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Opinion

Pre-eclampsia: a maternal manifestation of a fetal adaptive response?

More than 70 years ago, Ernest W. Page published what is perhaps one of the most insightful articles regarding the pathophysiology of pre-eclampsia[1]. 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 (PlGF)) and anti-angiogenic factors are associated with the maternal manifestations of pre-eclampsia, eclampsia and HELLP syndrome[4].

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[2,5–23]. 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[18,24,25]. For example, the combination of a low maternal plasma concentration of PlGF 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.*[26] report a negative correlation between the maternal serum concentration of PlGF, 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 PlGF, 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[18].

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[4]: 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 angiogenic 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 anti-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

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[4]. 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[27–30] and those with pre-eclampsia[27–29,31]. Thus, it is possible that abnormal trophoblast invasion of the spiral arteries[32,33] may lead to chronic trophoblast ischemia, which in turn may induce angiogenic imbalances during pregnancy. The magnitude of the imbalances, genetic predisposition[34] 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)[4].

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[35–37] or following correction of fetal hydrops in parvovirus infection[38]. 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)[39] 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[41]: 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[42] 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[43]. 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[44]. 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.

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REFERENCES

1. Page EW. The relation between hydatid moles, relative ischemia of the gravid uterus, and the placental origin of eclampsia. *Am J Obstet Gynecol* 1939; **37**: 291–293.
2. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, Sibai BM, Epstein FH, Romero R, Thadhani R, Karumanchi SA; CPEP Study Group. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med* 2006; **355**: 992–1005.
3. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, Libermann TA, Morgan JP, Sellke FW, Stillman IE, Epstein FH, Sukhatme VP, Karumanchi SA. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest* 2003; **111**: 649–658.
4. Espinoza J, Uckele JE, Starr RA, Seubert DE, Espinoza AF, Berry SM. Angiogenic imbalances: the obstetric perspective. *Am J Obstet Gynecol* 2010; **203**: 17.e1–8.
5. Tjoa ML, van Vugt JM, Mulders MA, Schutgens RB, Oudejans CB, van Wijk IJ. Plasma placenta growth factor levels in midtrimester pregnancies. *Obstet Gynecol* 2001; **98**: 600–607.
6. Tidwell SC, Ho HN, Chiu WH, Torry RJ, Torry DS. Low maternal serum levels of placenta growth factor as an antecedent of clinical preeclampsia. *Am J Obstet Gynecol* 2001; **184**: 1267–1272.
7. Chappell LC, Seed PT, Briley A, Kelly FJ, Hunt BJ, Charnock-Jones DS, Mallet AI, Poston. A longitudinal study of biochemical variables in women at risk of preeclampsia. *Am J Obstet Gynecol* 2002; **187**: 127–136.
8. Taylor RN, Grimwood J, Taylor RS, McMaster MT, Fisher SJ, North RA. Longitudinal serum concentrations of placental growth factor: evidence for abnormal placental angiogenesis in pathologic pregnancies. *Am J Obstet Gynecol* 2003; **188**: 177–182.
9. Polliotti BM, Fry AG, Saller DN, Mooney RA, Cox C, Miller RK. Second-trimester maternal serum placental growth factor and vascular endothelial growth factor for predicting severe, early-onset preeclampsia. *Obstet Gynecol* 2003; **101**: 1266–1274.
10. Krauss T, Pauer HU, Augustin HG. Prospective analysis of placenta growth factor (PlGF) concentrations in the plasma of women with normal pregnancy and pregnancies complicated by preeclampsia. *Hypertens Pregnancy* 2004; **23**: 101–111.
11. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, Schisterman EF, Thadhani R, Sachs BP, Epstein FH, Sibai BM, Sukhatme VP, Karumanchi SA. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004; **350**: 672–683.
