Explaining and Predicting Preeclampsia

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Preeclampsia, either alone or superimposed on another disorder, is a major cause of maternal and fetal death and the leading cause of premature delivery worldwide.[1] Underappreciated is the strain that preeclampsia places on the health care resources of all nations. This disease increases the need for neonatal intensive care; in addition, early birth may lead to health problems later in life. Considerable evidence suggests that premature delivery increases the incidence of remote cardiovascular and metabolic health problems, which themselves create enormous economic health burdens.[2,3] Thus, the ability to predict or prevent preeclampsia or the development of therapy that safely prolongs gestation would be a major advance in prenatal care.

Research on the disease was neglected and sporadic until about 20 years ago. Since then, both basic and translational research concerning preeclampsia have increased exponentially and, as a result, we now have a plethora of information supporting several plausible hypotheses about the cause of the disorder, including the roles of oxidative stress, inflammation, and circulatory maladaptation, as well as humoral, mineral, or metabolic abnormalities.[4] Here we focus on the roles of circulating antiangiogenic factors in the pathogenesis of the most dangerous phenotypes of preeclampsia, as well as on the article by Levine et al. in this issue of the *Journal*,[5] which suggests that the measurement of certain antiangiogenic proteins can predict preeclampsia months before its clinical onset.

In 2003, Maynard et al.[6] observed that soluble fms-like tyrosine kinase 1 (sFlt1), a protein that binds (and inactivates) the proangiogenic proteins vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), was among the genes up-regulated in the placentas of women with preeclampsia. These investigators, also involved in research on cancer and basic vascular biology, were familiar with the adverse effects (e.g., hypertension and proteinuria) of certain antiangiogenic compounds used to treat tumors. Thus, they focused on sFlt1, hypothesizing that it entered the maternal circulation, where it bound free (active) VEGF and PlGF, and that excessive circulating sFlt1 would create an imbalance between intravascular antiangiogenic and proangiogenic factors, leading to the preeclampsia syndrome.

Indeed, maternal sFlt1 levels were increased in women with preeclampsia, and levels of free VEGF and PlGF were decreased. Taking clinical observations to the bench, Maynard et al. then showed that serum from women with preeclampsia, as well as sFlt1 itself, inhibited both angiogenesis and renal arteriolar vasodilatation in vitro (these phenomena were reversed with VEGF). The highlight of their studies was the observation that adenoviral vector–mediated overexpression of sFlt1 in pregnant rats resulted in hypertension, albuminuria, and glomerular endotheliosis (the renal lesion characteristic of preeclampsia in humans), which established a plausible explanation for two of the phenotypes of the disease, hypertension and proteinuria, and created a potential animal model. However, preeclampsia is a multisystem disorder, and absent from this model were other serious manifestations of this disease seen in women, including liver involvement, microangiopathic hemolytic anemia, and generalized vascular "leakiness."

Karumanchi and his colleagues have continued to evaluate antiangiogenic proteins produced by the placenta. They showed recently that circulating levels of endoglin, a soluble coreceptor for transforming growth factor β1 (TGF-β1), are elevated in women with preeclampsia; therefore, endoglin may also be pathogenic but by a different mechanism.[7] Soluble endoglin may impair the binding of TGF-β1 to endothelial receptors, decreasing endothelial nitric oxide synthase–activated vasodilatation. They next showed that soluble endoglin decreased angiogenesis in vitro, but its overexpression in pregnant rats had only minimal effects. However, the simultaneous introduction of adenoviruses encoding both sFlt1 and soluble endoglin produced severe hypertension, heavy proteinuria, elevated liver-enzyme levels, and circulating schistocytes, in essence creating a powerful model that simulates most of the protean manifestations of preeclampsia in humans and has obvious implications for the study of mechanisms or therapy of the disease.

The angiogenic (both proangiogenic and antiangiogenic) chronicle in preeclampsia also relates to prediction. Authors of a large systematic review

concluded in 2004 that no single test to predict preeclampsia was sufficiently reliable for clinical use.[8] However, that survey explored neither combinations of markers nor the newly emerging literature about angiogenic proteins. The observations by Levine et al. place the measurement of angiogenic proteins at the forefront of tests that are potentially useful for predicting preeclampsia. These investigators had already suggested the use of angiogenic proteins for prediction when they measured samples stored from a previous prevention trial, noting elevated sFlt1 levels and decreased circulating free VEGF and free and urinary PlGF levels approximately 5 weeks before overt preeclampsia.[9,10] Others reported similar findings.[4,5]

Levine et al. have now combined soluble endoglin levels and sFlt1:PlGF ratios, measured in stored samples from the same study, and show that this combination markedly increases the odds ratio for predicting both early and late preeclampsia, the most striking observation being the prediction of severe outcomes (e.g., early preeclampsia, fetal growth restriction, and perhaps the HELLP syndrome [hemolysis, elevated liver enzymes, and low platelets]) as much as 10 weeks before the onset of clinical manifestations.[5] It is important to note that levels were not elevated in patients who were destined to have gestational hypertension or to remain normotensive but deliver growth-restricted neonates. Thus, the authors now have strong evidence to suggest the usefulness of these proteins in predicting preeclampsia, and they propose proceeding to prospective studies. They further conclude that their data, when combined with the reports of animal models,[6,7] constitute evidence that circulating soluble endoglin and sFlt1, each causing endothelial dysfunction by different mechanisms, act in concert to mediate the maternal syndrome of preeclampsia. What can we make of all this?

