thermo scientific

Pre-eclampsia management with biomarkers

Improved pre-eclampsia diagnosis and prognosis of adverse outcome with PlGF and sFlt-1 after week 20 of gestation

ThermoFisher SCIENTIFIC

Biomarkers for pre-eclampsia management

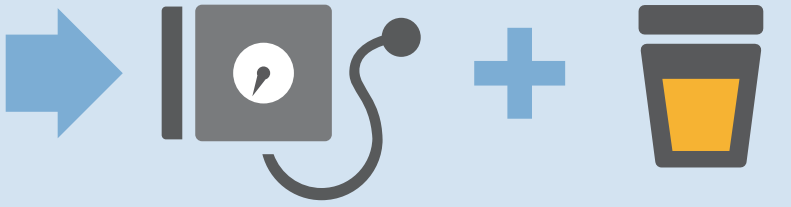
Improving the diagnostic tools for pre-eclampsia evaluation

Pre-eclampsia is a progressive, pregnancy-related disorder with severe complications for mother and child. A timely diagnosis is needed in order to prevent maternal and fetal morbidity or mortality. In the absence of a specific therapy other than delivery the main objective of frequent patient monitoring is to detect deterioration of a patient's condition and to counteract maternal and fetal risk.

10 % of pregnant women show unspecific signs and symptoms of pre-eclampsia

Only **one fifth of them** is actually developing pre-eclampsia [1]

Diagnostic standard for pre-eclampsia …



Blood pressure **Proteinuria**

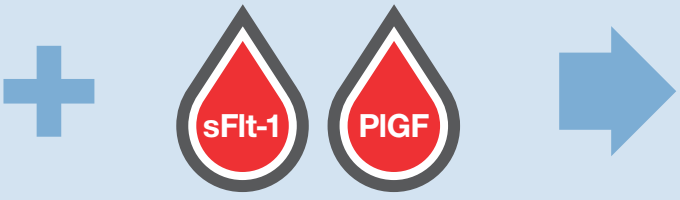
The "gold standard" for pre-eclampsia diagnosis – assessment of blood pressure and proteinuria – offers only a **poor sensitivity and specificity** with regards to origin of disease and prediction of maternal and perinatal outcome.[2,3]

Serum sFlt-1 and PlGF determination adds significant clinical benefit to standard procedures

Determination of the biomarkers sFlt-1 (soluble FMS-like Tyrosine Kinase) and PlGF (Placental Growth Factor) in maternal blood have shown to significantly improve risk stratification among women presenting for pre-eclampsia evaluation.

The high sensitivity assays Thermo Scientific™ B·R·A·H·M·S™ sFlt-1 KRYPTOR™ and Thermo Scientific B·R·A·H·M·S PlGF plus KRYPTOR detect serum levels of both biomarkers reliably throughout pregnancy and thus improve pre-eclampsia management.

… significantly improved by sFlt-1 and PlGF serum measurement



Biomarkers

- **Clearly differentiating** between pre-eclampsia and other forms of hypertensive disorders [4,5]
- **Reliable prognosis** of adverse outcome in women with suspected pre-eclampsia [5,6]
- Offering **potential savings** in hospital costs and resource use [7]

Measuring sFlt-1 and PlGF starting in mid pregnancy in women with suspected pre-eclampsia significantly improves the current evaluation of patients – for a better patient management and improved care.

