Pre-eclampsia: State of art

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ABSTRACT

The need to understand the etiology and pathogenesis of a disease process, so that a sound basis for management and possible prevention can be arrived at, continues to spur scholars of reproductive physiology to pursue the study of pre-eclampsia. Despite interesting observations involving many physiological systems, most theories on causation of this disorder have either been dismissed or remain unproven. Agreement on universal management for the pre-eclampsia is still unresolved in different countries, further complicating discussion on this topic. This paper is a review of the pathogenesis of pre-eclampsia. We tried to numerate the possible causative factors leading to pre-eclampsia with some scientific review of the associated syndromes.

Keywords: Pre-eclampsia.


Although pre-eclampsia was first described over 100 years ago, there are still difficulties surrounding its definition. The variety of names for the syndrome of hypertension peculiar to pregnancy associated with proteinuria, thrombocytopenia, hyperuricemia and compromised renal and hepatic function emphasis the confusion surrounding the condition.

As the debate continues, pre-eclampsia will be defined as a clinical syndrome in which a previously normotensive woman (with no pre-existing renal disease and after 20 completed weeks of gestation) develops a blood pressure of at least 140/90 mmHg on two occasions separated by at least four hours, in the presence of proteinuria of at least 0.3 g/l in a 24 hour collection of urine (in the absence of urinary tract infection), both of which resolve by sixth week post partum.1 Pregnancy induced hypertension (PIH) will be defined as the onset of hypertension in a previously normotensive woman of at least 140/90 mmHg on two occasions separated by at least four hours, after 20 completed weeks gestation, which is not associated with significant proteinuria.

Pathogenesis of pre-eclampsia. Intensive research in different fields has been conducted through out the last century, from epidemiological to cellular and biochemical studies. The etiology of pre-eclampsia is still obscure. The only consistent finding is the abnormal permeability of cell membranes, generalized or localized to specific organs. During recent years pathogenic research has focused on endothelial function and structure.

Endothelial function. The endothelium is the largest endocrine organ of the body and it has now been recognized as an important modulator of vascular tone among many other functions. Abnormal endothelial cell function in pre-eclampsia could contribute to an increase in peripheral resistance. Endothelium-derived relaxing factor (EDRF) and prostacyclin are produced by the endothelial cell layer and act locally on the underlying smooth muscle. EDRF, first described by Furchgott and Zawadski (1980), has later been recognized as nitric oxide (NO). There are only a few studies carried out in pregnant woman to confirm the physiological importance of NO in man.
Nitric oxide is a small lipophilic molecule that rapidly diffuses out of its cells of origin into nearby target cells, where it binds to the heme group of cytosolic guanylate cyclase and thereby causes enzyme activation with a resultant 50 to 200-fold increase in the velocity of conversion of guanosine triphosphate to cyclin guanosine monophosphate. The increase cyclic guanosine monophosphate levels cause vascular smooth muscle relaxation by accelerating the intracellular binding of free calcium. Cyclic guanosine monophosphate also inhibits platelet aggregation and adhesion to vascular endothelial surfaces. Nitric oxide is synthesized from the essential amino acid L-arginine by a cytosolic enzyme nitric oxide synthetase (NOS). Several isoforms of NOS have been identified. The endothelial isoform of this enzyme (eNOS) is found in both large and small vessel endothelium, platelets, endocardium, myocardium, and vascular smooth muscle cells. The production of NO requires molecular oxygen and at least four co-factors and is inhibited by L-arginine analogues, flavoprotein binders and calmodulin binders. As NOS activity is oxygen dependent, a reduction in oxygen saturation reduces NO synthesis. Endothelial nitric oxide synthetase activity is stimulated by serotonin and bradykinin, which are released during platelet activation, and, hence, prevent excessive platelet aggregation and adhesion. NOS is increased in pregnancy, reflected in the increased urinary excretion of nitrate, the stable NO metabolite. However, different groups have suggested that the increased sensitivity to vasopressors seen in pre-eclampsia could be explained by a decreased production of NO. Confirmation of these results await larger studies along with measurements of endothelial nitric oxide synthase in the placenta and umbilical cord in pre-eclamptic patients.

