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VARIABLES IN THE PATHOGENESIS OF PRE-ECLAMPSIA

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ABSTRACT

Preeclampsia remains a common complication of pregnancy that leads to unacceptable increases in fetal and maternal morbidity and mortality, particularly in less developed nations. Efforts continue to understand better the pathophysiology of the clinical manifestations of the disease. Recent findings on the role of circulating antiangiogenic factors have generated great optimism for being able to predict better the disease and develop therapeutic advances. If subsequent trials validate these theories, then future work should lead to renewed efforts finally to explain and treat this complex disease.

KEYWORDS: Pathogenesis, pre-Eclampsia.

INTRODUCTION

Preeclampsia, a multisystem pregnancy disorder characterized by gestational hypertension and often associated with proteinuria in the second trimester, threatens the safety of 2-5% of mothers and neonates worldwide.[1]

The progressive stage of preeclampsia with convulsions is defined as eclampsia. Although the mechanism of preeclampsia/eclampsia (PEE) is incompletely elucidated, placenta-induced immune and endothelial dysfunction is considered a key role in leading to pertinent pathogenesis and complications. The exquisite balance between proinflammatory and anti-inflammatory reactions in pregnancy is dramatically altered in the presence of PEE.

Growing evidence shows that systemic inflammation is induced by helper T-lymphocyte immune shifting and a subsequent series of evoked cytokine response during PEE

activation.[2] Even after delivery, PEE-mediated immune inflammation consistently increases the risks for systemic disorders.

Preeclampsia still ranks as one of the obstetrics major problems. Clinicians typically encounter preeclampsia as a maternal disease with variable degrees of fetal involvement. More and more the unique immunogenetic maternal–paternal relationship is appreciated, and as such also the specific 'genetic conflict' that is characteristic of haemochorial placentation. From that perspective, preeclampsia can also be seen as a disease of an individual couple with primarily maternal and fetal manifestations. Factors that are unique to a specific couple would include the length and type of sexual relationship, the maternal (decidual natural killer cells) acceptation of the invading cytotrophoblast (paternal HLA-C), and seminal levels of transforming growth factor-b and probably other cytokines. The magnitude of the maternal response would be determined by factors including a maternal set of genes determining her characteristic inflammatory responsiveness, age, quality of her endothelium.[3]

Pre-eclampsia occurs in pregnancy, and it is characterized by the new onset of hypertension with proteinuria or other organ dysfunctions after 20-weeks gestation. Pre-eclampsia is the leading cause of maternal and fetal morbidity and mortality worldwide. Pre-eclampsia occurs in 4–6% of pregnancies.[4] Certain pre-existing conditions such as type 1 and type 2 diabetes mellitus (DM) can increase the risk of preeclampsia up to 4-fold. Pre-eclampsia does not only have short-term risks, but long term can lead to cardiovascular disease and/or type 2 DM in both mothers and their offspring. Currently, there are no reliable and early predictive biomarkers, preventative measures or treatment strategies, other than delivery. The mechanistic data related to the development of pre-eclampsia is lacking, and, as a result, the pathogenesis of pre-eclampsia is poorly understood. Some of the processes which appear to be involved in the development of pre-eclampsia include inappropriate remodeling of spiral uterine artery (SUA) likely caused by inadequate function of trophoblast cells. Inadequate remodeling of SUA leads to the restricted supply of oxygen and nutrients to the placenta and, therefore, placental hypoxia.[5]

BACKGROUND

Epidemiology

Pre-eclampsia is a multisystem disorder that complicates 3%–8% of pregnancies in Western countries and constitutes a major source of morbidity and mortality worldwide. Overall, 10%–15% of maternal deaths are directly associated with preeclampsia and eclampsia.[6]

Some epidemiological findings support the hypothesis of a genetic and immunological etiology. The risk of pre-eclampsia is 2-fold to 5-fold higher in pregnant women with a maternal history of this disorder. Depending on ethnicity, the incidence of pre-eclampsia ranges from 3% to 7% in healthy nulliparas and 1% to 3% in multiparas. Moreover, nulliparity and a new partner have been shown to be important risk factors.

