Pre-eclampsia management from 1st to 3rd trimester of pregnancy

Improved patient care for early and late-onset pre-eclampsia with biomarkers

thermo scientific

Contents

What is pre-eclampsia?

Pre-eclampsia is a severe complication related to hypertension affecting pregnant women. This life-threatening disease can only be cured by the delivery of the baby and contributes largely to maternal and neonatal mortality and morbidity.[1]

Pre-eclampsia can start from week 20 and happens up to 6 weeks after delivery.[2]

Key facts on pre-eclampsia

- With an incidence between 2–8%, pre-eclampsia is a hypertensive disorder that occurs during pregnancy[3] and affect 4.1 million women per year worldwide.[4]
- Pre-eclampsia and eclampsia account for more than 50 000 maternal and 500 000 neonatal deaths each year worldwide.[2]
- Hypertensive disorders in low-income countries are responsible for 9% of maternal deaths in Africa and Asia and 26% in Latin America. Although maternal mortality, in high-income countries is much lower than in developing countries, 16% of maternal deaths can be attributed to hypertensive disorders. Being also related to race and ethnicity, it is most prevalent among African Americans and Latin American.[2]
- Pre-eclampsia is a severe disease and brings complications such as eclampsia, hemorrhagic stroke, hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, placental abruption, renal failure, and pulmonary oedema.[1]
- Women who survive pre-eclampsia have long-term consequences like increased risk of stroke, cardiovascular disease and diabetes.[1]

Risk factors[4,5]

African American

First pregnancy

IVF conception

Chronic hypertension

Diabetes mellitus

Previous pre-eclampsia

Generational pre-eclampsia

Systemic lupus erythematosus

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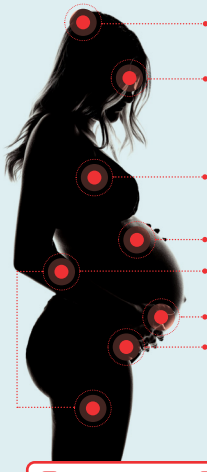
Signs and symptoms[6]



- Persistent and severe headache even with medication.
- Visual disturbances such as blurriness and flashing lights.
- Shortness of breath.
- Right sided abdominal pain.
- Sudden swelling of the face, hands or feet.
- Nausea, vomitting.
- Sudden weight gain (> 1kg per week).

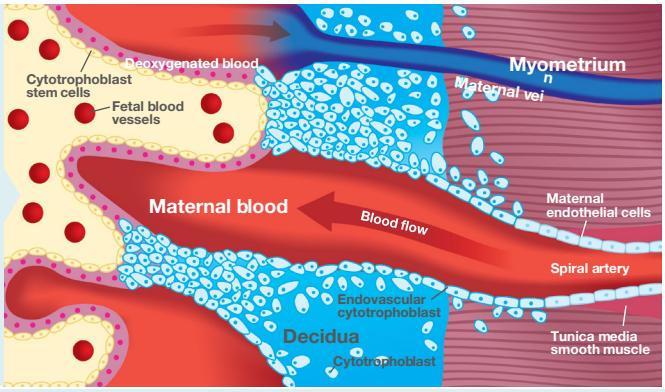
Click here to learn more

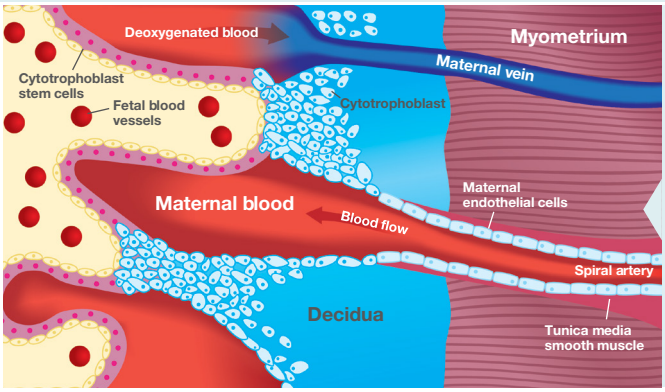
Imbalance of pro- and anti-angiogenic factors

