Endothelial Dysfunction in Preeclampsia and Eclampsia: Current Etiology and Future Non-Invasive Assessment

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Preeclampsia is a common, pregnancy-specific syndrome defined by clinical findings of elevated blood pressure combined with proteinuria and edema. The incidence has been reported in 2–7% of all pregnancies. The clinical findings manifest late in pregnancy, usually after the 20th week of gestation. The disease can progress rapidly, at times without warning, to a life-threatening convulsive phase – eclampsia. The pathologic changes in women dying with eclampsia are characterized by intense vasospasm, hypoperfusion and necrosis. Gross morphologic and histopathologic changes are observed in many organs including the heart, lungs, kidney, liver, brain and placenta, indicating that this syndrome is a multisystemic disease [1]. Generalized vasodilatation is the primary hemodynamic change in normal pregnancy and is already present during the luteal phase in women who subsequently become pregnant. In the 1980s, pregnancy-associated biological dominance of prostacyclin over thromboxane-A2 was thought to cause vascular refractoriness to vasoconstrictors and thus vasodilation. More recently, it was demonstrated that vasodilator prostaglandins do not mediate the attenuation of systemic and renal pressor responsiveness in pregnancy. Several peptide-regulatory factors (cytokines, binding proteins, growth factors) released in an appropriate steroid environment appear to play an integral part in this mediation, and nitric oxide may be important as a final messenger [2].

Immunology of normal pregnancy

The placenta is essentially an allograph; its implementation involves an allogenetic recognition system based on natural killer cells rather than T cells. About 75% of decidual cells express CD45, reflecting their bone marrow origin. Overall, natural killer cell and T lymphocyte activity is down-regulated in normal pregnancy [3]. In 1986, two distinct and mutually inhibitory types of T helper cells were described. The first type of cell, termed Th1, secretes interleukin-2, interferon gamma, and lymphotoxin. This contrasts with Th2 cells, which secrete IL-4, IL-6 and IL-10. Th1 cytokines are associated with cell-mediated immunity and delayed hypersensitivity reactions, whereas Th2 cytokines foster antibody responses and allergic reactions. Pregnancy is characterized by Th2 switch. During pregnancy, expression of both CD4 and CD8 is transiently down-regulated on αβ TcR+ splenic T cells specific for a paternal major histocompatibility complex class I antigen, which represents a reduced Th1 response. HLA-G expressed on cytotrophoblast induces a Th2 response in decidual leukocytes. Several substances such as prostaglandin E2, progesterone, tissue growth factor beta-2, granulocyte-macrophage colony-stimulating factor, and IL-10 play a part in the immunoendocrine network in pregnancy maintenance [3–5].

Preeclampsia

Development of preeclampsia begins with a loss of vascular refractoriness to vasoactive agents followed by vasoconstriction. Increased vascular sensitivity and subsequent vasoconstriction results in a decrease in intravascular volume. Intravascular volume is shunted, across the "leaky" capillaries, to extravascular spaces. Preeclampsia is characterized by a generalized dysfunction of the maternal endothelium, as demonstrated by increased levels of factor VIII, total and cellular fibronectin, thrombomodulin, endothelin, growth factor activity, and a disturbance of the tPA/PAI-1 and prostacyclin/thromboxane-A2 balance [6]. Preeclampsia is associated with an impairment of endothelium-dependent relaxation in maternal resistance arteries [7]. Several studies have found a decrease in urinary excretion of nitric oxide metabolites in preeclampsia [8,9].

The majority of studies reported so far found increased TNFα and IL-1 levels, and increased levels of soluble TNFα receptors and IL-1 receptor antagonist. Serum levels of IL-2 are also increased in preeclampsia [10]. Increases in plasma ceruloplasmin, complement activity, α1-antitrypsin and haptoglobin, and reduced albumin and transferrin in preeclampsia, are characteristic of an acute-phase reaction that may be related to the increased IL-6 levels [11]. Dysfunctional endothelial cells undergo activation and produce leukocyte-endothelial adhesion molecules that mediate adherence of inflammatory cells. This inductive process is mediated by cytokines produced by inflammatory cells and activated endothelial cells.

IL = interleukin

TNF = tumor necrosis factor

Preeclampsia is associated with increased levels of these adhesion molecules, and this increase may be an early event. Increased IL-6 and IL-1 receptor antagonist levels in preeclampsia correlate with elevated concentrations of these adhesion molecules [12].

Adhesion molecules in preeclampsia

Several studies reported increased levels of vascular cell adhesion molecule and E-selectin in the sera of patients with preeclampsia. Increased levels of VCAM-1 in patients with preeclampsia could be indicative of endothelial cell activation, and the soluble adhesion molecules in serum should reflect the concentration of membrane-bound adhesion molecules on the endothelium. E-selectin is considered more endothelium-specific than VCAM-1 because E-selectin can bind to activated neutrophilic granulocytes [13]. The pathophysiologic significance of soluble adhesion molecules, as well as the mechanisms causing shedding of the membrane, have not yet been clarified. According to one theory, adhesion molecules occupy specific receptors on activated leukocytes to prevent an excessive cell adhesion in the sense of downward regulation [14]. However, a cytokine-like function was defined, with a chemo-attractant potency of E-selectin to leukocyte integrins [15]. In addition to thrombin and histamine, the pro-inflammatory cytokines IL-1β and TNFα stimulate cultured human endothelial tissue to an increased production of adhesion molecules [16].

