Thermo Scientific
Early Prenatal Care

Pre-eclampsia screening

in 1st trimester of pregnancy

Early screening for pre-eclampsia enables optimal patient care • Placental Growth Factor (PlGF) screening: high detection rates and possible intervention • High sensitivity PlGF measurement with Thermo Scientific B·R·A·H·M·S PlGF KRYPTOR

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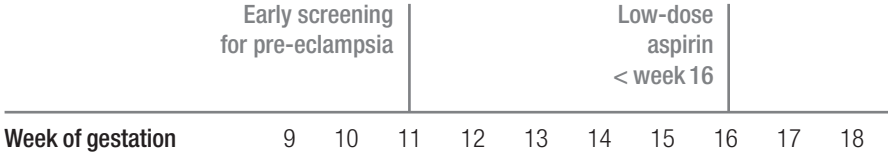
Early screening – early intervention

Pre-eclampsia screening in 1st trimester for optimal patient care

Serum PlGF determination in combination with other factors allows early prediction of pre-eclampsia

Pre-eclampsia is a leading cause of maternal morbidity and mortality. Early identification of women at high risk for pre-eclampsia allows intensified maternal and fetal monitoring which offers the potential of reducing an adverse outcome for mother and child. First trimester screening of Placental Growth Factor (PlGF) allows early detection of women at risk for early-onset pre-eclampsia before any clinical symptoms occur.

With the new high sensitivity assay Thermo Scientific™ B·R·A·H·M·S™ PlGF KRYPTOR™ maternal serum PlGF levels can be detected already at weeks 11-13 of gestation.



Early-onset pre-eclampsia causes severe complications

Pre-eclampsia is defined as new onset of hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on two occasions) and proteinuria (≥300 mg/day) after 20 weeks of gestation.[1] The degree of adverse maternal and fetal consequences is inversely related to the gestational age at onset.[2]

Therefore, pre-eclampsia can be classified as[2]

- Early-onset at 20-34 weeks (severe pre-eclampsia)
- Intermediate-onset at 34-37 weeks (medium pre-eclampsia)
- Late-onset after 37 weeks (moderate pre-eclampsia)

Low-dose aspirin can reduce the risk of pre-eclampsia

A recent meta-analysis has shown that the application of low-dose aspirin (<150 mg/day) started before week 16 of gestation caused a significant reduction in pre-eclampsia and intrauterine fetal growth restriction (IUGR) compared to control, while aspirin started after 16 weeks of gestation did not.[4,5]

Literature suggests that the use of low-dose aspirin during pregnancy is safe with regard to congenital anomalies and fetal, neonatal, and maternal cardiovascular physiologic state and hemostasis.[6]