Normal pregnancy

Placenta and developing fetus are provided with sufficient maternal oxygen and nutrients.[7]

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



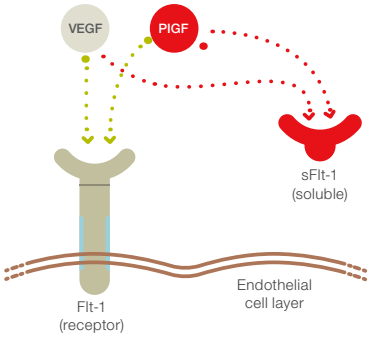


Pre-eclamptic pregnancy

Inadequate circulation between the placenta and uterus.[7]

- Invasion of cytotrophoblasts is incomplete; they can only be found in superficial layers of decidua.
- Maternal spiral arteries fail to be invaded and remodelled, resulting in vessels with a decreased capacity and increased resistance.
- As a consequence of the decreased blood flow the fetus is not supplied sufficiently with oxygen and nutrients.

Angiogenic and anti-angiogenic factors



Signal transduction (healthy)

Signal transduction inhibited

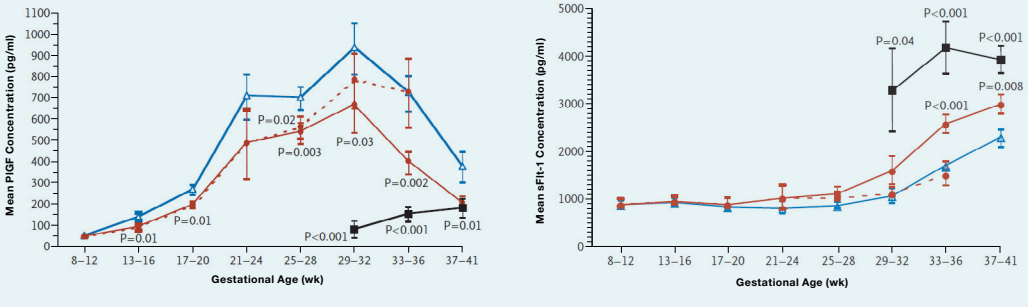
VEGF = Vascular Endothelial Growth Factor
PIGF = Placental Growth Factor
(s)Flt-1 = (soluble) fms like tyrosine kinase

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 neutralises their effects.[8]

PlGF belongs to the VEGF family, promoting proliferation and survival of endothelial cells and inducing vascular permeability.[8]

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

Measuring PlGF and sFlt-1 in pregnancy



Controls
Women who had pre-eclampsia > 5 weeks later
Women who later had pre-eclampsia
Women with clinical pre-eclampsia

