PREDICTION OF PREECLAMPSIA

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The signs and symptoms of preeclampsia are usually apparent at a relatively late stage in pregnancy, usually in the third trimester. However, the disorder results from abnormal interaction between the mother and the invading endovascular trophoblast much earlier in pregnancy. For that reason it seems logical to search for earlier indicators of this disorder, and indeed a multitude of tests have been proposed as a means of predicting the later development of the disease. In this presentation the various clinical, biochemical and biophysical tests that have been proposed for the early diagnosis of preeaclampsia that are presently available or feasible in most hospitals in developed countries will be reviewed briefly.

CLINICAL ASSESSMENT

Blood pressure: Hypertension is the most common sign and potentially the most dangerous clinical manifestation of pregnancy-induced hypertensive disorders. The increase in blood pressure is a rather early feature of the disease. However, measuring blood pressure or second-trimester MAP is not useful for the early diagnosis of preeclampsia. If an increased diastolic blood pressure, MAP or second-trimester MAP, or incremental changes in blood pressure predicts anything it is transient hypertension, but not the real disease preeclampsia-eclampsia with its associated perinatal morbidity and mortality.

Edema and weight gain: The one visible sign of pregnancy-induced hypertensive disorders in swelling, but this is not a reliable sign. Moderate edema can be detected in 60-80 % of normotensive pregnancies. Pathologic edema affects 85 % of women with a pregnancy-induced hypertensive disorder. Pathologic edema appears suddenly and is associated with an accelerated rate of weight gain. The diagnostic signs of pregnancy-induced hypertensive disorders usually antedate symptoms. The classic sequence of the signs is edema, increased blood pressure, and proteinuria. However, any order of appearance may occur, and edema is not a prerequisite for diagnosing pregnancy-induced hypertensive disorders. Weight gain cannot be used to predict the development of pregnancy-induced hypertensive disorders and excess weight gain alone impart no adverse prognosis to perinatal outcome.

Isometric exercise test: Isometric hand grip exercise increases arterial blood pressure by increasing systemic vascular resistance. Presently, no firm conclusion can be drawn with regard to the clinical value of the isometric exercise test or hand-grip test in the early diagnosis of preeclampsia. Several studies did report good results, but, conclusions of these studies were based on miscalculations or no definitions were reported for diagnosing preeclampsia. Further prospective studies are necessary.

Roll-over test: The roll-over test has gained some popularity because of its simplicity, and the good results that were reported in the initial studies. However, more recent studies demonstrated that a major part of the pressor response in the roll-over test is caused by the relative change in the position of the cuff in relation to the level of the heart when turning supine, and that the rollover test is of no use in predicting preeclampsia.

BIOCHEMICAL MARKERS

It is important to emphasize that the majority of women with a pregnancy-induced hypertensive disorder are asymptomatic. This lack of symptoms is, in fact, an important part of the rationale for the frequent antenatal care visits in late pregnancy. Laboratory tests have been used for prediction, diagnosis, and monitoring of disease progress. The diagnosis "preeclampsia" is even based on a laboratory test.

Uric acid: Preeclamptic hyperuricemia is caused by a decreased urate clearance by the kidneys and uric acid clearance drops disproportionally in preeclampsia as compared to urea clearance. The pathophysiologic explanation for this specific decrease in urate clearance is based on the biphasic pattern of renal involvement in preeclampsia. The tubular function is the first to be involved, later on in the disease process the glomerular function impairs. The impairment of tubular physiology, a rather early feature of renal involvement in preeclampsia, results in a reduced renal clearance of uric acid, and thus an increase of plasma uric acid levels. Later on in the development of the disease, about the time proteinuria appears, glomerular function and thus urea and creatinine clearance becomes impaired. Preeclamptic hyperuricemia has been shown to correlate more or less with the decrease in plasma volume and plasma

renin activity. Preeclamptic hyperuricemia is probably caused by a combination of intrarenal (peritubular) vasoconstriction and hypovolemia. Increments in urate levels have been demonstrated to correlate with the severity of the preeclamptic lesion in renal biopsies, the degree of uteroplacental vascular pathology, and with poor fetal outcome. Hyperuricemia has been reported to be a better predictor for adverse perinatal outcome than blood pressure. More recent studies report contradictory findings. Serum uric acid levels may begin to rise before the appearance of proteinuric hypertension. In most patients the increase in urate levels appears to coincide with the increase in blood pressure, and precedes the development of the proteinuric stage of the disease. As such uric acid levels have been used for the early diagnosis of preeclampsia, but not for hypertension as such. Uric acid may be used as an indicator of disease severity in pregnancy-induced hypertensive disorders.

