## PATHOPHYSIOLOGY OF PREECLAMPSIA

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Preeclampsia and eclampsia are important causes of maternal death worldwide. Preeclampsia/eclampsia constitutes the syndrome of vasoconstriction with elevated arterial blood pressure, edema, proteinuria and convulsions. Preeclampsia reduces uteroplacental perfusion, which places the fetus at high risk of (acute and/or chronic) hypoxemia, malnutrition, fetal growth retardation, preterm birth, and perinatal morbidity and mortality. In contrast, hypertension arising late in pregnancy, and not accompanied by proteinuria is neither associated with any increase in perinatal mortality or morbidity nor with a decreased birthweight.

Although preeclampsia has been studied extensively, its true cause remains unknown. Hypotheses have focussed on endogenous hormones, nutrition, and immunologic and genetic factors. There is increasing evidence that genetic and immune mechanisms are involved in the etiology of preeclampsia. Severe preeclampsia and eclampsia have a familial tendency. The development of preeclampsia-eclampsia may be based on a single recessive gene or a dominant gene with incomplete penetrance. Penetrance may be dependent on the fetal genotype. Multifactorial inheritance is another possibility. Future molecular genetic methods will provide information on the exact mode of inheritance. The possible involvement of the immune system in the pathogenesis of preeclampsia has attracted increasing attention. The fetoplacental unit serves as an allograft because it contains paternal antigenic tissue which is foreign to its maternal host. Pregnancy represents an unique state of mutual immunologic tolerance.

The decidua has been recognized as a mainly lymphoid tissue. Certain types of immune responses may be benefical to pregnancy and prevent 'rejection' by natural effectors such as lymphokine activated killer cells. Cytokines such as granulocyte-macrophage colony stimulating factor derived from T-cells or macrophages can stimulate trophoblast growth. Plenty of circumstantial evidence suggests that immune mechanisms ought to be involved in the etiology of preeclampsia. Involvement of immune alterations in the early development of preeclampsia, show a significantly lower proportion of T-helper cells than those who remain normotensive, already early in the second trimester. In addition, it was found that neutrophil activation occurs in preeclampsia, localized in part to the placental bed.

Immune maladaptation is an attractive, although still hypothetical, explanation for the disturbed endovascular trophoblast invasion in preeclampsia. In normotensive pregnancy the invasion of the uteroplacental arteries by non-villous trophoblast results in a significant reduction in peripheral vascular resistance in the uteroplacental vascular circulation allowing substantial blood flow under low pressure through the intervillous spaces of the placenta. In preeclampsia the physiologic changes in the uteroplacental arteries are confined to the decidual arteries, the myometrial segments remain anatomically intact and do not dilate. Adrenergic nerve supply to these arteries remains intact. The inhibition of trophoblastic invasion of the myometrial segments of the spiral arteries, and secondary lesions such as acute atherosis and thrombosis, may have the effect of curtailing the increased blood supply required by the fetoplacental unit in the later stages of pregnancy and cause further acute dearangements of uteroplacental perfusion.

In recent years evidence has been adduced to support the concept that the eicosanoid system plays an important part in the pathophysiology of pre-eclampsia. The imbalance between vasodilator prostaglandins and vasoconstrictors such as thromboxane-A2 and angiotensin-II, especially in the uteroplacental circulation and the kidney allows an explanation for many of the clinical manifestations of preeclampsia. The absence of the normal stimulation of the renin-angiotensin-aldosterone system, despite significant hypovolemia, and the increased vascular sensitivity to angiotensin-II and norepinephrine can be explained by a single mechanism: endothelial cell injury, resulting in a prostacyclin/thromboxaneA2 imbalance. In addition, the increased thromboxane-A2/prostacyclin ratio may be the cause of the selective platelet destruction, sometimes accompanied by microangiopathic haemolysis resulting in the syndrome of haemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome), and the reduced uteroplacental blood flow with arterial thrombosis and placental infarction. Because the platelet is the principal source of circulating serotonin, the increased platelet aggregation in preeclampsia may be the cause of the higher levels of serotonin reported in blood and placentas of women with preeclampsia as compared to normotensive pregnancies. The increased level of free circulating platelet-derived serotonin further facilitates platelet aggregation, but may also amplify the vasoconstrictor action of certain neurohumoral mediators, in particular catecholamines and angiotensin-II, and may cause direct contraction via S2-receptors on vascular smooth muscle itself.