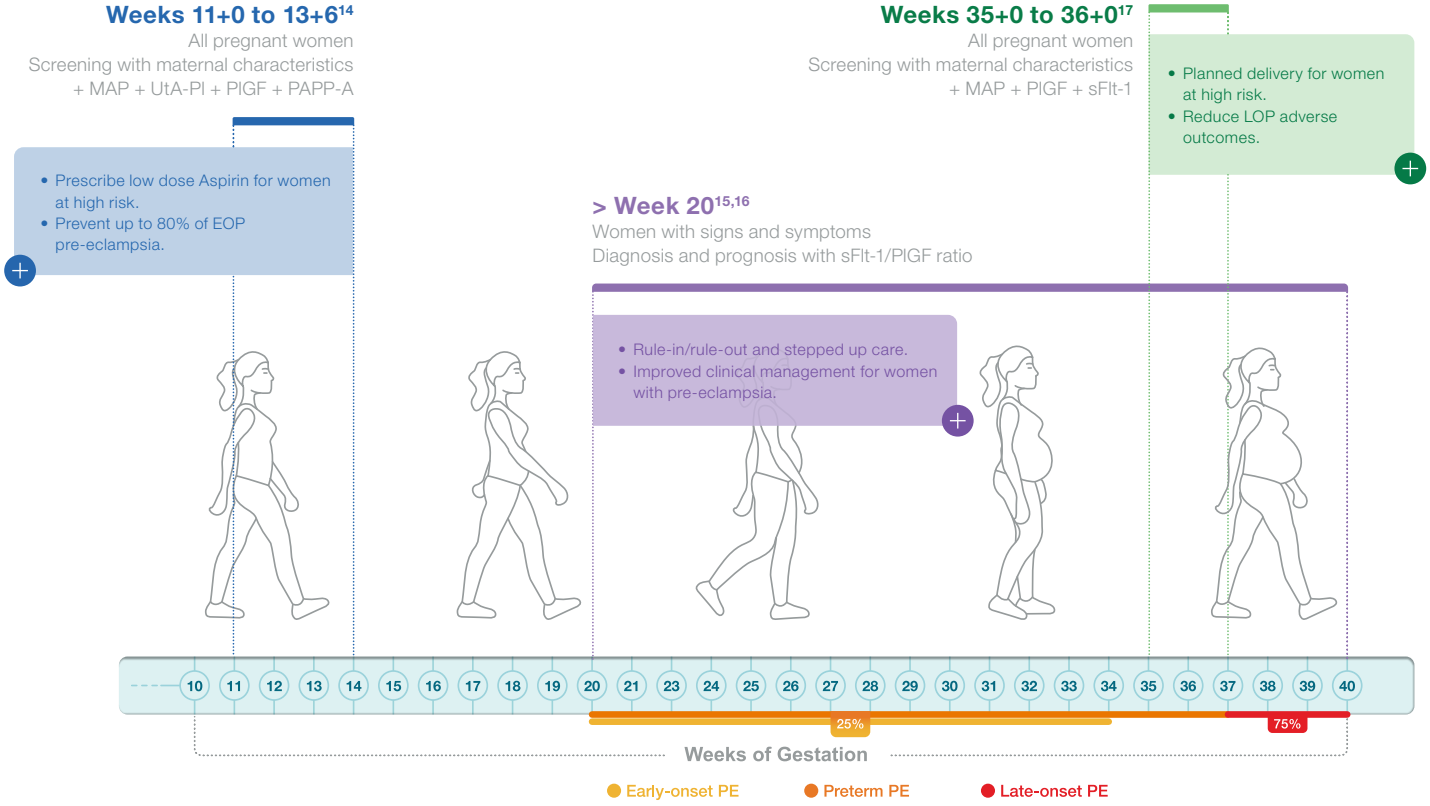
Mean PlGF and sFlt-1 concentrations in healthy and pre-eclamptic pregnancies.[8]

sFlt-1 in the control group remains constant until 33-36 weeks and PlGF increases during the first two trimesters, decreasing after week 32. In the women who developed pre-eclampsia later, the concentrations of sFlt-1 begin to increase at 21 to 24 weeks of gestation, with a steeper increase at 29 to 32 weeks, while PlGF increases during the first two trimesters but with significantly lower levels than the controls.[8]

Biomarkers can help to improve pre-eclampsia management throughout the pregnancy

Pre-eclampsia can be subdivided into early- and late-onset pre-eclampsia (EOP and LOP), depending on the time of onset. EOP is pre-eclampsia that develops before week 34 whereas LOP develops after week 34 and preterm is pre-eclampsia that ocurres before 37 weeks.[9] LOP accounts for 80 - 95% of all pre-eclampsia cases worldwide[10] associated with a high prevalence of eclampsia and HELLP syndrome, which are both life-threatening complications.[11] EOP, although less common, is associated with higher rates of neonatal mortality and maternal morbidity.[12]

These conditions have different implications for both the mother and the fetus, with a 10-fold higher risk of perinatal mortality in the EOP pre-eclampsia group and 1.5-fold increased risk among mothers with LOP disease, compared with mothers without pre-eclampsia.[18]



Prevent EOP[14]

- Identification of women at risk of developing EOP in first trimester with PAPP-A and PlGF.
- Prevention with low-dose Aspirin starting before week 16.

