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REVIEW ARTICLE

Serum markers in pre-eclampsia

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Abstract

Preeclampsia occurs approximately in 10% of pregnancies and remains a leading cause of maternal and neonatal mortality and morbidity worldwide, particularly in developing countries. The condition is usually diagnosed in late pregnancy by the presence of hypertension with proteinuria and/ or edema. Prevention of any disease process requires knowledge of its etiology and pathogenesis, as well as the availability of methods for prediction of those at high risk for this disorder. Numerous clinical, biophysical, and biochemical tests have been proposed for prediction or early detection of preeclampsia. This review will explore the current tests available in the evaluation of hypertensive complications of pregnancy.

Keywords: *Prreclampsia; serum markers; oxidative stress; haemostatic parameters; VEGF*

Introduction

Pre-eclampsia occurs in approximately 10% of pregnancies and remains a leading cause of maternal and neonatal mortality and morbidity worldwide, particularly in developing countries. The condition is usually diagnosed in late pregnancy by the presence of hypertension with proteinuria (Chesley 1985). Pre-eclampsia is characterized by *de novo* hypertension, blood pressure ≥ 140/90 mmHg and new-onset proteinuria (Chesley 1985).

Prevention of any disease process requires knowledge of its aetiology and pathogenesis, as well as the availability of methods for prediction of those at high risk for this disorder. Numerous clinical, biophysical and biochemical tests have been proposed for prediction or early detection of pre-eclampsia. This review will explore the current tests available in the evaluation of hypertensive complications of pregnancy.

Calcium and vitamin D

Alterations in calcium metabolism have been reported in human essential hypertension (August et al. 1992). It has also been suggested that calcium regulation may be abnormal in pre-eclampsia (August et al. 1992).

For the prediction of pre-eclampsia a good correlation has been shown between the calcium to creatinine ratio, single-voided urine samples and with 24-h urinary calcium excretion (Huikeshoven & Zuijderhoudt 1990).

The hypocalciuria observed in pre-eclamptic women appears long before the disease becomes clinically manifest and is a useful marker with good predictive value. Also, it could serve to differentiate those women who present with hypertension late in pregnancy or in labour when the diagnosis of pre-eclampsia versus gestational hypertension is uncertain.

Uric acid

Although hyperuricaemia is a useful confirmatory test for clinically evident pre-eclampsia, it is a poor predictor because serum concentrations rise only 1 week before the clinical appearance of disease (Fay et al. 1985). Presence of hyperuricaemia with severe pre-eclampsia is associated with poor fetal prognosis regardless of the maternal blood pressure (Varma 1992).

Proteinuria

Proteinuria is defined as ≥ 1+ on the dipstick assessment of a random urine sample. A 24-h collection of urine obtained from a patient with ≥ 1+ protein reading should contain > 300 mg of protein. The presence of > 5 g protein

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in a 24-h urine specimen is a criterion for the definition of severe pre-eclampsia (Sibai 1988). The finding of increasing urinary protein is usually a late manifestation of pre-eclampsia.

Fibronectin

Plasma fibronectin levels have been observed to be increased 3.6 ± 1.9 weeks earlier than the onset of hypertension and/or proteinuria (Ballegeer et al. 1989). Importantly, the increase occurs even in the first trimester of pregnancy before clinical evidence of pre-eclampsia becomes apparent.

Liver function tests

Severe pre-eclampsia can be associated with indicators of hepatic dysfunction that include increased concentrations of aspartate transaminase (AST), lactic dehydrogenase (LDH), indirect bilirubin and serum glutamic oxaloacetate transaminase (SGOT). These parameters in association with thrombocytopenia have been recognized as markers for HELLP syndrome (Weinstein 1985).

Haemostatic parameters

A number of haemostatic parameters have been assessed for their predictive value in the development of pre-eclampsia, including antithrombin III, tissue plasminogen activator, plasminogen activator inhibitor-I, β-thromboglobulin, fibrinogen, fibrin degradation products, D-dimer and euglobulin lysis time.