**Prostacyclin/Thromboxane A2 imbalance, endothelial dysfunction.** Endothelial cell (EC) injury causing a deficiency in the production and/or activity of vasodilatory prostaglandins, in particular PG12. The increased TXA2/PG12 ratio may be the cause of the selective platelet destruction, sometimes accompanied by microangiopathic hemolysis, and the reduced uteroplacental blood flow, with spiral artery thrombosis and placental infarction. However, in the past decade we have learned that pre-eclampsia is not simply a state of PG12 deficiency but is essentially a highly variable clinical syndrome caused by a complex disturbance of normal EC function. Beside the disturbance of the PG12/TXA2 balance, increased levels of factor V111:RAG, increased levels of total fibrinectin and endothelium specific, increased endothelin levels and a disturbance of the tissue plasminogen activator (TPA) and plasminogen activator inhibitor balance all demonstrate that endothelial damage is intimately involved with the pathogenesis of pre-eclampsia. The placenta. In normal pregnancy, as the result of trophoblastic invasion, there are striking changes in the arteries supplying the intervillous space. The diameter of spiral arteries increases to four to six times the diameter of the same vessels in non-pregnant woman. The muscular and elastic components are replaced by a fibrinoid layer in which trophoblasts are embedded. These vascular changes extend from the intervillous space to the inner third of the myometrium. By contrast these changes do not occur in pre-eclamptic women or are limited to the decidual portion of the vessels, with the myometrial portion maintaining their smooth muscle. Some spiral arteries in the decidua and myometrium are occluded by fibrinoid material and surrounded by foam cells, changes similar to those seen with allograft rejection. As the normal trophoblastic implantation in the spiral arteries is complete at 20-22 weeks of gestation, the deficient implantation process of pre-eclampsia must be complete at around that time even though the disorder is not manifest until later in pregnancy.

Trophoblastic invasion is associated with a modulation in the distribution of adhesion molecules, increased expression of HLA-G antigen and activity of a type IV collagenase. The end result of this abnormal trophoblastic invasion is an inadequate development of the uteroplacental blood supply, increased resistance in the placental vascular bed, and, consequently, diminished fetal perfusion.

**Platelets and coagulation.** The pathogenesis of pre-eclampsia-associated thrombocytopenia is equally unclear. Patients with pre-eclampsia who develop thrombocytopenia seem to manifest a state of accelerated platelet destruction which exceeds that observed in the course of normal pregnancy. Activation of both the coagulation and fibrinolytic systems, occasionally leading to the development of disseminated intravascular coagulation (DIC), occurs in some patients with pre-eclampsia, and may play a role in stimulating platelet activation and accelerated clearance. The level of antithrombin III (AT-III) were reported to be significantly reduced in pre-eclamptic patients. The levels of thrombin-ATIII (TAT) complexes have also been noted to be elevated, and those of protein C decreased in pre-eclamptic, compared with normal pregnant patients. Concentrations of fibrinogen-fibrin degradation products, and soluble fibrinogen-fibrin complexes are increased. Assays of plasminogen activators and their inhibitors have recently shown unchanged plasma plasminogen activator, but increased levels of tissue plasminogen activator in plasma. The increase in tissue plasminogen activator is accompanied by an increase in plasminogen activator inhibitors 1 and 2. Plasminogen activator inhibitor 2 is produced only from the placental and its increase...
reflect placental vascular damage and would predispose to local thrombosis by local inhibition of fibrinolysis in the abnormal vessels of the placental bed.

This increase in fibrinolysis may be a response to intravascular coagulation which may be prevented from reaching its full potential due to the concomitant increase in intravascular inhibitors of plasminogen activation.

**Endothelial activation.** Endothelial activation has been defined as (quantitative changes in the level of expression of specific gene products that endow endothelial cells with new capacities that cumulatively allow endothelial cells to perform new functions. In pre-eclampsia, extensive ultrastructural endothelial injury has been found in placental bed specimens, with changes in the spiral arteries termed, acute atherosclerosis. The increased capillary permeability seen in pre-eclampsia is consistent with alteration to normal vascular endothelium.

Pre-eclampsia is associated with alteration in prostaglandin metabolism, with a decrease in the PG12/thromboxane ratio. Various mechanisms have been proposed for alteration in PG12 metabolism. Lipid peroxidation, the oxidative conversion of unsaturated fatty acids to lipid peroxides, occurs in all cells and lipid peroxides are physiologically activators of prostaglandin endoperoxide synthase. However, as lipid peroxide levels become pathologically high, PG12 synthase is specifically impaired. Lipid peroxidation products have been shown to be elevated in women with pre-eclampsia which may inhibit PG12 synthase and explain the diminution in PG12 production. Lipid peroxides may therefore be involved in endothelial cell injury, vasoconstriction, and the imbalance between thromboxane and prostacyclin that is associated with pre-eclampsia. Lipid peroxides are neutralized by antioxidants, of which vitamin E and glutathion peroxidase are considered to be two of the most important in the placenta. Deficiencies in known antioxidant, are associated with increased incidence of pre-eclampsia. The acute atherosclerosis of pre-eclampsia resembles the atherogenic process in other arteries, in which a progressive deposition of lipid peroxide is associated with antibody directed against certain antigenic components, such as malondialdehyde-lysine. Antibody and complement have been demonstrated where there are lipid-containing macrophages.