Creatinine and creatinine clearance: Creatinine clearance is a glomerular function. Measuring serum creatinine or creatinine clearance is certainly not useful for early diagnosis of pregnancy-induced hypertensive disorders. A decrease in creatinine clearance, and elevated creatinine levels are late features of preeclampsia, more or less coinciding with the appearance of proteinuria. Measuring creatinine is essential not for diagnosis but to anticipate increasing renal impairment which might precede acute renal failure.

Proteinuria: Proteinuria is obligatory for the classic diagnosis of preeclampsia. Proteinuria is a late sign of pregnancy-induced hypertensive disorders, and is a reflection of advanced disease. HELLP syndrome and eclampsia (prior to seizures) may occur in the absence of proteinuria. The occurrence of proteinuria is an expression of glomerular dysfunction, and coincides more or less with a decrease in creatinine clearance. Proteinuria is associated with a poorer perinatal outcome, and a poorer prognosis for the mother. On average proteinuria appears about three weeks before intrauterine demise or mandatory delivery. Hypertension plus proteinuria is associated with a two-fold increased risk of perinatal death, as compared to normotensive pregnancy and hypertension without proteinuria. Because the development of proteinuria is a late feature of the disease routine use of dipsticks in a normotensive low-risk population is probably just as ineffective as measuring maternal weight gain.

Microalbuminuria tests have been tried in order to predict preeclampsia. On the whole there appears to be little value in using precise techniques of detecting proteinuria in the early diagnosis of preeclampsia. Other signs such as an increase in blood pressure, a fall in the number of platelets, and a rise in plasma uric acid levels appear to antedate the occurrence of detectable microalbuminuria.

Urinary calcium excretion: Hypocaiciuria is present in the majority of patients with severe stage of the disease. Preeclamptic hypocalciuria is, just as a decreased urate clearance, an expression of tubular dysfunction. Although initially several investigators reported very good results withk measuring urinary calcium excretion as a predictive test, later investigators could not demonstrate the occurrence of hypocalciuria preceding the onset of clinical symptoms.

Enzymes and Hormones:

Human chorionic gonadotrophin (hCG): Some studies found elevated levels of ß-HCG in pregnancy-induced hypertensive disorders, and it has been suggested that ß-HCG determination may have value for the early diagnosis of preeclampsia. However, levels of ß-HCG in normotensive and hypertensive pregnancies appear to overlap considerably, also levels show a large scatter. Therefore, the clinical value of ß-HCG measurements for predicting or monitoring pregnancy-induced hypertensive disorders seems limited at the most.

Placental proteins: The studies reported in the literature demonstrate that measuring placental proteins, such as PAPP-A, hPL, SP1 et cetera is of no use to predict pregnancy-induced hypertensive disorders.

Deoxycytidylate deaminase and cytidine deaminase: As a predictor for adverse perinatal outcome the clinical value of both enzymatic activities is similar, but the cytidine deaminase assay is much simpler. Measuring cytidine deaminase (PET-test) is a simple method that can be used as a routine laboratory test, but determination of serum uric acid levels appear to be just at least as least as good to monitor the course of the disease.

HEMATOLOGIC MARKERS

Factor VIII Related Antigen - Factor VIIIc: The ratio Factor VIII related antigen/Factor VIIIc (VIIIrag/fVIIIc) in healthy subjects is 1.0 per definition. An increase in the numerator of this ratio, the fVIIIrag, is associated with endothelial release of this antigen. Several authors have demonstrated an early rise of the fVIIIrag/fVIIIc ratio in pregnancy-induced hypertensive disease, and a positive correlation between the magnitude of increase of the ratio and the severity of the disease, the degree of hyperuricemia, placental infarcts, adverse perinatal outcome, and a strong negative correlation between this ratio and platelet life-span. The increase of fVIIIrag and thereby the ratio is most pronouced in preeclampsia associated with fetal growth retardation. Endothelial release of fVIIIrag is not increased in chronic

hypertension. In time the increase in fVIIIrag runs parallel with the increase in serum uric acid levels and the increase in blood pressure.

