INTRODUCTION

Preeclampsia is a hypertensive condition unique to pregnancy with both maternal and fetal manifestations. The maternal disease is characterized by vasospasm, endothelial dysfunction, activation of the coagulation system and high blood pressure. The maternal pathophysiologic changes are systemic and are mainly ischemic, affecting the placenta, kidney, liver and brain. Preeclampsia is diagnosed in a woman with new onset hypertension >140/90 mm Hg after gestational week 20 accompanied by proteinuria >300 mg/day. Other common clinical and lab abnormalities include facial and peripheral edema, thrombocytopenia, elevated uric acid levels (>5.5 mg/dl), and elevated transaminase levels (to >2 x normal). The greatest concern is that preeclampsia can progress to eclampsia, which are life-threatening convulsions associated with cerebral hemorrhage or to HELLP syndrome, which is Hemolysis, Elevated Liver enzymes and Low Platelets. Eclampsia is frequently preceded by severe headaches, visual disturbance (halos or auras) and hyperreflexia, while HELLP syndrome is frequently preceded by right upper quadrant or epigastric pain. The consequences of preeclampsia for the fetus are a result of decreased placental perfusion and include intrauterine growth restriction and fetal loss. Delivery is the only definitive cure of preeclampsia/eclampsia, and in order to prevent serious maternal complications premature delivery is often necessary, as such hypertensive disorders in pregnancy are the leading cause of indicated premature delivery. In this chapter the pathophysiology of preeclampsia and the pathogenesis of these manifestations will be examined.

PATHOPHYSIOLOGY

The pathophysiology of preeclampsia has been described divided into two stages: alterations in placental perfusion (stage 1) and the maternal syndrome (stage 2).

Placenta

The pathophysiology of preeclampsia begins with abnormalities in the development of the placenta, leading to the production of abnormal vasculogenic substances, which upon reaching the maternal circulation produce the maternal clinical syndrome. There is considerable evidence for the importance of the placenta in the pathogenesis of preeclampsia; preeclampsia can develop without a fetus in the case of molar pregnancies (a rapidly growing placenta with trophoblastic tissue) and in multiple gestations (increased placental mass). There are also case reports of twin pregnancies where preeclampsia is reversed upon termination of the severely growth restricted twin and involution of the pathologic placenta.
In normal gestation, the uterine artery’s terminal branches, the spiral arteries, invade the placenta and are transformed from muscular arteries into relaxed flaccid vessels to accommodate an eventual 10-fold increase in uterine blood flow. This transformation is dependent on the placental trophoblasts which invade and surround the uterine spiral artery’s vascular walls. The placental trophoblasts, normally epithelial cells, replace their adhesion molecules with those of endothelial cells to assume vascular endothelial cell phenotype prior to invading the uterine arteries, a process termed pseudo-vasculogenesis. This vascular remodeling results in increased blood flow and supply of nutrients and oxygen to the fetus by the end of the first trimester. In preeclampsia, pseudo-vasculogenesis is defective; cytotrophoblast invasion from the placenta is shallow, the arteries remain small and muscular and the ensuing placental ischemia is thought to trigger the release of placental-derived factors. Of considerable interest is the increased incidence of preeclampsia in women with medical conditions associated with microvascular disease such as hypertension, diabetes and collagen vascular disease, as the impaired placental perfusion leading to ischemia may be the common source of this disease.