12. Parra M, Rodrigo R, Barja P, Bosco C, Fernandez V, Munoz H, Soto-Chacón E. Screening test for preeclampsia through assessment of uteroplacental blood flow and biochemical markers of oxidative stress and endothelial dysfunction. *Am J Obstet Gynecol* 2005; **193**: 1486–1491.
13. Chaiworapongsa T, Romero R, Kim YM, Kim GJ, Kim MR, Espinoza J, Bujold E, Gonçalves L, Gomez R, Edwin S, Mazor M. Plasma soluble vascular endothelial growth factor receptor-1 concentration is elevated prior to the clinical diagnosis of pre-eclampsia. *J Matern Fetal Neonatal Med* 2005; **17**: 3–18.
14. Moore Simas TA, Crawford SL, Solitro MJ, Frost SC, Meyer BA, Maynard SE. Angiogenic factors for the prediction of preeclampsia in high-risk women. *Am J Obstet Gynecol* 2007; **197**: 244.e1–8.
15. Ohkuchi A, Hirashima C, Matsubara S, Suzuki H, Takahashi K, Arai F, Watanabe T, Kario K, Suzuki M. Alterations in placental growth factor levels before and after the onset of preeclampsia are more pronounced in women with early onset severe preeclampsia. *Hypertens Res* 2007; **30**: 151–159.
16. Poon LC, Zaragoza E, Akolekar R, Anagnostopoulos E, Nicolaides KH. Maternal serum placental growth factor (PlGF) in small for gestational age pregnancy at 11(+0) to 13(+6) weeks of gestation. *Prenat Diagn* 2008; **28**: 1110–1115.
17. Erez O, Romero R, Espinoza J, Fu W, Todem D, Kusanovic JP, Gotsch F, Edwin S, Nien JK, Chaiworapongsa T, Mittal P, Mazaki-Tovi S, Than NG, Gomez R, Hassan SS. The change in concentrations of angiogenic and anti-angiogenic factors in maternal plasma between the first and second trimesters in risk assessment for the subsequent development of preeclampsia and small-for-gestational age. *J Matern Fetal Neonatal Med* 2008; **21**: 279–287.
18. Poon LC, Kametas NA, Maiz N, Akolekar R, Nicolaides KH. First-trimester prediction of hypertensive disorders in pregnancy. *Hypertension* 2009; **53**: 812–818.
19. Thadhani R, Mutter WP, Wolf M, Levine RJ, Taylor RN, Sukhatme VP, Ecker J, Karumanchi SA. First trimester placental growth factor and soluble fms-like tyrosine kinase 1 and risk for preeclampsia. *J Clin Endocrinol Metab* 2004; **89**: 770–775.
20. Rana S, Karumanchi SA, Levine RJ, Venkatesha S, Rauh-Hain JA, Tamez H, Thadhani R. Sequential changes in antiangiogenic factors in early pregnancy and risk of developing preeclampsia. *Hypertension* 2007; **50**: 137–142.
21. Baumann MU, Bersinger NA, Mohaupt MG, Raio L, Gerber S, Surbek DV. First-trimester serum levels of soluble endoglin and soluble fms-like tyrosine kinase-1 as first-trimester markers for late-onset preeclampsia. *Am J Obstet Gynecol* 2008; **199**: 266.e1–6.
22. Romero R, Nien JK, Espinoza J, Todem D, Fu W, Chung H, Kusanovic JP, Gotsch F, Erez O, Mazaki-Tovi S, Gomez R, Edwin S, Chaiworapongsa T, Levine RJ, Karumanchi SA. A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate. *J Matern Fetal Neonatal Med* 2008; **21**: 9–23.
23. Schmidt M, Dogan C, Birdir C, Kuhn U, Gellhaus A, Kimmig R, Kasimir-Bauer S. Placental growth factor: a predictive marker for preeclampsia? *Gynakol Geburtshilfliche Rundsch* 2009; **49**: 94–99.
24. Espinoza J, Romero R, Nien JK, Gomez R, Kusanovic JP, Goncalves LF, Medina L, Edwin S, Hassan S, Carstens M, Gonzalez R. Identification of patients at risk for early onset and/or severe preeclampsia with the use of uterine artery Doppler velocimetry and placental growth factor. *Am J Obstet Gynecol* 2007; **196**: 326.e1–13.
25. Stepan H, Geipel A, Schwarz F, Kramer T, Wessel N, Faber R. Circulatory soluble endoglin and its predictive value for preeclampsia in second-trimester pregnancies with abnormal uterine perfusion. *Am J Obstet Gynecol* 2008; **198**: 175.e1–6.
26. Wortelboer EJ, Koster MPH, Kuc S, Eijkemans MJC, Bilardo CM, Schielen PCJI, Visser GHA. Longitudinal trends in fetoplacental biochemical markers, uterine artery pulsatility index and maternal blood pressure during the first trimester of pregnancy. *Ultrasound Obstet Gynecol* 2011; **38**: 383–388.
27. Lin S, Shimizu I, Suehara N, Nakayama M, Aono T. Uterine artery Doppler velocimetry in relation to trophoblast migration into the myometrium of the placental bed. *Obstet Gynecol* 1995; **85**: 760–765.
28. Olofsson P, Laurini RN, Marsal K. A high uterine artery pulsatility index reflects a defective development of placental