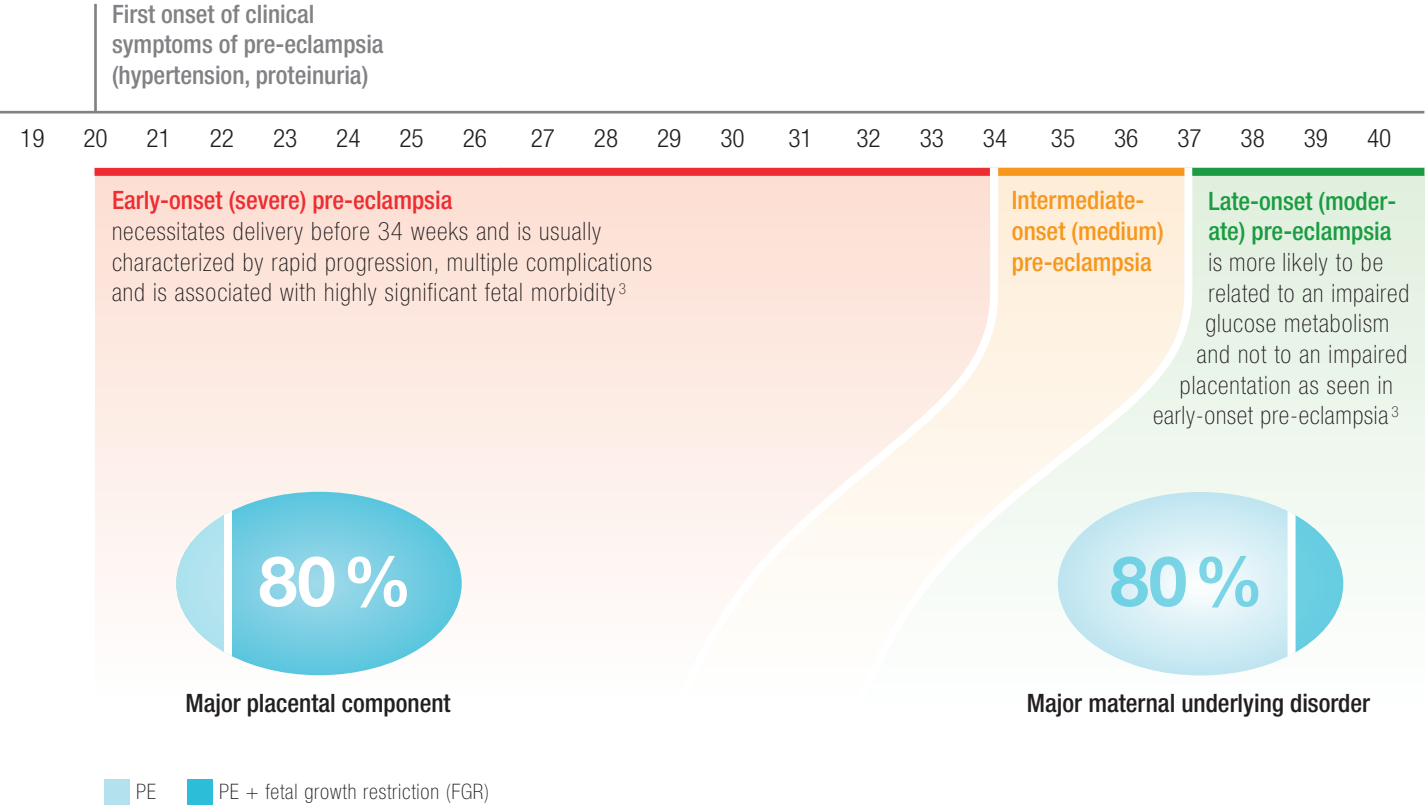


Figure 1 First clinical symptoms of pre-eclampsia are observed >20 weeks of gestation. The gestational age at onset correlates with the occurrence of maternal and fetal consequences.[2]

Pre-eclampsia: a leading cause of maternal morbidity and mortality

Severe complications for the mother

With an incidence between 2-8% pre-eclampsia is a frequent pregnancy disorder[7], affecting more than 4.1 million women per year worldwide.[8]
The severe pre-eclampsia variant HELLP syndrome (**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets) occurs in about 20% of the affected women and is defined by an additional affection of the liver and the coagulation system, resulting in symptoms such as abdominal pain, hemorrhage, placental abruption, hepatic infarction and rupture, intra-abdominal bleeding and edema. Eclampsia is the final and most feared stage of the disease, associated with severe tonic-clonic seizures and coma as well as brain injury, cerebral edema and stroke.[9]

HELPP syndrome and eclampsia account for more than 50 000 maternal deaths each year.[7]

Severe complications for the fetus

Due to an insufficient supply of oxygen and nutrients, pre-eclampsia also causes severe complications for the fetus, such as prematurity, IGUR, bronchopulmonary dysplasia and sometimes even death.[9]

About 15-20% of preterm deliveries are due to pre-eclampsia.[9]