Antithrombin III and Thrombin-Antithrombin III complexes: Decreased ATIII activity levels have been demonstrated to exist in a majority of patients with preeclampsia. However, a decrease in ATIII activity levels is not useful for early diagnosis, although occasionally a patient may show a decrease in ATIII activity more than 10 weeks prior to the development of clinical manifestations. Exacerbations and remissions of the disease process are excellently reflected in fluctuations of ATIII activity levels.

Fibronectin: Fibronectin is a major cell-surface glycoprotein. In normal pregnancy plasma levels of fibronectin are similar or just slightly increased as compared to non-pregnant individuals. The upper range of normal is 300 mg/L. in pregnancy-induced hypertensive disorders plasma fibronectin levels are elevated. In established preeclampsia most studies show an approximately 2-3 fold increase in plasma fibronectin levels. There is almost no overlap in plasma fibronectin levels between normotensive and hypertensive pregnancy. The high fibronectin levels in preeclampsia are caused by endothelial cell damage or activation that occurs e.g. in the uteroplacental vascular bed, kidneys, liver et cetera, and by increased hepatocyte production. Pregnancies in women with chronic hypertension have normal fibronectin levels, therefore the increase in plasma fibronectin is not simply a consequence of hypertension. Ballegeer et al. (1989) compared plasma fibronectin, PAI-1, fVIIIrag, and uric acid, and concluded that fibronectin is the best predictor of preeclampsia. Ballegeer et al. (1989), evaluated the presence of increased fibronectin levels (mean+2SD) at 25-32 week's gestation in the early diagnosis of preeclampsia and found a sensitivity of 96 % and ak specificity of 94 %. According to Ballegeer et al the increase in plasma fibronectin antedates the increase in blood pressure by 4-6 weeks on average. In our high-risk antenatal clinic at the Department of Obstetrics at the Free University, we found that elevated fibronectin preceded the increase in blood pressure by 4 weeks in patients with gestational hypertension and 12 weeks in patients with subsequent preeclampsia. Measuring fibronectin levels, is feasible with techniques that are available in most hospitals, and may be of great help in the early diagnosis of preeclampsias.

Platelet count: Platelet life-span is significantly shorter in pregnancy-induced hypertensive disorders, in particular when complicated by fetal growth retardation, as compared to uncomplicated pregnancy. In preeclamptic women the fall in the platelet count coincides more or less with the increase in uric acid levels, both precede the development of proteinuria by 3 weeks. However, the standard deviations in the number of circulating platelets in normotensive and hypertensive pregnant women preclude the use of platelet counts as an effective method for early detection in low-risk nulliparaous women. Prospective serial counts in selected high-risk patients are certainly useful when the patient's own baseline is established in early pregnancy.

Hemoglobin level, hematocrit: Abnormal high Hb/Htc levels are a better predictor of adverse perinatal outcome than abnormally low estriol or hPL levels. High maternal Hb/Htc levels are associated with low birth weight and placental weight, increased incidence of prematurity and perinatal mortality, as well as with peripheral vascular resistance, and the degree of maternal hypertension. Serial measurements of Hb/Htc are of definite use to monitor pregnancies at a high risk of developing uteroplacental insufficiency, and to monitor the course of disease in established pregnancy-induced hypertensive disorders and/or pregnancies complicated by fetal growth retardation. Marked elevation of hemoglobin leves in the second trimester have been demonstrated to precede the development of pregnancy-induced hypertensive disorders, and to be useful as a predictor. However, the predictive value of less pronounced hemoglobin levels is low.

