Novel drug development for pregnancy-specific conditions remains a challenge. The reasons for this sentiment are many, but lack of a sound understanding of the pathogenesis for various conditions in pregnancy ranks high among them. Preeclampsia, one of the most common medical complications of pregnancy, has thus far eluded comprehensive biological understanding. In the absence of a sound understanding of its biological underpinnings, our first attempts to alleviate the consequences of this disorder targeted the classic signs and symptoms of preeclampsia (hypertension and proteinuria) with agents such as antihypertensive compounds. Trials of these agents, numbering over a dozen, failed to demonstrate that control of blood pressure itself could reduce the systemic consequences of preeclampsia. Nevertheless, lack of success in these early efforts did not deter further attempts, and primary prevention trials premised on biochemical differences in women with and without preeclampsia represented the next generation of such clinical trials.

Low urine calcium and low calcium intake noted in preeclampsia, in combination with the vasodilatory activity of calcium itself, prompted primary prevention trials with calcium supplementation. Similarly, imbalances between prostacyclin and thromboxane led to large trials examining the use of aspirin to prevent preeclampsia. Primary prevention trials have been informative, and given that the incidence of preeclampsia is ~4% to 7% in nulliparous women, these have necessitated inclusion of thousands of women enrolled over an extended period of time. Although noteworthy in their magnitude and outstanding execution, these trials have, for the most part, been neutral or negative. Primary prevention studies, by their nature, require large numbers of subjects, especially in the setting of outcomes that are relatively infrequent. Furthermore, given the history of these trials in preeclampsia, mustering the appetite to initiate yet another challenge may represent a potentially insurmountable challenge.

Without a sound understanding of the underlying pathophysiology, therapies focused on pathways thought to be involved in the pathogenesis of preeclampsia will remain nonspecific.

The pathogenesis of preeclampsia is a 2-stage process: the first is an asymptomatic stage that involves abnormal placentation (placental stage), and the second is placentation of soluble factors that enter the maternal circulation and lead to widespread endothelial dysfunction (maternal stage). Soluble Fms-like tyrosine kinase 1 (sFlt-1) is a factor thought to be involved in the second stage of this process. sFlt-1 is a natural inhibitor of vascular endothelial growth factor (VEGF) and placental growth factor, both of which are present in maternal circulation during normal pregnancy. Recent data indicate that sFlt-1 levels are markedly elevated in patients diagnosed with preeclampsia; experimental sFlt-1 overexpression leads to hypertension, proteinuria, and glomerular endothelialosis, the hallmarks of human preeclampsia. This concept was advanced in proof-of-concept intervention studies by Li et al; VEGF121 administration in Sprague-Dawley rats with elevated sFlt-1 levels successfully ameliorated all 3 features of the disease, suggesting that this could represent a potential therapy in women with severe preeclampsia.

Proof-of-concept studies have not halted. In fact, the article by Gilbert et al published in this issue of *Hypertension* advances the existing antiangiogenic hypothesis. These investigators pioneered a novel model of preeclampsia in rats that involves induction of uteroplacental ischemia in the second trimester. Uteroplacental ischemia may be the critical initiating step in the pathogenesis of preeclampsia. These investigators demonstrated previously that this model develops several of the features of preeclampsia, including hypertension, fetal growth restriction, and decreased glomerular filtration rate. Of note, however, is the lack of significant proteinuria and glomerular endothelial changes in this model. These characteristic findings in human preeclampsia. This absence may be attributed to the limited exposure (2 to 3 days) of toxic mediators to the maternal vasculature. This contrasts with the model involving induced uterine artery ischemia in nonhuman primates where, in addition to gestational hypertension, there is definite proteinuria and glomerular endothelialosis.

Nevertheless, Gilbert et al reported previously that their model is associated with increased circulating levels of sFlt-1 and, building on previous work by Li et al, they now convincingly demonstrate improvement of hypertension and glomerular filtration rate by VEGF121. The VEGF-treated animals also improved the abnormal vascular reactivity noted in this model. Importantly, this therapeutic strategy appeared not to impose any adverse outcomes on the fetuses; in fact, fetal weights may have improved. Thus, in the setting of several pathways potentially altered in this model of preeclampsia, one specific intervention appeared to have a biologically and physiologically important effect. On the
basis of this study and that from Li et al.4 are we prepared to move forward to human trials with this single target?