Other risk factors have been identified, including a medical history of chronic hypertension, kidney disease, diabetes, obesity, birthplace in Africa, age 35 years, and pregnancy characteristics, such as twin or molar pregnancy, previous pre-eclampsia, or fetal congenital abnormality. High altitude has also been shown to increase the incidence of pre-eclampsia, and is attributed to greater placental hypoxia, smaller uterine artery diameter, and lower uterine artery blood flow. Pre-eclampsia may be life-threatening for both mother and child, increasing both fetal and maternal morbidity and mortality.

In the mother, pre-eclampsia may cause premature cardiovascular disease, such as chronic hypertension, ischemic heart disease, and stroke, later in life,9 while children born after pre-eclamptic pregnancies and who are relatively small at birth, have an increased risk of stroke, coronary heart disease, and metabolic syndrome in adult life. The sole curative treatment being delivery, management must continuously balance the risk-benefit ratio of induced preterm delivery and maternal-fetal complications. Screening women at high risk and preventing recurrences are also key issues in the management of pre-eclampsia.[7]

Table 1 Major risk factors for pre-eclampsia[49]

Risk factor	OR or RR (95% CI)
Antiphospholipid antibody syndrome	9.7 (4.3–21.7)
Renal disease	7.8 (2.2–28.2)
Prior pre-eclampsia	7.2 (5.8–8.8)
Systemic lupus erythematosus	5.7 (2.0–16.2)
Nulliparity	5.4 (2.8–10.3)
Chronic hypertension	3.8 (3.4–4.3)
Diabetes mellitus	3.6 (2.5–5.0)
High altitude	3.6 (1.1–11.9)
Multiple gestations	3.5 (3.0–4.2)
Strong family history of CV disease (heart disease or stroke in ≥2 first-degree relatives)	3.2 (1.4–7.7)
Obesity	2.5 (1.7–3.7)
Family history of pre-eclampsia in first-degree relative	2.3–2.6 (1.8–3.6)
Advanced maternal age (>40 years)	1.68 (1.23–2.29) for nulliparas 1.96 (1.34–2.87) for multiparas

Abbreviations: CI, confidence interval; OR, odds ratio; RR, relative risk; CV, cardiovascular.

Pathophysiology

During normal pregnancy, the villous cytotrophoblast invades into the inner third of the myometrium, and spiral arteries lose their endothelium and most of their muscle fibers. These structural modifications are associated with functional alterations, such that spiral arteries become low resistance vessels, and thus less sensitive, or even insensitive, to vasoconstrictive substances. Pre-eclampsia has complex pathophysiology, the primary cause being abnormal placentation. Defective invasion of the spiral arteries by cytotrophoblast cells is observed during pre-eclampsia. Recent studies have shown that cytotrophoblast invasion of the uterus is actually a unique differentiation pathway in which the fetal cells adopt certain attributes of the maternal endothelium they normally replace.[8]

In pre-eclampsia, this differentiation process goes awry.13 The abnormalities may be related to the nitric oxide pathway, which contributes substantially to the control of vascular tone. Moreover, inhibition of maternal synthesis of nitric oxide prevents embryo implantation.[9]

Increased uterine arterial resistance induces higher sensitivity to vasoconstriction and thus chronic placental ischemia and oxidative stress. This chronic placental ischemia causes fetal complications, including intrauterine growth retardation and intrauterine death. In parallel, oxidative stress induces release into the maternal circulation of substances such as free radicals, oxidized lipids, cytokines, and serum soluble vascular endothelial growth factor.[10]

These abnormalities are responsible for endothelial dysfunction15 with vascular hyperpermeability, thrombophilia, and hypertension, so as to compensate for the decreased flow in the uterine arteries due to peripheral vasoconstriction. Endothelial dysfunction is responsible for the clinical signs observed in the mother, ie, impairment of the hepatic endothelium contributing to onset of the HELLP (Hemolysis, Elevated Liver enzymes and Low Platelet count) syndrome, impairment of the cerebral endothelium inducing refractory neurological disorders, or even eclampsia. Depletion of vascular endothelial growth factor in the podocytes makes the endotheliosis more able to block the slit diaphragms in the basement membrane, adding to decreased glomerular filtration and causing proteinuria.[11]

Finally, endothelial dysfunction promotes microangiopathic hemolytic anemia, and vascular hyperpermeability associated with low serum albumin causes edema, particularly in the lower limbs or lungs. The crucial issue to understand is that the prime mover of pre-eclampsia is

abnormal placentation. Two common theories appear to be interlinked, ie, genetic theory and an immunological theory. Several susceptibility genes may exist for pre-eclampsia.[12]