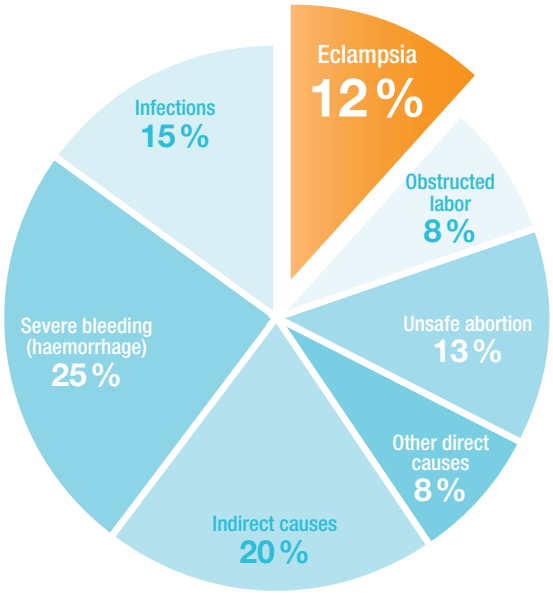


Figure 2 Causes of maternal death worldwide (Total is more than 100% due to rounding) [8]

Long-term complications for the women

Pre-eclampsia is responsible for long-term complications later in life. Large retrospective epidemiological studies have shown that women with a previous pre-eclampsia have a 3-4 times higher risk for cardiovascular disorders later in life than non pre-eclamptic women. The risk is even higher (4-8 fold) if the onset of pre-eclampsia was before 34 weeks of gestation or pre-eclampsia was combined with a preterm birth.[9]

The risk of death from cardiovascular and cerebrovascular disease is 50% greater in women with a history of pre-eclampsia.[9]

The underlying mechanism that accounts for the elevated risk is not yet well understood, but it was shown that endothelial dysfunction persists for many years in women with a former pre-eclampsia episode.[9]

Risk factors

The risk factors for pre-eclampsia are varied and unique to this condition and include[9]

- Maternal and paternal family history
- Previous pregnancy with pre-eclampsia
- Multiple pregnancy (triplets > twins)
- Maternal Age (>40 years)
- Body Mass Index (BMI >30)
- Pre-existing hypertension, Diabetes mellitus or renal disease
- Systemic inflammation
- Ethnical origin