The idea that impaired placental perfusion leads to release of ‘factors’ into the maternal circulation to cause the clinical manifestations of preeclampsia is not new, although the precise nature of these ‘factors’ awaits ultimate description. The placenta derived preeclampsia factors causing systemic endothelial dysfunction have for decades been elusive. Maynard et al have reported that angiogenic proteins such as placental growth factor (PIGF) and vascular endothelial growth factor (VEGF) are both required for normal angiogenesis and endothelial function in pregnancy, and are reduced in women with preeclampsia. Recent studies report elevated maternal serum levels of a protein which in preeclampsia appears to scavenge these factors and induce endothelial dysfunction: a soluble fms-like tyrosine kinase 1 (sFlt-1) (also called soluble vascular endothelial growth factor receptor 1; sVEGFR-1). This molecule is a circulating modified VEGF receptor which functions to neutralize VEGF and PIGF, and is found in excess quantities in both the placenta and the serum of preeclamptic women. When administered to pregnant rats, sFlt-1 has been shown to induce a preeclampsia-like phenotype with albuminuria, hypertension and renal pathologic changes of glomerular endotheliosis. In human studies, increased serum levels of sFlt-1 and reduced levels of PIGF have been found to predict the subsequent development of preeclampsia, and decreased urinary PIGF in the early second trimester is strongly associated with subsequent early development of preeclampsia. The mechanism for the upregulation of sFlt-1, and whether normalization of VEGF and PIGF levels might halt progression of preeclampsia are yet unknown.

Other factors that may be derived from the placenta, and are postulated to be related to preeclampsia are substances which increase oxidant stress, leptin, and a variety of cytokines including TNF alpha. Oxidative stress due to hypoxia driven free-radical generation at the fetal-maternal interface has been suggested as a cause of preeclampsia. The byproducts of increased oxidative stress, possibly released by the placenta in response to hypoxia or ischemia, have been implicated in the genesis of endothelial cell damage in preeclampsia. Small studies using antioxidants to prevent preeclampsia have been encouraging and vitamins E and C are currently being studied in larger trials to determine their potential role in prevention.

Pathologically, the lesion of the placenta is in preeclampsia is termed acute atherosis and is characterized by an accumulation of fat-laden macrophages and infiltrates in the arteries not invaded by trophoblast cells. In a study of 400 placentas from preeclamptic women, vascular lesions in the placenta correlated with the severity of clinical disease. Preeclampsia is also associated with a greater degree of placental infarction than in normal gestation, however the placenta has considerable reserve, explaining why some infants are growth restricted or die but more often are normal for gestational age.
Maternal Syndrome of Preeclampsia

Blood Pressure in Preeclampsia

High blood pressure in preeclampsia is due mainly to a reversal of the vasodilatation of normal pregnancy, replaced by a marked increase in peripheral vascular resistance. Preeclamptics do not develop overt hypertension until late gestation (after week 20, and usually not until the third trimester), but vasoconstrictor influences may be present much earlier. For instance longitudinal and epidemiologic surveys show that women destined to develop preeclampsia have slightly higher “normal” blood pressure (e.g., diastolic levels >70 mm Hg) as early as the second trimester.

The precise mechanism of preeclamptic hypertension is obscure. During normal pregnancy the renin-angiotensin system is stimulated, most likely in response to vasodilatation and lower blood pressure. In contrast with normal pregnancy, women with preeclampsia have suppressed plasma renin activity, aldosterone, urinary aldosterone excretion and angiotensin II levels. There is evidence that the renin-angiotensin system is stimulated early in pregnancy in women who later develop preeclampsia and that the developing vasoconstriction and hypertension turn off renin secretion. This decrease in renin has been used as a screening test to identify gravidas in midgestation who are at risk for the development of preeclampsia.

Fig. 88.1: Hypothesis on the role of sFlt1 in preeclampsia. (a) During normal pregnancy, the uterine spiral arteries are infiltrated and remodeled by endovascular invasive trophoblasts, thereby increasing blood flow significantly in order to meet the oxygen and nutrient demands of the fetus. (b) In the placenta of preeclamptic women, trophoblast invasion does not occur and blood flow is reduced, resulting in placental hypoxia. In addition, increased amounts of soluble Flt1 (sFlt1) are produced by the placenta and scavenge VEGF and PIGF, thereby lowering circulating levels of unbound VEGF and PIGF. This altered balance causes generalized endothelial dysfunction, resulting in multi-organ disease. It remains unknown whether hypoxia is the trigger for stimulating sFlt1 secretion in the placenta of preeclamptic mothers and whether the higher sFlt1 levels interfere with trophoblast invasion and spiral artery remodeling. Used with permission J. Clin. Invest 111:600-602 (2003) Luttun and Carmeliet
Blood pressure in preeclampsia is also characteristically labile, and exaggerated responses to norepinephrine and angiotensin despite normal plasma levels have been noted.\textsuperscript{18} There is a reversal of the normal circadian rhythm, with blood pressures often being higher at night.\textsuperscript{19} In addition, increases in peripheral vascular resistance and blood pressure that characterize preeclampsia have been found to be mediated, at least in part, by a substantial increase in sympathetic vasoconstrictor activity which reverts to normal after delivery.\textsuperscript{20} These observations lend mechanistic support for the use of methyldopa, which is metabolized to a-methylnorepinephrine and replaces norepinephrine to decrease sympathetic tone centrally.