These genes probably interact in the hemostatic and cardiovascular systems, as well as in the inflammatory response. Some have been identified, and in candidate gene studies they have provided evidence of linkage to several genes, including angiotensinogen on 1-q42–43 and eNOS on 7q36; other main important loci are 2p12, 2p25, 9p13, and 10q22.1.16 Pre-eclampsia can be perceived as an impairment of the maternal immune system that prevents it from recognizing the fetoplacental unit. Excessive production of immune cells causes secretion of tumor necrosis factor alpha which induces apoptosis of the extravillous cytotrophoblast.[13] The human leukocyte antigen (HLA) system also appears to play a role in the defective invasion of the spiral arteries, in that women with pre-eclampsia show reduced levels of HLA-G and HLA-E.18 During normal pregnancies, the interaction between these cells and the trophoblast is due to secretion of vascular endothelial growth factor and placental growth factor by natural killer cells. High levels of soluble forms-like tyrosine kinase 1 (sFlt-1), an antagonist of vascular endothelial growth factor and placental growth factor, have been found in women with pre-eclampsia.[14]

Accordingly, assays of sFlt-1, placental growth factor, endoglin, and vascular endothelial growth factor, all of which increase 4–8 weeks before onset of the disease, may be useful predictors of pre-eclampsia. Recent data show the protective role of heme oxygenase 1 and its metabolite, carbon monoxide, in pregnancy, and identify this as a potential target in the treatment of pre-eclampsia.[15]

Clinical presentation and workup findings

Clinical and laboratory tests are intended to define and determine the severity of pre-eclampsia. Headaches, tinnitus, phosphene signals, visual disorders, brisk tendon reflexes, and vigilance disorders are related to cerebral edema; oliguria to acute renal failure; uterine contraction, vaginal bleeding to placental abruption; vomiting to HELLP syndrome; bandlike epigastric pain to subcapsular hepatic hematoma; and dyspnea to cardiac failure. Eclampsia, the major neurological complication of pre-eclampsia, is defined as a convulsive episode or any other sign of altered consciousness arising in a setting of pre-eclampsia, and which cannot be attributed to a pre-existing neurological condition.[16]

Clinical examination should include resting blood pressure measurement using an appropriate cuff, and screening for weight gain, edema (including signs of acute pulmonary edema and cerebral edema), cardiomyopathy, and acute renal failure. The fetus should be assessed by electrocardiotocography. Laboratory tests include: a complete blood count with platelets, haptoglobin, and lactate dehydrogenase; a blood smear to test for schistocytes; bilirubin, aspartate transaminase, and alanine transaminase in order to identify potential HELPP syndrome; electrolyte, urea, and creatinine assessment to check for acute renal failure or uremia; 24-hour proteinuria; prothrombin, activated thrombin time, and fibrinogen (microangiopathic hemolytic anemia); blood group; and irregular antibody screening. Other examinations include fetal ultrasound with Doppler velocimetry of the umbilical, cerebral, and uterine arteries, estimation of fetal weight, assessment of fetal well-being by Manning score, and examination of the placenta.[17]

Although the definition of severe pre-eclampsia varies, several components of this definition are usually accepted: maternal systolic blood pressure 160 mmHg or diastolic blood pressure 110 mmHg; maternal neurological disorders such as persistent headaches, phosphene signals, tinnitus, and brisk, diffuse, polykinetic tendon reflexes, eclampsia, acute pulmonary edema, proteinuria 5 g/day, oliguria, 500 cc/day, creatinine. 120 µmol/L, HELLP syndrome, thrombocytopenia, 100,000/mm3, and fetal criteria, especially intrauterine growth retardation, oligohydramnios, or fetal death in utero.[18]

Mild pre-eclampsia is defined as diastolic blood pressure $90 mmHg measured on two occasions at least 6 hours apart, combined with proteinuria (two or more occurrences of protein on the dipstick, .300 mg total protein in a 24-hour urine collection, or a protein creatinine ratio .30 mg/mmol).[19]

Variables in the pathogenesis of pre-Eclampsia

The abnormal placentation that results from failure of trophoblast remodeling of uterine spiral arterioles is thought to lead to the release of secreted factors that enter the mother's circulation, culminating in the clinical signs and symptoms of preeclampsia. All of the clinical manifestations of preeclampsia can be attributed to glomerular endotheliosis, increased vascular permeability, and a systemic inflammatory response that results in end-organ damage and/or hypoperfusion. These clinical manifestations typically occur after the 20th week of pregnancy.[20]

Hypertension

Accommodation to normal pregnancy includes a decrease in both systolic and diastolic BP as a result of a decrease in systemic vascular resistance primarily secondary to vasodilation. Relaxin, which is released from the ovaries under the influence of human chorionic gonadotrophin, upregulates nitric oxide synthase (NOS)[21], the enzyme that generates NO from arginine, via the endothelial endothelin B receptor.

