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PERSPECTIVES IN RENAL MEDICINE

Preeclampsia: A renal perspective

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Preeclampsia: A renal perspective. Preeclampsia is a syndrome that affects 5% of all pregnancies, producing substantial maternal and perinatal morbidity and mortality. The aim of this review is to summarize our current understanding of the pathogenesis of preeclampsia with special emphasis on the recent discovery that circulating anti-angiogenic proteins of placental origin may play an important role in the pathogenesis of proteinuria and hypertension of preeclampsia.

Preeclampsia, the syndrome of hypertension and proteinuria that heralds the seizures of eclampsia, remains one of the great mysteries in the field of obstetrics. Although our understanding of the pathophysiology of preeclampsia has increased over the past 50 years, it is quite incomplete, and management remains supportive: close observation, treatment with antihypertensive agents and magnesium sulfate, and if progressive signs and symptoms occur, urgent delivery of the fetus. Preeclampsia is still one of the leading causes of maternal and neonatal mortality in the world.

Preeclampsia is characterized by a constellation of signs and symptoms, including the new onset of hypertension and proteinuria during the last trimester of pregnancy, usually associated with edema and hyperuricemia [1, 2]. It occurs only in the presence of the placenta, even when there is no fetus (as in hydatidiform mole) and remits dramatically postpartum [3]. The placenta in preeclampsia is usually abnormal, with evidence of hypoperfusion and ischemia. Although these placental changes are neither universal nor specific for preeclampsia, there appears to be a correlation between the severity of the disease and the extent of placental abnormalities. The clinical findings of severe preeclampsia are unified by the presence of systemic endothelial dysfunction and microangiopathy, in which the target organ may be the brain (seizures or eclampsia), the liver [the hemolysis, elevated liver function tests, and low platelet count (HELLP) syndrome], or the kidney (glomerular endotheliosis and proteinuria). Severe preeclampsia is also associated with small for gestational age (SGA) fetuses. Because of the strong clinical and experimental evidence of early placental involvement and dysfunction of the maternal endothelium, it is currently believed that preeclampsia has its origin in disordered vascular development of the placenta, which in turn leads to widespread maternal vascular endothelial effects [4, 5] (Fig. 1). This review will discuss mechanisms underlying the clinical manifestations of preeclampsia. In addition, we will describe evidence suggesting that placental secretion of an antiangiogenic protein may contribute to the endothelial dysfunction of preeclampsia.

Key words: pregnancy, HELLP syndrome, angiogenesis, pseudovasculogenesis, VEGF, PlGF, soluble Flt-1, soluble VEGFR-1, proteinuria, edema.

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RISK FACTORS FOR THE DEVELOPMENT OF PREECLAMPSIA

The risk factors for the development of preeclampsia are listed in Table 1 [1, 5–7]. Preeclampsia is more common not only in first pregnancies, but also in multigravidas who have a new partner, suggesting that prior exposure to paternal antigens may be protective [8, 9]. However, recent evidence from a large Norwegian birth registry suggests that prolonged interpregnancy interval, rather than primipaternity, accounts for this increase in risk [10], though why this occurs is unclear. Although preeclampsia is traditionally not considered to be a genetic disease, it is clear that genetic factors contribute to the susceptibility to preeclampsia [6]. A family history (mother, sister, or both) of preeclampsia is associated with a fourfold increased risk for preeclampsia [6]. Other epidemiologic studies suggest that paternal genetic contributions to the zygotic genotype in addition to

Table 1. Risk factors for the development of preeclampsia

Family history of preeclampsia
Nulliparity
Multiple gestation
Molar pregnancies
Older maternal age
Obesity
Preexisting hypertension
Chronic renal disease
Diabetes mellitus
Thrombotic vascular disease