With \( \approx 25,000 \) entries about preeclampsia in PubMed, the debate about pathogenesis and potential biomarkers remains in full force. Are we ready to use the markers thus far identified to inform clinical trials? Our understanding of the pathogenesis of preeclampsia has undergone tectonic advances in the past decade.6 Uncovering potential pathogenic mechanisms may satisfy some, but if we never build on these advances to develop therapies, we will merely continue to debate hypotheses without ever making a difference to our patients, both mother and infant. The first criticism in moving any hypothesis forward in preeclampsia will be whether the target of choice is the right target, especially given the number of alterations noted in women with preeclampsia.1,8 Indeed, innumerable alterations in preeclampsia have been described. Lessons from inflammatory arthritis, however, may help guide the preeclampsia community in such a situation.

When Feldmann and Maini9 decided to attack the proinflammatory cytokine storm in rheumatoid arthritis with a single agent, the prevailing view was that cytokines would not make good therapeutic targets. Targeting a single cytokine was believed to be ineffective, whereas blocking many cytokines was deemed impractical. Feldmann and Maini targeted one specific cytokine, tumor necrosis factor-\( \alpha \), because experimental studies suggested that tumor necrosis factor-\( \alpha \) inhibition would inhibit several downstream cytokines thought to be intimately involved in the inflammation and tissue destruction characteristic of rheumatoid arthritis. The cytokine considered most indicative of inflammatory arthritis was interleukin 1. When screening potential agents, their primary readout was inhibition of interleukin 1 production. Although other pathways almost certainly contribute to rheumatoid arthritis, the inhibition of a single pathway was sufficient to significantly alter the signs and symptoms of this devastating condition. Similarly, a multitude of pathways in preeclampsia may exist, but can we use sFlt-1 to guide the development of therapeutic agents in preeclampsia?

Although the debate about the pathogenesis of preeclampsia marches on and, frankly, may never end,10 biomarkers (whether they are mediators or simply biomarkers of the disorder) can be used to aid in our quest for therapies. Short-term proof-of-concept trials with an intermediate outcome (reduced serum levels of sFlt-1 or a rise in placental growth factor levels) may allow therapies to be tested in a shorter period of time. If a therapy appears not to effect potential intermediates such as sFlt-1, its value should be reconsidered. Prostate-specific antigen itself is not likely to be pathogenic for prostate cancer, yet this biomarker does inform intervention trials about efficacy, remission, and prognosis. The same can be said of troponin and high-sensitivity C-reactive protein levels for cardiovascular disease. In the case of sFlt-1, not only do epidemiological studies suggest that it may be a useful biomarker, sFlt-1 (unlike prostate-specific antigen, troponin, and high-sensitivity C-reactive protein) is likely involved in the pathogenesis of the disease. Therefore, another approach may be to develop therapies specifically targeting sFlt-1.

Therapeutic options include administration of small molecules that block sFlt-1 production, recombinant ligands for sFlt-1 (eg, VEGF, as in the case of Gilbert et al11), or neutralizing antibodies against sFlt-1 and/or angiogenic proteins. Alternatively, we could identify means of removing sFlt-1. sFlt-1 levels during normal pregnancy can reach levels \( \approx 50 \)-fold higher than levels seen in nonpregnant women,3 and levels increase even further among patients with preeclampsia.2 The function of sFlt-1 in “normal” pregnancy is not entirely known. sFlt1 inhibits trophoblast migration and differentiation in vitro, and, therefore, it has been hypothesized that this normal production of an antiangiogenic protein is nature’s way of slowing and reversing the placental angiogenesis that is a hallmark of normal mammalian pregnancy. Nevertheless, the goal for any intervention should be to bring levels back to a “normal range” in the event that a lower limit may be necessary for normal pregnancy and delivery to proceed. The study by Gilbert et al11 provides further support for targeting sFlt-1 in women with severe preeclampsia. The natural next steps, of course, would be to choose a safe and effective strategy and test this in nonhuman primates. If successful, the therapy could be moved to women with severe preeclampsia, particularly preterm preeclampsia. Although we continue to debate which pathway is most relevant and, thus, which specific one to target, targeting one pathway with strong biological support can have a marked effect on an otherwise complex disorder.

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R.T. has filed patents on the use of biomarkers for the prediction and diagnosis of preeclampsia through the Massachusetts General Hospital. R.T. is a consultant to Beckman Coulter and Roche Diagnostics in the area of biomarkers for the prediction and diagnosis of preeclampsia.

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Inching Towards A Targeted Therapy for Preeclampsia
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