In preeclampsia, derangement of endothelial-derived vasoactive factors is thought to result in the predominance of substances that are vasoconstrictors (endothelin, thromboxane A2) over vasodilators (NO, prostacyclin). Hypertension, defined as repeat BP measurements 140/90 mmHg, results from abnormal vasoconstriction. Normal pregnancy in the rat is accompanied by increased production of NO and its second messenger, cyclic guanosine 3-5 monophosphate with a parallel increase in renal expression of constitutive NOS.[22]

In the pregnant rat, an infusion of NG-nitro-l-arginine methyl ester (L-NAME), an exogenous inhibitor of NOS, has been shown to replicate some of the hemodynamic features of preeclampsia. l-Arginine supplementation reversed these adverse effects of L-NAME on pregnancy, attenuating hypertension, significantly decreasing proteinuria, and reducing the proportion of injured glomeruli.[23]

However, in humans, evidence to support a role of NO deficiency in the pathogenesis of hypertension in preeclampsia has been conflicting. Although elevated circulating levels of asymmetric dimethylarginine, an endogenous inhibitor of NOS, has been a consistent finding in pregnancies that are complicated by preeclampsia, plasma concentrations are typically very low with a narrow distribution among healthy adults, making quantification extremely challenging and the clinical significance of the finding uncertain.[24]

Furthermore, l-arginine supplementation has not conferred significant benefit in women with pregnancies that are complicated by preeclampsia. Another hypothesis considered the possibility that an early gestational exaggeration of the normal accommodation to pregnancy can be used to identify and may be pathogenic in preeclampsia.[25] A longitudinal study that used Doppler echocardiography in 400 primigravidas throughout pregnancy noted a significantly increased cardiac output without any difference in peripheral vascular resistance in the 24 women who eventually developed preeclampsia compared with healthy control subjects.[26]

This increased cardiac output was followed by a marked reduction in the cardiac output and increased peripheral vascular resistance with the onset of the clinical syndrome. This notion of a crossover in the hemodynamic profile in women who develop preeclampsia resulted in a handful of studies that used blockers in a preventive manner.[27] These studies were typically small and/or uncontrolled. Furthermore, reduced fetal growth was noted in the women who received the blockers, possibly because of an overaggressive decrease in the cardiac output.

Decreased GFR

Healthy pregnant women exhibit marked glomerular hyperfiltration, peaking above normal, nongravid levels by 40 to 60% (39,40). This hyperfiltration seems to result primarily from the depression of the plasma oncotic pressure (GC) in the glomerular capillaries. The reduction of GC in pregnancy is attributable to two phenomena. The first is a hypervolemia-induced hem dilution that lowers the protein concentration of plasma that enters the glomerular microcirculation. The second is an elevated rate of RPF.[28] Hyperperfusion of glomeruli blunts the extent to which the oncotic pressure can increase along the glomerular capillaries during filtrate formation. In preeclampsia, variable degrees of renal insufficiency is associated with a characteristic glomerular lesion, "glomerular endotheliosis." Precise physiologic measurements in conjunction with immediate postpartum biopsies were used to examine the determinants of the GFR in women with preeclampsia as compared with healthy gravid control subjects. The GFR was significantly depressed to 91 ml/min per 1.73 m2 in women with preeclampsia compared with a value of 149 ml/min per 1.73 m in the control subjects. Of interest, no significant differences were found in either RPF or GC.

