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Editorial

Detection of Pregnant Women with a Risk of Preeclampsia during the First Trimester

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Preeclampsia (PE) is a leading cause of maternal and perinatal death worldwide, and it's affects 2 - 5% of all pregnancies [1,2]. 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 [3]. This multisystem disorder is a common, yet incompletely understood syndrome, unique to humans, which appears after 20 weeks of gestation and has spontaneous resolution after delivery. It can be distinguished as early (< 34 weeks of gestation) and late (> 34 weeks of gestation) onset phenotypes. Also, PE is a major cause of iatrogenic preterm birth [4,5]. The aetiology of PE is still not completely understood, although many facts of the disease have been illuminated. Endothelial cell dysfunction would seem to be the common denominator in the various stages of PE and appears to be present from the first trimester of pregnancy [6-9].

Women with PE develop hypertension, proteinuria, and varying degrees of ischemic end-organ damage, caused by widespread endothelial dysfunction. Also, PE is associated with abnormalities of the coagulation system, disturbed liver function, renal failure and cerebral ischemia. This condition is characterized by vasospasm, increased peripheral vascular resistance, and thus reduced organ perfusion [9].

Prediction and prevention of PE is a very important contribution for maternal health. Although the PE doesn't appear until 20 weeks of gestation, the root of the cause develops much earlier during the first trimester of pregnancy. The only guaranteed primary prevention of PE is avoidance of pregnancy. There are identified risk factors (maternal age, interval between pregnancies and maternal weight). Prevention of PE demands knowledge of the pathophysiological mechanism. Availability of techniques for early detection and intervention in the pathophysiological process are necessary. Finally, prevention of PE is a proper antenatal care which provides screening for hypertension and proteinuria, making intervention, such as timely deliver. With an organised antenatal care, such as in most high in-come countries, the maternal mortality and serious morbidity have decreased [8].

Combination of information from maternal characteristics and medical history (included obstetrical history), uterine pulsatility index (PI), mean arterial pressure (MAP), biochemical markers (plasma protein-A PAPP-A, placental growth factor PlGF) at 11 - 13 weeks of gestation can identify a high proportion of pregnancies at risk for early onset of PE [10]. The performance of the different methods of screening and prediction of PE are summarized in the following text.

Maternal history is the first step in prediction and prevention of PE. Major risk factors for PE are: nuliparity, extremes of reproductive age (young primiparas and adult multiparas), antiphospholipid antibody syndrome, family history of PE in first-degree relative, renal disease, chronic hypertension, diabetes mellitus, multiple gestations, strong family history of cv diseases (heart disease or stroke in ≥2 first-degree relatives), obesity etc [1,4,11].

Numerous studies have shown that high maternal pre-pregnancy body mass index (BMI; weight (kg)/height $(m)^2$) is a strong risk factor for preeclampsia. Overweight is associated with alterations in lipid concentrations and an activation of inflammatory markers and both of these metabolic abnormalities are characteristic of preeclamptic pregnancies before the onset of clinically evident disease [12]. BMI and obesity is a validated and independent risk factor for preeclampsia, but the mechanism of how it imparts increased risk is not completely understood. Obesity might act thought its association with insulin resistance, a syndrome of metabolic derangement characterized by hyperinsulinemia, hyperlipidemia, hypertension, and endothelial dysfunction [13,14].

Cigarette smoking is associated with lower maternal sFlt-1 concentrations during pregnancy and PE. Based on this data, cigarette smoke exposure may decrease the risk of PE in part by moderating the anti-angiogenic phenotype observed in syndrome [14,15].

The fact that parity plays a role for the development of preeclampsia is not new. The increased risk of PE is associated with a longer interbirth interval. In Norwegian population of women who had two, three or more singleton deliveries (1967 - 1998), the association between the risk of PE and the interval was more significant than the association between the risk and a change of partner. When the interval was 10 years or more, the risk of PE was about the same as that in nulliparous women [16]. A Danish cohort study found that a long interval between pregnancies was associated with a significantly higher risk of PE in a second pregnancy when PE had not been presented in the first pregnancy and paternity had not been changed [17].

The maternal demographic characteristics, including medical and obstetric history, are potentially useful in screening for PE, but only when the various factors are incorporated into a combined algorithm derived by multivariate analysis [1].