Pre-eclampsia diagnosis and prognosis of adverse outcome

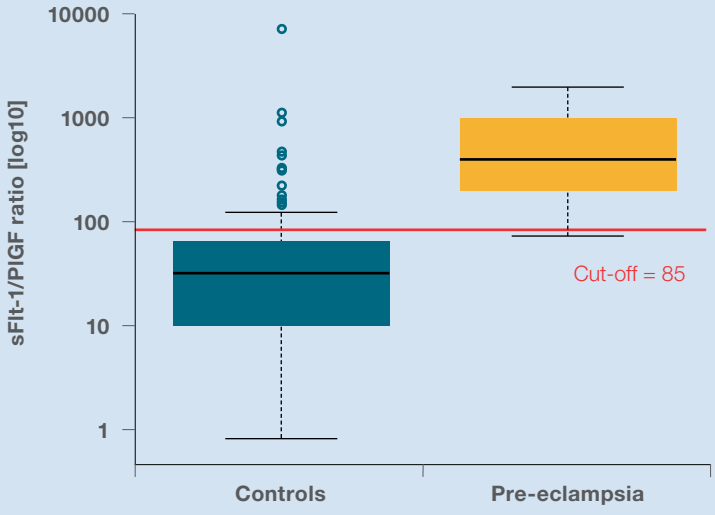
The added value of sFlt-1 and PlGF

Improved diagnosis of pre-eclampsia with sFlt-1/PlGF ratio

Studies proved the additional benefit of the sFlt-1/PlGF ratio in diagnosing pre-eclampsia:

- In women presenting with hypertension, the sFlt-1/PlGF ratio is able to **distinguish between those who will develop pre-eclampsia and those with chronic or gestational hypertension**. Women with pre-eclampsia have a significantly higher sFlt-1/PlGF ratio than women with other hypertensive disorders or controls.[4,5]
- The addition of sFlt-1/PlGF ratio to Doppler ultrasound measurement **improves the sensitivity and specificity** in diagnosing pre-eclampsia compared to the Doppler measurement alone.[8]
- Measurement of sFlt-1 and PlGF levels in maternal serum, starting in mid pregnancy, can **confirm pre-eclampsia diagnosis**, with the sFlt-1/PlGF ratio having a superior diagnostic ability compared to either of the biomarkers alone.[8,9]

Therefore, the sFlt-1/PlGF ratio is a valuable additional tool for confirming or excluding the diagnosis of pre-eclampsia.



PlGF and sFlt-1 were measured on KRYPTOR in parallel on samples from pregnant women with normal pregnancy outcome and patients with pre-eclampsia. At a cut-off of 85 for the sFlt-1/PlGF ratio, the sensitivity was calculated at 95% and the specificity at 84% for diagnosing pre-eclampsia. Latest studies show identical clinical performance and high accuracy in diagnosing pre-eclampsia when applying recently published cut-offs by using the sFlt-1/PlGF ratio on KRYPTOR.[6,10,11]

The higher the sensitivity of a test the more women with pre-eclampsia are identified correctly and can be advised for closer monitoring.

Figure 1 Improved pre-eclampsia diagnosis with sFlt-1/PlGF ratio [12]

Prognosis of adverse outcome with sFlt-1/PlGF ratio

Recent studies showed that **women with any subsequent adverse outcome** in addition to hypertension had a significantly higher sFlt-1/PlGF ratio than those women without, especially when presenting before week 34 (Figure 2).[5,6]

Women who needed to be delivered within the next 2 weeks after presentation had a significantly higher sFlt-1/PlGF ratio than women who could continue with their pregnancy (Figure 3).[5,6]

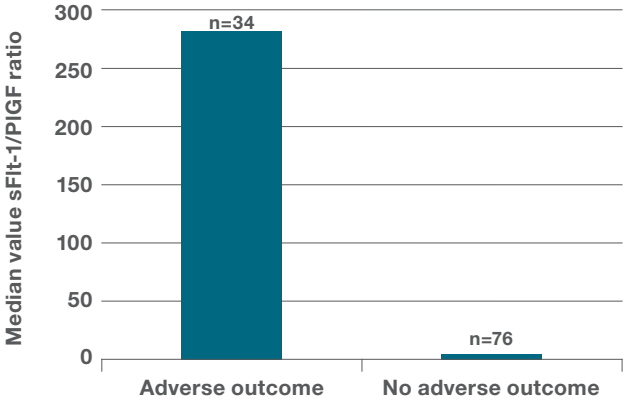


Figure 2 Prediction of adverse outcome with sFlt-1/PlGF ratio in women presenting < 34 weeks' gestation[6]