The morphometric analysis revealed significant ultrastructural differences, including swelling of the endothelial cells, subendothelial fibrinoid deposition, and mesangial cell interposition. Scanning electron microscopy was used to characterize the endothelial fenestral dimensions, allowing the authors to conclude that a reduction in the density and the size of the endothelial fenestrae and subendothelial accumulation of fibrinoid deposits severely lowered glomerular hydraulic permeability in patients with preeclampsia. Mesangial cell interposition also decreased available surface area for filtration, thereby resulting in a cumulative depression of Kf that was exactly proportional to the GFR.[29]

A more controversial conclusion was that the hyperfiltration in preeclampsia does not have a hemodynamic basis. A recent study used a semiquantitative scale to grade the endotheliosis that was present on biopsy specimens that were taken from women with preeclampsia

approximately 1 wk before delivery.[30] They noted moderate to severe endotheliosis in all women with significant hypertension and proteinuria before delivery. Of interest, women with nonproteinuric gestational hypertension and normal pregnant women also exhibited endotheliosis but to lesser degrees, suggesting that pregnancy-induced hypertension may in some cases reflect an earlier or milder form of the same pathology.[31] Subendothelial fibrinoid deposits and mesangial cell interposition were found only in women with preeclampsia. Unfortunately, the authors never published any images or acquired confirmation from a second blinded pathologist to ensure interobserver reliability. In a second article that examined the same patient population, the authors found a linear trend between glomerular volume reflecting the degree of endotheliosis and cystatin C[32], suggesting that the basis for the hyperfiltration in preeclampsia is largely secondary to structural changes in the glomerulus as opposed to renal vasoconstriction and depression in RPF. However, the utility of cystatin C as a marker of GFR is unclear in this patient population. A recent study found that cystatin C correlated poorly with third-trimester creatinine clearance (r 0.27) (45), and another study that used inulin clearances for comparison found that the measurement is not independent of body composition as previously assumed. To date, cystatin C has not been validated as a marker of GFR in pregnancy, with several studies suggesting that it may be imprecise.[33]

Coagulopathy and HELLP Syndrome

In preeclampsia, the endothelial injury may also become manifest as a low-grade coagulopathy with increased fibronectin, increased platelet aggregation, shortened platelet survival, and depressed antithrombin III levels. The HELLP syndrome develops in up to 10% of pregnancies with severe preeclampsia, and evidence exists to suggest that it is not simply an epiphenomenon of extreme hypertension. Plasma concentrations of cellular fibronectin have been shown to be consistently higher throughout pregnancy in a woman who develops preeclampsia compared with healthy control subjects. In addition, markers of platelet activation, including -thromboglobulin, as well as assays of platelet aggregation have been demonstrated to precede the clinical manifestations of the disease.[34]

Eclampsia

Seizures with other neurologic symptoms, including headache and visual disturbances, complicate approximately 5 of every 10,000 live births, with a declining incidence as a result of improved prenatal care with expedited delivery and, possibly, the widespread use of

magnesium sulfate. The precise mechanism that is responsible for the development of seizures is not clear, but proposed theories include cerebral vasospasm, edema, and the possibility that severe hypertension might disturb cerebral autoregulation and disrupt the blood-brain barrier. The cerebral edema of eclampsia predominantly involves the posterior, parieto-occipital lobes and is similar to images described in reversible posterior leukoencephalopathy syndrome.[35] This finding on magnetic resonance imaging has been noted to correlate better with markers of endothelial dysfunction, including lactate dehydrogenase, red blood cell morphology, and creatinine than the level of hypertension (58,59). Of interest, reversible posterior leukoencephalopathy syndrome in patients with thrombotic thrombocytopenic purpura has also been found to be independent of the level of hypertension in some cases.[36]

Proteinuria

In 1843, John Lever of Guy's Hospital in London discovered the presence of albumin by boiling the urine from pregnant women with puerperal convulsions. Preeclampsia is differentiated from gestational hypertension by the presence of proteinuria and is the most common cause of nephrotic syndrome in pregnancy. The quantity of protein that is excreted in the urine varies widely. Significant protein excretion is defined as 300 mg in a 24-h urine collection or 1 or greater on urine dipstick testing of two random urine samples that are collected at least 4 h apart.[37]

Numerous studies have used a variety of methods to examine the biochemical constitution of preeclamptic urine, including protein selectivity indices, with variable results. Generally, urine from preeclampsia has demonstrated poor selectivity and has not differed significantly from other forms of primary renal disease.[38] Glomerular proteins of intermediate sizes, such as albumin, have been identified alone or in combination with varying degrees of tubular proteins, such as B2-microglobulin, reflecting the tubular damage that can occur in severe preeclampsia.[39]