Changes in eicosanoid metabolism occur in normal pregnancy, particularly prostacyclin (PGI\textsubscript{2}) and thromboxane (TXA\textsubscript{2}) production, and further alterations arise in pre-eclampsia. Prostaglandins such as PGI\textsubscript{2} are increased in normal pregnancy, particularly vasodilatory prostanoids (mostly PGI\textsubscript{2}) by vascular endothelial cells\textsuperscript{21}, and this may contribute to the generalized vasodilatation characteristic of pregnancy. Reduced PGI\textsubscript{2}, but not TXA\textsubscript{2}, has been found to occur months before the clinical onset of preeclampsia.\textsuperscript{22,23} There is substantial literature suggesting that alterations in prostaglandin metabolism underlie the pathogenesis of pre-eclampsia.\textsuperscript{21-25} Manifestations such as increments in vascular reactivity and blood pressure, as well as intravascular coagulation, have been proposed to be due to an imbalance between PGI\textsubscript{2} and TXA\textsubscript{2} synthesis, resulting in a relative or absolute PGI\textsubscript{2} deficiency. These findings are consistent with evidence that pre-eclampsia is characterized by generalized vascular endothelial cell dysfunction, leading to diminished production of PGI\textsubscript{2}, as well as other vasodilatory endothelial cell products.

In spite of the large body of evidence supporting a role for alterations in prostaglandin metabolism in pre-eclampsia, it is important to emphasize that these substances are difficult to measure, and act locally, so measurements from peripheral blood may not reflect local effects. Nevertheless, the notion that pre-eclampsia is characterized by a deficiency of PGI\textsubscript{2} with stable or increased TXA\textsubscript{2} production has been the basis of several large multicenter randomized trials evaluating low-dose aspirin (which inhibits platelet TXA\textsubscript{2} generation but spares vascular PGI\textsubscript{2} production) in the prevention of pre-eclampsia. Despite early, small relatively small studies that reported striking reductions in the risk of preeclampsia in women treated with low dose aspirin, a recent Cochrane review including data from 36,500 women did not reveal overall beneficial effect of aspirin on pregnancy outcome.\textsuperscript{26}

**Endothelial Cell Function**

In recent years, the role of the vascular endothelial cells in the modulation of vascular smooth muscle contractile activity, as well as in coagulation and regulation of blood flow, has increased understanding of endothelial cell function in the pathophysiology of pre-eclampsia, and other chronic cardiovascular conditions, such as atherosclerosis and essential hypertension. Endothelial cells, which have receptors for numerous vasodilators and constrictors, produce hormones, autacoids, and mitogenic cytokines, including PGI\textsubscript{2}, nitric oxide, and endothelin. The pathophysiologic changes of preeclampsia, particularly those present before clinically apparent disease, support the hypothesis that altered endothelial function contributes to many of the changes observed in the preeclamptic syndrome.\textsuperscript{27} Women with preeclampsia manifest increased circulating markers of endothelial activation (von Willibrand Factor, cellular fibronectin, thrombomodulin, endothelin, V-CAM).\textsuperscript{28} Preeclamptic blood vessels demonstrate reduced endothelial mediated vasodilation in vitro\textsuperscript{28}, and in vivo studies have shown that flow mediated (endothelium dependent) dilatation is impaired in women with previous preeclampsia.\textsuperscript{25} Most recently, raised plasma concentrations of asymmetric dimethylarginine (ADMA) the endogenous inhibitor of endothelial nitric oxide synthase, has been shown to be elevated in women with evidence of abnormal endothelial function prior to the development of preeclampsia.\textsuperscript{29}
There are numerous reports of a hypertensive syndrome produced by inhibiting nitric oxide synthase in various experimental models of gestation, with some features similar to human pre-eclampsia. Results from women with pre-eclampsia are conflicting, with reports of increased as well as decreased serum and urinary metabolites of nitric oxide in pre-eclampsia.