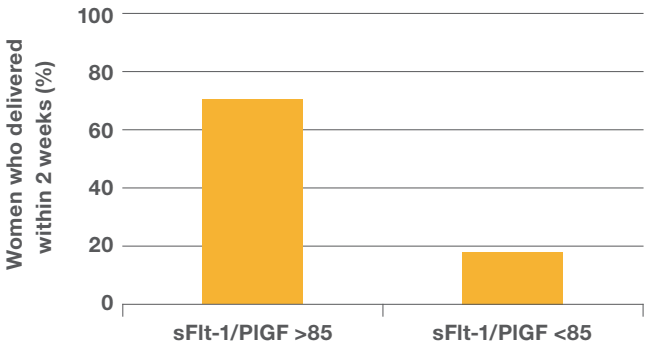


Figure 3 Prediction of duration of pregnancy with sFlt-1/PlGF ratio in women presenting < 34 weeks' gestation[6]

The sFlt-1/PlGF ratio is also a potent predictor for subsequent maternal and fetal adverse outcome in women already diagnosed with pre-eclampsia and can support clinical decisions.

The role of angiogenic factors

Biomarker levels correlate with severity of disease

sFlt-1 and PlGF are counterparts

Although the cause of pre-eclampsia remains unclear, it is likely that the syndrome is initiated by an imbalance of angiogenic factors secreted by the placenta that induce endothelial dysfunction.

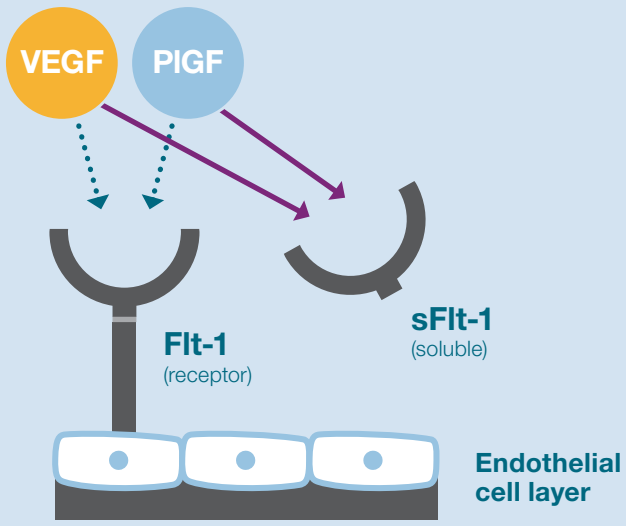


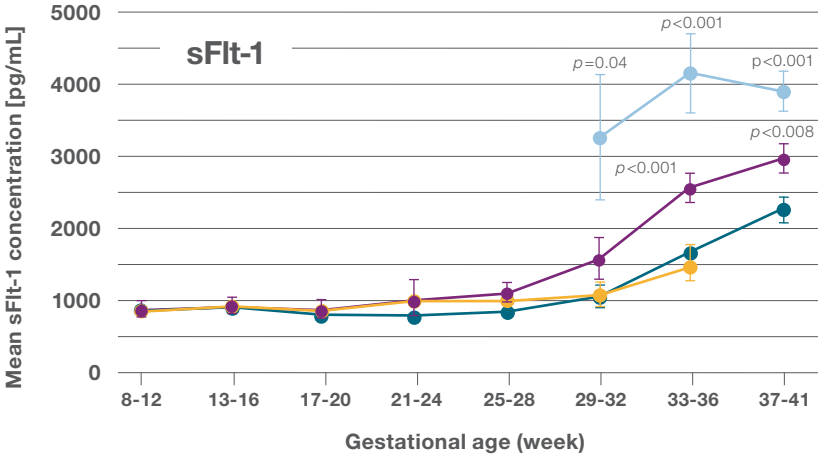
Figure 4 sFlt-1 acts as potent antagonist of PlGF and VEGF by adhering to the receptor-binding domains, thus preventing interaction with endothelial receptors and inducing endothelial dysfunction