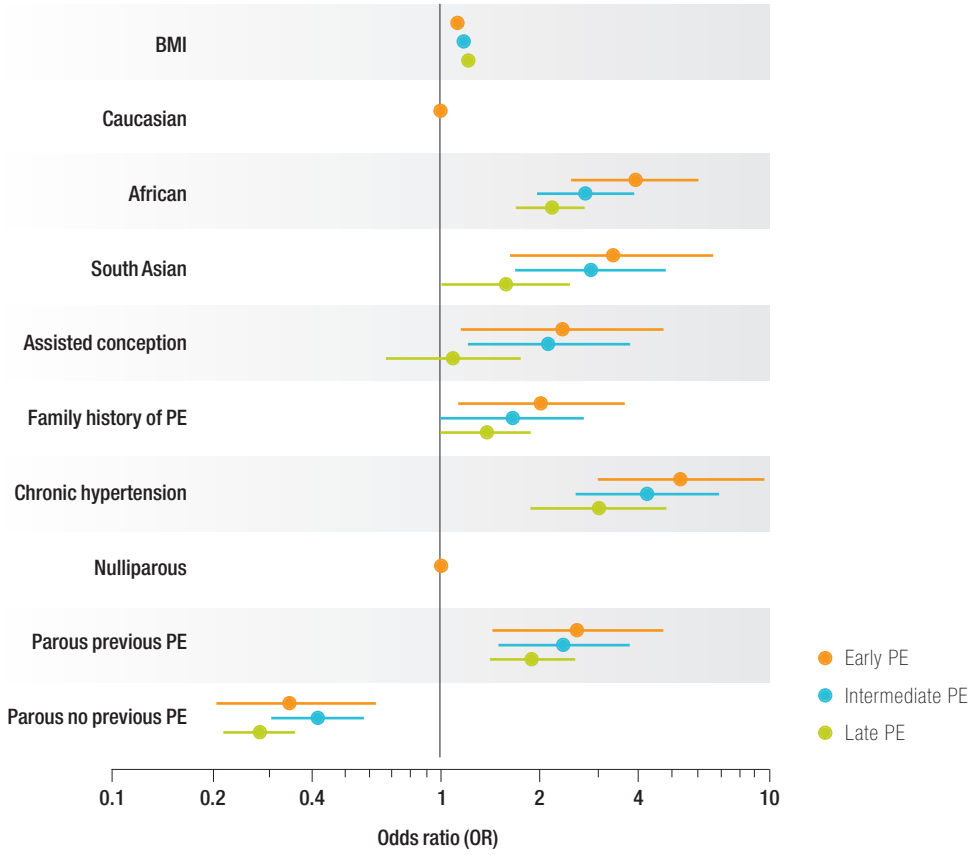


Figure 3 Odd ratios and 95% confidence interval (CI) of risk factors for development of pre-eclampsia (PE) [10]

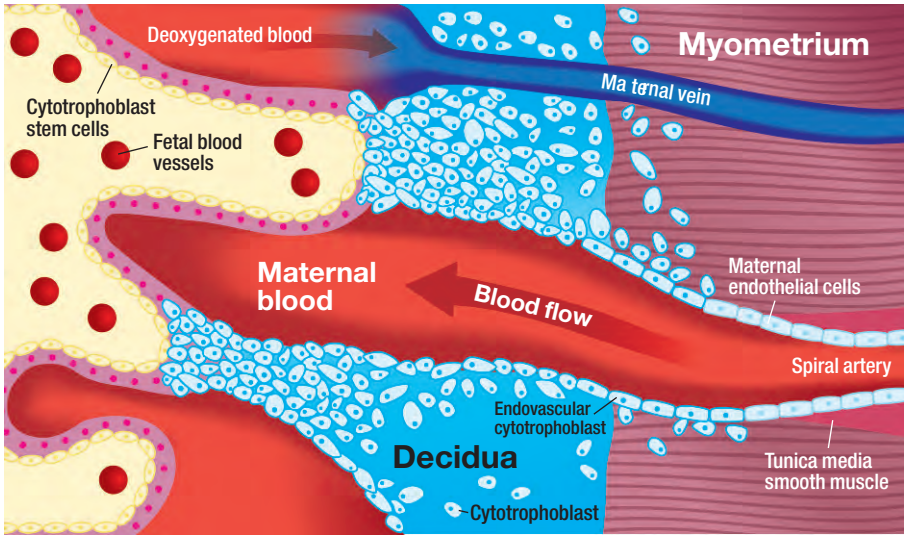
Imbalance of pro- and antiangiogenic proteins

A key factor for developing pre-eclampsia

Normal pregnancy

Placenta and developing fetus are provided with sufficient maternal oxygen and nutrients[11]

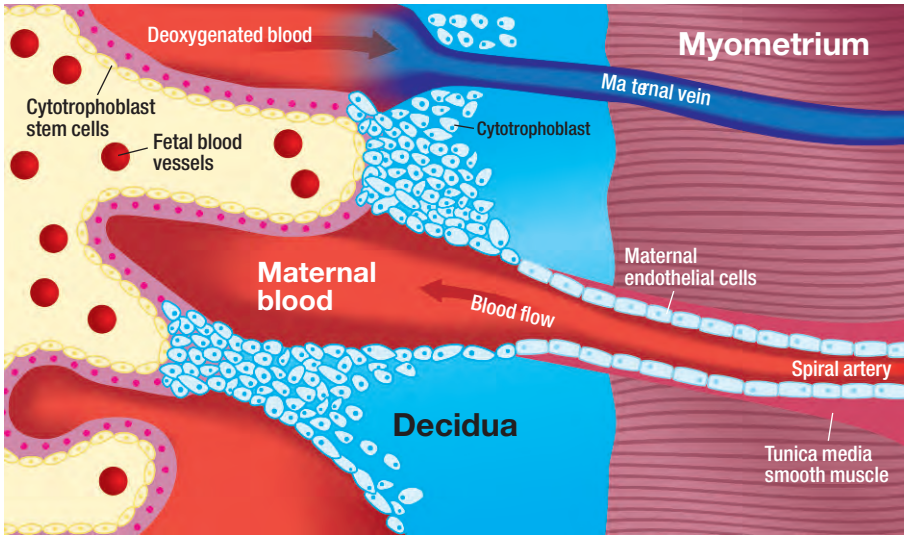
- Fetal cytotrophoblast cells invade maternal uterine wall (into smooth muscle and endothelial layer)
- Maternal spiral arteries are remodeled into large vessels with high capacity and low resistance



