Advances in the pathophysiology of pre-eclampsia and related podocyte injury

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Pre-eclampsia is a pregnancy-specific hypertensive disorder that may lead to serious maternal and fetal complications. It is a multisystem disease that is commonly, but not always, accompanied by proteinuria. Its cause(s) remain unknown, and delivery remains the only definitive treatment. It is increasingly recognized that many pathophysiological processes contribute to this syndrome, with different signaling pathways converging at the point of systemic endothelial dysfunction, hypertension, and proteinuria. Different animal models of pre-eclampsia have proven utility for specific aspects of pre-eclampsia research, and offer insights into pathophysiology and treatment possibilities. Therapeutic interventions that specifically target these pathways may optimize pre-eclampsia management and may improve fetal and maternal outcomes. In addition, recent findings regarding placental, endothelial, and podocyte pathophysiology in pre-eclampsia provide unique and exciting possibilities for improved diagnostic accuracy. Emerging evidence suggests that testing for urinary podocytes or their markers may facilitate the prediction and diagnosis of pre-eclampsia. In this review, we explore recent research regarding placental, endothelial, and podocyte pathophysiology. We further discuss new signaling and genetic pathways that may contribute to pre-eclampsia pathophysiology, emerging screening and diagnostic strategies, and potential targeted interventions.

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Pre-eclampsia, a hypertensive disorder unique to pregnancy, remains a leading cause of fetal and maternal morbidity and mortality worldwide.[1] Unlike other hypertensive pregnancy disorders, pre-eclampsia is a systemic disease with multi-organ involvement, which is commonly, but not always, accompanied by either sudden onset or worsening of preexisting proteinuria. It is estimated that 5% of otherwise uncomplicated pregnancies will be affected by pre-eclampsia, and that as many as 25% of pregnant women with preexisting hypertension will develop superimposed pre-eclampsia. Pre-eclampsia commonly is viewed as one of the hypertensive pregnancy disorders, which cover a spectrum of clinical presentations from chronic hypertension (i.e., hypertension occurring prior to 20 weeks of gestation) and gestational hypertension (hypertension occurring after 20 weeks of gestation) to more severe forms, including pre-eclampsia, eclampsia (its convulsive form), and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). The rationale to treat these disorders as a continuum comes from clinical evidence demonstrating that either chronic or gestational hypertension may progress to pre-eclampsia (commonly evidenced by new-onset or worsening of proteinuria), whereas pre-eclampsia may progress to more severe forms, such as eclampsia or HELLP syndrome. An alternative approach views pre-eclampsia as a separate disease entity. Either way, it is recognized that pre-eclampsia is a heterogeneous disease. Different clinical subtypes may reflect distinct underlying pathological mechanisms.[2] For example, it is common in clinical practice to subcategorize pre-eclampsia as early versus late (before and after 34 weeks of gestation, respectively),[3] and mild versus severe,[4] based on the absence/ presence of severe hypertension, defined as a blood pressure $\geqslant$160/110 mm Hg, neurological/renal/cardiac impairment, or signs of HELLP. Recent evidence suggests that women with early severe pre-eclampsia, who are at a particularly high risk for adverse pregnancy outcomes, may have a more pronounced antiangiogenic imbalance than those with late pre-eclampsia and more favorable outcomes.[5] Active research in this field may delineate the mechanisms of the subtypes of pre-eclampsia, commonly referred to as placental versus maternal pre-eclampsia, based on their etiologies and origins.[6,7]

Renal pathology in pre-eclampsia in the form of endotheliosis has long been recognized, and the kidney manifestations of pre-eclampsia form the basis for a 'nephrocentric' view in the research and clinical arenas.[8] In contrast, obstetric literature questions the importance of kidney injury (as demonstrated by proteinuria) in the diagnosis of pre-eclampsia, suggesting that a subclass of 'nonproteinuric pre-eclampsia' should be added,[9] or that detection of proteinuria should not be mandatory for a pre-eclampsia diagnosis.[10] Most recently, the Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy has eliminated the dependence of the diagnosis of pre-eclampsia on proteinuria.[11] In addition, massive proteinuria (greater than 5 g/24 hours) is no longer considered as a sign of disease severity. However, similar to other renal diseases, proteinuria in pre-eclampsia may represent a late marker of renal injury. Our recent data suggest that podocyturia, i.e., the urinary loss of viable glomerular epithelial cells (podocytes), may occur before the clinical features of pre-eclampsia, potentially representing an earlier marker of renal injury than proteinuria.[12] These findings set the stage for future studies of podocyturia in women who meet all of the clinical criteria for the diagnosis of pre-eclampsia, except proteinuria.