Although the concept of a prostacyclin/thromboxane-A2 imbalance, as a major pathogenetic mechanism, allows an

explanation for many of the clinical manifestations of pregnancy-induced hypertensive disorders and provides a framework for further investigations, the hypothesis remains unproven.

Endothelial cell injury and altered endothelial cell function play an important role in the pathogenesis of preeclampsia. Serum from preeclamptic women injures endothelial cells in vitro. Preeclampsia is characterized by a generalized disturbance in normal endothelial physiology, and not merely by an isolated defect in vascular prostacyclin synthesis. It might be that the physiologic vasodilation in pregnancy is mediated by other autocoids instead of prostacyclin. Recent animal and in-vitro studies support the hypothesis that endothelium-derived relaxing factor (EDRF) is the major "antihypertensive factor" in normal pregnancy rather than prostacyclin. If this hypothesis is correct, prostacyclin synthesis in the uteroplacental circulation may be "just" a rescue mechanism in those pregnancies where uteroplacental perfusion is endangered because of inadequate conversion of spiral arteries to uteroplacental arteries and a decrease in uteroplacental EDRF release. The adequacy of the uteroplacental rescue mechanism (S1-receptors, prostacyclin, EDRF, uteroplacental renin-angiotensin system) may determine the final clinical and perinatal outcome.

Neutrophil activation occurs in preeclampsia, localized in part to the placental bed. Plasma neutrophil elastase, a marker for neutrophil activation, is significantly higher in plasma from preeclamptic patients than in normotensive controls. The number of elastase containing neutrophils in the fibrin of the decidua is significantly greater in preeclampsia than in normal pregnancies, and correlates with plasma urate. Concentration of neutrophil elastase in umbilical venous plasma is similar in normotensive and hypertensive pregnancies, which implies that neutrophil activation in preeclampsia is confined to the maternal circulation.

What might be the connection between these activated neutrophils and endothelial cell dysfunction in preeclampsia? Neutrophils have been implicated in the pathogenesis of vascular damage in the non-pregnant situation. Activated neutrophils release a variety of substances, capable of mediating vascular damage. These include the contents of neutrophil granules such as elastase and other proteases which can destroy the integrity of endothelial cells, vascular basement membrane and subendothelial matrix. Endothelial cells convert leukotriene-A4 generated by neutrophils to leukotriene-C4, a molecule capable of smooth-muscle constrictor activity. Leukotriene-C4 is known to cause a sustained formation of platelet activating factor (PAF). In addition, toxic oxygen free radicals are released which results in membrane lipid peroxidation, lysis of endothelial cells, disruption of the endothelium and increased vascular permeability and reactivity. Oxygen free radicals inhibit endothelium-dependent relaxation in vitro and in vivo by chemical inactivation of EDRF and inhibition of the production and release of relaxing factors due to oxidant injury of endothelial cells. Lipid peroxides activate cyclo-oxygenase and impair endothelial prostacyclin synthetase. Therefore the increased lipid peroxide levels in preeclampsia favour production of platelet-derived thromboxane-A2 above vascular prostacyclin production. Also, an increased production of oxygen free radicals may cause "Up" regulation of endothelin receptors with a subsequent increased reactivity to endothelin.

Oxygen free radicals and lipid hydroperoxides are increased in preeclampsia. Erythrocyte glutathione peroxidase activity and erythrocyte glutathion levels, major lipid hydroperoxide scavenger systems, are increased in preeclampsia. This increase is probably compensatory.

The increased production of oxygen free radicals, or other products released by activated lymphoid cells in the pregnant decidua may be the link between the hypothetical immunologic maladaptation and the generalized endothelial injury occurring in preeclampsia.