Thermo Scientific
Early Prenatal Care

Pre-eclampsia diagnosis

in 2nd and 3rd trimester of pregnancy

Improved pre-eclampsia diagnosis with sFlt-1 and PlGF • Prognosis of adverse outcome in women with suspected pre-eclampsia • Sensitive and reliable measurement on Thermo Scientific B·R·A·H·M·S KRYPTOR

Fardiotop

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Biomarkers for pre-eclampsia management

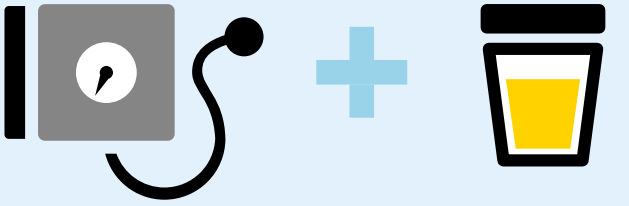
Improving the diagnostic tools for pre-eclampsia evaluation

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** are actually developing pre-eclampsia [1]

Diagnostic standard for pre-eclampsia …



Blood pressure **Proteinuria**

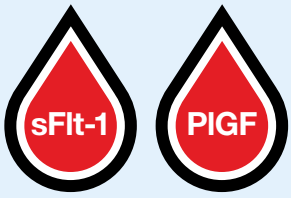
The "gold standard" for pre-eclampsia diagnosis – assessment of blood pressure and proteinuria – offers only a **poor sensitivity and specificity** with regards to origin of disease and prediction of maternal and perinatal outcome.[2,3]

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.

With the new 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 it is now possible to 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 prediction** of adverse outcome in women with suspected pre-eclampsia [5]
- Offering **potential savings** in hospital costs and resource use [6]

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

Pre-eclampsia diagnosis and prognosis of adverse outcome

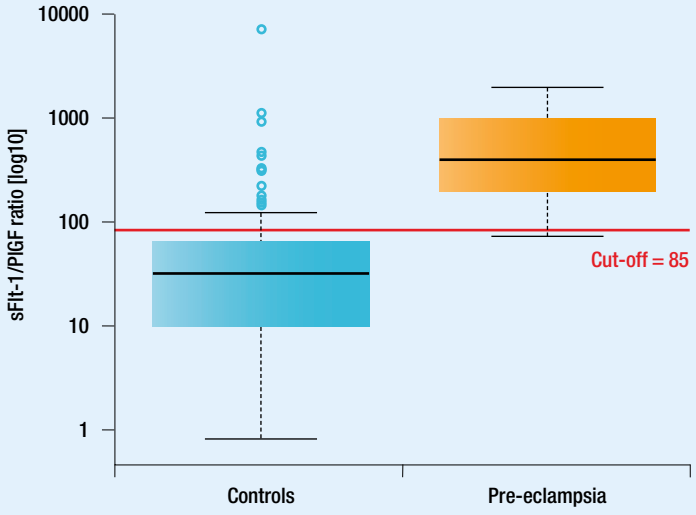
The added value of sFlt-1 and PlGF

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

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

- 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.[7,8]
- 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]
- 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]

Therefore, the sFlt-1/PlGF ratio is a valuable tool for confirming or excluding the diagnosis of pre-eclampsia and offers a high clinical value for clinical management, counseling and risk anticipation.



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.

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

Figure 1 Improved pre-eclampsia diagnosis with sFlt-1/PlGF ratio [9]

Prognosis of adverse outcome with sFlt-1/PlGF ratio

Rana et al. 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]

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]

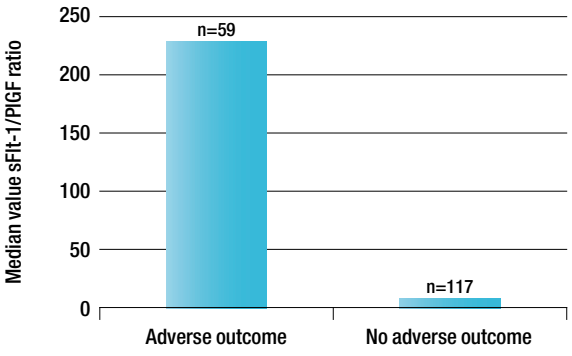


Figure 2 Prediction of adverse outcome with sFlt-1/PlGF ratio in women presenting < 34 weeks' gestation[5]

