thermoscientific


# Pre-eclampsia diagnosis

Study overview on improved pre-eclampsia diagnosis and prediction of adverse outcome with sFlt-1 and PlGF

ThermoFisher SCIENTIFIC

# Content

# Improved pre-eclampsia diagnosis and prediction of adverse outcome

Pre-eclampsia, which complicates about 2-3% of pregnancies, is a major cause of perinatal and maternal morbidity and mortality. Routine 1st trimester combined screening can identify women at high risk for developing pre-term pre-eclampsia in weeks 11-13+6 of gestation.

This literature review provides an overview of **why and how to implement the biomarkers sFlt-1 (soluble FMS-like tyrosine kinase) and PlGF (Placental growth factor)** into clinical practice for **women with suspected pre-eclampsia after 20 weeks of gestation** in order to improve patient management and patient care.

Main findings supported in the studies are:

- In patients with pre-eclampsia sFlt-1 levels are significantly increased while PlGF levels are significantly decreased compared to healthy pregnancies
- The sFlt-1/PlGF ratio is a useful tool as an aid to confirm the diagnosis of pre-eclampsia
- The sFlt-1/PlGF ratio improves the predictive value of Doppler ultrasound alone
- The sFlt-1/PlGF ratio is useful in the differential diagnosis of hypertensive pregnancy-related disorders
- The sFlt-1/PlGF ratio is useful in predicting the development of an adverse outcome in women with diagnosed pre-eclampsia

The determination of maternal serum sFlt-1 and PlGF together with other biological and clinical data improves the diagnostic possibilities in pre-eclampsia management in second and third trimester of pregnancy.

**Therefore, the sFlt-1/PlGF ratio is an important tool to better monitor and care for women with suspected pre-eclampsia or women already suffering from this severe pregnancy-related disorder.**

## Angiogenic Factor Estimation as a Warning Sign of Preeclampsia-Related Peripartum Morbidity Among Hospitalized Patients

Lopes Perdigao J, Chinthala S, Mueller A, Minhas R et al.
*Hypertension. 2019 Apr;73(4):868-877*

### Abstract

Preeclampsia-related morbidity and mortality is rising predominantly because of delayed identification of patients at risk for preeclampsia with severe features and associated complications. This study explored the association between angiogenic markers (sFlt1 [soluble fms-like tyrosine kinase-1]) and PlGF [placental growth factor]) and preeclampsia-related peripartum complications.

Normotensive women or those with hypertensive disorders of pregnancy were enrolled. Blood samples were collected within 96 hours before delivery, and angiogenic markers were measured on an automated platform.

Our study included 681 women, 375 of which had hypertensive disorders. Of these, 127 (33.9%) had severe preeclampsia, and 71.4% were black. Compared with normotensive women, women with severe preeclampsia had higher levels of sFlt1 (9372.5 versus 2857.0 pg/mL; P<0.0001), lower PlGF (51.0 versus 212.0 pg/mL; P<0.0001), and a high sFlt1/PlGF (212.0 versus 14.0; all P<0.0001).
A similar trend in sFlt1, PlGF, and sFlt1/PlGF was found in those women with complications secondary to preeclampsia (all P<0.001). The highest tertile of sFlt1/PlGF was strongly associated with severe preeclampsia in a multivariable analysis. Among patients with a hypertensive disorder of pregnancy, 340 (90.7%) developed postpartum hypertension, of which 50.4% had mild, and 40.3% had severe postpartum hypertension. The sFlt1/PlGF ratio was significantly higher for severe and mild postpartum hypertension compared with women with normal postpartum blood pressures (73.5, 46.0, and 13.0, respectively; P values<0.0001). Furthermore, the highest tertile of antepartum sFlt1/PlGF was associated with postpartum hypertension (P=0.004).

This study demonstrates a significant association between an abnormal angiogenic profile before delivery and severe preeclampsia and peripartum complications.

## Intrauterine growth restriction, soluble fms-like tyrosine kinase-1 to placental growth factor ratio increase and preeclampsia

Boulanger H, Drouin D, Largilliere C, Lefèvre G

*J Gynecol Obstet Hum Reprod. 2019 May 11. pii: S2468-7847(18)30509-9*

**Background**

Intrauterine growth restriction (IUGR) and preeclampsia (PE) share common features such as ischemic placental disease but also differ in their clinical expression regarding maternal diseases. The reason why IUGR remains isolated in some cases yet is followed by clinical manifestations of PE in other cases remains unexplained.

**Case report**

A 40-year old woman, gravida two, para one, experienced early-onset IUGR with a significant increase in the ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF) but, surprisingly, without any maternal clinical manifestations of PE.

**KEY FACTS**

**IUGR and a significant increase in sFlt-1/PlGF ratio without PE raise the issue of a missing factor enabling IUGR, a significant increase in sFlt-1/PlGF ratio, and PE to be linked. TEACHING POINTS: (1) Early-onset IUGR and a significant increase in sFlt-1/PlGF ratio do not necessarily mean the onset of PE. (2) Combining early-onset IUGR and a significant increase in sFlt-1/PlGF ratio without PE raises the question of an additional factor responsible for the onset of PE.**

## Midpregnancy prediction of pre-eclampsia using serum biomarkers sFlt-1 and PlGF

Black C, Al-Amin A, Stolarek C, Kane SC, Rolnik DL, White A, da Silva Costa F
*Brennecke S Pregnancy Hypertens. 2019 Apr;16:112-119*

**Objective**
Pre-eclampsia remains a significant cause of morbidity and mortality. Placental biomarkers soluble Fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) have been investigated previously for their ability to predict pre-eclampsia. We compared the performance of these biomarkers for midpregnancy pre-eclampsia prediction using three different immunoassay platforms.

**Study design**
Prospective study including singleton pregnancies 19-22 weeks' gestation. Maternal bloods were collected at recruitment. Screening performances using receiver operating characteristic (ROC) curves for PlGF and sFlt-1/PlGF ratio raw data and MoM values in isolation were evaluated for three immunoassay platforms using selected cut-off values.

**Main outcome measures**
Pre-eclampsia was defined as early-onset (<34 weeks' at delivery) and preterm (<37 weeks' at delivery).

**Results**
For prediction of preterm pre-eclampsia, PlGF MoM and sFlt-1/PlGF ratio MoM performed similarly, with areas under the curve (AUC), detection rates (DR) and false positive rates (FPR) for PlGF MoM and sFlt-1/PlGF ratio MoM being 0.77-0.79 and 0.71-0.74, 62.5% for both and 9.7-14.9 and 10.7-17.7, respectively. For the prediction of early-onset pre-eclampsia, sFlt-1/PlGF ratio raw data and MoM values performed similarly, with AUC, DR and FPR being 0.92-0.97 and 0.93-0.96, 100% for both, and 4.13-16.9 and 9.4-12.2, respectively.

