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# *GEORGE EMIL PALADE* UNIVERSITY OF MEDICINE, PHARMACY, SCIENCE AND TECHNOLOGY OF TÂRGU MUREȘ, ROMANIA

**DOCTORAL SCHOOL OF MEDICINE AND PHARMACY**
**ABSTRACT OF PhD THESIS**

## Prediction of preeclampsia and fetal growth restriction risk based on serum and Doppler parameters

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**BACKGROUND:** Regarding the hypertensive disorders of pregnancy, preeclampsia remains one of the leading causes of severe and life-threatening maternal and fetal complications, such as uncontrollable severe hypertension, eclampsia, stroke, myocardial infarction, pulmonary edema, acute respiratory distress syndrome, HELLP syndrome, disseminated intravascular coagulation, severe renal failure, retinal lesions, abruptio placentae, fetal growth restriction, antepartum fetal demise or preterm birth, as well as long-term neonatal morbidities, such as cerebral palsy and chronic pulmonary hypertension of the newborn. Screening of early-onset preeclampsia (< 34 weeks of pregnancy), as well as late-onset preeclampsia (≥ 34 weeks), shows poor performance if based solely on traditional risk factors (first-degree relative with medical history of the disorder, previous pregnancy complicated by preeclampsia personal history of thrombophilia, multifetal gestation - triplet gestation carries an increased risk compared to twin gestation - as well as in vitro fertilization, advanced maternal age (over 40 years), diabetes mellitus type I or II, obesity with a BMI > 35 kg/m2, pre-existing chronic hypertension or chronic kidney disease, autoimmune disease such as systemic lupus erythematosus, significantly increased serum uric acid levels (more than 1.5 times higher than normal after 20 weeks of gestation), and the more recently described serum uric acid-to-creatinine ratio, which is significantly higher in all three trimesters among pregnant women who later develop preeclampsia). The vast majority of preeclampsia cases affect healthy nulliparous women with none of the clinical factors mentioned above. Moreover, the prediction of preeclampsia using these traditional risk factors has shown poor predictive value, with a 37% detection rate for early-onset preeclampsia and a 29% detection rate for late-onset preeclampsia. In recent years, biochemical markers from maternal blood—the pro-angiogenic protein placental growth factor (PlGF) and the antiangiogenic protein soluble fms-like tyrosine kinase 1 (sFlt-1) - and uterine Doppler velocimetry indices - primarily the mean uterine pulsatility index (PI) and the uterine resistivity index (RI) have all shown improved screening performance.

**AIM:** The aim of the current research was to assess the role of algorithms based on the combination of the two biochemical parameters – sFlt-1 and PlGF – with the two uterine artery Doppler ultrasound parameters – mean PI and mean RI – in the second and third trimester prediction of hypertensive disorders of pregnancy, mainly preeclampsia and its associated complications – fetal growth restriction, premature delivery and antepartum fetal demise.

**MATERIAL and METHDOS:** Two prospective observational studies were carried out on a group of 160 pregnant patients, who were admitted to the Obstetrics and Gynaecology Department of Mures Clinical County Hospital between January 2021 and September 2022. Inclusion criteria consisted of the following: gestational age of 24 or 32 weeks, singleton pregnancy, the existence of at least one traditional risk factor for preeclampsia. Meanwhile, pregnancies already diagnosed with any form of hypertensive disorders of pregnancy were excluded from the studies.

**STUDY 1:** In the first study, all pregnant women had their sFlt-1 and PlGF levels determined once, at 24 weeks of gestation, in the moment of study enrollment, from a venous blood sample. For the study purpose, the sFlt-1/PlGF ratio was determined in each case. Moreover, Doppler ultrasound evaluation of the uterine arteries was also performed in each case at the moment of incluson, using a transabdominal approach. All the patients enrolled were followed-up until delivery. A special focus was placed on the

cases who developed gestational hypertension or preeclampsia during later stages of pregnancy, as well as related complications such as early-onset fetal growth restriction and antepartum fetal demise. Pregnant women who remained normotensive until delivery formed the control group, while patients who developed elevated blood pressure (≥140/90 mmHg) during the pregnancy, after the inclusion in the study, but with no other criterion for preeclampsia were considered part of the gestational hypertension group. Women who developed hypertension alongside at least one other diagnostic criterion for preeclampsia, formed the preeclampsia group, which was further divided into mild preeclampsia group and severe preeclampsia group. As far as the results are concerned, the algorithm comprising the combination of sFlt-1/PlGF cut-off 102.74 with mean uterine PI cutoff 1.44 and mean uterine RI cutoff 0.69 significantly enhanced the prediction accuracy of severe, early-onset preeclampsia complicated by fetal growth restriction and preterm delivery or antepartum fetal demise, meanwhile the algorithm based on the combination of sFlt-1/PlGF cutoff 59.55 with mean uterine PI cutoff 1.25 and mean uterine RI cutoff 0.62 significantly enhanced the prediction accuracy of preeclampsia compared to screening based on traditional risk factors. Finally, an algorithm based on the combination of sFlt-1/PlGF cutoff 59.55 with mean uterine PI cutoff 1.44 and mean uterine RI cutoff 0.74 significantly enhanced the prediction accuracy of uncomplicated gestational hypertension.

**STUDY 2:** In the second study, the pregnant women had their sFlt-1/PlGF ratio evaluated once, at 32 weeks of gestation, in the moment of study inclusion. Moreover, third trimester Doppler ultrasound evaluation of the uterine arteries was also performed in each case at 32 weeks, using a transabdominal approach. All the patients enrolled were followed-up until delivery. A special focus was placed on the cases who developed gestational hypertension or late-onset preeclampsia during later stages of pregnancy. As far as the results are concerned, the third trimester predictive algorithm based on the combination of sFlt-1/PlGF cut-off 64.76 with mean uterine PI cutoff 1.15 and mean uterine RI cutoff 0.65 significantly improved the prediction accuracy of late-onset preeclampsia compared to traditional risk factors, while the algorithm consisting of sFlt-1/PlGF cut-off 239.09 with mean uterine PI cutoff 1.48 and mean uterine RI cutoff 0.76 significantly improved the prediction the severe late-onset form of the condition.

**ORIGINALITY:** The originality of the current research is represented by the development of predictive algorithms of hypertensive disorders of pregnancy, mainly early- and late-onset preeclampsia occurrence and also its severity, based on the addition of two uterine artery Doppler ultrasound parameters – mean PI and mean RI – to serum biomarkers sFlt-1 and PlGF, for the second trimester screening, at 24 weeks, as well as the third trimester screening, at 32 weeks. As far as I know, no other published scientific paper created such predictive algorithms based on the combination of these ultrasound with biochemical parameters in the second or third trimester of pregnancy. The previously published literature either focused either on sFlt-1/PlGF ratio or Doppler ultrasound markers superiority compared to traditional risk factors in preeclampsia screening. Moreover, as gestational hypertension can unpredictably evolve into preeclampsia, the present studies also created distincitve algorithms for the prediction of uncomplicated gestational hypertension, with specific cut-offs.