Endothelins represent another vasoactive endothelial cell product postulated to play a role in pre-eclampsia. In this respect, circulating levels of endothelin-1 are generally (but not universally) reported as increased in this disorder, but it is unclear if such levels have pathogenic significance or are a byproduct of endothelial damage.

The evidence for endothelial cell dysfunction in the pathogenesis of the maternal manifestations of pre-eclampsia is strong; and its cause continues to be actively investigated. As mentioned circulating factors of placental origin e.g s-Flt 1, are likely involved. Indeed, sera from women destined to develop or manifest pre-eclampsia alter endothelial cell function or cause endothelial cell activation in vitro (assessed by nitric oxide and PGI2 generation). Sera from pre-eclamptic patients are also mitogenic and increase messenger RNA for, as well as production of, the growth factor PDGF-β in culture.

There is also a growing body of evidence implicating increased lipid peroxides as well as byproducts of increased oxidative stress, possibly released by the placenta in response to hypoxia or ischemia, in the genesis of endothelial cell damage in pre-eclampsia.

**Metabolic Disturbances in Pre-eclampsia**

Hyperinsulinemia, obesity, glucose intolerance and dyslipidemia (e.g., increased triglycerides, reduced HDL) are associated with cardiovascular disease and essential hypertension. Insulin resistance and hyperinsulinemia (mediated by hormonal changes) are also characteristic of normal pregnancy, and are maximal in the third trimester. Several laboratories have reported exaggerated metabolic disturbances in patients with pre-eclampsia, including hyper-triglyceridemia, increased levels of free fatty acids, decreased levels of lipoprotein a, increased insulin levels, and glucose intolerance. These observations are intriguing, particularly because they may be related to the evidence for increased oxidative stress in pre-eclampsia (lipid abnormalities may result in increased oxidative stress.

Obesity remains an important risk factor for preeclampsia, with strong positive association between maternal prepregnancy body mass index and the risk of preeclampsia. Early pregnancy dyslipidemia and gestational diabetes are also associated with an increased 2-3 fold risks of preeclampsia. At this time it is uncertain if these are cause or markers for endothelial dysfunction, or if they may be cause or evidence of increased oxidative stress in preeclampsia.

**Cardiac Function in Preeclampsia**

Blood pressure normally declines in early pregnancy; systolic pressure changes little, while diastolic pressure falls by 10 mm Hg at 13 to 20 weeks, then rises again to prepregnancy levels in the third trimester. Normal pregnancy is characterized by primary vasodilatation and increased cardiac output is due in part to the decreased afterload. As noted high blood pressure in preeclampsia is due mainly to a reversal of the vasodilatation of normal pregnancy, replaced by marked increases in peripheral vascular resistance. Most studies of cardiovascular hemodynamics in women with preeclampsia have been performed in women with established disease and may be confounded by ongoing treatment. Invasive hemodynamic monitoring of untreated preeclampsics as well as limited careful echocardiographic studies demonstrate that women with preeclampsia have either normal or slightly decreased cardiac output in association with increased systemic vascular resistance and increased afterload. Serial echocardiographic studies throughout gestation have shown that in women who eventually developed preeclampsia, increased cardiac outputs and decreased peripheral vascular resistance were found early in pregnancy followed by high
resistance low cardiac output states when preeclampsia developed. Other studies of nulliparous gravidas with preeclampsia in the third trimester using pulmonary artery catheter, show decreased cardiac output in preeclamptic patients compared with controls. Peripheral vascular resistance was increased, and pulmonary capillary wedge pressure was low normal. This has been confirmed in other studies, and amounts to a normal ventricle contracting normally against a markedly increased afterload. Peripartum heart failure can occur in this setting, though it is usually a complication of preexisting heart disease.