**KEY FACTS**

**For midpregnancy prediction of preterm pre-eclampsia, PlGF MoM for all three platforms and sFlt-1/PlGF ratio MoM for the two platforms that tested sFlt-1 performed similarly. For midpregnancy prediction of early-onset pre-eclampsia at midpregnancy, sFlt-1/PlGF ratio raw data and MoM values using the early-onset cut-off for the two platforms that tested sFlt-1 gave similar performance from a clinical perspective.**

## The soluble fms-like tyrosin kinase-1 (sFLT-1) to placental growth factor (PlGF) ratio as a possible indicator for the severity of preeclampsia - single institution experience

Müller A, Horvat V, Vulin M, Mandić S, Šerić V, Vidosavljević D

*Med Glas (Zenica). 2019 Feb 1;16(1):53-59*

**Aim**

To investigate a potential of the clinical use of the soluble fms-like tyrosine kinase 1 (sFLT-1) to placental growth factor (PlGF) ratio from the perspective of a small hospital centre.

**Methods**

Maternal serum samples were analysed at 241/7-28 0/7, and 281/7-320/7 weeks of gestation. The level of sFLT-1 and PlGF was determined by immunoassay platform and used to calculate the sFLT-1/PlGF ratio in 35 pregnant women, and divided into subgroups according to preeclampsia occurrence at the time of delivery: preterm (≤37 weeks) or term (37-42 weeks'), and matched a control group.

**Results**

Patients in the preterm delivery group had a significantly higher incidence of intrauterine growth restriction, lower gestational age at the time of delivery, and lower infant birth weight compared to the other two groups. There was a negative correlation between the sFLT-1/PlGF ratio and GA and between the sFLT-1/ PlGF ratio and birth weight at the time of delivery. The value of the sFLT-1/PlGF ratio was significantly higher in the preterm delivery PE group. All the PE group pregnancies ended with caesarean delivery compared to 25% in the control group. However, none of the patients from the PE group had any of the possible complications of preeclampsia nor did they require additional therapy such as blood transfusion or additional non-standard hypertensive therapy.

**KEY FACTS**

**The sFLT-1/PlGF ratio could be used as an indicator for the development and estimation of the severity of PE to provide objective evidence for the management of preeclampsia patients, and as a predictive marker of preeclampsia at low cost.**

## Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women With Suspected Preeclampsia

Cerdeira AS, O'Sullivan J, Ohuma EO, Harrington D, Szafranski P et al

*Hypertension. 2019 Aug 12:HYPERTENSIONAHA11912739*

### Abstract

The ratio of maternal serum sFlt-1 (soluble fms-like tyrosine kinase 1) to PlGF (placental growth factor) has been used retrospectively to rule out the occurrence of preeclampsia, a pregnancy hypertensive disorder, within 7 days in women presenting with clinical suspicion of preeclampsia.

A prospective, interventional, parallel-group, randomized clinical trial evaluated the use of sFlt-1/PlGF ratio in women presenting with suspected preeclampsia. Women were assigned to reveal (sFlt-1/PlGF result known to clinicians) or nonreveal (result unknown) arms. A ratio cutoff of 38 was used to define low (≤38) and elevated risk (>38) of developing the condition in the subsequent week. The primary end point was hospitalization within 24 hours of the test. Secondary end points were development of preeclampsia and other adverse maternal-fetal outcomes.

We recruited 370 women (186 reveal versus 184 nonreveal). Preeclampsia occurred in 85 women (23%). The number of admissions was not significantly different between groups (n=48 nonreveal versus n=60 reveal; P=0.192). The reveal trial arm admitted 100% of the cases that developed preeclampsia within 7 days, whereas the nonreveal admitted 83% (P=0.038). Use of the test yielded a sensitivity of 100% (95% CI, 85.8-100) and a negative predictive value of 100% (95% CI, 97.1-100) compared with a sensitivity of 83.3 (95% CI, 58.6-96.4) and negative predictive value of 97.8 (95% CI, 93.7-99.5) with clinical practice alone. Use of the sFlt-1/PlGF ratio significantly improved clinical precision without changing the admission rate. Clinical Trial Registration-URL: http://www.isrctn.com. Unique identifier: ISRCTN87470468.

## Analytical validation of soluble fms-like tyrosine and placental growth factor assays on B·R·A·H·M·S KRYPTOR Compact Plus automated immunoassay platform

Chan SL, Rana S, Chinthala S, Salahuddin S, Yeo KJ

*Pregnancy Hypertens. 2018 Jan;11:66-70*

**Background**

Preeclampsia is one of the leading hypertensive disorders of pregnancy. Angiogenic biomarkers such as anti-angiogenic factor soluble fms-like tyrosine kinase 1 (sFlt1) and pro-angiogenic factor placental growth factor (PlGF) are involved in the pathophysiology of preeclampsia.

**Objective**

The aim of this study is to validate the analytical performance of sFlt1 and PlGF on the B·R·A·H·M·S KRYPTOR Compact Plus (ThermoFisher Scientific).

**Study design**

We examined K2-EDTA plasma samples from 50 patients on B·R·A·H·M·S KRYPTOR Compact Plus, an automated immunoassay platform. QC materials were used to assess intra- and inter-precision of the assay. Lower limit of quantitation and interference studies were determined using pooled patient plasma.

**Results**

The sFlt1 and PlGF assays demonstrated an analytical measuring range of 90-69,000 pg/mL and 11-7000 pg/mL, respectively ($r2 > 0.99$). Lower limit of quantitation (20% CV) was interpolated to be 35 pg/mL for sFlt1 and 10 pg/mL for PlGF. Total precision for both assay displayed CVs of <10%. Interference studies showed that both assays were not significantly affected by hemolysis up to an H-index of 1100 for sFlt1 and 300 for PlGF; L- and I-index of 800 and 80 respectively for both assays. The Passing-Bablok regression analysis for sFlt1/PlGF yielded an equation of $y = 1.05x + 0.02$, and the Bland Altman analysis showed an average bias of 0.84.

**KEY FACTS**

**Plasma levels of sFlt1 and PlGF measured on the B·R·A·H·M·S KRYPTOR Compact Plus platform demonstrate excellent analytical performance and are acceptable as clinical grade assays.**

## Evaluation of sFlt-1/PlGF Ratio for Predicting and Improving Clinical Management of Pre-eclampsia: Experience in a Specialized Perinatal Care Center

Caillon H, Tardif C, Dumontet E, Winer N, Masson D

*Ann Lab Med. 2018 Mar;38(2):95-101*

**Background**

Management of pregnant women at high risk of pre-eclampsia (PE) requires frequent monitoring, with referral to specialized perinatal care centers. Reliable tests are necessary to improve prediction of PE and related complications and to assess disease severity and progression. An imbalance in two biomarkers, soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF), is involved in PE pathogenesis. The sFlt-1 to PlGF ratio is increased in pregnant women before the onset of PE. An elevated ratio is highly predictive of PE, whereas the diagnosis of PE can be ruled out within one week for low ratios. The main objective of this study was to assess whether a low sFlt-1/PlGF ratio, below a cutoff of 38, can predict the absence of PE within one week.