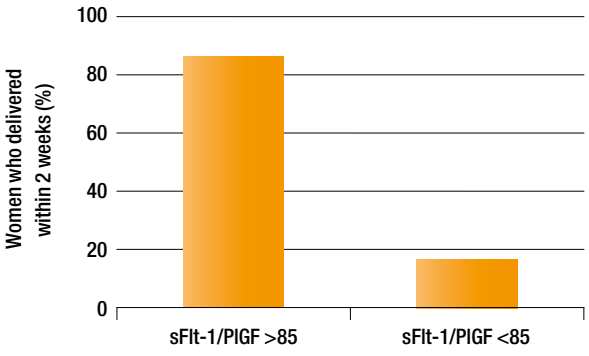


Figure 3 Prediction of duration of pregnancy with sFlt-1/PlGF ratio in women presenting < 34 weeks' gestation[5]

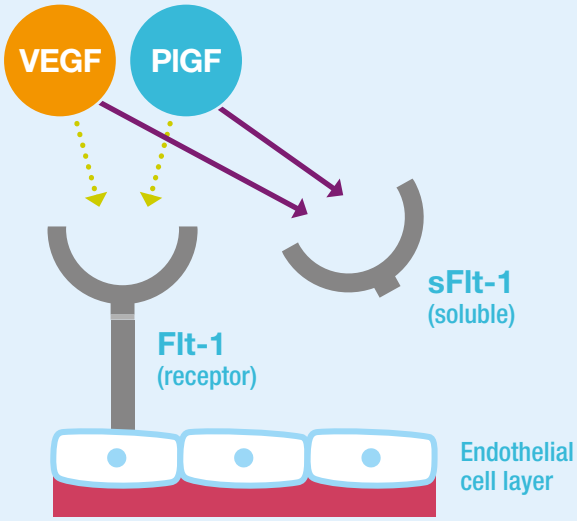
The sFlt-1/PlGF ratio is also a potent predictor for subsequent maternal and fetal adverse outcome in women already diagnosed with pre-eclampsia and can support clinical decisions to avoid severe pregnancy complications.

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 may be initiated by an imbalance of placental factors that induce 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.[10]

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

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.[10]

Pre-eclamptic pregnancy

In women with pre-eclampsia, sFlt-1 levels are significantly increased while concentrations of circulating free PlGF are significantly decreased.[10,11]

