More than 70 years ago, Ernest W. Page published what is perhaps one of the most insightful articles regarding the pathophysiology of pre-eclampsia. In this article, using a combination of induction and deduction, Dr Page advanced key concepts consistent with the notions of ‘failure of physiologic transformation of the spiral arteries’, ‘the fetal–maternal conflict’ and the need for a ‘placental pressor substance’ as part of the mechanisms of disease of pre-eclampsia. Since the publication of this seminal paper, there has been an accumulation of evidence to support the validity of these postulates.

Using teleologic reasoning, Dr Page wrote that, ‘if the placenta should be unable to obtain a sufficient maternal circulation for its demands, it might be capable of increasing this supply by raising the systemic blood pressure. Since there are no nervous connections by which the placenta could accomplish this, such a postulate necessitates the concept of a placental pressor substance.’ This revolutionary concept, described so eloquently in 1939, has proven to be correct, as demonstrated by a growing body of evidence indicating that anti-angiogenic factors of placental origin (including the soluble form of vascular endothelial growth factor (VEGF) receptor 1 (sFlt-1), soluble endoglin (s-Eng)2, 3 and others) play a central role in the pathophysiology of pre-eclampsia. Indeed, clinical and experimental evidence indicates that an imbalance between angiogenic factors (such as VEGFs and placental growth factor (PIGF)) and anti-angiogenic factors are associated with the maternal manifestations of pre-eclampsia, eclampsia and HELLP syndrome.

Changes in the maternal plasma/serum concentrations of angiogenic-related factors occur before presentation of pre-eclampsia: elevated maternal serum/plasma concentrations of anti-angiogenic factors have been described in the first and second trimesters in patients who then developed pre-eclampsia in the index pregnancy. Moreover, the measurement of angiogenic factors in combination with uterine artery Doppler velocimetry and other parameters has been reported to play an important role in the identification of patients at risk of developing pre-eclampsia. For example, the combination of a low maternal plasma concentration of PIGF and abnormal uterine artery Doppler velocimetry in the second trimester confers a very high risk for the development of early-onset pre-eclampsia (<34 weeks) (odds ratio (OR), 43.8 (95% CI, 18.48–103.89))24. In this issue of the Journal, Wortelboer et al. report a negative correlation between the maternal serum concentration of PIGF, among other biochemical markers, and impedance of blood flow in the uterine arteries during the first trimester of pregnancy.

This is consistent with a report indicating that a combination of low maternal serum concentrations of PIGF, high uterine artery pulsatility index and other parameters in the first trimester identified 93.1% of patients who developed pre-eclampsia requiring delivery before 34 weeks.

Uteroplacental ischemia may result in maternal hypertension and increased circulating concentrations of anti-angiogenic factors (sFlt-1 and s-Eng, among others). Evidence supporting this view includes: 1) reduced uterine perfusion in pregnant non-human primates and rats is associated with hypertension and increased placental expression of anti-angiogenic factors; 2) cytotrophoblast cultured under hypoxic conditions upregulates mRNA expression and production of sFlt-1 in the supernatant; 3) increased expression of human placental sFlt-1 is mediated by hypoxia inducible factor-1 (HIF-1); 4) among patients with pre-eclampsia, the higher the impedance to blood flow in the uterine arteries (a surrogate maker of chronic uteroplacental ischemia), the higher the maternal plasma concentration of anti-angiogenic factors; and 5) histological lesions suggestive of chronic trophoblast ischemia have been associated with hypertension, proteinuria and angiogetic imbalances. These lesions include decidual arteriolopathy, central villi infarction and hypermaturity of villi in ‘classic pre-eclampsia’, severe villous edema in ‘mirror syndrome’ and ‘avascular’ villi in mole and partial mole.

Dr Page wrote that the placenta ‘appears to be a ruthless parasitic organ existing solely for the maintenance and protection of the fetus, perhaps too often to the disregard of the maternal organism’. According to the conceptual framework of the ‘fetomaternal conflict’, fetal growth and development can sometimes happen at the expense of maternal wellbeing. Using this framework, it is difficult to believe that reproductive evolution allowed chronic trophoblast ischemia to lead to angiogenic imbalances which may endanger the survival of both the mother and the fetus. We speculate that, in pre-eclamptic patients, chronic uteroplacental ischemia limits the amount of substrates available for fetal growth. In turn, the fetus may signal the placental release of angiogenic factors in order to increase the maternal blood pressure in an attempt to compensate for the limited blood flow to placental and fetal tissues. The magnitude of angiogenic imbalances, gene–environment interaction and other factors may determine whether a patient with chronic trophoblast ischemia presents with pre-eclampsia, fetal growth restriction or both, or any of the other intermediate phenotypes. Chronic trophoblast ischemia appears to be less relevant in the pathophysiology of pre-eclampsia.
late-onset pre-eclampsia (> 34 weeks). Indeed, the latter is frequently associated with fetuses that are adequate or large-for-gestational age. Thus, we propose that, in late-onset pre-eclampsia, an increased fetal demand for substrates that surpasses the placental ability to sustain fetal growth may induce fetal signaling for placental overproduction of anti-angiogenic factors and subsequent ‘compensatory’ maternal hypertension. This is in keeping with Dr Page’s proposal that a ‘relative ischemia of gravid uterus may, of course, result from an increased demand for blood supply, an actual decrease of maternal blood supply, or a failure of the developing uterine circulation to keep pace with the increasing demand.’ The latter of these three is consistent with observations that high impedance to blood flow in both uterine arteries is associated with failure of physiologic transformation of the spiral arteries in placental bed biopsies from patients delivering small-for-gestational age (SGA) neonates and those with pre-eclampsia. Thus, it is possible that abnormal trophoblast invasion of the spiral arteries may lead to chronic trophoblast ischemia, which in turn may induce angiogenic imbalances during pregnancy. The magnitude of the imbalances, genetic predisposition or other factors may determine whether a patient with chronic trophoblast ischemia delivers an SGA neonate, develops pre-eclampsia or both, or develops one of the intermediate phenotypes (such as gestational hypertension, gestational proteinuria or pre-eclampsia associated with mirror syndrome and molar pregnancy).