**Methods**

We performed a prospective, monocentric, observational study to evaluate serum sFlt-1/PlGF ratio (Roche Diagnostics Cobas e411 system) for predicting -PE in a group of 67 high-risk pregnant women (20-37 gestation weeks).

**Results**

Among the 67 patients included, 53 had a sFlt-1/PlGF ratio lower than 38; none developed subsequent PE leading to a negative predictive value of 100%. Eight patients developed clinical PE. The positive predictive value was 21% at one week and 18% at four weeks, in accordance with previous studies.

**KEY FACTS**

**The serum sFlt-1/PlGF ratio showed highly predictive performances for ruling out PE. Using these biomarkers in routine management of PE may improve clinical care and avoid inappropriate hospitalization, which has a significant economic impact.**

## Soluble fms-like tyrosine kinase-1, placental growth factor and their ratio as a predictor for pre-eclampsia in East Asians

Cheng YKY, Law LW, Leung TY, Chan OK, Sahota DS

*Pregnancy Hypertens. 2018 Jan;11:61-65*

**Objective**

To assess the clinical utility of the sFlt-1:PlGF ratio rule-in/rule-out pre-eclampsia either directly or after correcting each marker for gestation and maternal weight.

**Methods**

This was a prospective cohort study. sFlt-1, PlGF were measured in 965 women randomized to undergo a single blood withdraw between 20 and 39 weeks of gestation. sFlt-1, PlGF and the sFlt-1:PlGF ratio temporal relationship was determined. sFlt-1 and PlGF were converted to multiples of the expected gestational median (MoM) and adjusted for maternal weight. The 90th centile of the adjusted sFlt-1MoM:PlGFMoM ratio was determined. Clinical utility of the sFlt-1:PlGF ratio (≥38) to rule in/rule-out pre-eclampsia (PE) after 20 weeks of gestation versus that of the sFlt-1MoM:PlGFMoM 90th percentile was assessed in 81 women admitted for management of antenatal hypertension.

**Results**

The sFlt-1:PlGF ratio had quadratic relationship with gestation whereas the sFlt-1MoM:PlGFMoM ratio log distribution that was Gaussian with a mean of zero and a standard deviation of 0.85 with a 90th percentile equal to 1.08. Thirty-four (42%) of the 81 women admitted for management of their antenatal hypertension had PE, 26 (76.4%) had a sFlt-1:PlGF ratio ≥ 38. Four of the remaining 8 PE affected pregnancies with sFlt-1:PlGF ratio <38 delivered within 7 days, 3 were preterm. Two of the 3 preterm PE pregnancies had sFlt-1MoM:PlGFMoM exceeding 90th percentile.

**KEY FACTS**

**The relative level of the sFlt-1 to PlGF carries prognostic value. A sFlt-1MoM:PlGFMoM ratio exceeding the 90th centile resulted in additional detection of pregnancies which developed PE compared to the conventional sFlt-1:PlGF ratio.**

## Diagnosis of preeclampsia and fetal growth restriction with the sFlt-1/PlGF ratio: Diagnostic accuracy of the automated immunoassay KRYPTOR

Dröge LA, Höller A, Ehrlich L, Verlohren S, Henrich W, Perschel FH

*Pregnancy Hypertens. 2017 Apr;8:31-36.*

**Objective**

We aimed to characterize the diagnostic accuracy of the KRYPTOR assay for sFlt-1 and PlGF in maternal serum samples of uneventful singleton pregnancies and subjects with preeclampsia (PE) and PE-related outcomes such as fetal growth restriction (FGR). Longitudinal reference ranges of the sFlt-1 and PlGF level in the course of normal pregnancies were generated.

**Methods**

A cohort of subjects with PE and PE-related outcomes including FGR in the third trimester was compared to a cohort of women with uneventful outcome. Serum levels of sFlt-1, PlGF level as well as the sFlt-1/PlGF ratio was analysed with the KRYPTOR assay and compared between the case- and control groups. Cut-off values were generated and diagnostic accuracy examined.

**KEY FACTS**

**Longitudinal reference ranges of the sFlt-1 and PlGF level in healthy pregnancies were in line with those levels measured with other immunoassays. Comparison of the sFlt-1/PlGF ratio between PE-related outcomes including FGR or PE and healthy controls showed a high diagnostic accuracy with an area under the curve (AUC) of 0.917 for PE-related outcomes and 0.919 for PE.**

## Angiogenic Markers Predict Pregnancy Complications and Prolongation in Preeclampsia: Continuous Versus Cutoff Values

Saleh L, Vergouwe Y, van den Meiracker AH, Verdonk K et al.
*Hypertension. 2017 Nov;70(5):1025-1033*

**Abstract**

To assess the incremental value of a single determination of the serum levels of sFlt-1 (soluble Fms-like tyrosine kinase 1) and PlGF (placental growth factor) or their ratio, without using cutoff values, for the prediction of maternal and fetal/neonatal complications and pregnancy prolongation.

620 women with suspected/confirmed preeclampsia, aged 18 to 48 years, were included in a prospective, multicenter, observational cohort study. Women had singleton pregnancies and a median pregnancy duration of 34 (range, 20-41) weeks. Complications occurred in 118 women and 248 fetuses. The median duration between admission and delivery was 12 days.

To predict prolongation, PlGF showed the highest incremental value (R2=0.72) on top of traditional predictors (gestational age at inclusion, diastolic blood pressure, proteinuria, creatinine, uric acid, alanine transaminase, lactate dehydrogenase, and platelets) compared with R2=0.53 for the traditional predictors only.

sFlt-1 showed the highest value to discriminate women with and without maternal complications (C-index=0.83 versus 0.72 for the traditional predictors only), and the sFlt-1/PlGF ratio showed the highest value to discriminate fetal/neonatal complications (C-index=0.86 versus 0.78 for the traditional predictors only).

Applying previously suggested cutoff values for the sFlt-1/PlGF ratio yielded lower incremental values than applying continuous values. In conclusion, sFlt-1 and PlGF are strong and independent predictors for days until delivery along with maternal and fetal/neonatal complications on top of the traditional criteria. Their use as continuous variables (instead of applying cutoff values for different gestational ages) should now be tested in a prospective manner, making use of an algorithm calculating the risk of an individual woman with suspected/confirmed preeclampsia to develop complications.

## Using the angiogenic factors sFlt-1 and PlGF with Doppler ultrasound of the uterine artery for confirming preeclampsia

Bahlmann F, Al Naimi A

*Arch Gynecol Obstet. 2016 Nov;294(6):1133-1139*

### Purpose

The aim of this study is to assess the value of the angiogenic factors for diagnosing preeclampsia and predicting the severity of manifestation. A secondary aim is assessing the combination of the uterine artery Doppler with the angiogenic factors for improving the diagnostic power.

