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## Preeclampsia: Should be Predict and Prevent?

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"A women is never closer to death than when giving a life"

## Lev Nikolayevich Tolstoy

Preeclampsia continues to be a massive cause of maternal and perinatal morbidity and mortality. Preeclampsia is a common, incompletely understood syndrome yet, unique for humans only and it is one of the most common complications of pregnancy worldwide. Over 4 million women will develop the disorder worldwide every year, 50.000-100.000 women die from the preeclampsia each year and it's responsible for approximately 300.000 perinatal deaths [1-3].

Women with preeclampsia usually develop hypertension, proteinuria and varying degrees of ischemic end-organ damage, caused by widespread endothelial dysfunction. Preeclampsia is also associated with abnormalities of coagulation system, disturbed liver function, renal failure and cerebral ischemia. It's characterized by vasospasm, increased peripheral vascular resistance and thus reduced organ perfusion [4,5]. Preeclampsia complicates 2–30% of pregnancies and it is a major cause of maternal morbidity, prenatal death and premature delivery, although outcome for most women is good [5,6].

Mild preeclampsia is defined by the occurrence of two or more systolic pressure  $\geq$ 140 mmHg and/or diastolic pressure  $\geq$ 90 mmHg, diastolic blood pressure measurements, with the first elevated blood pressure occurring after 20 weeks' gestation up to 24 hours after delivery, combined with proteinuria at least 0.3 g or "1+ protein" per 24 hours [7,8]. Severe preeclampsia is defined as a systolic blood pressure of 160 mmHg or greater and diastolic blood pressure of 110 mmHg or greater on at least two occasions at least 4 hours apart or on one occasion if antihypertensive therapy was administered. Severe proteinuria was defined with a 24-hour urine sample containing  $\geq$ 3.5 g of protein or two urine samples of "3+ protein" or greater taken at least 4 hours apart. The syndrome of haemolysis, elevated liver enzymes and low platelets and eclampsia was also categorized as severe preeclampsia [7,8].

Women with preeclampsia usually develop raised blood pressure and proteinuria after 20 week of gestation, but it can be distinguished as early (<34 weeks gestation) and late (>34 weeks) onset phenotypes [9,10].

The pathogenesis of preeclampsia is complex. It has been suggested that preeclampsia is a two-stage disease: stage 1: asymptomatic, characterized by abnormal placental development during the first trimester resulting in placental insufficiency. This in turn leads to symptomatic stage 2: where in the pregnant women develops characteristic hypertension, renal impairment and proteinuiria and is at risk for the HELLP syndrome, eclampsia and other end-organ damage [11].

Major risk factors for preeclampsia are: nuliparity, maternal age >40, prior preeclampsia, antiphospholipid antibody syndrome, family history of preeclampsia, renal disease, chronic hypertension, diabetes mellitus, multiple gestations, strong family history of CV disease (heart disease or stroke in  $\geq$ 2 first-degree relatives), obesity etc [12].

Prediction and prevention of preeclampsia is very important contribution for maternal health. Primary prevention of preeclampsia is identification of the risk factors. Prevention of preeclampsia demands knowledge of the pathophysiological mechanism. Availability of techniques for early detection and intervention in the pathophysiological process are necessary. Finally, prevention of pre-eclampsia is a proper antenatal care which provides screening for hypertension and proteinuria, making intervention, such as timely delivery possible. With an organised antenatal care, such in developed countries, the maternal mortality and serious morbidity have decreased. The major value of prevention is to identify women at high risk of preeclampsia and to make a medical intervention so that the disorder never occurs or is postponed. The ultimate predictor of preeclampsia should presumably identify women with an increased risk of the disorder as early as in the first trimester [13].

Blood pressure measurement is a screening test routinely used in antenatal care to detect or predict hypertensive disease. Accurate prediction of women at risk for preeclampsia is crucial for judicious allocation of monitoring resources and use of preventive treatment, with the prospect of improving maternal and neonatal outcome. Studies investigate the predictive accuracy of blood pressure measurement report conflicting results. In the period within 20 week of gestation the values of MAP over 85-90 mmHg and values of diastolic blood pressure over 75 mmHg are important predictive indicator for determination the risk of hypertensive disorders in pregnancy, especially preeclampsia [14]. In view of these conflicting reports it is uncertain whether blood pressure measurement should be used routinely as a predictive test or should only be used to diagnose hypertensive disorders in pregnancy once they are suspected [15].

Normal placentation is process who starts in the first trimester and it's more or less completed at the end of the second trimester. In preeclampsia, abnormal invasion of the spiral arteries by cytotrophoblast cells is associated with inadequate uteroplacental blood flow [11]. Doppler ultrasonography might be used to assess the velocity of uterine blood flow and indirectly evaluate the trophoblastic invasion of the spiral arteries.

Cnossen et al. report the results of their systematic review and meta-analysis of studies in which Doppler assessment of the uterine arteries was used to predict pre-eclampsia and intrauterine growth restriction. One of the widest Doppler study shows that the pulsatility index is leading predictor for preeclampsia. An increased pulsatility index has been associated with an increased risk for pre-eclampsia and intrauterine growth restriction. The presence of an early diastolic notch in the waveform has also been shown in several studies to be associated with adverse outcomes. The likelihood ratio, sensitivity and for each Doppler index and specific outcome have varied among studies, but the predictive relationship for adverse outcomes has been consistently reported. Cnossen and colleagues found that uterine artery Doppler ultrasonography more accurately predicted preeclampsia than

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intrauterine growth restriction and that the most powerful Doppler index for predicting preeclampsia was an increased pulsatility index with notching in the second trimester. For severe preeclampsia, they found that an increased pulsatility index or bilateral notching are the best predictors for this condition [16].

Several biochemical markers (PAPP-A, PIGF, PP13, sEndoglin, Inhibin-A, Activin-A, Pentraxin 3 and P-Selectin) as potential predictors describe the foetal and placental endocrine functions and the maternal endothelial dysfunction [17].

Antiplatelet aspirin therapy as secondary prevention reduces the risk of pre-eclampsia by 10% in women who have at least one risk factor. Aspirin should be initiated as early as possible (before 12–14 weeks- to the beginning of the first phase of trophoblast invasion). Calcium supplementation at a dosage of 1.5 g/day, beginning at 15 weeks and continued throughout the pregnancy is recommended for prevention of preeclampsia. Other treatments, such as antioxidant treatment by vitamins C and E, oligoelements and nitric oxide have no proven efficacy. Omega-3 fatty acids, as found in marine fats, have been suggested to be important in the prevention of preeclampsia. The possibility of the beneficial effect of these fatty acids was suggested by differences in rates of preeclampsia in population ingesting large quantities of fish oil [2,3,10].

Delivery is the only curative treatment for pre-eclampsia. Antihypertensive treatment is useful only in severe preeclampsia because the sole proven benefit of such management is to diminish the risk of maternal complications (cerebral hemorrhage, eclampsia, or acute pulmonary edema). There is no international consensus concerning antihypertensive treatment in preeclampsia. The mostly used drugs authorized for the treatment of hypertension in severe preeclampsia are Methyldopa, Labetalol, Nifedipine and Hydralazine [2,3].

Future research should concentrate on the development of algorithms that combine biochemical and biophysical markers, including blood pressure measurement, ultrasound and Color Doppler as diagnostic process used in clinical care. These may help improve the predictive accuracy of the tests to clinically important values [15].

An integrated first hospital visit at first trimester combining data from maternal characteristics, biophysical markers and biochemical predictors can define the patient at risk for preeclampsia.

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