Prevent LOP[17]

- Identification of women at risk of developing LOP in third trimester with PlGF and sFlt-1.
- Prevention with timed birth.

Improve management of women with signs and symptoms of pre-eclampsia[18]

- Use the sFlt-1/PlGF ratio from week 20 to aid in:
  - Pre-eclampsia diagnosis.
  - Pre-eclampsia short-term prediction.
  - Prognosis of adverse outcomes.

Prevent EOP pre-eclampsia with first trimester screening and low dose Aspirin

Combine PlGF and PAPP-A with MAP and UtA-PI to assess the risk of developing EOP, between week 11+0 and 13+6.

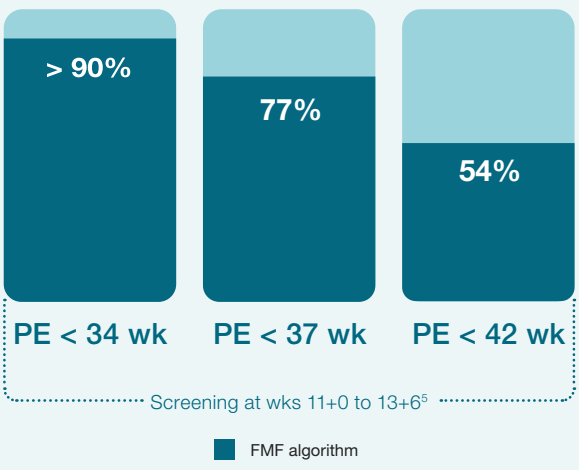
The Fetal Medicine Foundation

1. Maternal characteristics including medical and obstetric history
2. **Serum Biomarkers B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S PAPP-A KRYPTOR**
3. Mean arterial blood pressure (MAP)
4. Uterine artery pulsatility index (UtA-PI)
5. Risk assessment with appropriate PNS software to calculate individual risk to develop pre-eclampsia

Combined first trimester screening can be easily integrated into clinical routine pregnancy assessment. Risk assessment for trisomies and pre-eclampsia can be performed at the same time with PAPP-A, Free βhCG and PlGF.

Combined screening efficiently identifies women at risk of developing EOP and preterm pre-eclampsia

Using the traditional screening method, based on maternal risk factors has a poor performance, achieving only 34-41% detection rates with a FPR of 10%.[13]
Detection rates become more accurate when maternal factors are combined with PlGF measurement as well as other biomarkers such as serum PAPP-A (both measured in weeks 11+0 to 13+6), mean arterial pressure (MAP), and uterine artery Doppler (UtA-PI), resulting in a detection rate of >90% for cases of EOP pre-eclampsia (before week 34) for a fixed false positive rate (FPR) of 10%.[5]
Therefore, an effective prediction of preterm pre-eclampsia can be achieved already in first trimester.[5,19]



Depending on the setting and resources, different screening strategies can be implemented

Screening combination	Detection Rate (%)		
	PE < 34 wk	PE < 37 wk	PE < 42 wk
Maternal characteristics +	50.5	43.3	40.3
MAP	72.9	59.3	53.5
UtA-PI	75.2	55.1	42.2
PAPP-A	54.7	48.2	42.1
PlGF	72.4	54.4	40.1
UtA-PI, MAP and PlGF	95.8	77.3	52.9
UtA-PI, MAP, PAPP-A and PlGF	96.3	76.6	53.6

Estimated detection rates of pre-eclampsia requiring delivery before 34, 37 and 42 weeks' gestation, at false-positive rate (FPR) of 10%.[5]