### Methods

This is a prospective single center study in a tertiary referral hospital. This study includes 728 individual patients. Inclusion criteria were singleton pregnancies, a referral to the hospital with suspicion of preeclampsia and any one or combination of the following symptoms: headache, upper abdominal pain, edema, and hypertension. Patients with complications that would affect the course of the pregnancy, such as placenta praevia, premature preterm rupture of membranes, breech presentation, and fetal chromosomal or structural anomalies, were excluded from the study. Blood samples collection and uterine artery Doppler ultrasound were performed at time of recruitment. The differences in sFlt-1, PlGF, and their quotient among normal collective and patients with preeclampsia were analyzed. Doppler ultrasound was performed by one of four highly qualified sonographers. Wilcoxon-Mann-Whitney U test, Spearman's rank correlation, receiver operating characteristic curves, Chi-square test, and logistic regression were used in the analysis.

### Results

A total of 1003 individual samples for the angiogenic factors were included in the analysis. 584 out of the recruited 728 patients had follow-up data with delivery information at the study hospital. Patients with preeclampsia show a significant increase in sFlt-1, which directly correlate with the increased severity of manifestation (Spearman's ρ 0.49). The sFlt-1 cut-off value of 5424 pg/ml confirms preeclampsia with 83.7 % sensitivity, 68.1 % specificity, and 24 % misclassification rate. Preeclampsia patients also show a significant decrease in PlGF, which negatively correlates with the increased severity of manifestation (Spearman's ρ -0.39). A PlGF cut-off value of 118 pg/ml confirms preeclampsia with 47.6 % sensitivity, 71.4 % specificity, and 27 % misclassification rate. Logistic regression shows that a combination of the quotient from sFlt-1/PlGF with notching and uterine artery PI provides a valid model for diagnosing preeclampsia with a diagnostic power of 74.4 %.

**KEY FACTS**

**The study confirms the use of the sFlt-1 and PlGF for diagnosing preeclampsia. It also shows their significance in differentiating between different categories of preeclampsia according to severity. This study shows that the use of angiogenic factors in combination with ultrasound findings provides valid models for confirming preeclampsia.**

## Soluble fms-Like Tyrosine Kinase-1-to-Placental Growth Factor Ratio and Time to Delivery in Women With Suspected Preeclampsia

Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M et al
*Obstet Gynecol. 2016 Aug;128(2):261-9*

**Objective**
To assess the association of a serum soluble fms-like tyrosine kinase 1-to-placental growth factor (sFlt-1-to-PlGF) ratio of greater than 38 with time to delivery and preterm birth.

**Methods**
Secondary analysis of an observational cohort study that included women 18 years of age or older from 24 to 36 6/7 weeks of gestation at their first study visit with suspected (not confirmed) preeclampsia. Participants were recruited from December 2010 to January 2014 at 30 sites in 14 countries. A total of 1,041 women were included in time-to-delivery analysis and 848 in preterm birth analysis.

**Results**
Women with an sFlt-1-to-PlGF ratio greater than 38 (n=250) had a 2.9-fold greater likelihood of imminent delivery (ie, delivery on the day of the test) (Cox regression hazard ratio 2.9; P<.001) and shorter remaining time to delivery (median 17 [interquartile range 10-26] compared with 51 [interquartile range 30-75] days, respectively; Weibull regression factor 0.62; P<.001) than women with an sFlt-1-to-PlGF ratio of 38 or less, whether or not they developed preeclampsia. For women who did not (n=842) and did develop preeclampsia (n=199), significant correlations were seen between an sFlt-1-to-PlGF ratio greater than 38 and preterm birth (r=0.44 and r=0.46; both P<.001). Among women who did not develop preeclampsia, those who underwent iatrogenic preterm delivery had higher median sFlt-1-to-PlGF ratios at their first visit (35.3, interquartile range 6.8-104.0) than those who did not (8.4, interquartile range 3.4-30.6) or who delivered at term (4.3, interquartile range 2.4-10.9).

**KEY FACTS**

**In women undergoing evaluation for suspected preeclampsia, a serum sFlt-1-to-PlGF ratio greater than 38 is associated with a shorter remaining pregnancy duration and a higher risk of preterm delivery.**

## Influence of the sFlt-1/PlGF Ratio on Clinical Decision-Making in Women with Suspected Preeclampsia

Klein E, Schlembach D, Ramoni A, Langer E, Bahlmann F et al.
*PLoS One. 2016 May 31;11(5):e0156013*

**Objective**
To evaluate the influence of the soluble fms-like tyrosine kinase 1/placental growth factor ratio in physicians' decision making in pregnant women with signs and symptoms of preeclampsia in routine clinical practice.

**Methods**
A multicenter, prospective, open, non-interventional study enrolled pregnant women presenting with preeclampsia signs and symptoms in several European perinatal care centers. Before the soluble fms-like tyrosine kinase 1/placental growth factor ratio result was known, physicians documented intended clinical procedures using an iPad® application (data locked/time stamped). After the result was available, clinical decisions were confirmed or revised and documented. An independent adjudication committee evaluated the appropriateness of decisions based on maternal/fetal outcomes. Clinician decision making with regard to hospitalization was the primary outcome.

**Results**
In 16.9% of mothers (20/118) the hospitalization decision was changed after knowledge of the ratio. In 13 women (11.0%), the initial decision to hospitalize was changed to no hospitalization. In seven women (5.9%) the revised decision was hospitalization. All revised decisions were considered appropriate by the panel of adjudicators (McNemar test; $p < 0.0001$).

**KEY FACTS**

**The use of the soluble fms-like tyrosine kinase 1/placental growth factor test influenced clinical decision making towards appropriate hospitalization in a considerable proportion of women with suspected preeclampsia. This is the first study to demonstrate the impact of angiogenic biomarkers on decision making in a routine clinical practice.**

## Longitudinal changes in maternal serum placental growth factor and soluble fms-like tyrosine kinase-1 in women at increased risk of pre-eclampsia

Khalil A, Maiz N, Garcia-Mandujano R, Penco JM, Nicolaides KH
*Ultrasound Obstet Gynecol. 2016 Mar;47(3):324-31*

**Objective**
To investigate longitudinal changes in maternal serum levels of placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) in pregnant women who develop pre-eclampsia (PE) or gestational hypertension (GH).

**Methods**
This was a prospective longitudinal study in women with singleton pregnancies identified by screening at 11 + 0 to 13 + 6 weeks' gestation as being at high-risk of PE. Blood samples were taken every 4 weeks until delivery. Values were compared in women who developed preterm PE (requiring delivery before 37 weeks' gestation), term PE or GH and those who remained normotensive.