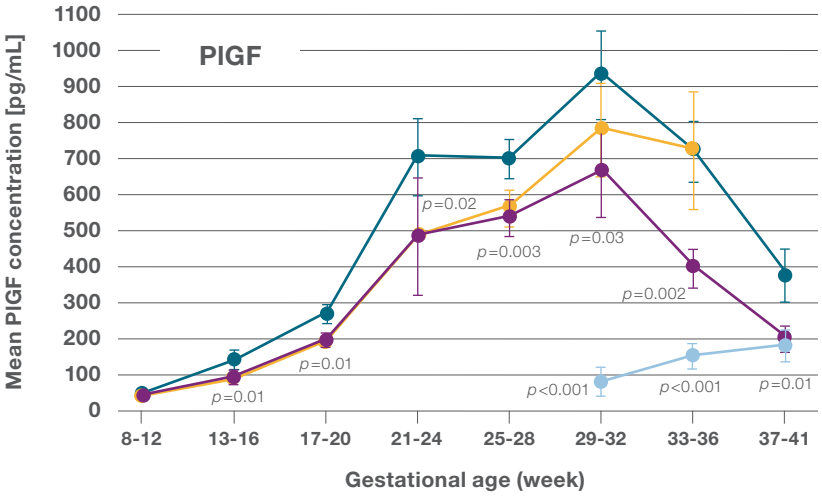
sFlt-1 is a truncated form of the VEGF receptor Flt-1, circulating freely in the blood. sFlt-1 is produced in the placenta and secreted into the bloodstream, where it binds VEGF and PlGF with high affinity and therefore neutralizes their effects.[8]

PlGF belongs to the Vascular Endothelial Growth Factors (VEGF) family, promoting proliferation and survival of endothelial cells and inducing vascular permeability.[13]

Signal transduction (healthy)

Signal transduction inhibited





Controls

Women who had pre-eclampsia >5 weeks later

Women who later had pre-eclampsia

Women with clinical pre-eclampsia

Figure 5 Mean sFlt-1 and PlGF concentrations of healthy women and those women who later developed pre-eclampsia [13]

Angiogenic factors during pregnancy

Normal pregnancy

During pregnancy, sFlt-1 levels are stable until weeks 20–24, when they rise steadily until delivery. In contrast, PlGF levels increase progressively in first and second trimester and decrease towards term.[13]

Pre-eclamptic pregnancy

In women with pre-eclampsia, sFlt-1 levels are significantly increased while concentrations of circulating free PlGF are significantly decreased.[13,14] In contrast to PlGF where the difference between healthy and pre-eclamptic pregnancies is measurable throughout pregnancy, sFlt-1 levels only start to separate after week 20.

Measuring maternal serum concentrations of sFlt-1 and PlGF can differentiate healthy women from women with pre-eclampsia.[9,15] Changes in sFlt-1 and PlGF levels also reflect the severity of the disease: early-onset pre-eclampsia is associated with greater changes compared to late-onset pre-eclampsia.[16]

Pre-eclampsia management throughout pregnancy

Improving the outcomes for mother and child

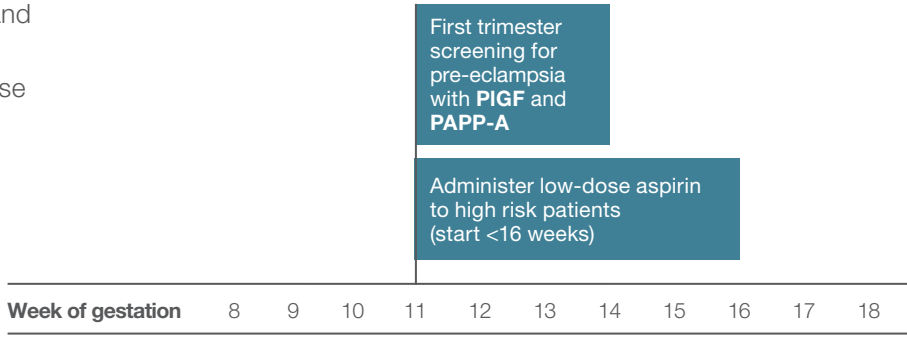
PIGF and PAPP-A: First trimester screening for timely intervention