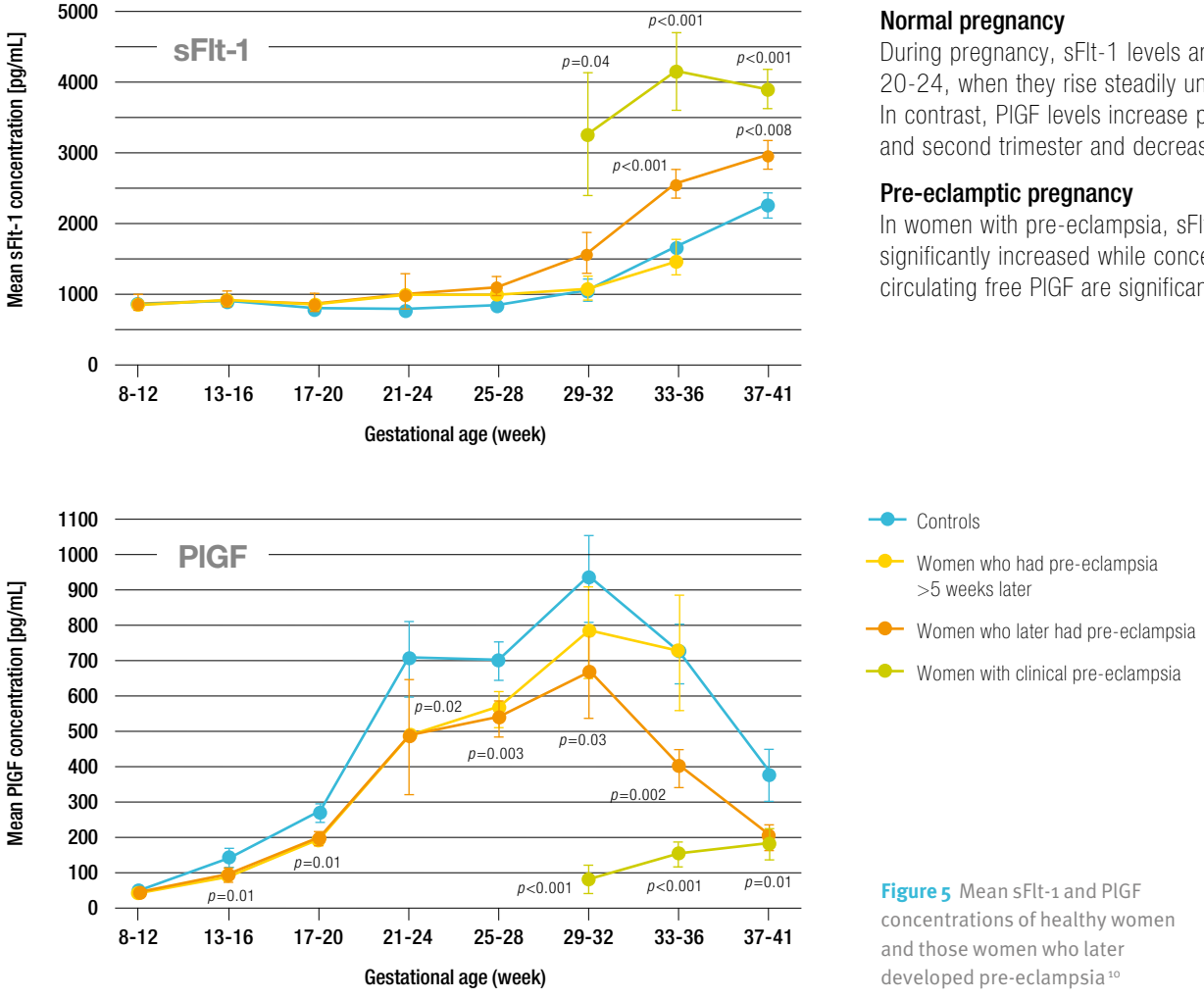


Figure 5 Mean sFlt-1 and PlGF concentrations of healthy women and those women who later developed pre-eclampsia[10]

Measuring maternal serum concentrations of sFlt-1 and PlGF can differentiate healthy women from women with pre-eclampsia.[7,12] Changes in sFlt-1 and PlGF levels also appear to reflect the severity of the disease: early-onset pre-eclampsia is associated with greater changes in PlGF and sFlt-1 compared to late-onset pre-eclampsia.[13]

Pre-eclampsia management throughout pregnancy

Improving the outcomes for mother and child

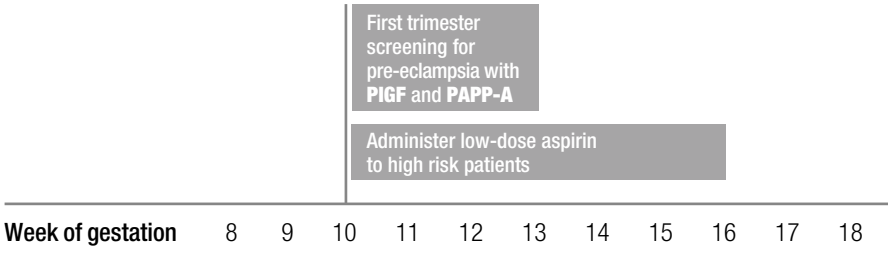
PIGF and PAPP-A: First trimester screening for timely intervention

Combined screening for pre-eclampsia in weeks 10-13 can reliably identify women at risk for developing pre-eclampsia.

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

resulting in a detection rate of >90% for a fixed false positive rate of 5%.[14]

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 reduce the incidence of pre-eclampsia by 50%.[15]



Facts on pre-eclampsia

- Multisystem, life-threatening pregnancy-related disorder
- A main reason for maternal and fetal morbidity and mortality [16,17]
- **Incidence:** 2-8% of pregnancies
- **Definition:** New onset hypertension and proteinuria >20 weeks of gestation in previously normotensive women [18]
- **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 [20]
- **Eclampsia:** Final stage of disease, associated with severe tonic-clonic seizures and coma as well as brain injury, cerebral edema and stroke [20]

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.[20]

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]

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]