Antithrombin III

Antithrombin III (At III) concentrations are decreased in patients with pre-eclampsia/eclampsia and normal in gravid patients with chronic hypertension (Weiner & Brandt 1982). Also, AT III levels are inversely related to the severity of proteinuria with lowest levels observed in patients with severe proteinuria. AT III when compared with other haemostasis system markers (prothrombin 1 and 2, fibrin fragment D-dimers, Von Willebrand factor antigen and platelet count) seems to be the most sensitive marker for detecting pregnancies complicated by hypertension or pre-eclampsia (Cadroy et al. 1993).

Plasminogen activator inhibitors

Plasminogen activator inhibitors (PAI) are not altered during a normal pregnancy. However, PAI-2 levels have been observed to decline significantly in pre-eclamptic pregnancies and the PAI-1/PAI-2 ratio and PAI-1 levels seem to be useful in separating pregnancies complicated by pre-eclampsia from normal pregnancies (Reith et al. 1993).

C-1 esterase inhibitor

Low levels of C-1 esterase inhibitor (C_1-INH) have been observed in normal pregnancy and a further reduction was noted with pre-eclampsia (Inglis et al. 1982). It seems to be a more sensitive indicator of the haemostatic impact of pre-eclampsia than other such recognized markers such as AT III and platelet count.

Thrombocytopenia

The most common cause of moderate to severe thrombocytopenia ($\leq 100\,000\,\mu l^{-1}$) in pregnancy is pre-eclampsia/eclampsia (Burrows & Kelton 1990). Endothelial damage associated with microangiopathic haemolytic anaemia or fibrin-deposition/consumptive coagulopathy have been two suggested mechanisms (Burrows et al. 1987). Lower platelet counts with evidence of haemolysis and elevated liver enzymes define the HELLP syndrome form of severe pre-eclampsia (Weinstein 1982).

Other haematological laboratory parameters

Red blood cell morphology, serum iron and haemoglobin/haematocrit

An increased proportion of abnormal to normal red blood cells (schistocytes, echinocytes and spherocytes) is a well-recognized phenomenon in patients with pre-eclampsia/eclampsia when compared with non-pregnant women and normal pregnant women (Cunningham et al. 1985).

An increase in serum iron concentration can occur in women with pre-eclampsia (Entman et al. 1982), and, it is a predictor of the disease. The degree of haemoconcentration seems to parallel the severity of pre-eclampsia.

Oxidative stress markers

Recent research has supported the view that oxidative mechanisms may be responsible for pre-eclampsia (Hubel et al. 1989). Pre-eclampsia on that basis would be a disease of antioxidant inadequacy appearing when normal antioxidant equilibrium is upset. This equilibrium is normally maintained by antioxidants such as: vitamin E, both intramembraneously and in the plasma; glutathione peroxidase, constitutive and inducible superoxide dismutase and catalase, intracellularly; and ceruloplasmin, extracellularly.

Markers of oxidative stress in the maternal circulation

Nitrotyrosine in maternal vasculature

Immunohistochemical analysis of microvessels from biopsies of subcutaneous fat suggests increased peroxynitrite formation in pre-eclampsia (Roggensack et al. 1999). The percentage of vascular endothelial staining for nitrotyrosine was greater in pre-eclampsia than normal pregnancy.

Lipid peroxidation products

Increased plasma/serum levels of lipid peroxidation products primarily measured as thiobarbituric acid-reactive substances (BARS) which include malonaldehyde (MDA) are reported in pre-eclamptic women (Hubel et al. 1989, Walsch 1994, Kharb et al. 1998). However, most lipid peroxidation assays have problems of sensitivity and specificity.