Unfortunately, the exact role of the endothelial cell layer in the regulation of glomerular permselectivity remains the least well defined. Endothelial cells are difficult to acquire for in vitro studies, and, unlike the podocyte, there are no specific markers for this cell line. Perforated by large fenestrae, the endothelial cell layer does not contribute to size selectivity, allowing the passage of neutral molecules with a radius up to approximately 375 Å. Therefore, the mechanism for proteinuria in preeclampsia is not well understood. The

glomerular basement membrane and podocytes typically appear normal. Few investigators have used dextran-sieving techniques to elucidate the properties of the glomerular filtration barrier in women with preeclampsia. In the 1970s, MacLean et al. confirmed the glomerular origin of proteinuria in preeclampsia demonstrating dextran-sieving coefficients in the intermediate range.[40]

Circulating Antigenic Factors in Preeclampsia

Recently, two endogenous antiangiogenic proteins of placental origin— circulating soluble forms-like tyrosine kinase 1 (sFlt1) and soluble endoglin have been suggested, on the basis of rodent models, to play a causal role in the pathogenesis of preeclampsia.[41]

sFlt1 is a secreted protein, a splice variant of the vascular endothelial growth factor (VEGF) receptor Flt1, which lacks the transmembrane and cytoplasmic domain of the membrane-bound receptor. Circulating in the blood, it acts as a potent antagonist to VEGF and placental growth factor (PlGF). Both VEGF and PlGF are made by the placenta and circulate in high concentration during pregnancy. Circulating sFlt1 levels are greatly increased in women with preeclampsia even before the onset of clinical symptoms.[42]

Consistent with the action of the circulating protein to bind PlGF, free PlGF levels are also decreased in preeclamptic women before the onset of clinical symptoms. When administered to pregnant and nonpregnant rats, sFlt1 produces a syndrome of hypertension, proteinuria, and glomerular endotheliosis that resembles preeclampsia.[43] It has also been shown that VEGF induces endothelial fenestrae in vitro, and the loss of 50% of VEGF production in the mouse glomerulus leads not only to glomerular endotheliosis but also to the loss of glomerular endothelial fenestrae similar to what is noted in human preeclampsia.[44] Antagonists of VEGF, used in antiangiogenic oncology trials, sometimes produce hypertension and proteinuria in humans.

Finally, higher circulating levels of the chromosome 13– encoded gene product sFlt1 in pregnancies with trisomy 13 may explain the increased risk for preeclampsia in women who carry fetuses with trisomy 13. In addition to its role in the pathogenesis of preeclampsia, circulating concentration of sFlt1 and PlGF may have important predictive and diagnostic implications. The concentration of sFlt1 starts to rise near the end of the second trimester in women who are destined to have preeclampsia, a full 4 to 5 wk before clinical manifestations are first detected.[45]

By the time preeclamptic manifestations are pronounced, plasma concentrations of sFlt1 are greatly elevated, from two to four times the levels found in normal pregnancy, and are greatest in patients with severe preeclampsia. In women who develop preeclampsia, there is a modest but significant decrease in PlGF levels beginning as early as the first trimester. From mid-pregnancy onward, the concentration of unbound PlGF in plasma falls significantly lower at the time when sFlt1 levels are rising. Unbound PlGF is also freely filtered into the urine and thus may also serve to predict the subsequent development of preeclampsia.[46] Endoglin (Eng) is an angiogenic receptor that is expressed on the surface of endothelial cells and placental syncytiotrophoblasts. Eng acts as a co-receptor for TGF-, a potent proangiogenic molecule. Eng mRNA is up-regulated in the preeclamptic placenta.[47]

Moreover, the extracellular region of Eng is proteolytically cleaved, and soluble Eng (sEng) is released in excess quantities into the circulation of preeclamptic patients. In pregnant rats, sEng exacerbates the vascular damage that is mediated by sFlt1, resulting in severe preeclampsia-like illness, including the development of a HELLP-like syndrome and fetal growth restriction.[48] In explant cultures of trophoblasts from 5 to 8 wk of gestation, mAb to Eng and antisense Eng oligonucleotides stimulated trophoblast outgrowth and migration.