bed spiral arteries in pregnancies complicated by hypertension and fetal growth retardation. *Eur J Obstet Gynecol Reprod Biol* 1993; **49**: 161–168.
29. Aardema MW, Oosterhof H, Timmer A, van Rooy I, Aarnoudse JG. Uterine artery Doppler flow and uteroplacental vascular pathology in normal pregnancies and pregnancies complicated by pre-eclampsia and small for gestational age fetuses. *Placenta* 2001; **22**: 405–411.
30. Madazli R, Somunkiran A, Calay Z, Ilvan S, Aksu MF. Histomorphology of the placenta and the placental bed of growth restricted foetuses and correlation with the Doppler velocimetries of the uterine and umbilical arteries. *Placenta* 2003; **24**: 510–516.
31. Voigt HJ, Becker V. Doppler flow measurements and histomorphology of the placental bed in uteroplacental insufficiency. *J Perinat Med* 1992; **20**: 139–147.
32. Espinoza J, Romero R, Mee KY, Kusanovic JP, Hassan S, Erez O, Gotsch F, Than NG, Papp Z, Jai Kim C. Normal and abnormal transformation of the spiral arteries during pregnancy. *J Perinat Med* 2006; **34**: 447–458.
33. Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. *Placenta* 2006; **27**: 939–958.
34. Sandrim VC, Palei AC, Cavalli RC, Araujo FM, Ramos ES, Duarte G, Tanus-Santos JE. Vascular endothelial growth factor genotypes and haplotypes are associated with pre-eclampsia but not with gestational hypertension. *Mol Hum Reprod* 2009; **15**: 115–120.
35. Audibert F, Salomon LJ, Castaigne-Meary V, Alves K, Frydman R. Selective termination of a twin pregnancy as a treatment of severe pre-eclampsia. *BJOG* 2003; **110**: 68–69.
36. Hagay ZJ, Levy R, Zalel Y, Weissman A. Single fetal demise in twin gestation resulting in the resolution of severe pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol* 1994; **56**: 137–138.
37. Sarhanis P, Pugh DH. Resolution of pre-eclampsia following intrauterine death of one twin. *Br J Obstet Gynaecol* 1992; **99**: 159–160.
38. Duthie SJ, Walkinshaw SA. Parvovirus associated fetal hydrops: reversal of pregnancy induced proteinuric hypertension by in utero fetal transfusion. *Br J Obstet Gynaecol* 1995; **102**: 1011–1013.
39. Chaiworapongsa T, Espinoza J, Gotsch F, Kim YM, Kim GJ, Goncalves LF, Edwin S, Kusanovic JP, Erez O, Than NG, Hassan SS, Romero R. The maternal plasma soluble vascular endothelial growth factor receptor-1 concentration is elevated in SGA and the magnitude of the increase relates to Doppler abnormalities in the maternal and fetal circulation. *J Matern Fetal Neonatal Med* 2008; **21**: 25–40.
40. Schlembach D, Wallner W, Sengenberger R, Stiegler E, Mortl M, Beckmann MW, Lang U. Angiogenic growth factor levels in maternal and fetal blood: correlation with Doppler ultrasound parameters in pregnancies complicated by pre-eclampsia and intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2007; **29**: 407–413.
41. Slegel P, Kitagawa H, Maguire MH. Determination of adenosine in fetal perfusates of human placental cotyledons using fluorescence derivatization and reversed-phase high-performance liquid chromatography. *Anal Biochem* 1988; **171**: 124–134.
42. George EM, Cockrell K, Adair TH, Granger JP. Regulation of sFlt-1 and VEGF secretion by adenosine under hypoxic conditions in rat placental villous explants. *Am J Physiol Regul Integr Comp Physiol* 2010; **299**: R1629–R1633.
43. Espinoza J, Espinoza AF, Power GG. High fetal plasma adenosine: A role for the fetus in preeclampsia? *Am J Obstet Gynecol* 2011; DOI: 10.1016/j.ajog.2011.06.034.
44. Trapani Jr A, Gonçalves LF, Pires MM. Transdermal nitroglycerin in patients with severe pre-eclampsia with placental insufficiency: effect on uterine, umbilical and fetal middle cerebral artery resistance indices. *Ultrasound Obstet Gynecol* 2011; **38**: 389–394.

