Prediction and prevention of pre-eclampsia

ABSTRACT

Pre-eclampsia is a pregnancy-specific disorder affecting 2-8% of all pregnancies. Every year approximately 70 000 women die due to pre-eclampsia and its complications. It accounts for nearly one fifth of all maternal deaths. The only treatment for pre-eclampsia is delivery, which may lead to a premature birth. The aim of this study was to find ways to predict pre-eclampsia and test the performance of low dose aspirin in the prevention of pre-eclampsia in women at high risk.

This thesis includes data from two study cohorts. Participants of Study I comprise 21 nulliparous, pre-eclamptic women and 11 normotensive, non-proteinuric women recruited between January 1996 to February 1998 in the maternity clinics, the prenatal clinic and the antenatal ward of Helsinki University Central Hospital. The participants of Studies II-V consist of 947 pregnant women with and 117 without known risk factors for pre-eclampsia who were included in the PREDO project between September 2005 and December 2009 from 12^{+0} to 13^{+6} weeks of gestation in 1 of the 10 participating hospital maternity clinics.

To study the role of different combinations of risk factors in predicting pre-eclampsia, we studied 903 women using cluster analysis (Study IV). Of these, 86 (9.5%) developed pre-eclampsia, 10 (11.6%) had early-onset disease and 36 (41.9%) had severe disease. Women who have had pre-eclampsia, or small for gestational age (SGA) newborn in an earlier pregnancy, or who have chronic hypertension (CHT) or type 1 diabetes mellitus were at highest risk of early-onset pre-eclampsia, severe pre-eclampia and preterm pre-eclampsia. Pre-eclampsia in a previous pregnancy and a body mass index over 30 kg/m^2 were the most important risk factors for term pre-eclampsia. Early-onset and late-onset pre-eclampsia had different risk profiles. Moreover, the risk of pre-eclampsia increased exponentially with respect to the number of risk factors.

To assess the role of vasoactive agents in the prediction of pre-eclampsia, we studied placental growth factor (PlGF) and soluble vascular endothelial growth factor receptor-1 (VEGF-1 or sFlt-1) and their ratio, at 12-14, 18-20 and 26-28 weeks of gestation in a total of 53 women at high risk for pre-eclampsia and healthy controls (Study III). Of these, 27 developed pre-eclampsia: 6 early-onset and 21 late-onset forms of the disease. By the second measurement, differences in PlGF concentrations, and by the third measurement, differences in sFlt-1 concentrations were discovered between those who developed early-onset pre-eclampsia and others. With a cut-off point of 40 the ratio of sFlt-1/PlGF identified all women who developed early-onset pre-eclampsia, with no false positives, 4 to 6 weeks before the clinical diagnosis.

To study the predisposing factors to superimposed pre-eclampsia in women with CHT (Study V) we assessed markers of placental and endothelial function, and maternal cardiac function, and renal tubular injury at all three timepoints in women with CHT (n=90) and healthy controls (n=90). Superimposed pre-eclampsia was diagnosed in women with CHT with new proteinuria over 0.3g per day after 20^{+0} weeks of gestation. In women who subsequently developed superimposed pre-eclampsia, plasma syndecan-1 concentrations were lower at 26^{+0}-27^{+6} weeks (p=0.03) and plasma PlGF concentrations were lower (p=0.002) across gestation, compared to women with CHT without superimposed pre-eclampsia. Urine albumin creatine ratio (ACR) was elevated across gestation in women with CHT who subsequently developed superimposed pre-eclampsia compared with women with CHT only (p=0.007) or healthy controls (p=0.002). At the first timepoint receiver operator curve (ROC) value for ACR for prediction of pre-eclampsia was 0.87 (CI 0.73-1.0).

We investigated the concentrations of total and individual free fatty acids (FFA) in pre-eclamptic and normotensive pregnant women and the relationship between FFA concentrations and insulin sensitivity (Study I). Total FFA concentrations at baseline were 67% higher in pre-eclamptic than normotensive pregnancies (P = 0.0002). This difference was no longer significant after an oral glucose load. At the baseline, the differences between pre-eclamptic and normotensive pregnancies were largest in the concentrations of the oleic (75%), linoleic (129%) and arachidonic (315%) acids.

In the aspirin trial (Study II), we randomised 152 women with risk factors for pre-eclampsia and abnormal uterine artery flow upon Doppler velocimetry to low dose aspirin (100 mg per day) or placebo. We could not demonstrate any differences in the primary or secondary outcomes. Because the number of women identified as high risk by ultrasound was lower than expected, we concluded a meta-analysis of placebo-controlled aspirin trials with women whose uterine artery measurement indicated a high risk. According to the meta-analysis (3 trials, 346 women) low dose aspirin started at or before 16 weeks of gestation reduced the risk of pre-eclampsia (Risk ratio (RR) 0.6, 95% confidence interval (CI) 0.37-0.83), and severe pre-eclampsia (RR 0.3, 95%CI 0.11-0.69).

In conclusion, the risk of pre-eclampsia increased exponentially with respect to the number of risk factors. The sFlt-1/PlGF ratio identified women who develop early-onset pre-eclampsia weeks before the onset of clinical findings. The association between ACR in early pregnancy and superimposed pre-eclampsia is an evidence that pre-existing endothelial dysfunction in women with CHT may contribute to development of pre-eclampsia. It may be used in the prediction of pre-eclampsia in women with CHT already at the 12 weeks of gestation. Reduced syndecan-1 and PlGF antedate the development of pre-eclampsia in women with CHT, which implicate endothelial glycocalyx disturbance and reduced angiogenic capacity in the pathophysiology of superimposed pre-eclampsia. Women with established pre-eclampsia had higher FFA concentrations, which may influence several characteristics of pre-eclampsia, for example increased insulin resistance, endothelial cell dysfunction and altered production of vasoactive substances. According to the meta-analysis, low dose

aspirin reduced the risk of pre-eclampsia and severe pre-eclampsia in women with abnormal uterine artery flow. Consequently, low dose aspirin at a dose of 100 mg per day should be recommended to initiate before the 16^{th} week of gestation in high-risk women and continued until 35^{+0} weeks of gestation.