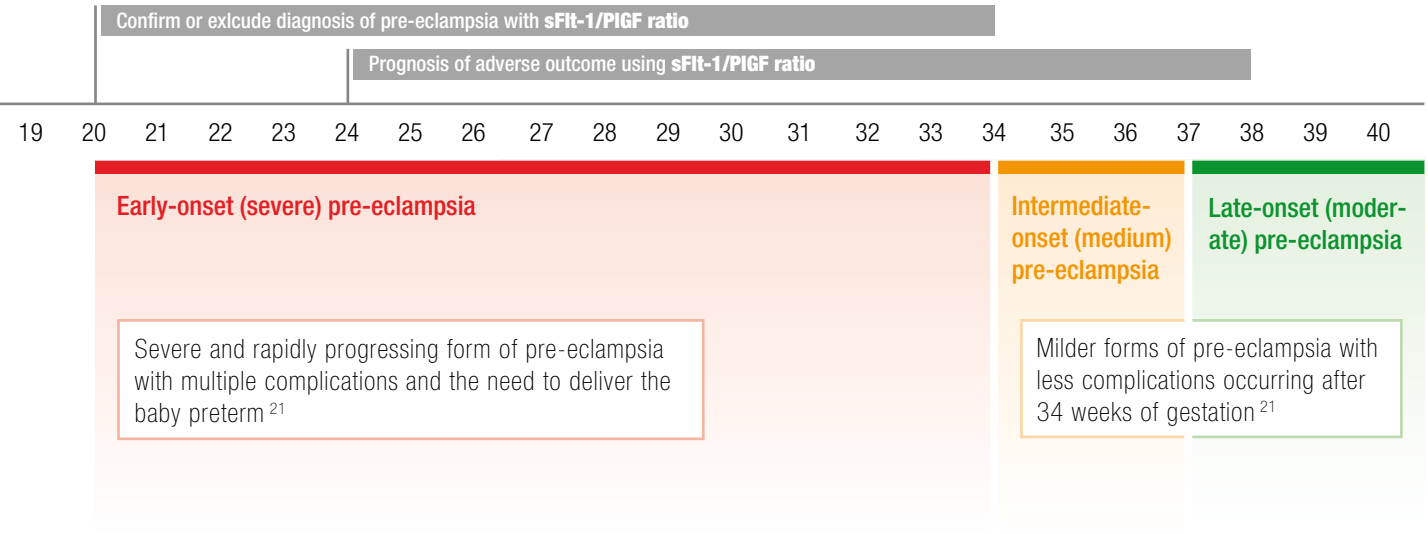


Figure 6 First clinical symptoms of pre-eclampsia are observed >20 weeks of gestation. The gestational age at onset correlates with the severity of maternal and fetal consequences.[2]

Complete pre-eclampsia portfolio

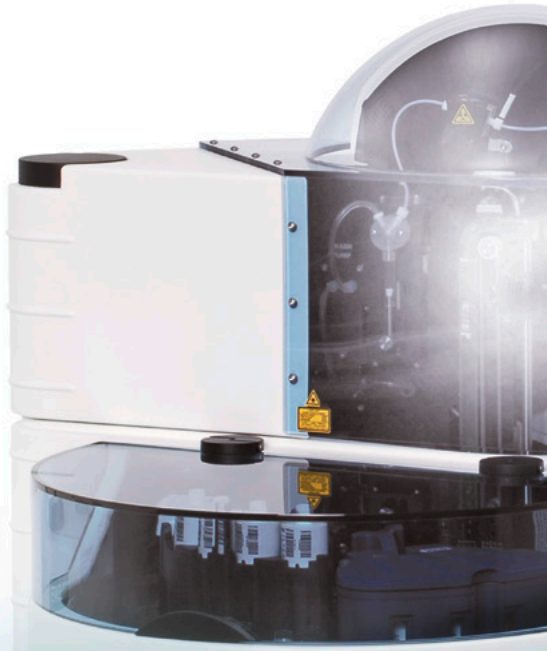
From safe screening to improved diagnosis with B·R·A·H·M·S sFlt-1 and PlGF

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**
- **Two-point calibration**
- **Monoparametric control kit, 3 levels**
- **Wide measuring range: 22-90000 pg/mL**
- **Excellent precision**

With the lower and upper detection limits of 22 and 90000 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 PIGF plus KRYPTOR

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

- **75 determinations per kit**
- **29 min incubation time**
- **Single-point calibration**
- **Monoparametric control kit, 3 levels**
- **Wide measuring range: 3.6-7000 pg/mL**
- **Excellent precision**

With a detection limit of 3.6 pg/mL and an upper limit of 7000 pg/mL B·R·A·H·M·S PIGF plus KRYPTOR provides the high sensitivity needed for **measuring PIGF levels in first trimester** as well as a wide measuring range to **reliably measure clinical values in second and third trimester**.

Exceptionally precise, fast and easy

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

15 Years Reliable Results
15 Years Confident Decisions

- **All KRYPTOR platforms FMF approved**
- **In routine use in labs worldwide since 1999**
- **Excellent precision and data stability**

Thermo Scientific B·R·A·H·M·S Biomarkers Prenatal Screening Markers on KRYPTOR Systems

• B·R·A·H·M·S **AFP** KRYPTOR	Art. no.: 816.075
• B·R·A·H·M·S **Free βhCG** KRYPTOR	Art. no.: 809.075
• B·R·A·H·M·S **hCG+β** KRYPTOR	Art. no.: 841.050
• B·R·A·H·M·S **Inhibin A** KRYPTOR	(under development)
• B·R·A·H·M·S **PAPP-A** KRYPTOR	Art. no.: 866.075
• B·R·A·H·M·S **PlGF** KRYPTOR*	Art. no.: 844.075
• B·R·A·H·M·S **PlGF plus** KRYPTOR*	Art. no.: 859.075
• B·R·A·H·M·S **sFlt-1** KRYPTOR*	Art. no.: 845.075
• B·R·A·H·M·S **uE3** KRYPTOR	(under development)
• B·R·A·H·M·S **Fast Screen pre I plus Software**	Art. no.: 105750

* Available on KRYPTOR compact PLUS

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