Addition of MAP, UtA-PI and PlGF significantly improves the detection rate compared to maternal factors only.[5]

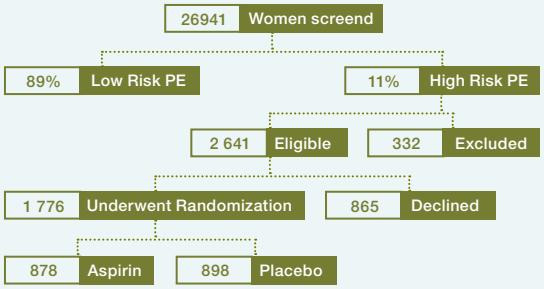
Combined 1st trimester screening with Thermo Scientific™ B·R·A·H·M·S™ PlGF plus KRYPTOR™ biomarkers has been validated most recently in PREVAL and PRESIDE studies in a total of near 19 000 pregnancies.[20,21]

Low-dose Aspirin prescribed for high-risk patients after first trimester screening reduces risk for preterm pre-eclampsia.[14]

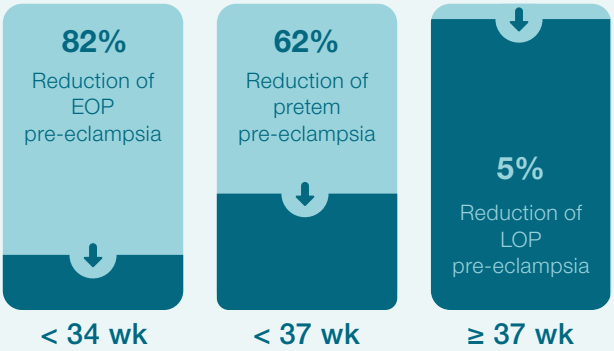
Study design

- Multicenter, double-blind, placebo-controlled trial
- Administration of low-dose Aspirin or placebo **150 mg/day at bedtime**
- Start intake after screening test before wk 16 until week 36 or onset of labor

Study Population



ASPRE trial has proven that low-dose Aspirin can reduce effectively the development of preterm pre-eclampsia[14]



The trial demonstrated that, the administration of low-dose Aspirin (150 mg) every day starting before 16 weeks until 36 weeks, to women identified in first trimester combined screening as being at high risk for preterm pre-eclampsia, effectively reduces the incidence of preterm pre-eclampsia.[14]

Prevent LOP pre-eclampsia with third trimester screening and timed birth

Combine PIGF and sFlt-1 with MAP to assess the risk of developing LOP between week 35+0 and 36+6.

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1

Maternal characteristics including medical and obstetric history

2

Serum Biomarkers B·R·A·H·M·S PIGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR

3

Mean arterial blood pressure (MAP)

4

Risk assessment with appropriate PNS software to calculate individual risk to develop late-onset pre-eclampsia

Combined screening in third trimester can be easily integrated into clinical routine pregnancy assessment.

Competing-risk model is a valuable tool for predicting LOP pre-eclampsia

In the weeks prior to the clinical onset of pre-eclampsia, the maternal serum level of PIGF is decreased and sFlt-1 is increased.[22]

In women with signs or symptoms of hypertensive disorders the use of the ratio sFlt-1/PIGF has been used to predict the development of pre-eclampsia within the subsequent 1 to 4 weeks. Although the simplicity of this approach doesn't take into account previous risk factors of the patient neither measurement of blood pressure.[22]

An alternative to this approach is to assess the risk of development of pre-eclampsia is the use of the competing-

