Placental Growth Factor
A Step Forward in the Search for a Treatment for Preeclampsia

Lucinda M. Hilliard, Kate M. Denton

See related article, pp 1263–1272

Preeclampsia, a pregnancy-related condition characterized by hypertension and proteinuria after 20 weeks of gestation, is an enormous global health problem. It is a major cause of maternal and neonatal morbidity and mortality and is closely linked to fetal growth retardation. Moreover, preeclampsia heralds an elevated risk of cardiovascular disease for both the mother and the baby in later life. Yet, despite the fact preeclampsia has been recognized as a serious health concern for millennia, we remain at a standstill when it comes to prevention and treatment of preeclampsia largely because of uncertainties regarding its pathogenesis. Accordingly, early delivery of the fetus and removal of the placenta remain the only recognized effective cure, which is of course undesirable for the child. Preeclampsia research is, therefore, of paramount importance.

In the current issue of Hypertension, the study by Makris et al takes a vital step toward confirming the potent angiogenic factor, placental growth factor (PIGF), as a suitable therapeutic target to combat preeclampsia. Certainly, extensive research during the past few decades has led to the recognition that maternal endothelial abnormalities underlie many of the clinical manifestations of preeclampsia. It is commonly thought that, as a result of poor vascularization during placental development, the inadequately perfused placenta releases vasoactive factors that subsequently enter the maternal circulation and damage the maternal endothelium. Moreover, recent advances in our understanding of the pathogenesis of preeclampsia have revealed that an imbalance of angiogenic factors induced by the ischemic placenta may drive the pathogenesis of maternal endothelial dysfunction. Findings from both human and experimental animal studies indicate that the antiangiogenic protein, soluble fms-like tyrosine kinase 1 (sFLT-1), plays a key pathogenic role by binding and antagonizing the proangiogenic proteins, PIGF and vascular endothelial growth factor in the circulation, which are critical to the maintenance of the vascular endothelium (Figure). Maternal circulating levels of sFLT-1 are increased in women with preeclampsia, even before the onset of clinical symptoms, and correlate with the severity of the disease. Furthermore, increases in sFLT-1 are paralleled by decreases in circulating levels of PIGF and vascular endothelial growth factor. Although, in the experimental setting, administration of sFLT-1 to pregnant rats has been shown to induce hypertension, proteinuria, and glomerular endotheliosis. Accordingly, there is much interest in the notion that correcting the imbalance in the angiogenic axis may prove fruitful in treating preeclampsia and eliminate the need for premature delivery of the baby.

In particular, PIGF has recently become a large focus of preeclampsia research. It has been demonstrated that a reduction in circulating PIGF, as early as the first trimester, strongly correlates with the development of preeclampsia in women later in pregnancy. Moreover, investigations into the temporal relationship between maternal PIGF levels and placental perfusion in early pregnancy in humans have revealed that increases in PIGF correlate to increased placental perfusion. Such evidence gives credence to the theory that targeting this effector protein could correct the angiogenic imbalance in the setting of preeclampsia.

To investigate the potential therapeutic benefit of PIGF administration to restore angiogenic balance in the setting of preeclampsia, Makris et al utilized a nonhuman primate (baboon) model of uteroplacental ischemia, which demonstrates phenotypes analogous to that observed in preeclamptic women, including hypertension, proteinuria, and endotheliosis, as well as increased circulating sFLT-1 levels. The first key finding of their study was that induction of uteroplacental ischemia produced a decrease in circulating PIGF levels; thus providing direct evidence for a causal relationship between reduced placental perfusion and modulation of angiogenic balance in the clinical manifestation of disease. However, it was noted that PIGF levels rose back to baseline levels after 10 days of uteroplacental ischemia. The investigators attribute this to partial reperfusion of the ischemic placenta based on the observations of others that increases in PIGF correlate to increased placental perfusion.

Remarkably, Makris et al also demonstrated that administration of recombinant human PIGF reduced arterial pressure and proteinuria and improved endotheliosis (as observed on renal biopsy) in their baboon model of preeclampsia (Figure). This provides strong evidence that targeting the angiogenic imbalance in preeclampsia by increasing PIGF levels can improve endothelial function. The dose of recombinant human PIGF administered was reportedly at the upper limit of what is considered the normal circulating PIGF range in uncomplicated pregnancy.
Notably, these findings extend the recent observations of several other research groups whom have investigated the outcomes of PIGF therapy on the clinical manifestations of preeclampsia in nonprimate experimental models. This includes a recently published in *Hypertension*, in which Spradley et al. demonstrated the ability of recombinant human PIGF therapy to abolish placental ischemia–induced hypertension and improve renal function in rats.

Of course, the strength of the investigation by Makris et al. is the use of a nonhuman primate model to interrogate the therapeutic effects of PIGF therapy on the clinical manifestations of preeclampsia. Animal studies are pivotal to the successful translation of scientific research from bench to bedside. This is particularly true in the case of pregnancy because there is a natural reticence to trial new therapies in human pregnancy. As such, the selection of an animal model relevant to the human condition of interest is of utmost importance. When it comes to pregnancy and preeclampsia research, studies in nonhuman primates represent an important translational link. As pointed out by Makris et al., although dissimilarities exist between human and nonhuman primates when it comes to the establishment of pregnancy including placenta pathology, mechanistic studies investigating the pathogenesis of preeclampsia in nonhuman primates offer advantages over other species (mice, rats, and sheep) that are commonly utilized in this field. For instance, the placenta is hemochorial and the implantation is essentially similar to that observed in humans. Furthermore, each pregnancy in a nonhuman primate typically involves a single fetus, and there is a similarity in the pattern of uterine blood flow between humans and nonhuman primates.

So, where do we go from here? Much work remains to be done. Although the findings of Makris et al. provide new insights into the therapeutic potential of targeting PIGF to treat preeclampsia, at the same time they raise new questions that will require interrogation in future studies before such treatments could be introduced to the clinic. In particular, although this study investigated the effects of recombinant human PIGF on the mother, a limitation of the work was that fetal wellbeing was not assessed as an end point. However, any treatment given to the mother may affect the fetus. Another limitation of the model was this it was not possible to examine the impact of the treatment on the placenta because the mothers ingested this at the time of birth. It was noted by the investigators that all animals delivered at term and seemed normal on physical examination. However, a more thorough investigation is certainly required. It would also be of interest to follow-up the long-term outcomes of PIGF treatment on renal and cardiovascular health in the mum, as well as the offspring into adulthood, given that preeclampsia heralds an elevated risk of cardiovascular disease for both the mother and the baby in later life.

In summary, the findings of Makris et al. add new insight to the growing body of evidence that targeting PIGF in the setting of preeclampsia may offer significant therapeutic benefit, at least in patients in which aberrations exist in the angiogenic axis. We now eagerly await the outcomes of further investigations in this field, with the hope that these new discoveries will lead to the implementation of therapies that can be used to safely treat preeclampsia in the clinic and minimize the need for preterm delivery.

**Disclosures**

None.

**References**

2. Heida KY, Franx A, van Rijn BB, Eijkemans MJ, Boer JM, Verschuren MW, Oudijk MA, Bots ML, van der Schouw YT. Earlier Age of Onset of
Chronic Hypertension and Type 2 Diabetes Mellitus After a Hypertensive Disorder of Pregnancy or Gestational Diabetes Mellitus. Hypertension. 2015;66:1116–1122. doi: 10.1161/HYPERTENSIONAHA.115.06005.


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