In his original paper, Dr Page put emphasis on the role of the placenta in the pathophysiology of pre-eclampsia. However, there is growing evidence that the fetus may play a central role in the mechanisms of disease in pre-eclampsia; after all, the placenta is considered to be of fetal origin. A striking example of the role of the fetus is the remission of pre-eclampsia following the death of the growth-restricted fetus in discordant twins or following correction of fetal hydrops in parvovirus infection. Moreover, increased impedance to blood flow in the umbilical artery (a surrogate marker of impaired fetal perfusion of the placenta) is associated with elevated maternal plasma concentration of anti-angiogenic factors (sFlt-1) and reduced maternal plasma concentrations of angiogenic factors (PlGF)40. Recent studies suggest that, in the context of chronic uteroplacental ischemia, the fetus may use the adenosine system and/or other signaling mechanisms to increase the maternal blood pressure in an attempt to increase uteroplacental blood flow. An elegant in-vitro study provides compelling evidence in support of this view: the authors determined the adenosine concentrations in fetal venous perfusates using isolated dual-perfused human placental cotyledons, with the fetal compartment and the intervillous space being perfused under controlled conditions. They reported that cessation of ‘maternal’ perfusion was associated with a two- to six-fold increase in fetal venous perfusate concentrations of adenosine and a concomitant increase in fetoplacental perfusion pressure. Furthermore, perfusate pressure and the concentration of adenosine in the fetal compartment returned to baseline levels on reperfusion of the ‘maternal’ circuit. A more recent study using placental explants from rats found that exogenous adenosine administration significantly increased the concentration of sFlt-1 in normoxic conditions, and that the addition of dipyridamole (an adenosine transporter antagonist which increases extracellular adenosine concentration) to cell cultures led to a 1.6-fold increase in the concentration of sFlt-1. Moreover, although hypoxia was associated with a two-fold increase in the concentrations of sFlt-1 in the supernatant, blockade of adenosine signaling (using a non-specific adenosine receptor antagonist) blunted the hypoxic effect on the concentrations of sFlt-1 and VEGF to a level similar to that in normoxic conditions. These results indicate that adenosine signaling is important for placental overexpression and release of sFlt-1 under both normoxic and hypoxic conditions. This is consistent with another recent study comparing the fetal plasma concentrations of adenosine from normal pregnancies with those from pre-eclamptic ones, which found that adenosine levels were significantly higher in patients with pre-eclampsia than in those with normal pregnancies. Moreover, this study sub-classified pre-eclamptic patients into those with and those without abnormal uterine artery Doppler velocimetry (UADV) and found that fetal plasma concentrations of adenosine in patients with pre-eclampsia and abnormal UADV, but not in those with pre-eclampsia and normal UADV, were significantly higher than in normal pregnancies. The authors concluded that patients with pre-eclampsia and with sonographic evidence of chronic uteroplacental ischemia have high fetal plasma concentrations of adenosine, and proposed that in patients with chronic uteroplacental ischemia the fetus may use the adenosine system and/or other signaling mechanisms to increase the maternal blood pressure in an attempt to increase uteroplacental blood flow.

Visionaries such as Dr Page advanced our understanding of complex pregnancy complications such as pre-eclampsia and the role of the placenta in its mechanisms of disease. However, the role of the fetus in the maternal manifestations of pregnancy complications deserves more attention. Recent evidence suggests that the fetus may play a central role in the clinical manifestations of pre-eclampsia which might have fetal survival value in the context of uteroplacental ischemia. It is possible that the combination of ultrasound and biochemical markers in the first and second trimesters of pregnancy may contribute to the identification of patients at high risk for early-onset and/or severe pre-eclampsia, who may benefit from interventions such as the one described by Trapani Jr et al. in this issue of the Journal. These authors reported that transdermal administration of nitroglycerin in patients with severe pre-eclampsia is associated with a significant reduction in the impedance to blood flow in the uterine and umbilical arteries as well as a significant reduction in the maternal mean arterial blood pressure. Future randomized controlled trials would determine whether this or other similar interventions could improve maternal and neonatal outcomes.
REFERENCES


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