Circulating antioxidized LDL antibodies

Increased autoantibodies to an epitope of oxidized low-density lipoprotein (LDL) have been described in women with pre-eclampsia relative to normal pregnancy although a negative report also exists (Armstong et al. 1994, Branch et al. 1994). Uotila et al. (1998) found increased titres of serum autoantibodies against copper-oxidized LDL, but not against MDA-LDL, in pre-eclampsia. Kurki et al. (1996) found that antibodies to MDA-LDL and anticardiolipin were not increased in early in gestation in women who subsequently developed pre-eclampsia compared with women whose pregnancies remained normal.

Plasma antioxidants reserves

Several reports have shown that in severe pre-eclampsia peroxide levels are increased and vitamin E levels are decreased (Hubel et al. 1989, Kharb et al. 1998). On the other hand, other authors did not find decreased vitamin E levels in pre-eclampsia (Uotila et al. 1993). Devidge et al. (1992) found an increased serum antioxidant capacity during uncomplicated pregnancy, whereas antioxidant capacity in pre-eclampsia was found to be reduced by 50%.

Erythrocyte glutathione levels and glutathione peroxidase activity are increased in pre-eclampsia (Uotila et al. 1993). Ascorbic acid, α-tocopherol and β-carotene are antioxidant nutrients and have been shown to be decreased in pre-eclampsia (Wisdom et al. 1991, Kharb 2000a, 2000b).

Lipid changes

Lipid alterations may promote oxidative stress in pre-eclampsia (Hubel 1998). In particular, the insulin resistance syndrome ('Syndrome X' a cluster of abnormalities including dyslipidaemia, obesity and resistance to insulin-stimulated glucose uptake) may have an important role in the pathogenesis of pre-eclampsia (Kaaja 1998).

Tumour necrosis factor

Hypoxia promotes excess production of placental tumour necrosis factor (TNF) which might promote endothelial dysfunction in pre-eclampsia (Benyo et al. 1997).

Inflammatory response in pre-eclampsia

Placental lipid peroxidation products, TNF-α and syncytiotrophoblast membrane fragments are candidate blood-borne agents with the potential to cause endothelial cell dysfunction (Redman 1975). Elastase-positive neutrophils are found to be increased in deciduas of the placental bed in pre-eclamptic women (Butterworth et al. 1999).

Vascular endothelial growth factor and vascular cell adhesion molecule

Vascular endothelial growth factor (VEGF) and vascular cell adhesion molecule-1 (VCAM-1) have been reported to be increased in pre-eclampsia (Higgins et al. 1998). VCAM-1 levels are not elevated in gestational hypertension, suggesting that VCAM-1 dysregulation is specific for pre-eclampsia.

There is mounting evidence that an imbalance between angiogenic factors, such as VEGF or placental growth factor, and factors inhibiting angiogenesis, such as sFlt1 (soluble fms-like tyrosine kinase 1) and sEng (soluble endoglin) are closely related to the pathogenesis of pre-eclampsia (Stepan 2009, Steinberg et al. 2009, Levine et al. 2004).

Many workers have presented evidence that circulating sFlt1 begins to rise during last 2 months of normal pregnancy and this process is exaggerated in pre-eclampsia (Stepan 2009, Steinberg et al. 2009, Levine et al. 2004). An excess of soluble VEGF receptor 1 (sVEGFR-1) is released into the maternal circulation of patients with pre-eclampsia and those with small-for-gestational-age (SGA) fetuses, as abnormalities of impedance to blood flow involve the uterine and umbilical circulation. Chaiworapongsa et al. (2008) provided support for the participation of sVEGFR in the pathophysiology of SGA with abnormal uterine artery Doppler velocimetry and pre-eclampsia.

Plasma cell-free fetal DNA, activin A and heat shock proteins

Maternal plasma cell-free fetal DNA (cffDNA) levels have been reported to be elevated in early pregnancies which later develop into pre-eclampsia (Zhong et al. 2002, Hahn & Holzgreve 2002). Measurement of cffDNA in maternal plasma and activin A could be an independent biomarker for early identification and monitoring

of pre-eclampsia (Watanganara & Bianchi 2004). As the placenta is one of the major sources of activin A in pregnancy, this increase in activin A in pre-eclampsia may be reflection of underlying placental hypoxic condition (Madazli et al. 2005). Diesch et al. (2006) examined prospectively the concentration of activin A before the clinical manifestation of pre-eclampsia and compared the data with those of cffDNA levels in the maternal plasma and suggested that circulatory activin A could be an independent biomarker for the early identification and monitoring of pre-eclampsia. Plasma cffDNA level, serum levels of inflammatory markers (CRP) and heat shock protein 70 are also increased in pre-eclampsia (Molvarec et al. 2006, 2007, 2009).