**Results**
A total of 1069 samples were analyzed in 234 women, including 172 who remained normotensive, 18 who developed GH, 22 who developed preterm PE and 22 who developed term PE. In the preterm PE group, compared to the normotensive group, sFlt-1 levels were significantly higher from 15 weeks' gestation onward and the difference increased with gestational age ($P < 0.001$). In the preterm PE group, compared to the normotensive group, PlGF levels were significantly lower from 11 weeks' gestation onward and the difference increased significantly with gestational age ($P < 0.001$). Similarly, in the term PE and GH groups, PlGF levels were lower from 13 and 27 weeks onward, respectively, and the differences increased significantly with gestational age ($P < 0.001$ for both groups). In the preterm PE group, compared to the normotensive group, the sFlt-1/PlGF ratio was significantly higher from 11 weeks onward and the difference increased significantly with gestational age ($P < 0.001$). A random slope model provided a significantly better fit to the data than did a single-level model for sFlt-1 (likelihood ratio (LR) = 516; degrees of freedom (df) = 3; $P < 0.001$), PlGF (LR = 542; df = 3; $P < 0.001$) and the sFlt-1/PlGF ratio (LR = 468; df = 3; $P < 0.001$).

**KEY FACTS**

**Repeat measurements of the biochemical markers used in this study are likely to be better predictors of PE than are measurements at a single time point during pregnancy, as the differences between normotensive and hypertensive pregnancies increase with gestational age. In screening for preterm PE, maternal serum level of PlGF is a useful marker from the first trimester onward, while the level of sFlt-1 is likely to have a predictive value from the second trimester onward.**

## KRYPTOR-automated angiogenic factor assays and risk of pre-eclampsia-related adverse outcomes

Salahuddin S, Wenger JB, Zhang D, Thadhani R, Karumanchi SA, Rana S
*Hypertens Pregnancy. 2016 Aug;35(3):330-45*

**Objective**
To evaluate KRYPTOR assays for circulating soluble fms-like tyrosine kinase-1 (sFlt1) and placental growth factor (PlGF) in risk assessment of adverse outcomes in women with suspected pre-eclampsia.

**Methods**
We studied 412 women carrying a singleton pregnancy from a previous study cohort who were evaluated for suspected pre-eclampsia. Another 434 nonpre-eclamptic patients with plasma samples drawn throughout pregnancy were used to derive normative data. Plasma sFlt1 and PlGF levels were measured on the automated KRYPTOR platform and evaluated for prediction of adverse maternal and perinatal outcomes within 2 weeks. Normative values were used to create a ratio of markers and these values were reported as multiples of median (MoM) for women with and without adverse outcomes. The KRYPTOR assay results were also compared with previously reported measurements obtained using the automated Elecsys platform.

**Results**
Among participants presenting at <34 weeks (N = 110), patients with subsequent adverse outcome had higher sFlt1, lower PlGF, and higher sFlt1/PlGF ratio compared with women without adverse outcomes: the median (25th, 75th centile) sFlt1 (pg/ml), 9030 (3197, 12,140) versus 1976 (1248, 2937); PlGF (pg/ml), 36 (16, 111) versus 318 (108, 629); and ratio, 285.6 (32.2, 758.5) versus 6.1 (2.3, 20.3) (all $p < 0.0001$). Higher sFlt1/PlGF ratio correlated negatively with timing of delivery ($r = -0.60$, $p < 0.001$) and the risk of adverse outcomes was markedly elevated among women in highest tertile compared with lower tertile (odds ratio, 14.77; 95% confidence interval (CI), 4.28-51.00). The addition of sFlt1/PlGF ratio (≥85) to hypertension and proteinuria significantly improved the prediction for subsequent adverse outcomes (AUC 0.89 (95% CI): 0.82, 0.95) for hypertension, proteinuria, and sFlt1/PlGF (AUC = 0.75 (0.65, 0.85)) for hypertension alone ($p = 0.002$). Compared with normative controls, women who were evaluated for pre-eclampsia without adverse outcomes had higher MoM for sFlt1/PlGF ratio; these values were further elevated in women with adverse outcomes. sFlt1/PlGF ratios measured on the KRYPTOR platform were highly correlated with measurements obtained using Elecys platform ($r = 0.97$, $p < 0.001$).

**KEY FACTS**

**In women with suspected pre-eclampsia presenting prior to 34 weeks of gestation, KRYPTOR assays for circulating sFlt1 and PlGF when used in conjunction with standard clinical evaluation performs well in the prediction of adverse maternal and perinatal outcomes occurring within 2 weeks of presentation.**

## The sFlt-1/PlGF ratio associates with prolongation and adverse outcome of pregnancy in women with (suspected) pre-eclampsia: analysis of a high-risk cohort

Saleh L, Verdonk K, Jan Danser AH, Steegers EA, Russcher H et al.
*Eur J Obstet Gynecol Reprod Biol. 2016 Apr;199:121-6*

### Objective

To evaluate the additive value of the sFlt-1/PlGF ratio for diagnosing pre-eclampsia (PE) and predicting prolongation of pregnancy and adverse outcome in a cohort of women with PE or at high risk of PE.

### Study design

Patients with suspected or confirmed clinical PE were recruited. At time of inclusion blood for measurement of sFlt-1and PlGF was taken. Values were determined after delivery. A cut-off ratio of ≥85 was defined as a positive test.

### Results

A total of 107 patients were included. Of the patients, 62 (58%) met the clinical criteria of PE at time of blood sampling. In 10% of these patients (n=6) the ratio was <85 (false negative), whereas in 7% (n=3) of patients without clinical PE the ratio was ≥85 (false positive), resulting in positive and negative predictive values of 95% and 88% respectively.

One patient with false positive ratio developed superimposed PE and 2 developed gestational hypertension, and adverse outcome occurred in all three. An adverse pregnancy outcome was only encountered in 1 of the 6 patients with a false negative ratio.

Using a binary regression model with adjustment for gestational age <34 weeks, the adverse outcome risk was 11 times increased on the basis of clinical PE, and 30 times on the basis of an elevated ratio (P=0.036).

**KEY FACTS**

**The additive value of an increased ratio for diagnosing PE is limited since most patients with clinical PE also have a positive ratio. However, an elevated ratio is superior to the clinical diagnosis of PE for predicting an adverse pregnancy outcome. Furthermore, irrespective of clinical PE, a low ratio is inversely correlated with prolongation of pregnancy.**

## Predictive Value of the sFlt-1: PlGF Ratio in Women with Suspected Pre-eclampsia

Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M et al.
*N Engl J Med. 2016 Jan 7;374(1):13-22*

**Background**
The ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF) is elevated in pregnant women before the clinical onset of pre-eclampsia, but its predictive value in women with suspected pre-eclampsia is unclear.

**Methods**
We performed a prospective, multicenter, observational study to derive and validate a ratio of serum sFlt-1 to PlGF that would be predictive of the absence or presence of pre-eclampsia in the short term in women with singleton pregnancies in whom pre-eclampsia was suspected (24 weeks 0 days to 36 weeks 6 days of gestation). Primary objectives were to assess whether low sFlt-1:PlGF ratios (at or below a derived cutoff) predict the absence of pre-eclampsia within 1 week after the first visit and whether high ratios (above the cutoff) predict the presence of pre-eclampsia within 4 weeks.