The main objective of this review is to discuss emerging theories regarding pre-eclampsia pathophysiology, focusing on the different causal pathways that translate into different subtypes (clinical phenotypes) of pre-eclampsia; highlight animal models that may advance the understanding of the roles of specific mechanisms in pre-eclampsia; examine emerging evidence indicating that different signaling pathways may converge at the point of podocyte damage, which may be at the core of renal injury and ultimately lead to proteinuria; and discuss their possible implications for pre-eclampsia diagnosis and management.

ENDOTHELIAL DYSFUNCTION IN PRE-ECLAMPSIA

The prediction and treatment of pre-eclampsia is complicated by the fact that many pathophysiological processes may contribute to this syndrome. These causal pathways are believed to converge at the point of systemic endothelial dysfunction, which leads to hypertension and proteinuria

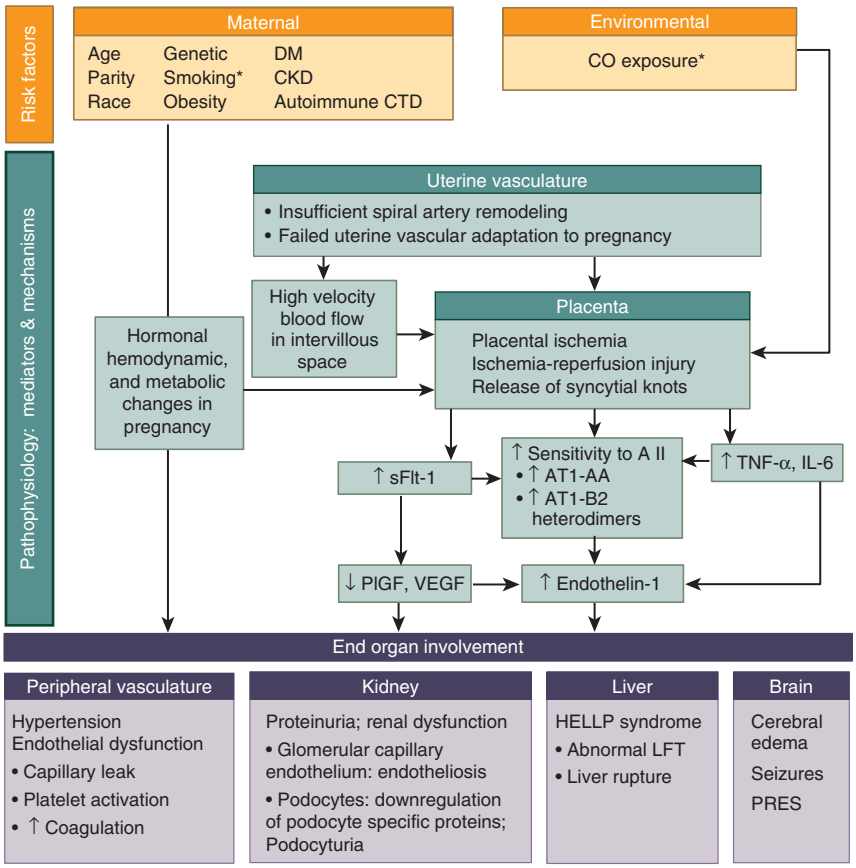

Figure 1 | Etiologies and pathophysiology of pre-eclampsia. Several different signaling pathways may have a role, ultimately converging at the point of systemic endothelial dysfunction, hypertension, and proteinuria. AT1-AA, autoantibodies to the angiotensin II type 1 receptor; AT1-B2 heterodimers, angiotensin II type 1 receptor-bradykinin type 2 receptor heterodimers; CO, carbon monoxide; CKD, chronic renal disease; CTD, connective tissue disease; DM, diabetes mellitus; HELLP, hemolysis, elevated liver enzymes, low platelet count; IL-6, interleukin 6; LFT, liver function tests; PlGF, placental growth factor; PRES, posterior reversible encephalopathy syndrome; sFlt-1, soluble fms-like tyrosine kinase 1; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor. *Reduced risk for pre-eclampsia.