Pre-eclamptic pregnancy

Inadequate circulation between placenta and uterus[11]

- Invasion of cytotrophoblasts is incomplete, they can only be found in superficial layers of decidua
- Maternal spiral arteries fail to be invaded/ remodeled, resulting in vessels with a decreased capacity and increased resistance



Maternal PlGF serum concentration is decreased in pre-eclampsia

Pre-eclampsia is a disease that begins in the placenta and ends at the maternal endothelium.[9] The cause of pre-eclampsia is still not well understood, but the placenta has been identified as the central organ in pathogenesis.[9] The inadequate blood supply explains the consequences for the fetus in pre-eclampsia.

Recent studies suggest that an imbalance of proangiogenic and antiangiogenic proteins accounts for many maternal complications with respect to pre-eclampsia. Antiangiogenic factors such as sFlt-1 (soluble FMS-like Tyrosine Kinase) and sEng (soluble Endoglin) are released by an abnormal placenta into the blood, where they antagonize the effects of proangiogenic factors such as VEGF (Vascular Endothelial Growth Factors) and PlGF (Placental Growth Factor).[9]

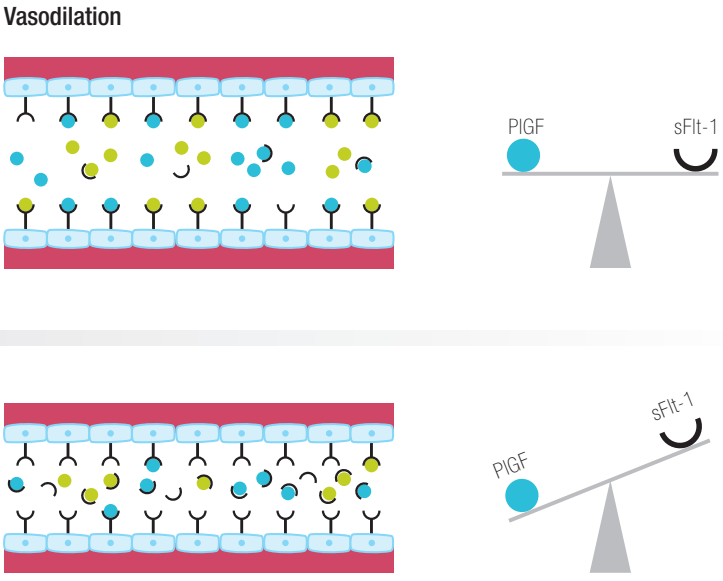


Figure 4 In pre-eclampsia, sFlt-1 is released by an abnormal placenta and concentrations are increased, whereas concentration of free PlGF is decreased. This imbalance of circulating factors is assumed to be responsible for an increased maternal vascular inflammation, finally resulting in endothelial dysfunction and hence clinical signs of pre-eclampsia.[12]