Plasma volume and red blood cell mass are increased in normal pregnancy, as physiologic vasodilatation leads to stimulation of the renin angiotensin system, and volume retention ensues. In preeclampsia however, plasma volume is decreased, this documented by measurement with Evans blue dye. The decrease in plasma volume may be secondary to vasoconstriction and hypertension, although there are some reports that decreases in plasma volume may precede hypertension. These latter reports have led to the use of volume expansion therapy with vasodilator drugs in the treatment of preeclampsia. In view of the suppressed renin-angiotensin system in preeclampsia, the decreased plasma volume seems likely secondary to vasoconstriction and a “smaller” intravascular compartment. Reports that the decreased plasma volume may have preceded hypertension led to the experimental use of volume expansion therapy, although in Cochrane analysis, this treatment remains unproven.

Renal Changes in Preeclampsia

Consistent with the effects of preeclampsia on the endothelium, the renal lesion characteristic of preeclampsia is glomerular endotheliosis. The glomeruli are enlarged and swollen but not hypercellular, due primarily to hypertrophy of the intracapillary cells (mainly endothelial but mesangial as well), which encroach on the capillary lumina, giving the appearance of a bloodless glomerulus. The basement membrane is usually not thickened and foot process are usually well preserved, even when severe proteinuria is present. Interestingly sFlt-1, which is elevated in women with preeclampsia, has been administered to pregnant rats and induces hypertension, proteinuria, and glomerular endotheliosis, the classic lesion of preeclampsia. Similarly, these renal alterations are also observed in experimental models that are characterized by reduced VEGF levels in the case of VEGF knockout mice.

Localized lesions resembling those of focal and segmental glomerulosclerosis (FSGS) are present in about 20% of women with preeclampsia. The significance of this finding is not clear; some consider it to be a sequelae of preeclampsia, a form of secondary FSGS, whereas others consider that it may be a manifestation of preexisting subclinical nephrosclerosis.

In preeclampsia, both glomerular filtration rate and renal blood flow decrease, the former more so than the later, leading to a decrease in filtration fraction. The decrement is usually modest (25%) even when morphologic changes are pronounced. Because renal function normally rises 35-50% during pregnancy, creatinine levels are usually still below the upper limits of normal. The basis for the altered renal hemodynamics is not certain, renal histological and hormonal changes are probably involved. Recent evidence suggests that the hormone relaxin, a natural vasodilator produced by the corpus luteum and placenta, is reduced in women with preeclampsia and may contribute to the renal changes observed. Fractional urate clearances decrease, often before overt disease is apparent, with a uric acid level greater than 5.5 mg/dl (327 mmol/L) being an important marker of pre-eclampsia. This appears to be a sensitive marker of decreased renal clearance and glomerular filtration. Proteinuria > .3g/day (but in some cases nephrotic range i.e. >3g/day), is another hallmark which may appear late in the clinical course of the disease. Rarely, renal insufficiency may develop due to acute tubular or cortical necrosis associated with pre-eclampsia.
Sodium excretion appears to be impaired in preeclampsia, documented in studies of renal excretory ability after saline infusion, though the reduction in intravascular volume and decreased placental perfusion are major reasons to avoid diuretics in preeclampsia. Renal handling of calcium is also abnormal in pre-eclampsia, with hypocaliuria, low plasma 1,25-dihydroxyvitamin D3 and high parathyroid hormone noted.