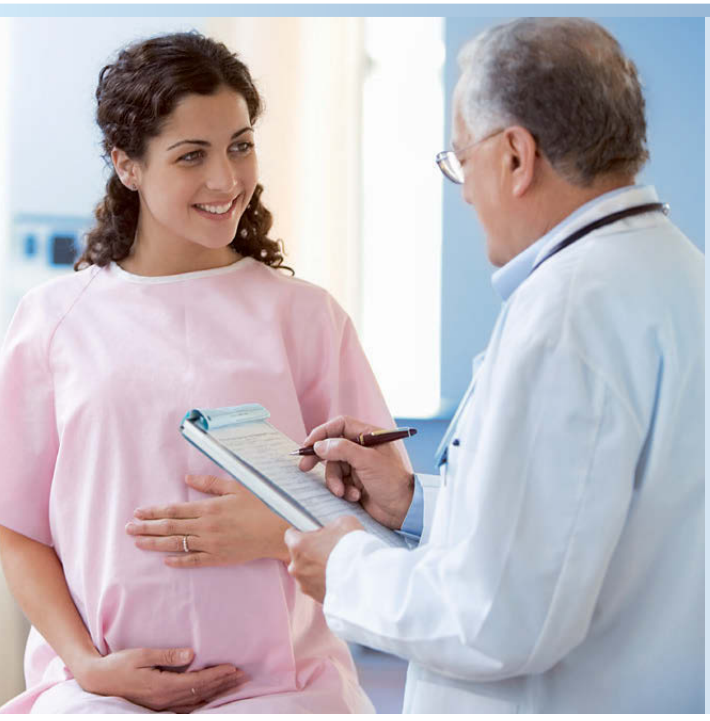
Combined screening for pre-eclampsia in weeks 11–13+6 can reliably identify women at risk for developing pre-eclampsia.

Combined first trimester screening includes
- serum PlGF and PAPP-A measurement,
- determination of mean arterial pressure (MAP), and
- Uterine Artery Pulsatility Index (UtA-PI)

resulting in a detection rate of >90% for a fixed false positive rate of 5%.[17]

An early identification of high-risk women allows for preventive measures and intensified monitoring. Administering low-dose aspirin (<150 mg/day) to high-risk women before 16 weeks of gestation can significantly reduce the incidence of pre-eclampsia by 50%–90%.[18,19]





Facts on pre-eclampsia

- Multisystem, life-threatening pregnancy-related disorder
- A main reason for maternal and fetal morbidity and mortality[20,21]
- **Incidence:** 2-8% of pregnancies[20]
- **Definition:** New onset hypertension and proteinuria >20 weeks of gestation in previously normotensive women[22]
- **HELLP** (Hemolysis, Elevated Liver enzymes, Low Platelets): Severe pre-eclampsia variant occurring in ≈20% of symptomatic women; defined by additional affection of liver and coagulation system[23]
- **Eclampsia:** Final stage of disease, associated with severe tonic-clonic seizures and coma as well as brain injury, cerebral edema and stroke[23]

sFlt-1/PlGF ratio: Improved diagnosis and prognosis of adverse outcome

First symptoms of pre-eclampsia (hypertension, proteinuria) are observed after 20 weeks of gestation.[23]

Diagnosis of pre-eclampsia is difficult, as pre-eclampsia can be confused with other diseases such as pregnancy-induced hypertension.

By adding sFlt-1/PlGF ratio to the current diagnostic standard, the **diagnosis of pre-eclampsia** in a symptomatic woman can be confirmed or excluded.[2,10,11]

In women with diagnosed pre-eclampsia, the sFlt-1/PlGF ratio is a potent **predictor of subsequent maternal and fetal adverse outcome** and can be useful for further patient management.[5,6]