Multicentre study:
10 maternity hospitals in England, Spain and Belgium

Biomarker Platform:
KRYPTOR Analyzer

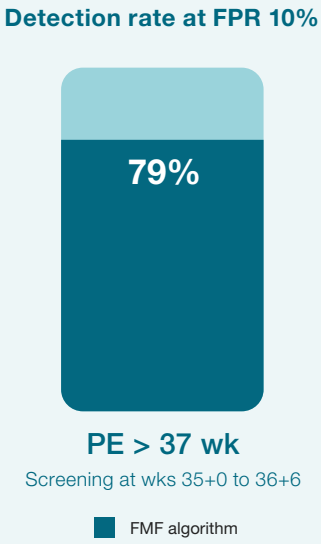
Study population:
29 670 pregnant women between 35+0 and 36+6 weeks

In a prospective multicenter study including more than 29 000 pregnancies it was demonstrated that screening at week 35+0 to 36+6 using a combined approach including maternal risk factors, MAP, PIGF and sFlt-1 is effective predicting LOP pre-eclampsia, resulting in a detection rate of 79% with a false positive rate of 10%.[23]

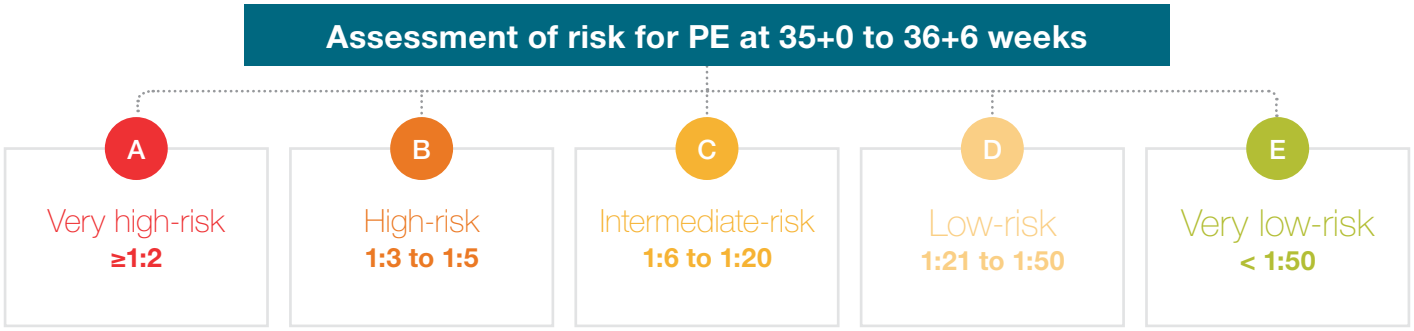
The combination of Maternal Factors, MAP, PlGF and sFlt-1 identifies 79% of LOP.

Screening test	Detection rate (%)
Maternal Factors +	36
MAP	63
PlGF	63
sFlt-1	68
PlGF + sFlt-1	72
MAP + PlGF + sFlt-1	79

Performance of screening for pre-eclampsia at 35+0 to 36+6 gestation, at a false-positive rate (FPR) of 10%.[23]



Screening for the risk of developing pre-eclampsia at 35+0 to 36+6 weeks can effectively identify a significant number of women who are likely to experience term pre-eclampsia. To mitigate the risk of pre-eclampsia, a proposed approach involves categorising the population into five risk groups and scheduling early births based on the assigned risk category. This entails planning deliveries at 37+0 weeks for group A, 38+0 weeks for group B, 39+0 weeks for group C, 40+0 weeks for group D, and 41+0 weeks for group E.[17]



Improving pre-eclampsia management for pregnant women with signs and symptoms

B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR assays after week 20 can help clinicians make the right decisions

10%

of pregnant women show unspecific signs and symptoms of pre-eclampsia.[24]