Increased cytokine levels (IL-1β ,and TNFα) have been found in the serum of patients with preeclampsia [17,18]. In addition to cytokines, however, other factors such as hypoxia [19,20] or hyperthermia can also lead to an increased expression of adhesion molecules, as can co-incubation of human endothelial cells with monocytes or mast cells [21,22].

VCAM-1 was also found to be elevated in preeclampsia [23]. VCAM-1 is present on a number of activated cells, including activated endothelial cells. Since the common pathologic feature of preeclampsia is endothelial damage and dysfunction, one likely source of the circulating adhesion molecules is the endothelium. Increased concentrations of VCAM-1 may reflect increased expression of this molecule on the endothelial surface. The expression of VCAM-1 on cells is regulated, at least in part, by multiple micro-environmental influences, such as changes in cytokine concentrations. For example, VCAM-1 expression on endothelial cells is induced by IL-1β, IL-4, TNFα and IFNγ. Interestingly, the cytokine IL-4, produced by a subset of T cells, induces VCAM-1-mediated binding of T lymphocytes to endothelium without stimulating E-selectin or intracellular cell adhesion molecule-mediated attachment. VCAM-1 mediates the adhesion of lymphocytes, monocytes and eosinophils to activated endothelium via the integrin α4β1 (VLA-4). However, normal neutrophils express little, if any, VLA-4. VCAM-1 could contribute to neutrophil recruitment to the endothelium as a secondary event following recruitment of other leukocytes [23].

Plasma GMP-140 levels were found to be significantly elevated in preeclamptic and eclamptic patients compared with normotensive controls [24]. P selectin, or GMP-140, is a member of a family of cell adhesion receptors, termed selectins, that mediate cellular interactions [25,26]. It is expressed in the α granules of platelets and the Weibel-Palade bodies of endothelial cells [27]. GMP-140 is secreted from the activated platelets and circulates in plasma as a soluble and functional form [28]. The hypothesis of endothelial dysfunction is also supported by the increased level of factor VIII-related antigen and fibronectin and an imbalance of tissue plasminogen activator and its inhibitors, vasoconstrictors and vasodilators, that are present in this disease [29]. Elevated plasma thrombin-antithrombin complexes and a decrease in plasma antithrombin III activity were reported in preeclampsia [30] and eclampsia [31]. A characteristic fall in platelet counts occurs because of the increased consumption of platelets in preeclampsia [32].

Levels of von Willebrand factor and fibronectin were found to be higher in preeclampsia than in normal pregnancy [33], and these levels were still elevated 5 weeks postpartum in women with severe preeclampsia [33]. This may indicate an ongoing vascular disease with increased risk for preeclampsia in subsequent pregnancies.

The "brachial artery method"

There is a new non-invasive method that evaluates endothelial function based on the basic knowledge that a high shear stress causes an endothelial dependent vasodilation. It is based on the technique of Celermajer and Deanfield [34]. Endothelium-dependent vasodilation can be assessed by measuring the maximum increase in diameter of the brachial artery during reactive hyperemia created by an inflated cuff (to at least 50 mmHg above systolic pressure to occlude arterial inflow for 5 minutes) on the forearm [35]. After cuff deflation, flow velocity is measured for the first 15 seconds, then the longitudinal image of the artery is recorded continuously from 30 seconds before to 2 minutes after cuff deflation to assess hyperemic velocity [36].

This method, known as the "brachial artery method," is capable of accurately measuring the endothelial function and enables us to predict the future clinical outcome of patients with endothelial dysfunction.

Clinical studies

Several studies used the brachial artery reactivity method to examine endothelial function in preeclampsia. Chambers et al. [37] conducted a case-control study in London and found that the brachial artery reactivity was impaired in women with previous preeclampsia (without established maternal risk factors), and most importantly, that it was reversed by ascorbic acid administration.

Yoshida et al. [38] noted that flow-mediated vasodilation in preeclamptic women was significantly less than in women with normal pregnancies. They also found that the flow-mediated vasodilation was significantly less than in women with normal pregnancies, but more than in preeclamptic women.

Another review [39] has suggested a two-step vascular dysfunction mechanism. In the early stage, there is suboptimal development of the placenta and a hemodynamic maladaptation to pregnancy. At this stage, maternal constitutional factors such as

VCAM = vascular cell adhesion molecule
IFNγ = interferon-gamma

genetic and immunologic factors and preexisting vascular diseases may play a role. Due to this defective placentation a factor is released from the placenta, supposedly under the influence of ischemia. This factor results in the late vascular dysfunction characterized mainly by generalized endothelial dysfunction, leading to the clinical syndrome of preeclampsia [39].

Conclusion

Eclampsia is an endothelial cell disease that begins under the endocrine and rheologic stress of pregnancy but may continue thereafter in women with the "appropriate" genetic predisposition. Today, non-invasive methods are used to diagnose endothelial function, and it is hoped that the near future will bring us improved non-invasive means for diagnosing and detecting eclampsia, thereby enabling us to identify women at high risk of developing eclampsia in an early stage of pregnancy, thereby preventing dangerous life-threatening complications.

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