**Results**
In the development cohort (500 women), we identified an sFlt-1:PlGF ratio cutoff of 38 as having important predictive value. In a subsequent validation study among an additional 550 women, an sFlt-1:PlGF ratio of 38 or lower had a negative predictive value (i.e., no pre-eclampsia in the subsequent week) of 99.3% (95% confidence interval [CI], 97.9 to 99.9), with 80.0% sensitivity (95% CI, 51.9 to 95.7) and 78.3% specificity (95% CI, 74.6 to 81.7). The positive predictive value of an sFlt-1:PlGF ratio above 38 for a diagnosis of pre-eclampsia within 4 weeks was 36.7% (95% CI, 28.4 to 45.7), with 66.2% sensitivity (95% CI, 54.0 to 77.0) and 83.1% specificity (95% CI, 79.4 to 86.3).

**KEY FACTS**

**An sFlt-1:PlGF ratio of 38 or lower can be used to predict the short-term absence of pre-eclampsia in women in whom the syndrome is suspected clinically.**

## Removal of Soluble Fms-Like Tyrosine Kinase-1 by Dextran Sulfate Apheresis in Pre-eclampsia

Thadhani R, Hagmann H, Schaarschmidt W, Roth B, Cingoez T, Karumanchi SA et al
*J Am Soc Nephrol. 2016 Mar;27(3):903-13*

**Abstract**

Pre-eclampsia is a devastating complication of pregnancy. Soluble Fms-like tyrosine kinase-1 (sFlt-1) is an antiangiogenic protein believed to mediate the signs and symptoms of pre-eclampsia.

We conducted an open pilot study to evaluate the safety and potential efficacy of therapeutic apheresis with a plasma-specific dextran sulfate column to remove circulating sFlt-1 in 11 pregnant women (20-38 years of age) with very preterm pre-eclampsia (23-32 weeks of gestation, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, new onset protein/creatinine ratio >0.30 g/g, and sFlt-1/placental growth factor ratio >85).

We evaluated the extent of sFlt-1 removal, proteinuria reduction, pregnancy continuation, and neonatal and fetal safety of apheresis after one (n=6), two (n=4), or three (n=1) apheresis treatments.

Mean sFlt-1 levels were reduced by 18% (range 7%-28%) with concomitant reductions of 44% in protein/creatinine ratios. Pregnancy continued for 8 days (range 2-11) and 15 days (range 11-21) in women treated once and multiple times, respectively, compared with 3 days (range 0-14) in untreated contemporaneous pre-eclampsia controls (n=22). Transient maternal BP reduction during apheresis was managed by withholding pre-apheresis antihypertensive therapy, saline prehydration, and reducing blood flow through the apheresis column. Compared with infants born prematurely to untreated women with and without pre-eclampsia (n=22 per group), no adverse effects of apheresis were observed.

**KEY FACTS**

**In conclusion, therapeutic apheresis reduced circulating sFlt-1 and proteinuria in women with very preterm pre-eclampsia and appeared to prolong pregnancy without major adverse maternal or fetal consequences. A controlled trial is warranted to confirm these findings.**

## Diagnosis of pre-eclampsia with soluble Fms-like tyrosine kinase 1/placental growth factor ratio: an inter-assay comparison

Andersen LB, Frederiksen-Møller B, Work Havelund K, Dechend R et al.
*J Am Soc Hypertens. 2015 Feb;9(2):86-96*

**Objective**
The angiogenic factor ratio soluble Fms-kinase 1 (sFlt-1)/placental growth factor (PlGF) is a novel diagnostic tool for pre-eclampsia. We compared the efficacy of the KRYPTOR (BRAHMS) automated assays for sFlt-1 and PlGF with the Elecsys (Roche) assays in a routine clinical setting.

**Methods**
Pre-eclamptic women (n = 39) were included shortly after the time of diagnosis. Normotensive control pregnancies were matched by gestational age (n = 76).

**Results**
The KRYPTOR assays performed comparably or superior to Elecsys (sFlt-1/PlGF area under the curve 0.746 versus 0.735; P = .09; for non-obese 0.820 versus 0.805, P = .047). For early-onset pre-eclampsia, KRYPTOR area under the curve increased to 0.929 with a 100% specificity for pre-eclampsia at cut-off 85 and an 88.9% sensitivity for pre-eclampsia at cut-off 33. For women with pre-eclampsia and preterm delivery or Hemolysis, Elevated Liver enzymes, Low Platelet count (HELLP) syndrome, the KRYPTOR sFlt-1/PlGF ratio was manifold increased (P < .01).

**KEY FACTS**

**The sFlt-1/PlGF ratio proved especially useful in early-onset pre-eclampsia.**

## Placental growth factor (PlGF) and sFlt-1 during pregnancy: physiology, assay and interest in pre-eclampsia

Lecarpentier É, Vieillefosse S, Haddad B, Fournier T, Leguy MC et al.
*Ann Biol Clin (Paris). 2016 Jun 1;74(3):259-67*

The placental growth factor (PlGF) and its soluble receptor (sFlt-1) are circulating angiogenic factors. During pregnancy these factors are released by the placenta into the maternal circulation. Pre-eclampsia affects 2-7% of pregnant women according to their risk factors and is characterized by high blood pressure and the onset of de novo proteinuria in the second half of pregnancy.

Alterations of the sFlt-1/PlGF ratio in pre-eclampsia correlate with the diagnosis and adverse outcomes, particularly when the disease presents prematurely (<34 weeks). These factors can be assayed in maternal blood and measuring the sFlt-1/PlGF ratio is now available. We propose in this work to update the knowledge of these two molecules, describe their roles and evolution during normal pregnancy and pre-eclampsia, and finally to focus on the available assays.

## Angiogenesis-Related Biomarkers (sFlt-1/PLGF) in the Prediction and Diagnosis of Placental Dysfunction: An Approach for Clinical Integration

Herraiz I, Simón E, Gómez-Arriaga PI, Martínez-Moratalla JM, García-Burguillo A et al. *Int J Mol Sci. 2015 Aug 13;16(8):19009-26*

Placental dysfunction is involved in a group of obstetrical conditions including pre-eclampsia, intrauterine growth restriction, and placental abruption. Their timely and accurate recognition is often a challenge since diagnostic criteria are still based on nonspecific signs and symptoms.

The discovering of the role of angiogenic-related factors (sFlt-1/PlGF) in the underlying pathophysiology of placental dysfunction, taking into account that angiogenesis-related biomarkers are not specific to any particular placental insufficiency-related disease, has marked an important step for improving their early diagnosis and prognosis assessment. However, sFlt-1/PlGF has not been yet established as a part of most guidelines. We will review the current evidence on the clinical utility of sFlt-1/PlGF and propose a new protocol for its clinical integration.

## Analytical evaluation of the novel soluble fms-like tyrosine kinase 1 and placental growth factor assays for the diagnosis of pre-eclampsia

van Helden J, Weiskirchen R
*Clin Biochem. 2015 Nov;48(16-17):1113-9*

**Objective**
Performance evaluation of the novel BRAHMS KRYPTOR soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF) assays.