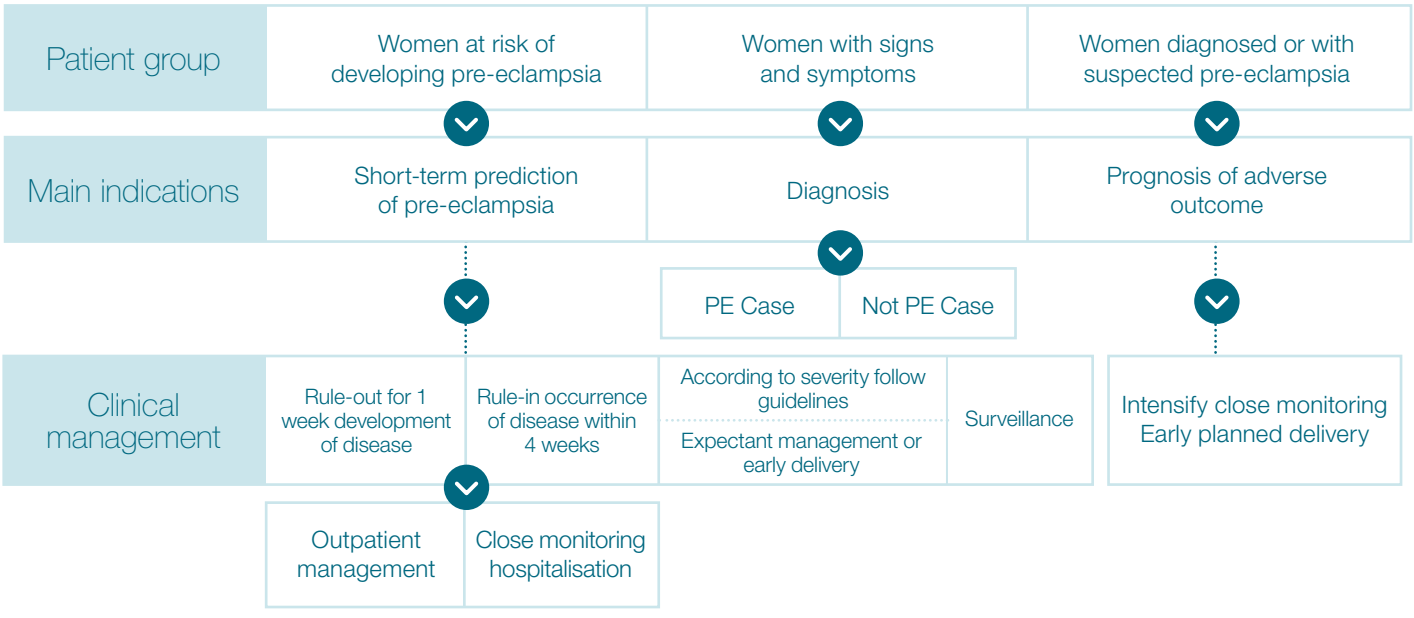
1/5

only **(1/5) of them** is actually developing pre-eclampsia.[24]

sFlt-1/PlGF ratio from week 20 can support identification and stratification of women with pre-eclampsia

When is a woman developing pre-eclampsia?	The ratio sFlt-1/PlGF is an aid **in short-term prediction** for rule-in /rule-out women at high risk of developing pre-eclampsia[18]
When is hospitalisation required?	The ratio is an aid in improving accuracy when **diagnosing** pre-eclampsia.[18]
When planning an early delivery?	The ratio is an aid in the **prognosis of adverse outcomes**, to intensify close monitoring and decide the best delivery timing.[18]

Clinical management depending on patient status[18,25,26]



Identifying pregnant women at risk of developing pre-eclampsia reduces severe maternal and neonatal morbidity and mortality

Assessment of pre-eclampsia is difficult and hospitalisations across all risk levels is not possible.[27]

High-risk women with any signs or symptoms may develop pre-eclampsia and a short-term prediction can help to decide on an outpatient setting or hospitalisation.[18]

sFlt-1/PlGF can help to improve diagnostic accuracy and to prevent overdiagnosis and over-treatment in women with suspected pre-eclampsia.[27]

Test interpretation[15,16]