1st trimester PlGF measurement

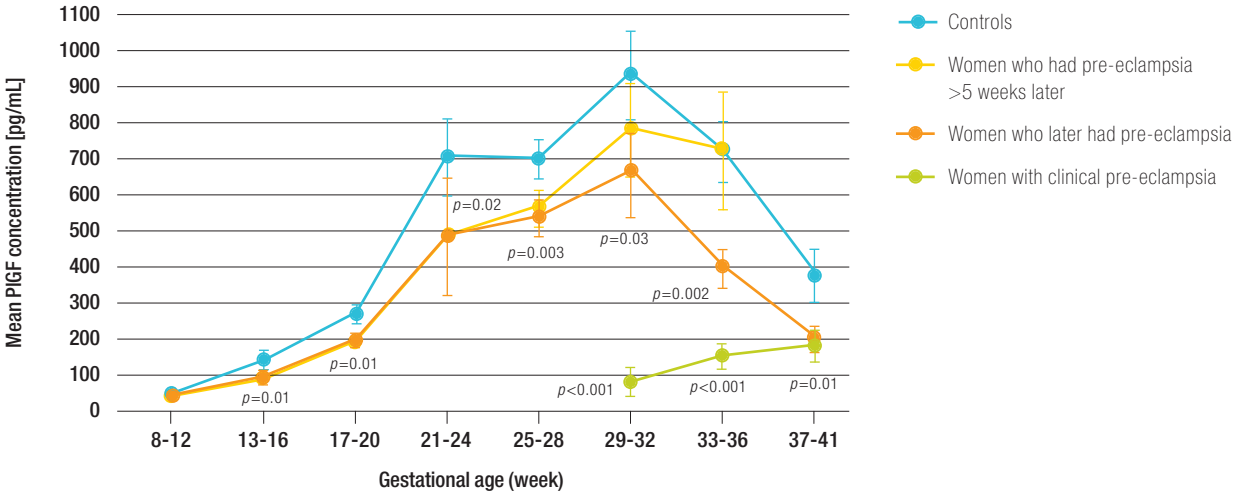
identifies women at risk for pre-eclampsia before clinical symptoms appear

PlGF – a proangiogenic factor

Placental Growth Factor (PlGF) belongs to the Vascular Endothelial Growth Factors (VEGF) family, which are promoting proliferation and survival of endothelial cells and inducing vascular permeability. During pregnancy, the placenta releases high amounts of PlGF. PlGF binds to the Vascular Endothelial Growth Factor Receptor 1 (VEGFR-1) also known as FMS-like Tyrosine Kinase-1 (Flt-1).

Low PlGF levels indicate increased risk for pre-eclampsia

In normal pregnancy, the concentration of PlGF increases progressively from week 12, reaching a peak during weeks 29-32 and declining thereafter. Compared to controls, the PlGF concentrations of those women who later develop pre-eclampsia are significantly lower, and can be measured as early as week 12.[13]



No. of specimens								
Controls	20	44	56	9	72	21	70	21
Before pre-eclampsia	21	43	56	6	75	23	57	19
>5 weeks before pre-eclampsia	21	43	56	6	71	19	8	–
During pre-eclampsia	–	–	–	–	–	2	14	26

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

High detection rate of pre-eclampsia by combining maternal characteristics with a high sensitivity PlGF assay

Using the traditional screening method, based on maternal history only, the detection rate for women who are at risk for developing pre-eclampsia is about 30%. Detection rates become more accurate when maternal characteristics are combined with PlGF measurement as well as other factors such as serum PAPP-A (both measured in weeks 11-13), mean arterial pressure (MAP), and uterine artery Doppler (uA-PI), resulting in a detection rate of >90% for cases of early pre-eclampsia for a fixed false positive rate of 5% before any clinical symptoms appear.[2]
An effective prediction of pre-eclampsia can be achieved already at weeks 11-13 of gestation.[3]

DR	Detection rate
FPR	False positive rate
History	Maternal history
MAP	Mean arterial blood pressure
uA-PI	Uterine artery pulsatility index

DR at 5% FPR	History	MAP	uA-PI	PAPP-A	PlGF
33	●				
38			●		
47	●			●	
54	●				●
60	●		●	●	
78	●		●		●
78	●	●	●	●	●
84	●	●	●	●	
89	●	●	●		●
93	●	●	●	●	●

Table 1 Different studies with resulting detection rates by using different screening methods[14]

With a high sensitivity assay PlGF levels can already be detected in weeks 11-13 of gestation.