**Design and Methods**
Intra- and inter-assay imprecision, functional sensitivity, linearity in dilution, method comparison, and diagnostic capacity were evaluated.

**Results**
Intra-assay coefficient of variations (CVs) were between 1.1% and 5.3% and inter-assay CVs between 3.9% and 11.1%. Functional sensitivity was 6.7ng/L for PlGF and 34ng/L for sFlt-1, respectively. The linearity in dilution was excellent (r>0.995) in the assay-specific relevant range of concentration.

The KRYPTOR assay correlated well with the Elecsys sFlt-1 (r=0.996), Elecsys PlGF (r=0.990) and the Elecsys sFlt-1/PlGF ratio (r=0.947) with partially high mean bias values. The optimal cut points for diagnosis of pre-eclampsia were calculated for KRYPTOR assays at: 60.5ng/L (PlGF), 4725ng/L (sFlt-1), and 99.2 (sFlt-1/PlGF ratio) which were different with the corresponding Elecsys cut points.

Nevertheless, the sensitivity, specificity, positive predictive values (PPVs), negative predictive values (NPVs), and areas under the curves (AUCs) were completely comparable in both assay platforms, even when applying the standard cut-off of 85 for sFlt-1/PlGF ratio or gestational age specific "rule in-rule-out" cut-offs for early and late onset pre-eclampsia.

**KEY FACTS**

**The new B·R·A·H·M·S KRYPTOR sFlt-1 and PlGF immunoassay show excellent precision and reliability. The assay results and the diagnostic capacity were highly comparable to established fully automated immunoassays (Elecsys). Hence, sFlt-1/PlGF ratio generated on KRYPTOR immunoassay platform should be suitable for diagnosing pre-eclampsia in clinical routine laboratory.**

## Maternal serum sFlt-1/PlGF ratio in twin pregnancies with and without pre-eclampsia in comparison with singleton pregnancies

Dröge L, Herraìz I, Zeisler H, Schlembach D, Stepan H, Küssel L, Henrich W et al.
*Ultrasound Obstet Gynecol. 2015 Mar;45(3):286-93*


### Objective

In singleton pregnancies, soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF) and the sFlt-1/PlGF ratio have shown utility as a diagnostic test for pre-eclampsia (PE). The objective of this study was to characterize the maternal serum levels of sFlt-1, PlGF and sFlt-1/PlGF ratio in normal and pre-eclamptic twin pregnancies.

### Methods

In a European multicenter case-control study, 49 women with a twin pregnancy were enrolled, including 31 uneventful and 18 pre-eclamptic pregnancies. sFlt-1 and PlGF were measured and receiver-operating characteristics (ROC) analysis was performed. The median sFlt-1 and PlGF serum concentrations and sFlt-1/PlGF ratio were compared with those of a singleton cohort, matched for gestational age, with PE (n = 54) and with an uncomplicated pregnancy outcome (n = 238).

### Results

In twin pregnancies with PE, sFlt-1 levels and the sFlt-1/PlGF ratio were increased and PlGF levels were decreased as compared with those of twin gestations with an uneventful pregnancy outcome (20 011.50 ± 2330.35 pg/mL vs 4503.00 ± 2012.05 pg/mL ($P \leq 0.001$), 164.22 ± 31.35 vs 13.29 ± 319.64 ($P \leq 0.001$), and 138.80 ± 20.04 pg/mL vs 403.00 ± 193.10 pg/mL ($P \leq 0.001$), respectively). The sFlt-1/PlGF ratio did not differ between twin pregnancies with PE and singleton pregnancies with PE. In twin pregnancies with an uneventful outcome, sFlt-1 levels and sFlt-1/PlGF ratio were increased, but no differences in PlGF concentration were found when compared with that of singleton controls. ROC analysis determined 53 as an optimal cut-off of the sFlt-1/PlGF ratio for diagnosing PE in twin gestations, yielding a sensitivity of 94.4% and a specificity of 74.2%. The cut-off values established for singleton pregnancies, of 33 and 85, led to sensitivities of 100% and 83.3%, and specificities of 67.7% and 80.6%, when used to detect PE in twin pregnancies.


**KEY FACTS**

**Significant differences in the serum marker levels in singleton vs twin pregnancies were detected. Reference ranges of sFlt-1, PlGF and their ratio in singleton pregnancies are therefore not transferable to twin pregnancies.**

## Prediction of pre-eclampsia and induced delivery at <34 weeks gestation by sFLT-1 and PlGF in patients with abnormal midtrimester uterine Doppler velocimetry: a prospective cohort analysis

Stubert J, Ullmann S, Bolz M, Külz T, Dieterich M, Richter DU, Reimer T
*BMC Pregnancy Childbirth. 2014 Aug 28;14:292*

**Background**
Women with bilateral abnormal uterine artery Doppler velocimetry (UtADV) are at increased risk for an adverse pregnancy outcome. This study aimed to determine if additional assessment of midtrimester angiogenic factors improves the predictive accuracy of Doppler results for various outcome parameters.

**Methods**
Women with a bilateral abnormal UtADV, which was defined as a postsystolic incision and/or an increased pulsatility index greater than the 95th centile, and a singleton pregnancy were prospectively recruited between 19 + 0 and 26 + 6 weeks of gestation. Maternal serum levels of placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFLT-1) were measured with a fully automated immunoassay and their ratio was calculated.

**Results**
Angiogenic factors could predict the development of pre-eclampsia (PE), as well as induced delivery at <34 weeks of gestation, but failed to predict the development of normotensive intrauterine growth restriction. Twelve (24.0%) of the 50 recruited women developed PE. Nine of these patients had early-onset disease (<34 + 0 weeks). Six (12.0%) patients were delivered at <34 + 0 weeks.

The most useful test results in the prediction of PE and induced delivery at <34 + 0 weeks were observed using the sFLT-1/PlGF >95th centile ratio with a sensitivity, specificity, positive predictive value, and negative predictive value (NPV) of 66.7%, 89.5%, 66.7%, and 89.5% for PE, and 85.7%, 86.1%, 50.1%, and 97.4% for induced delivery, respectively.

Positive and negative likelihood ratios were 6.33 (95% CI 2.31-17.38) and 0.37 (95% CI 0.17-0.84) for PE, and 6.14 (95% CI 2.76-13.69) and 0.17 (0.03-1.02) for induced delivery, respectively. Corresponding odds ratios were 17.0 (95% CI 3.5-83.0) and 37.0 (95% CI 3.8-363.9), respectively.