First some caution — these data, both retrospective and cross-sectional (like most of the related literature), come from samples stored for about 10 years, and the reader is given little information about sample stability and assay validation. Some might question the arbitrary post hoc breakdown of the analysis according to quartiles. The conclusions on causality seem ambitious, since not only is correlation weak evidence for causality, but also a disease can be subclinical long before the onset of clinical manifestation. Nevertheless, these findings are exciting, since they direct the next critical steps in the research of preeclampsia — prospective observational studies — and research toward prevention and treatment.

The World Health Organization (WHO) has just initiated a large prospective, observational study to evaluate the usefulness of sFlt1, soluble endoglin, and PlGF in the prediction of preeclampsia (Villar J, Widmer M: personal communication). The WHO study will take place in developing nations, where maternal and fetal deaths from preeclampsia are greatest and tertiary care facilities are limited. Validating tests to predict preeclampsia before onset could conceivably reduce maternal and fetal deaths in these nations by guiding the allocation of their limited capacities for tertiary care or the close surveillance by appropriate caregivers. Therapeutic studies involving the animal models described above are under way, and preliminary results suggest that VEGF-121 can reverse the hypertension, proteinuria, and renal lesions in the sFlt1 model.[11]

In conclusion, growing evidence links antiangiogenic factors to preeclampsia phenotypes. There are still unknowns — for example, why is sFlt1 up-regulated in the placentas of women with preeclampsia, and what is the mechanism of proteolytic cleavage leading to an increased generation of soluble endoglin? But we can now confidently state that a disorder once considered a mysterious disease is sufficiently understood to permit mechanistically rational studies of its prediction, diagnosis, prevention, and treatment.

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Risk of Bleeding after Elective Percutaneous Coronary Intervention

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About 2.2 million percutaneous coronary interventions (PCIs) were performed worldwide in 2004 (Mead D: personal communication). Success rates of more than 97%, mortality rates of less than 0.5%, and rates of emergency bypass surgery of less than 0.5% can be anticipated with elective procedures. Major obstacles initially confronting the field — including the inability to reach complex or tortuous lesions, to cross lesions, and to dilate lesions, as well as bifurcation disease, occlusive dissection, and abrupt closure — have largely been overcome. Restenosis has been markedly reduced with the advent of drug-eluting stents.[1]

As the technical obstacles to safe, effective, and sustained coronary dilatation are overcome, attention is focusing on the remaining safety issues. One of the most important risks associated with PCI is the risk of bleeding after the procedure. Major bleeding has been reported in 7% of cases of PCI for unstable angina in the Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial[2] and in 4% of elective cases in which unfractionated heparin was used in the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial.[3] This complication costs in excess of $10,000 per event,[4] adding an average of $400 to the cost of each PCI.[5] In addition to the economic cost, the length of stay of the patient in the hospital is prolonged, the incidence of ancillary diagnostic testing is increased, and reparative surgical procedures are frequently required.

Blood loss most often occurs at the femoral access site. Percutaneous access is achieved by means of fluoroscopic visualization of bony landmarks and is guided by palpation of the femoral pulse. This technique has not changed since the inception of angioplasty. Since arterial access is largely a blind procedure, anatomical variation, obesity, and incorrect needle positioning can all lead to perivascular hematoma, arteriovenous fistula, arterial pseudoaneurysm, rectus-sheath hematoma, or retroperitoneal hemorrhage. In addition to the anatomical factors that enhance the risk of bleeding, systemic anticoagulation further increases the risks of perivascular and systemic bleeding.

As a result of bleeding, rates of blood transfusion as high as 16% have been reported in major trials.[2] Transfusion carries the inherent risk of transmission of blood-borne illnesses and has been shown to increase mortality rates after PCI. Increased mortality rates after transfusion have been reported during procedures performed for acute myocardial infarction,[6] during acute coronary syndrome,[7] and during elective procedures.[8] Thus, transfusion has adverse economic effects, results in prolonged and complicated admissions, and is associated with an increased mortality rate.

In this issue of the *Journal*, Montalescot et al.[9] address the effect of anticoagulation on the risk of bleeding after elective PCI. The authors describe a well-designed, open-label, randomized trial of intravenous unfractionated heparin, as compared with two doses of intravenous enoxaparin (0.5 mg per kilogram and 0.75 mg per kilogram). Elective PCI was performed in a setting of oral aspirin and thienopyridine therapy. About 40% of patients received intravenous glycoprotein IIb/IIIa inhibitors. The population studied was at low risk for ischemic and bleeding complications. With regard