Coagulation System

Pregnancy is associated with an increase in hemostatic factors and decrease in fibrinolytic proteins; factors II, VII, X, VIII, XII and fibrinogen increase 20-200% whereas the fibrinolytic protein S has a 40% decrease during pregnancy. The inherited coagulopathies are major causes of thromboembolic disease in both pregnant and nonpregnant individuals; the most common are autosomal dominant deficiencies of antithrombin III, protein C, protein S, as well as activated protein C resistance due to the factor V Leiden mutation, and a function-enhancing mutation in the prothrombin gene (Prothrombin G20210A) and hyperhomocystinemia. The pregnancy associated changes in hemostatic and fibrinolytic proteins exacerbate the clinical effect of heritable coagulopathies. A postulated mechanism for preeclampsia in relation to the coagulopathies is the development of microthrombi in the placental circulation, with decreased placental perfusion leading to preeclampsia, hypertension and proteinuria. Factor V Leiden mutation is the most common heritable coagulopathy, affecting 5-9% of European populations, though is rare in Asian and African populations. A recent meta-analysis suggests that factor V Leiden mutation is the most common heritable coagulopathy, affecting 5-9% of European populations, though is rare in Asian and African populations.

Hepatic Abnormalities

The liver dysfunction that may accompany preeclampsia is correlated to the histological findings, which include periportal hemorrhages, ischemic lesions and fibrin disposition. These are consistent with both endothelial damage and activation of the coagulation system leading to some amount of liver tissue edema or necrosis. Involvement may range from mild enzyme abnormalities, to HELLP with markedly elevated transaminase levels, to subcapsular bleeding or hepatic rupture. HELLP syndrome - Hemolysis, Elevated Liver enzymes, Low Platelets is well described in the clinical literature and requires the presence of hemolysis on peripheral smear and platelet counts below 100,000/mm³ and transaminase levels > 2 x normal for diagnosis. Liver involvement in preeclampsia generally signifies more serious disease and is associated with an increased risk of maternal complications compared to preeclampsia alone.
Central Nervous System

Eclampsia, seizures in preeclampsia which can not be attributed another cause, are the most common central nervous system complication and are responsible for the most maternal deaths in this disease. In one small series, seizures were preceded by headache in 64% and by visual changes in 32%. Visual disturbances include blurred vision, scotomas, and rarely, reversible cortical blindness (reversible posterior leukencephalopathy). In these cases, CT and MRI studies showed extensive bilateral white-matter abnormalities suggestive of vasogenic edema without infarction in the occipital and posterior parietal lobes of the cerebral hemispheres.

Pathologic specimens postmortem of eclampsia reveal hemorrhages and petechiae, vasculopathy, and ischemia with microinfacts. The cause of cerebral hemorrhage is debated; vasospasm, thrombosis and rupture have been postulated and transcranial Doppler studies document increased cerebral blood flow velocity consistent with vasospasm in women with preeclampsia and eclampsia. Convulsions have been observed in women with only mild to moderate hypertension; the mechanisms for the seizures are not known, though by computed tomography and magnetic resonance imaging cerebral edema has been described, as have hemorrhage and edema in the vascular watershed areas of the posterior hemispheres. Predominance of posterior lesions may explain the increased incidence in preeclampsia-eclampsia of visual disturbances. Rarely, hemorrhages may be major and associated with permanent neurologic sequelae. Cerebral edema observed on some transcranial tomography studies may be a consequence of excess administration of fluids in patients with low oncotic pressure due to hypoalbuminemia. Rarely, reversible posterior leukoencephalopathy may develop in patients with eclampsia, which is transient blindness which resolves completely in most cases. The findings on neuroimaging are characteristic of subcortical edema without infarction.

LONG-TERM SEQUELAE OF PREECLAMPSIA

The pathophysiologic changes of preeclampsia appear to confer long-term risk for cardiovascular disease in the mother. In an analysis of follow up of over 30,000 hypertensive pregnant women, gestational hypertension, mild preeclampsia and severe preeclampsia were associated with 2.8-, 2.2- and 3.3-fold greater risks for premature cardiovascular events; a magnitude of excess risk which is on par with smoking. Severe preeclampsia was also associated with a 2.3 greater risk for thromboembolic events and in a separate study the rate ratio for later death from stroke for the pre-eclampsia/ eclampsia group was 3.59. Whether this is a result of permanent endothelial injury or if preeclampsia is a manifestation of an underlying predisposition to vascular disease is not known.

REFERENCES