maternal genes may contribute susceptibility to preeclampsia [11]. Polymorphisms of genes involved in the regulation of blood pressure or coagulation, such as renin, angiotensinogen (T235), endothelial nitric oxide synthase (eNOS), prothrombin, factor V Leiden, and methyltetrahydrofolate (MTHFR), though promising in early studies [12–15], have not been confirmed in larger studies [16–20]. Genome-wide scanning of Icelandic families revealed a significant locus on chromosome 2p13 [logarithm of the odds (LOD) score 4.70] [21]. More recently, the 2p locus was confirmed in a study of patients from New Zealand and Australia [22]. Finally, a Dutch study reported linkage of HELLP syndrome, but not preeclampsia, with a locus on 12q, suggesting that genetic factors important in HELLP (hemolysis, elevated liver function tests, low platelets) syndrome may be distinct from those in preeclampsia [23]. Women with trisomy 13 fetuses have a higher incidence of preeclampsia, regardless of parity, suggesting that a gene on chromosome 13 may be important in preeclampsia [24]. An activating mineralocorticoid receptor mutation was described in a rare group of patients who have only pregnancy-induced hypertension without proteinuria [25]. The incidence of preeclampsia is also higher in women who live at high altitudes and in the third world, suggesting that hypoxia and/or hitherto unknown environmental factors may also contribute to the development of preeclampsia [26, 27].

CLINICAL MANIFESTATIONS AND THEIR PATHOPHYSIOLOGIC UNDERPINNINGS

Hypertension

While in normal pregnancy peripheral vascular resistance and blood pressure are decreased, in preeclampsia these changes are reversed. Increased peripheral vascular resistance, rather than increased cardiac output, is the chief cause of hypertension [28]. Sympathetic activation is noted in preeclampsia as it is in other forms of hypertension, a conclusion supported by electrical recordings of sympathetic nerve impulses [29] and by reports of increased concentrations of circulating catecholamines [30]. Sympathetic activation may be responsible for the increase in cardiac output noted by some in the early stages of preeclampsia [31]. Preeclampsia is also notable for an exaggerated response to angiotensin II, catecholamines, and other hypertensive stimuli when compared to normal pregnant controls [32, 33]. One group has reported that this response may precede the onset of overt hypertension by weeks to months [34] (a finding disputed by others [35]), reminiscent of the exaggerated response to vasoconstrictors described in normotensive relatives of patients with essential hypertension [36].

Although total plasma volume has been reported to be low in preeclampsia [37], there may be increased "effective circulating volume" as evidenced by suppressed renin and aldosterone [38, 39] and elevated brain natriuretic hormone [40] relative to normal pregnancy. These findings are reminiscent of the fall in plasma volume and rise in blood pressure produced by infusion of vascoconstrictors suggesting that peripheral vasoconstriction, especially of small venules, shifts blood to the arteries and central veins while elevating capillary pressure [41]. Blood pressure rises, and renin and aldosterone levels fall as a secondary phenomenon.

Generalized vascular constriction is universally present in preeclampsia, at least compared to the physiologic vasodilation of normal pregnancy [28]. There is substantial evidence that this may be due to endothelial dysfunction. A myriad of markers for endothelial activation and dysfunction, including endothelin, cellular fibronectin, plasminogen activator inhibitor-1 (PAI-1), and von Willebrand's factor, are altered in preeclampsia. Women with preeclampsia have enhanced responsiveness to vasopressors as compared with normal pregnant women. Women with a history of preeclampsia exihibit evidence of impaired endothelial-dependent vasorelaxation as measured by brachial artery flow–mediated dilatation up to 3 years after delivery, implying these changes in the maternal endothelium may be more than transient [42, 43]. Alterations of endothelial function have been noted in preeclamptic vessels examined in vitro, supporting the hypothesis that endothelial dysfunction may underlie the hypertension of preeclampsia [4, 5]. The increased incidence of preeclampsia in women with chronic diseases such as diabetes and hypertension also suggests some factor in the maternal milieu may also lend susceptibility to preeclampsia. In addition to increased vascular reactivity, the vasoconstriction appears to be mediated at least in part by alterations in local concentrations of several vasoactive molecules, including the vasoconstrictors norepinephrine, endothelin, and perhaps thromboxane, and the vasodilators prostacyclin and perhaps nitric oxide.

Prostaglandin I_2 (PGI_2) (prostacyclin), a circulating vasodilator produced primarily by the endothelial and smooth muscle layers of blood vessels, is