**The immune system.** Pre-eclampsia is a disorder of the first pregnancies, but the protective effect of multiparity may be lost after a change of partner. This has led to an immunologically mediated pathogenesis for pre-eclampsia to be proposed. Recently, it has been suggested that the immune mechanism operate at a local level (i.e. the placenta) rather than a wide spread immune activation. In the first trimester, the decidua is primarily an immune tissue containing many cells of bone marrow origin, including macrophages, T cells and large granular lymphocytes. The subpopulation of cytotoxic lymphoblast cells that invade the uterus express a unique class 1 HLA antigen of the non classical HLA-G locus, which is thought to confer resistance of natural killer cell activity in the first trimester decidua. At present there is no direct evidence that abnormal recognition of this antigen occurs in pre-eclampsia.

**Genetic.** The familial nature of pre-eclampsia was first recognized over a century ago. Population studies show that the susceptibility to eclampsia is highly heritable and that a single recessive gene may be responsible. However, discordance between monozygotic twin sisters shows that maternal genotype cannot be the only determining factor. The fetal genotype has been shown to play a role, with an association between pre-eclampsia and trisomy 13 and an excess of male fetuses in pregnancies complicated by pre-eclampsia. The interaction between maternal and fetal genotypes in pre-eclampsia may mimic that seen in recurrent miscarriage and is characterized by an increased incidence of histocompatibility local A antigen sharing between maternal and paternal genotypes.

Availability of methods of early detection. Concerning the development of an easy, reliable test for the early detection of pre-eclampsia, measuring total or endothelium specific fibrinectin levels, Doppler flow studies of the uteroplacental circulation and measuring platelet angioteensII receptors are the most promising.

**Pre-eclampsia associated syndromes. HELLP syndrome.** Hemolysis, elevated liver enzymes, and low platelets have received much attention in recent years; however, this syndrome does not appear to be a unique disorder, but rather a variant of pre-eclampsia. The criteria for diagnosis of this syndrome include: (1) microangiopathic hemolytic anemia with schistocytes on the peripheral blood film, bilirubin >1.2 mg/dL, and LDH >600 U/L; (2) serum glutamic oxaloacetic transaminase (SGOT) >70 U/L; and (3) thrombocytopenia, with platelet count less than 100,000/uL. Because many patients with HELLP syndrome also manifest hypertension and proteinuria, the clinical overlap with pre-eclampsia is evident; indeed, 4% to 12% of patients with pre-eclampsia will also meet the diagnostic criteria for HELLP. While approximately 80% to 95% of patients with HELLP present with malaise, right upper quadrant and/or epigastric pain, and nausea, only 70% to 85% of patients with this disorder have proteinuria, which often is minimal and only approximately 50% of patients have edema and/or hypertension. The lack of hypertension and significant proteinuria, in addition to the observation that the HELLP syndrome develops more frequently...
in older (>25 years), white, multiparous women than does pre-eclampsia, may lead to erroneous diagnosis. Patients may misdiagnosed with such disorders as viral hepatitis, pyelonephritis, or cholecystitis, leading to delays in the institution of appropriate therapy. Thus the presence of thrombocytopenia in a nonhypertensive pregnant patient with malaise, right upper quadrant pain, and no or minimal proteinuria should be considered as potentially indicative of the HELLP syndrome, although the possibility of other general illnesses should not be disregarded.

**Hemolytic uremic syndrome.** Hemolytic uremic syndrome (HUS) is increasingly being recognized as occurring in adults and may present in association with pregnancy. It present with the triad of acute renal failure, microangiopathic hemolytic anaemia and thrombocytopenia. Prior to the introduction of plasmapheresis and plasma therapy, mortality was high with many cases requiring renal dialysis. It usually occurs in primigravida but has also been reported in multiparous patients. The adult presentation typically occurs during the postpartum period. Only occasional causes of HUS developing antepartum have been reported. Thus the time of onset of this syndrome may be of use in differentiating HUS from pre-eclampsia or the HELLP syndrome as it is difficult to distinguish between them on laboratory or physical findings alone. The primary defect is a platelet aggregating factor which causes deposition of microthrombi in the vessel wall, microangiopathic hemolytic anaemia and thrombotic occlusion in the microvasculature of the kidney resulting in acute renal failure. The pro-aggregatory factor is thought to be an infectious agent, most commonly the verotoxin producing E.coli O157:H7, but in the postpartum period HUS it is suggested that there is an additional oestrogen effect which is supported by the association with oral contraceptive pill. More recently, it is thought that plasma infusion or plasma exchange may be the most effective treatments as they remove the factor that promotes aggregation. An uncontrolled trial showed that plasma infusion alone, was effective. Others have found that plasma exchange was necessary.