TGF1 and/or TGF-3 inhibits trophoblast migration and invasion, and it seems that Eng mediates this effect. Therefore, it has been speculated that the production of sEng by the placenta may be a compensatory mechanism to limit the effects of surface Eng. In recent clinical studies, sEng was elevated not only during the disease but also before the onset of symptoms.[49] Elevations in sEng were particularly pronounced—and, therefore, potentially most useful for prediction—in women who developed preterm preeclampsia or preeclampsia with an infant who was small for gestational age. Although the gestational pattern of sEng concentration tended to parallel the trajectory of the sFlt1/PlGF ratio, multivariate analysis indicated that each was significantly associated with preeclampsia. Indeed, a composite measure that incorporated all three angiogenic molecules (sFlt1, sEng, and PlGF) was more strongly predictive of preeclampsia than the individual biomarkers.[50] (Figure 1).

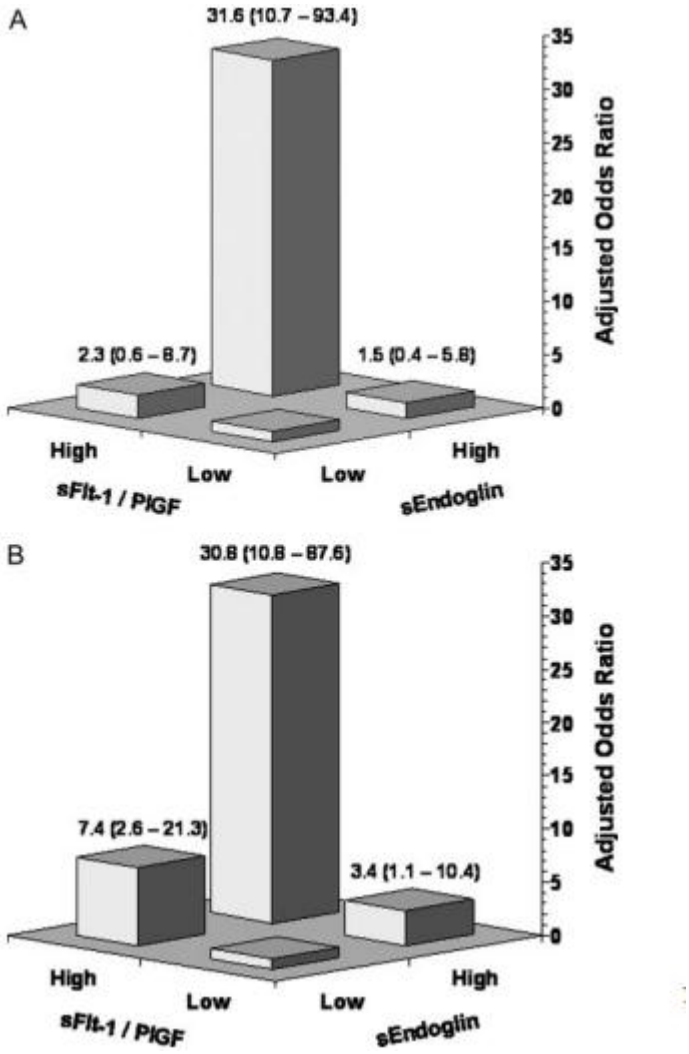

Figure 1: Adjusted odds ratios for preterm (A) or term (B) preeclampsia according to soluble forms-like tyrosine kinase 1: placental growth factor (sFlt1: PlGF) ratios and soluble endoglin levels.

CONCLUSION

Pre-eclampsia is a rare pregnancy-related disease with an unpredictable course that can have serious consequences for both the mother and the fetus. The treatment is simple, ie, delivery. Nonetheless, induced preterm delivery requires careful weighing of both maternal and fetal risk-benefit. Accordingly, identifying delivery criteria in case of pre-eclampsia is crucial to optimal management.

The pathogenesis of preeclampsia is complex; numerous genetic, immunologic, and environmental factors interact. It has been suggested that preeclampsia is a two-stage disease. The first stage is asymptomatic, characterized by abnormal placental development during the first trimester resulting in placental insufficiency and the release of excessive amounts of

placental materials into the maternal circulation. This, in turn, leads to the second, symptomatic stage, wherein the pregnant woman develops characteristic hypertension, renal impairment, and proteinuria and is at risk for the HELLP syndrome (hemolysis, elevated liver function enzymes, and low platelets), eclampsia, and other end-organ damage.

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