Maternal biophysical markers

Blood pressure (BP) measurement is a screening test routinely used in antenatal care to detect or predict hypertensive disease. Studies investigating the predictive accuracy of BP measurement report conflicting results. In view of these conflicting reports it is uncertain whether BP measurement should be used routinely as a predictive test or should only be used to diagnose hypertensive disorders in pregnancy once they are suspected [18]. Cnossen SJ., *et al*. (2008), worked on 34 studies and they concluded that the diastolic blood pressure over 75 mmHg in the period of 13 – 20 wg has predictive importance. They also concluded that in the same period the MAP values over 85 - 90 mmHg also has predictive importance for the development of PE [18,19]. Walsh AC. and Baxi VL. (2008), found out that values of DBP over 75 mmHg, have limited predictive importance for pre-eclampsia and the MAP values in the second quarter are a better predictor in relation to PE, as well as DBP and even more on SBP [20].

Blood pressure (BP) measurement is a screening test routinely used in antenatal care to detect or predict hypertensive disorders. BP measurement should be used routinely as a predictive test in the first trimester of pregnancy.

Normal placentation is a process that starts in the first trimester and is more or less completed at the end of the second trimester. In PE, defective invasion of the spiral arteries by cytotrophoblast cells is associated with inadequate uteroplacental blood flow [1,11,21]. Doppler ultrasonography might be used to assess the velocity of uterine blood flow and indirectly evaluate the trophoblastic invasion of the spiral arteries. The impaired placental perfusion reflects in increased uterine artery pulsatility index (PI). The ability to achieve a reliable measurement of uterine artery PI is dependent on appropriate training of sonographers [1,10]. One of the most widely studied Doppler indices is the pulsatility index (calculated as the peak systolic flow minus specificity of the end diastolic flow divided by the mean flow). The increased PI has been associated with an increased risk for PE 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. Cnossen and colleagues found that uterine artery Doppler ultrasonography is a much more accurate predictor for PE than for intrauterine growth restriction, and that the most powerful Doppler index for predicting PE was an increased PI with notching in the second trimester. For severe PE, they found that an increased PI or bilateral notching best predicted the condition [8,10,22].

Maternal biochemical markers

A large number of biochemical markers have been investigated for a prediction of PE. Several biochemical markers (PAPP-A, PlGF, 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 [23]. Some studies have concluded that the major phenotype of PE, hypertension and proteinuria, may be due to an excess of circulating anti-angiogenic growth factors, most notably soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin (sEng), and reduced levels of placental growth factor (PlGF) [24]. Maternal serum PAPP-A and PlGF are two biochemical markers that have been investigated extensively and have shown promising results in the early prediction of PE. They both have proven to be useful in screening for aneuploidies at 11 - 13 weeks' gestation [1]. In chromosomally normal pregnancies, there is evidence that low maternal serum PAPP-A in the first- and second-trimester is associated with increased risk for subsequent development of PE. Measurement of PAPP-A alone isn't an effective method of screening for PE [8].

Several studies reported that during the clinical phase of PE, the maternal serum PlGF concentration is reduced. These reduced levels of serum PlGF precede the clinical onset of the disease and are evident from both the first and second-trimester of pregnancy. First-trimester maternal serum concentrations of PAPP-A and PlGF have shown to be affected by gestational age at screening, maternal weight, maternal age, racial origin, cigarette smoking, conception by IVF, nulliparity and pre-existing diabetes mellitus. Consequently, the measured concentrations of PAPP-A and PlGF must be adjusted for these variables before comparing results with pathological pregnancies. The MoM values of PAPP-A and PlGF are significantly reduced at 11 - 13 weeks' gestation in women who subsequently develop PE [1,10,23].

There are some new biochemical markers. Further promising targets for the first-trimester screening are PP - 13, soluble endoglin, inhibin A, activin A, pentraxin 3, P-selectin, IGFBP-1 and IGFBP-3, adiponectin, resistin, l-arginine, asymmetric dimethylarginine (ADMA), and homoarginine. However, sFlt-1 is not suitable for screening in the first trimester [25].

Worldwide, prediction of PE in the first-trimester of pregnancy is of great interest. Early and improved prediction of PE would allow early administration of Aspirin, appropriate antenatal surveillance and better target research into preventive interventions [1,26]. The combination of maternal, biophysical and biochemical markers at 11 - 13 week of gestation could effectively identify women at high risk for PE [1,27]. An integrated first hospital/office visit at first trimester combining data from maternal characteristics and history, biophysical and some biochemical markers, can define the patient at risk for PE [10,18]. These may help improve the predictive accuracy of the tests to clinically important values [8].

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