**KEY FACTS**

**Measurement of angiogenic factors improves the specificity of an abnormal UtADV for prediction of PE. Compared with prediction of PE an abnormal sFLT-1/PlGF ratio revealed higher sensitivity for prediction of induced delivery at <34 + 0 weeks. The NPV of 97% will help to reassure most patients with an abnormal UtADV and a normal sFLT-1/PlGF ratio.**

## Characterization of the Soluble fms-Like Tyrosine Kinase-1 to Placental Growth Factor Ratio in Pregnancies Complicated by Fetal Growth Restriction

Herraiz I, Dröge LA, Gómez-Montes E, Henrich W, Galindo A, Verlohren S
*Obstet Gynecol 2014 Aug;124(2 Pt 1):265-73*

**Objective**
To characterize the values of the soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) ratio in pregnancies with fetal growth restriction with or without concurrent pre-eclampsia or hemolysis, elevated liver enzymes and low platelets syndrome (HELLP) and in pregnancies with normally grown fetuses with or without concurrent pre-eclampsia or HELLP.

**Methods**
This is a case-control study performed in two centers (Berlin and Madrid) consisting of 171 singleton pregnancies complicated by

- fetal growth restriction (n=27),
- pre-eclampsia or HELLP (n=105) or
- pre-eclampsia or HELLP and fetal growth restriction (n=39)

pairwise matched by gestational age with 171 healthy control pregnancies.

Automated measurement of sFlt-1 and PlGF in maternal serum samples was performed after diagnosis (cases) and in gestational-age matched healthy control samples. Samples were analyzed for two timeframes: before and at or after 34 weeks of gestation.

**Results**
Pregnancies with fetal growth restriction, pre-eclampsia or HELLP, and pre-eclampsia or HELLP and fetal growth restriction showed higher median values of sFlt-1/PlGF ratio than control pregnancies both before 34 weeks of gestation (90, 231, 514, and 3, respectively, P<.001) and at or after 34 weeks of gestation (117, 66, 165, and 11, respectively, P<.001). The differences among the case subgroups were not statistically different.

**KEY FACTS**

**Fetal growth restriction is characterized by elevated maternal sFlt-1/PlGF ratio, reaching values as high as those observed in pre-eclampsia or HELLP.**

## New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for pre-eclampsia

Verlohren S, Herraiz I, Lapaire O, Schlembach D, Zeisler H, Calda P et al.
*Hypertension 2014 Feb;63(2):346-52*

**Abstract**

To establish gestational phase adapted cutoffs for the use of the soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PlGF) ratio as a diagnostic tool for pre-eclampsia in the clinical setting, a multicenter case-control study including a total of 1149 patients was performed.

We report normal values of sFlt-1, PlGF, and the sFlt-1/PlGF ratio based on the analysis of a total of 877 patients with uneventful pregnancy outcome. A total of 234 patients with pre-eclampsia and a matched cohort consisting of 468 patients with normal pregnancy outcome were compared, and sFlt-1 and PlGF were measured on an automated platform.

Separate cutoffs for the sFlt-1/PlGF ratio were determined for the early (20+0-33+6 weeks) and the late gestational phase (34+0 weeks-delivery). For each of the 2 gestational phases, 2 independent cutoffs framing an equivocal zone were determined: the first cutoff with focus on high sensitivity, and the second focusing on high specificity.

Between 20+0 and 33+6 weeks, the cutoffs at ≤33 and ≥85 resulted in a sensitivity/specificity of 95%/94% and 88%/99.5%, respectively. An sFlt-1/PlGF ratio of ≤33 had the lowest likelihood of a negative test (0.05; 95% confidence interval, 0.02-0.13), whereas values ≥85 had the highest likelihood of a positive test (176; 95% confidence interval, 24.88-1245).

After 34+0 weeks, the cutoffs at ≤33 and ≥110 yielded a sensitivity/specificity of 89.6%/73.1% and 58.2%/95.5%, respectively.

**KEY FACTS**

**The approach to use multiple cutoffs for the early and late gestational phase enhances the diagnostic accuracy of the sFlt-1/PlGF ratio as a diagnostic tool for pre-eclampsia.**

## The importance of repeated measurements of the sFlt-1/PlGF ratio for the prediction of pre-eclampsia and intrauterine growth restriction

Schoofs K, Grittner U, Engels T, Pape J, Denk B, Henrich W, Verlohren S
*J Perinat Med 2014 Jan;42(1):61-8*

**Aims**
The sFlt-1/PlGF ratio has been evaluated as a diagnostic marker for pre-eclampsia (PE). The aim of this study was to explore the use of the sFlt-1/PlGF ratio as an aid in prediction for PE.

**Methods**
150 patients with a high risk for PE were enrolled in this prospective study. Groups were compared according to the pregnancy outcome: controls (n=114), intrauterine growth restriction (IUGR) (n=14) and PE (n=22) with subclassification early PE<34 weeks (n=6). Measurements of sFlt-1 and PlGF were performed on an automated system. Statistical comparison of the sFlt-1/PlGF ratio in different outcome groups and a mixed model analysis using random intercept models were performed.

**Results**
The sFlt-1/PlGF ratio was significantly higher in pregnancies complicated by PE up to 4 weeks before clinical diagnosis compared to controls (106.7 ± 47.7 vs. 21.0 ± 4.1; P=0.02).

Levels of the sFlt-1/PlGF ratio were higher throughout pregnancy in women with IUGR compared to PE/control patients (intercept 1.57 vs. 1.30/0.67; P<0.05).

The slope for the sFlt-1/PlGF ratio was significantly higher in PE and IUGR pregnancies compared to controls, indicating that a steep increase of the sFlt-1/PlGF ratio correlates with pathologic pregnancy outcomes.

**KEY FACTS**

- **The sFlt-1/PlGF ratio can identify pathologic pregnancy outcomes such as IUGR and PE before clinical diagnosis.**
- **Repeated measurements are necessary to assess the dynamics in serum values.**
- **The time-dependent slope of the sFlt-1/PlGF ratio is predictive for future pregnancy outcome and risk of developing pre-eclampsia.**

thermoscientific

# Thermo Scientific™ B·R·A·H·M·S™ sFlt-1 KRYPTOR™

Automated immunofluorescent assay for the quantitative determination of soluble FMS-like Tyrosine Kinase (sFlt-1) in human serum

- Excellent precision
- Wide measuring range: 22-90000 pg/mL
- Incubation time of only 9 minutes

# Thermo Scientific™ B·R·A·H·M·S™ PlGF plus KRYPTOR™

Automated immunofluorescent assay for the quantitative determination of Placental Growth Factor (PlGF) in human serum

- Excellent precision
- Best functional assay sensitivity (FAS): 6.7 pg/mL
- Very low detection limit: 3.6 pg/mL

► **Fast and reliable detection of clinical values throughout pregnancy**

---

**Clinical Diagnostics**

Thermo Fisher Scientific
B·R·A·H·M·S GmbH
Neuendorfstr. 25
16761 Hennigsdorf
Germany

+49 (0)3302 883 0
+49 (0)3302 883 100 fax
info.brahms@thermofisher.com
www.thermoscientific.com/brahms

Find out more at **thermoscientific.com/brahms**

**Products are CE marked but not 510(k)-cleared and not available for sale in the U.S. Availability of products in each country depends on local regulatory marketing authorization status.**



ThermoFisher SCIENTIFIC

900227.4