Homocysteine

Total homocysteine (Hcyt) concentration has been reported to be increased in pre-eclampsia and correlated significantly with cellular fibronectin concentration suggesting that Hcyt plays a role in promoting endothelial dysfunction in pre-eclampsia (Powers et al. 1998).

Miscellaneous

A number of other laboratory assays have been reported to reflect the presence of pre-eclampsia. Most of these are generally unavailable in routine clinical laboratories. Factor VIII consumption has been shown to correlate with the severity of pre-eclampsia (Redman et al. 1977). Serum prolactin has been found to be elevated in pre-eclamptic women, especially in those with elevated uric acid (Redman et al. 1975, 1977, Kharb & Singh 2001). β-thromboglobulin, a platelet-specific protein, increases in patients with pre-eclampsia and further increments are observed in association with worsening pre-eclampsia (Ayhan et al. 1990). Atrial natriuretic peptide (ANP) is elevated in hypervolaemic states, e.g. end-stage renal disease and congestive heart failure. Paradoxically, ANP is increased significantly in patients with progressively worse pre-eclampsia (Elias et al. 1988), but the inability of ANP to differentiate between pre-eclampsia and essential hypertension have rendered it unusable for evaluation of pre-eclampsia. Fibrin degradation products, prothrombin time, partial thromboplastin time and fibrinogen are highly variable in normal and pre-eclamptic women and are useful in patient management (Kitzmiller et al. 1973).

Future assays on the horizon

Human chorionic gonadotropin

Plasma levels of total, α and β human chorionic gonadotropin (hCG) are increased in patients with pre-eclampsia. α-hCG may be the best marker for pre-eclampsia among the three hCG markers (del Valle 1993).

Haptoglobin

Haptoglobin is a sensitive marker of haemolysis in the evaluation of HELLP syndrome. Mid-gestational hyperinsulinaemia may play a role in the development of pre-eclampsia (Kaaja 1998, Kharb 2000c).

Conclusion

Thus, a number of laboratory tests are available which reflect the severity of pre-eclampsia. These tests can be used to either predict and/or prognosticate between pre-eclampsia and other hypertensive disorders of pregnancy. The management of pre-eclampsia with its great risk for increased perinatal morbidity and mortality render this differentiation very important.

Understanding the mechanisms of disease responsible for the syndrome of pre-eclampsia as well as early risk assessment is still a major challenge. Risk factors for pre-eclampsia are nulliparity, a family or own history of pre-eclampsia, pre-existing diabetes or increased body mass index, multiple pregnancy, maternal age, renal disease, hypertension or raised blood pressure at booking and chronic autoimmune disease. Other factors are thrombophilias and insulin resistance together with obesity. A number of biochemical agents have been assessed as markers for predicting pre-eclampsia; none has yet been proved to be of clinical value. Much effort has been put into evaluating novel potential markers and their combination with other screening methods such as Doppler sonography. The most promising biochemical markers, to date, are placenta protein 13 as well as sFlt-1 and sEng. These markers allow screening at a relatively early stage and, most importantly, show relatively high predictive values and improved diagnostic performance if combined with first-trimester Doppler sonography. However, until now, too few data are available to justify the clinical use of these markers. Large-scale prospective studies, assessing these markers, are important to advance progress in reducing maternal and perinatal morbidity and relieving the heavy burden of pre-eclampsia. Currently no reliable early marker is available for pre-eclampsia with high sensitivity and specificity, which can predict the disease in early pregnancy.

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