

ABSTRACT OF DOCTORAL THESIS

UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
DOCTORAL DEPARTMENT

**ANGIOGENIC AND ANTIANGIOGENIC FACTORS
IN THE PREDICTION OF PREECLAMPSIA**

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Keywords:

preeclampsia, screening, sFLT, PIGF, first trimester screening, third trimester screening, angiogenic factors, antiangiogenic factors, prediction of preeclampsia, prevention of preeclampsia.

Background

Preeclampsia (PE) is a major pregnancy complication with increased maternal and perinatal mortality and morbidity and long term risks for cardiovascular disease. Screening for PE at 11-13 weeks' gestation by a combination of maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PLGF) identifies 75% of pregnancies that develop preterm-PE but only 40% of term-PE. Prophylactic use of aspirin in the high-risk group identified by first-trimester screening prevents 90% of PE <32 weeks and 62% of PE <37 weeks, but it has no significant effect on the incidence of term-PE. There is some evidence that in high-risk pregnancies useful prediction of PE in the third trimester of pregnancy is provided by the serum soluble fms-like tyrosine kinase-1 (sFLT-1) to PLGF ratio.

Objectives

There are three objectives of this thesis. First, to examine the value of the sFLT-1 to PLGF ratio in third trimester screening for PE. Second, to compare the performance of the sFLT-1 to PLGF ratio in screening for PE at 31-34 versus 35-37 weeks' gestation. Third, to estimate the patient-specific risk of PE at 30-34 weeks' gestation by a combination of maternal characteristics and medical history with multiple of the median (MoM) values of MAP, UtA-PI, PLGF and sFLT-1 and stratify women into high-, intermediate- and low-risk management groups.

Methods

This thesis is based on data derived from routine third trimester screening for PE and is divided into three studies that aim to fulfill each of the three objectives. In the first

study we examined 12,305 singleton pregnancies at 30-37 weeks' gestation. In the second study, we examined 8,063 singleton pregnancies at 31⁺⁰-33⁺⁶ weeks' gestation and 3,703 at 35⁺⁰-36⁺⁶ weeks. In these two studies we examined the performance of the sFLT-1/PLGF >38 in the prediction of delivery with PE at <1 week, at <4 weeks and at \geq 4 weeks after assessment.

In the third study, we examined 8,128 singleton pregnancies at 30-34 weeks' gestation. Patient-specific risks of delivery with PE at <4 weeks from assessment and at <40 weeks' gestation were calculated using the competing risks model to combine the *prior* risk from maternal characteristics and medical history with MoM values of MAP, UTPI, PLGF and sFLT-1. On the basis of these risks the population was stratified into high-, intermediate- and low-risk groups. Different risk cut-offs were used to vary the proportion of the population stratified into each risk category and the performance of screening for delivery with PE at <4 weeks and delivery with PE from 4 weeks after assessment and up to 40 weeks' gestation (PE 4w-40GW) was estimated.

Results

In the first study, the detection rate (DR) and false positive rate (FPR) of sFLT-1/PLGF >38 in the prediction of delivery with PE at <1 week were 79% and 4.5%; the values for delivery with PE at <4 weeks were 77% and 4.1% and for delivery with PE at \geq 4 weeks were 21% and 4.3%.

In the second study we found that in the non-PE group, the median sFLT-1/PLGF increased with gestational age at screening and the ratio of 38 was just below the 99th percentile at 32 weeks' gestation and just below the 90th percentile at 36 weeks. In the two gestational windows the DR of PE at <4 weeks was similar (76%, 95% CI 57, 90 vs. 80%, 95% CI 64, 91), but the FPR was substantially lower at 31-34 than at 35-37 weeks (1.7% vs. 9.6%). The number of cases with PE at <1 week was small, but as above, in the two gestational windows the DR was similar (80%, 95% CI 28, 100 vs. 86%, 42, 100), but the FPR was substantially lower at 31-34 than at 35-37 weeks (1.9% vs. 10.2%).

In the third study, use of a risk cut-off for PE at <4 weeks of 1 in 50 and a risk cut-off of 1 in 150 for PE at <40 weeks' gestation the proportion of the population stratified into high-, intermediate- and low-risk was about 3%, 26% and 71%, respectively. The high-risk group contained 90% of pregnancies with PE at <4 weeks and 40% of those with PE at 4w-40GW. The intermediate-risk group contained a further 49% of women with PE at 4w-40GW. In the low-risk group, none of the women developed PE at <4 weeks and only 0.3% developed PE at 4w-40GW.

Conclusion

The first study demonstrated that in routine screening of singleton pregnancies at 30-37 weeks' gestation, the performance of sFLT-1/PLGF >38 is modest for prediction of delivery with PE at <1 and <4 weeks and poor for prediction of PE at ≥ 4 weeks. A policy of hospitalizing patients with sFLT-1/PLGF >38 would potentially lead to unnecessary hospitalization in 4.5% of pregnancies and a ratio of ≤ 38 would falsely reassure one fifth of the women that will deliver with PE at <1 week from assessment. The sFLT-1 to PLGF ratio as a method of screening for PE both in the general population and in high-risk pregnancies is attractive because of its simplicity. However, a ratio of ≤ 38 does not rule out the development of PE during the subsequent one week and a ratio of >38 has only a modest performance in identifying women that will develop PE within the subsequent four weeks.

The second study demonstrated that the performance of sFLT-1/PLGF >38 in prediction of delivery with PE at <1 and <4 weeks is substantially different when assessment is carried out at 31-34 weeks compared to assessment at 35-37 weeks. A precondition for effective use of a fixed cut-off is that the distribution of values in both the PE and unaffected cases does not change with gestation; as demonstrated in this study this is not the case for unaffected pregnancies. Consequently, use of sFLT to PLGF ratio of >38 in identifying a high-risk group in need for intensive monitoring in the subsequent four weeks would lead to five times more pregnancies being falsely classified as high-risk when screening is carried out at 35-37 weeks than at 31-34 weeks.

The third study, provides the framework for stratification of risk for PE based on screening at 30-34 weeks. The high-risk group can be monitored by measurement of blood pressure and urinalysis at least on a weekly basis and the women can be advised to report any of the symptoms associated with severe PE, such as visual disturbance and epigastric pain. In the intermediate-risk group, intensive monitoring would begin four weeks after the initial assessment but these women would also be advised to report any symptoms associated with severe PE. The low-risk group can be reassured that development of PE at <40 weeks' gestation is very unlikely. In all pregnancies, the routine ultrasound examination carried out at 30-34 weeks would have already identified any possible impairment of fetal growth and in such case the decision on timing of delivery would be based on fetal heart rate patterns and / or Doppler findings in the umbilical artery, middle cerebral artery and ductus venosus.