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

High sensitivity and exceptional precision

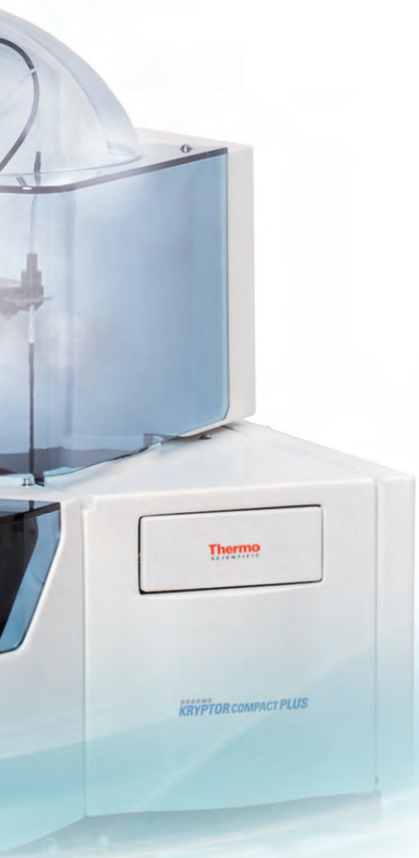
B·R·A·H·M·S PIGF KRYPTOR is an automated immunofluorescent assay for the quantitative determination of the concentration of human PIGF (Placental Growth Factor) in human serum. The assay is specific for the measurement of human free PIGF-1.

- **75 determinations per kit**
- **29 min incubation time**
- **FAS: 6.7 pg/mL**
- **Single-point calibration**
- **Monoparametric control kit, 3 levels**
- **Wide measuring range: 3.6-7000 pg/mL**
- **Excellent precision**

With a detection limit of less than 4 pg/mL B·R·A·H·M·S PIGF KRYPTOR provides the high sensitivity needed for measuring PIGF levels in the first trimester of pregnancy.

Thermo Scientific B·R·A·H·M·S PlGF KRYPTOR
Early pre-eclampsia screening provides optimal patient care

Best assay sensitivity + **Excellent precision** = **Reliable detection of clinical values in the very low range!**



Exceptionally precise, fast and easy

Thermo Scientific B·R·A·H·M·S KRYPTOR compact PLUS
Article number: 106172

14 Years Reliable Results
14 Years Confident Decisions

The Fetal Medicine Foundation

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

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

• 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 **PAPP-A** KRYPTOR	Art. no.: 866.075
• B·R·A·H·M·S **AFP** KRYPTOR	Art. no.: 816.075
• B·R·A·H·M·S **PlGF** KRYPTOR	Art. no.: 844.075
• B·R·A·H·M·S **sFlt-1** KRYPTOR	(soon available)
• B·R·A·H·M·S **Fast Screen pre I plus Software**	Art. no.: 105750

References

1. Definition of the American College of Obstetrics and Gynaecology
2. Akolekar R et al. Prenat Diagn 2011; 31: 66-74
3. Poon LCY et al. Hypertension 2009; 53: 812-818
4. Bujold E et al. J Obstet Gynaecol 2010; 116: 402-14
5. Bujold E et al. J Obstet Gynaecol can 2009; 31: 818-26
6. Dekker GA et al. Am J Obstet Gynaecol 1993; 168(1 Pt 1): 214-27
7. Ghulmiyyah L and Sibai B. Seminars in Perinatology 2012; 36: 56-59
8. The World Health Report 2005; p62
9. Powe CE et al. Circulation 2011; 123: 2856-69
10. Nicolaides KH. Fetal Diagn Ther 2011; 29(3): 183-96
11. Lam C et al. Hypertension 2005; 46: 1077-85
12. Yuan HT et al. Curr Top Dev Biol 2005; 71: 297-312
13. Levine RJ et al. N Engl J Med 2004; 350: 672-83
14. Costa FS et al. Rev Bras Ginecol Obstet 2011; 33 (11): 367-75

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