complex model (PIERS [Preeclampsia Integrated Estimate of Risk]) that uses clinical signs and laboratory tests to predict adverse outcomes has been advocated. However the model, not robust at presentation, is useful only after 48 hours of admission.56 Thus, it is fair to conclude that, as of 2013, protocols designed to determine risk stratification for suspected or diagnosed preeclampsia are far from ideal.57 Such assessments, too often, are directed by expert opinion–based guidelines that perform rather poorly as predictors of imminent adverse maternal or fetal outcomes.58 Needed are better approaches to predict complications and guide care. Thus, rather than relying on signs, symptoms, and nonspecific tests, biomarkers that are reproducible and quickly obtained, pathogenically linked to the disease, demonstrating high specificity to predict complications, and requiring less expertise to interpret, should have significant clinical usefulness.

Accurate risk stratification will help clinicians focus on the appropriate patients whether their disease classification is definitely apparent or not when first evaluated and should also reduce unnecessary interventions on women at low risk for adverse outcomes. In fact, because the latter group did not suffer any adverse outcomes except a few iatrogenic preterm deliveries,25 we anticipate that using angiogenic biomarkers for evaluation of preeclampsia will help avoid unnecessary preterm deliveries. Thus, the compelling and promising data cited this far should be followed by larger prospective studies to confirm whether use of angiogenic factors in clinical decision making can decrease the incidence of preterm delivery and reduce resource utilization without increasing the risk of adverse maternal and neonatal outcomes.

Therapeutic Studies Targeting the Angiogenic Pathway

Studies of angiogenic pathways are helping devise specific therapies for preeclampsia. In a pilot study limited to 3 severe early preeclampsics (24–32 weeks of gestation), Thadhani et al39 depleted sFlt1 30% by apheresis and prolonged pregnancy by 2 to 4 weeks. If confirmed, this approach could lead to targeted therapy for a specific group of patients, those with an abnormal angiogenic profile. More recently, statin therapy that promotes PlGF expression and angiogenesis was shown to prevent or ameliorate disease in an animal model of preeclampsia.60,61 Pilot human trial to test safety and efficacy of statins in severe preeclampsia is ongoing.62 Relaxin increases production of local vascular endothelial growth factor, its therapeutic potential also being investigated.63 Finally, dietary choline supplementation, shown to reduce placental sFlt1 expression, has been suggested as a strategy to improve placental angiogenesis.64 The future for specific therapies that antagonize sFlt1’s action or reduce its production and those that enhance PlGF levels are therefore promising.
Are There Multiple Causes of Phenotypic Preeclampsia?

Some suggest that searching for a single biomarker to predict or diagnose preeclampsia is fruitless because the disease has multiple causes.\(^2\)\(^4\)\(^6\)\(^8\)\(^6\). If preeclampsia phenotypes were heterogeneous, both angiogenic and nonangiogenic forms\(^2\)\(^4\)\(^6\)\(^7\) should manifest multisystemic involvement and similar adverse maternal and perinatal outcomes. Whether this is true or not would require large prospective data, but in our studies patients diagnosed with preeclampsia, without angiogenic imbalance, showed no risk for any major preeclampsia-related adverse outcomes other than what seemed to be unnecessary decisions to deliver prematurely.\(^2\)\(^9\) This forms the basis of our view that preeclampsia, or at least the form of the disorder that should most concern us, is a single and specific entity whose phenotypes relate to angiogenic imbalance and that measurements of these proteins help identify the severe form of the disease, and its management, and identify the best populations for follow-up research. This does not mean that other hypertensive proteinuric diseases (at times designated suspected preeclampsia) should not be watched carefully, but that angiogenic factor measurements will by identifying what we consider “true preeclampsia” not only will help caregivers in management decisions but also improve classification, the latter improving research on causality, prediction, and epidemiological surveys of both immediate and remote outcomes.

Our view of preeclampsia’s specificity, its phenotypes explained by angiogenic imbalance, and the magnitude of which influences the severity of adverse outcomes brings to mind the validity of older morphological studies in which a single pathological entity of preeclampsia seemed apparent. Sheehan and Lynch\(^6\)\(^8\) in a 1973 monograph discuss 67 autopsies of pregnant women, often performed within 3 hours after death, thus avoiding the confusion of postmortem changes. The text focuses on a detailed reanalysis of material from 377 cases, 159 of whom had either preeclampsia or eclampsia (Generally, eclampsia assures the clinical diagnosis of preeclampsia was correct, whereas autopsy, of course, confirms the disease’s severity!). The authors detail the gross and histological pathology of virtually every organ, the observations most unique to preeclampsia/eclampsia, greatest in liver and kidney (the latter further detailed by electron microscopy in numerous biopsy reports). These were the same lesions that investigators produced in rodents with sFlt1 overproduction several decades later and reversed the glomerular endotheliosis by administering recombinant proangiogenic proteins.\(^3\)\(^6\)

We suggest that the triage studies reviewed here\(^6\)\(^7\)\(^6\)\(^8\)\(^4\)\(^0\)\(^4\)\(^2\) delineate, with a high degree of success (certainly superior to current approaches), the “true preeclampsia” that is a disease with organ-specific histopathologies that lead to major adverse outcomes, including hepatic and renal disease, and fetal jeopardy, and the other outcomes classically associated with the severest forms of preeclampsia is associated with markedly elevated sFlt1/PlGF ratio in serum/plasma. We further suggest that many of the patients with sFlt1/PlGF ratios below the cutoff were misdiagnosed clinically,\(^2\)\(^6\) one reason they could be managed expectancy.

In summary, we posit that altered angiogenic factors allow clinicians to discriminate a serious from a more benign form of hypertension and proteinuria in a manner that defines a specific and multisystemic form of preeclampsia with a definitive organ pathology or the true preeclampsia.

Concluding Thoughts

This commentary focused on newer uses of angiogenic factors, most notably for accurately diagnosing and managing preterm preeclampsia. We discussed pitfalls in preeclampsia research that may underlie disputes regarding whether preeclampsia phenotypes have heterogeneous causes, or our view that they represent angiogenic factor imbalance, alone. Thus, we conclude by suggesting that even if multiple factors lead the placenta to produce excess amounts of antiangiogenic factors, these proteins alone account for the disease’s major phenotypes and therefore are extremely specific for both diagnosis and prognosis. Also, measuring these factors whose results can be produced rapidly with automated platforms will be important for triage may prevent unnecessary early deliveries in preeclamptic women with normal angiogenic profile. Based on our data, we also suggest that future screening studies should focus on prediction of angiogenic form of preeclampsia rather than disease diagnosis based on nonspecific clinical criteria. Measurement of angiogenic factors may also aid in designing specific preventive, and therapeutic trials, and for adequate short- and long-term follow-up studies.

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S.K. Karumanchi is a coinventor on multiple patents for preeclampsia markers and reports service as a consultant to Roche, Siemens, Beckman Coulter, and has financial interest in Aggamin LLC. The other authors report no conflicts.

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