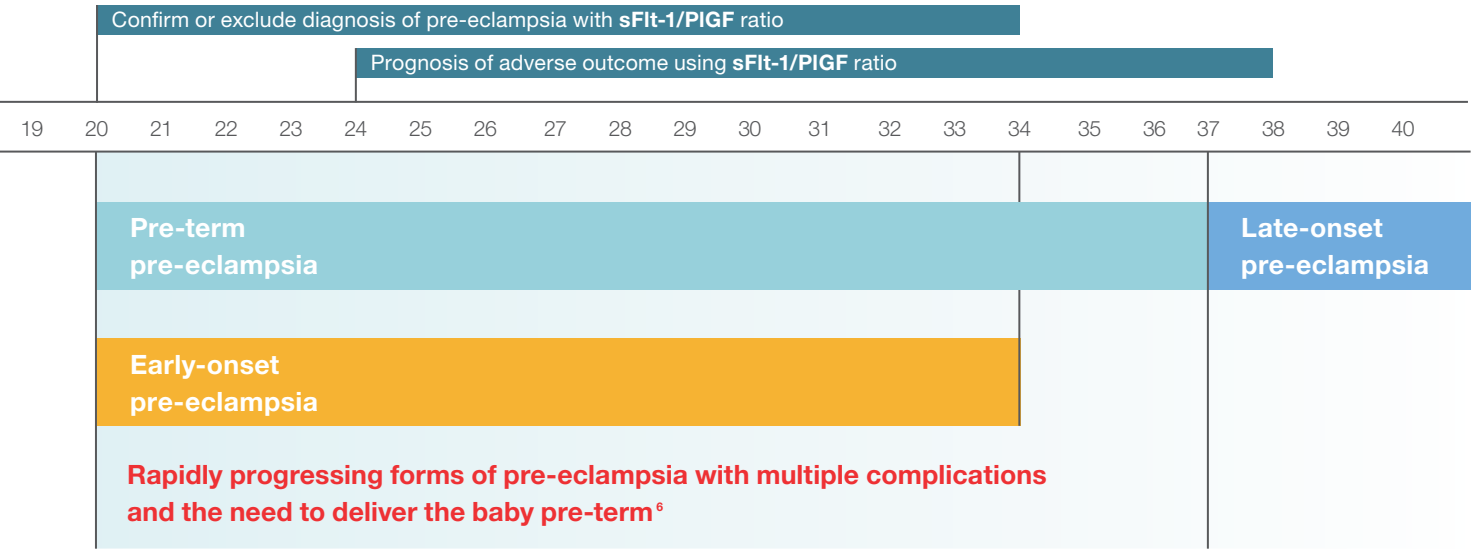


Figure 6 First clinical symptoms of pre-eclampsia are observed >20 weeks of gestation. The gestational age at onset correlates with the severity of maternal and fetal consequences.[2]

Complete pre-eclampsia portfolio

From safe screening to improved diagnosis with B·R·A·H·M·S sFlt-1 and PlGF plus

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

Automated immunofluorescent assay for the quantitative determination of the concentration of sFlt-1 (soluble FMS-like Tyrosine Kinase 1, also known as VEGF receptor-1) in human serum.

- **75 determinations per kit**
- **9 min incubation time**
- **Monoparametric control kit, 3 levels**
- **Wide measuring range: 22–90 000 pg/mL**
- **Excellent precision**

With the lower and upper detection limits of 22 and 90 000 pg/mL B·R·A·H·M·S sFlt-1 KRYPTOR provides the measuring range needed for a **reliable detection of clinical sFlt-1 values throughout pregnancy**.

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

Automated immunofluorescent assay for the quantitative determination of the concentration of PlGF (Placental Growth Factor) in human serum. The assay is specific for the measurement of human free PlGF-1.

- **75 determinations per kit**
- **29 min incubation time**
- **Monoparametric control kit, 3 levels**
- **Wide measuring range: 3.6–7 000 pg/mL**
- **Excellent precision**

With a detection limit of 3.6 pg/mL and an upper limit of 7 000 pg/mL B·R·A·H·M·S PlGF plus KRYPTOR provides the high sensitivity needed for **measuring PlGF levels in first trimester** as well as a wide measuring range to **reliably measure clinical values throughout pregnancy**.

Exceptionally precise, fast and easy

B·R·A·H·M·S KRYPTOR analyzers

- **All KRYPTOR platforms FMF approved**
- **In routine use by FMF since 1999**
- **Excellent precision and proven median stability**

Thermo Scientific
B·R·A·H·M·S KRYPTOR GOLD

Thermo Scientific
B·R·A·H·M·S KRYPTOR compact PLUS

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Your BENEFITS by adding the sFlt-1/PlGF ratio into clinical routine

- **Improved clinical accuracy** in diagnosing pre-eclampsia in symptomatic patients
- **Potent prognostic tool** for subsequent adverse pregnancy outcome

Your ACCESS to our interactive e-detail

Get more information on pre-eclampsia management throughout pregnancy:

http://prenatal.world-of-biomarkers.com

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