**Disseminated intravascular coagulopathy.** Disseminated intravascular coagulopathy (DIC) is not a single, distinct entity; rather, it is an intermediary manifestation of other diseases. DIC is said to exist whenever intravascular activation of clotting components results in excess consumption of at least the soluble coagulation components. The symptoms of DIC often predict the laboratory findings. Activation of the clotting cascade does not occur without concurrent plasmin generation. Should the intravascular clotting process dominate and the secondary fibrinolysis be minimal, the clinical presentation will be thrombosis.

Should secondary fibrinogenolysis dominate and fibrin/fibrinogen degradation products circulate at high concentration, the clinical presentation will be hemorrhage. On occasion, thrombosis and hemorrhage occur simultaneously. Lately, DIC may exist without clinical evidence and be detectable only by specific laboratory evaluation.

The morbidity and mortality of DIC result from both the coagulopathy and the underlying illness. The primary therapeutic goal, whether it be acute or chronic DIC, is treatment of the underlying disorder accompanied by aggressive support of blood volume and pressure. Activation of both the coagulation and fibrinolytic systems, leading to the development of DIC occurs in some patients with pre-eclampsia, and may play a role in stimulating platelet activation and accelerated clearance. In the antepartum state, procoagulant processes appear to predominate and may contribute to the development of microthrombi and fibrinoid-necrosis, which occur primarily in the liver and placenta. However, clinically evident DIC occurs only in the most severe cases of pre-eclampsia.

Antithrombin III (AT III) levels were reported to be significantly reduced (<70% normal activity) in a series of 22/25 pre-eclamptic patients, suggesting that reductions of AT III to this degree may be useful diagnostically in pre-eclampsia.

The levels of thrombin/AT III (TAT) complexes have also been noted to be elevated, and those of protein C decreased in pre-eclamptic, compared with normal pregnant patients. Significant elevation in fibrin D-dimer levels were observed in 39% of pre-eclamptic patients, although only approximately one third of these had concurrent elevations in fibrin degradation products. Finally, the factor V11-related antigen/factor VIIIc ratio has been reported to be elevated in most patients with severe pre-eclampsia.

**Acute fatty liver of pregnancy.** This is a rare condition; the estimated incidence is 1 in 15,000 pregnancies. Despite the fact that acute fatty liver of pregnancy occurs infrequently, it is important to have an understanding of it because it is associated with such a poor prognosis for both mother and fetus. Recent reports indicate that with prompt diagnosis and immediate institution of treatment the maternal and perinatal prognosis can be improved. It usually occurs in primigravid women late in the third trimester of pregnancy. There is an increased frequency of twin gestation and male fetuses. Prodromal symptoms and signs include malaise, anorexia, lethargy, nausea and vomiting. After one to three weeks, jaundice develops usually associated with right upper quadrant pain, hepatic tenderness and ascites. Pre-eclampsia is present in approximately 40% of affected patients. Eighty percent of patients experience prominent central nervous system aberration, including confusion, seizures, and ultimately coma.
Laboratory abnormalities include elevated white blood cell count, decreased platelets, and anaemia with typical normoblasts in the peripheral blood smear. Serum transaminase concentrations are increased, and alkaline phosphatase level and bilirubin concentration also are elevated moderately. Serum ammonia levels typically are elevated. In the presence of acute hepatic failure, synthesis of coagulation factors is impaired severely, and DIC may occur also. Renal dysfunction frequently is associated with hepatic failure.

Three principal disorders should be considered in the differential diagnosis of acute fatty liver of pregnancy: acute viral hepatitis, cholestasis of pregnancy, and pre-eclampsia. In many situations, the distinction between pre-eclampsia and acute fatty liver of pregnancy may not be possible on the basis of clinical presentation and laboratory evaluation. In many situations, liver biopsy may be the only diagnostic test. Unfortunately, the presence of coagulation defects may make liver biopsy impossible during the acute phase of the patient’s illness. The goals of therapy of acute fatty liver of pregnancy are to normalise liver function tests, electrolytes, clotting profile, and serum ammonia, to prevent renal failure, to return patient to normal mental status, and to deliver the fetus.

In conclusion, pre-eclampsia is still a major cause of perinatal and maternal morbidity and mortality, in developed as well as in developing parts of the world. It is a specific human pregnancy complication, unpredictable in onset and progression. It is a multiorgan syndrome complex, variable in organ affection. The disorder is recognised by the occurrence of pregnancy-induced changes, which are clinically obvious in the second half of pregnancy, and which regress after delivery. Differential diagnosis between pre-eclampsia and other associated syndrome is often difficult due to the overlap of these syndromes. Early presentation and understanding of the pathophysiology of these syndromes is important for an early diagnosis. Further studies are definitely needed to explore how the disease can be prevented or how it can be diagnosed early.

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