DOPPLER ULTRASOUND ASSESSMENT OF THE UTEROPLACENTAL CIRCULATION

The absence or presence of physiologic changes in the uteroplacental vessels is the pathophysiologic basis for the use of Doppler-flow studies in the early diagnosis of preeclampsia. The increase of the uteroplacental flow velocity waveform resistance indices has been found to correlate with the results of pathologic examination of the placental bed and placentas. It is important to note that these pathologic vascular changes have been demonstrated to exist in a significant proportion of normotensive pregnancies complicated by fetal growth retardation. Indices of uteroplacental blood flow velocity waveforms (resistance index) decrease in early pregnancy until 20-26 weeks' gestation and the remain stable to term. The high end-diastolic blood flow velocity and low ratios during the last half of pregnancy reflect the low peripheral resistance of the uteroplacental vascular bed. There is an ongoing discussion concerning the use of continuous wave (CW) versus pulsed Doppler ultrasound for the study of the uteroplacental circulation. Although pulsed waved ultrasonography with a range gate may demonstrate the exact depth of insonation, it does not necessarily visualize the vessels accurately, and so presently there is no convincing reason to advocate its use for the study of the uteroplacental circulation. In the third trimester, narrow branching vessels can be identified with real-time ultrasound in the lateral uterine wall, which, in most instances, represent the arcuate arteries. The sample gate is then placed over such a pulsating vessel, and FVWs are obtained. However, in the second trimester, the arcuate arteries are difficult to visualize without colour doppler flow equipment. In this setting, pulsed Doppler has no clear advantage as compared to CW equipment. CW has the advantages of cost, manouvrability of the probe, and smaller ma-

chine size. In the study of the uteroplacental circulation CW and pulsed wave ultrasonography have shown consistent results. In screening for uteroplacental insufficiency CW ultrasonography has to be preferred. In using CW for the studying the uteroplacental vascular bed, it is impossible to determine which vessel produces the signal. Therefore, the signals are best described as coming from a uteroplacental vessel.

There is no standard method of reporting uteroplacental FVWs. Pearce and McParland (1991) have suggested that both sides of the uterus should be examined and the FVWs reported as follows:

1. Uniform low resistance: FVWs from both sides of the uterus have a RI < 0.58
2. Uniform high resistance: FVWs from both sides of the uterus have a RI > 0.58
3. Mixed resistance pattern: One waveform (almost invariably that from the placental side) is of low resistance (RI < 0.58) while the waveform from the other side is of high resistance.

There is more information in the waveform shape than just a FVW index. Especially the presence or absence of a notch is very important in this respect. The early diastolic notch of uteroplacental FVWs has been reported in normal pregnancy until approximately 26 weeks gestation. However, on the placental side of the uterus it has been reported to be rarely found after 20 weeks'gestation. Presently, the studies reported in the literature concerning the clinical value of Doppler ultrasound evaluation of the uteroplacental circulation, have resulted in widely varying results. These differences may be related to wide differences in technique, different definitions of pregnancy-induced hypertensive disorders, fetal growth retardadation, fetal distress and adverse perinatal outcome. However, the major reason for the different conclusions concerning the value of Doppler FVWs of the uteroplacental vessels is probably given by the fact that investigators used different selection processes in dividing populations with a normal or abnormal uteroplacental Dopler flow pattern. Abnormality was sometimes based on the worst FVW, an average, the four-site averaged resistance index or even the best FVW. The scattered occurrence of "preeclamptic lesions" in the spiral arteries suggest that it is more logic to look for the worst doppler-flow patterns, and indeed investigators that used the worst FVW have consistently reported the best results with uteroplacental Doppler in the early-detection of preeclampsia.

In 1986, Campbell et al. were the first to report on the use of uteroplacental Doppler velocimetry as a screening test in early pregnancy for hypertension, fetal growth retardation, and fetal asphyxia. This first yielded extremely promising results. However, the excellent predictive value found in this study was caused by a complication rate of 25 % in the study group. Similar results were reported form other studies concerning high-risk patients. The results from subsequent larger studies in low-risk patients demonstrated a low predictive value. However, the majority of these studies did not look for the worst FVW, or evaluated the use of uteroplacental Doppler in predicting the occurrence of any degree of hypertension. In the early detection of severe preeclampsia associated with adverse perinatal outcome uteroplacental Doppler has been demonstrated to have a very high sensitivity.

In conclusion, Doppler-flow studies of the uteroplacental circulation are easy, inexpensive, and noninvasive. Doppler-flow studies can be done in early pregnancy and are suitable for therapeutic intervention in an attempt to reduce the incidence of preeclampsia and its complications. The results of Doppler ultrasound examination of the uteroplacental circulation as a screening test for any degree of hypertension are somewhat disappointing. In the early diagnosis of severe preeclampsia and/or severe fetal growth retardation Doppler ultrasound has demonstrated a high sensitivity, but this may be sufficient for clinical purposes because most hypertension in pregnancy probably represent an enhanced physiologic adaptation to pregnancy.