Evidence shows optimal predictive performance with a KRYPTOR-specific cut-off at 66 for the sFlt-1/PlGF ratio.[18]

sFlt-1/PlGF < 66 low risk of developing pre-eclampsia | **66** | sFlt-1/PlGF ≥ 66 high risk of developing pre-eclampsia

If the ratio sFlt-1/PlGF < 66, women are at low risk for progression to pre-eclampsia within 1-4 weeks and standard care including expectant management is expected.[18]

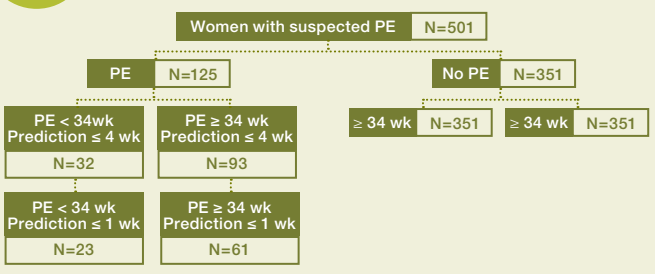
If the ratio sFlt-1/PlGF is ≥ 66, women are at high risk for progression to pre-eclampsia within 1-4 weeks and intensified surveillance and care are needed before pre-eclampsia develops.[18]

Evidence for the use of a single KRYPTOR-specific, gestation-independent threshold value for ruling out and ruling in developing pre-eclampsia[18]

Study design

- Observational retrospective study
- Evaluation of sFlt-1/PlGF predictive performance in women with suspected pre-eclampsia after 20
- Prediction PE ≤ 4 weeks
  Prediction PE ≤ 1 week
  Pre-specified cut-offs:
  Rule-out 33
  Rule-in 85

Study Population



sFlt-1/PlGF was implemented and evaluated retrospectively in a clinical routine setting.
Published data for KRYPTOR analyzer ratio suggested a cut-off value of 33 for rule-out and 85 for rule-in before wk 34, and 33 for rule-out and 99 to 110 for rule-in after wk 34.[18,28,29] An optimal KRYPTOR analyzer ratio threshold of 66 may be used with similar clinical performances providing evidence for the use of a single KRYPTOR-specific ratio cut-off.[18]

sFlt-1/PlGF Ratio < 66	sFlt-1/PlGF Ratio ≥ 66
Low risk of developing PE in the next 4 weeks	High risk of developing PE in the next 4 weeks
Rule-out (outpatient management)	Rule-in (hospitalisation)

B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR assays predictive performance evaluation in short-term prediction of pre-eclampsia

Clinical performances using the single 66 cut-off compared with those using the dual-threshold cut-off at 85 and 33, to rule-in and rule-out patients with suspected pre-eclampsia[18]

	Positive predictive value	All PE N=125	PE < 34 wk N=32	PE ≥ 34 wk N=93
Prediction PE ≤ 4 weeks	Cut-off at 85	75	72	76
	Cut-off at 66	75	73	76
Prediction PE ≤ 1 week	Cut-off at 85	70	69	71
	Cut-off at 66	70	69	70

	Negative predictive value	All PE N=125	PE < 34 wk N=32	PE ≥ 34 wk N=93
Prediction PE ≤ 4 weeks	Cut-off at 33	93	97	88
	Cut-off at 66	90	95	86
Prediction PE ≤ 1 week	Cut-off at 33	97	99	95
	Cut-off at 66	96	98	93

Good evidence for KRYPTOR-specific rule-out

Unique sFlt-1/PlGF threshold at 66 provides clinicians with a simple alternative to gestation specific dual- threshold values, for clinical decision-making.

KRYPTOR-specific 66 cut off has been **clinically validated** in a **routine setting** on a cohort of 500 women with signs and symptoms including both **EOP and LOP pre-eclampsia** cases showing good performances for safe clinical decisions.[18]

Clinically validated sFlt-1/PlGF ratio cut-off at 66 for short-term prediction of pre-eclampsia, allows a simple implementation in clinical practice

Benefits in clinical management

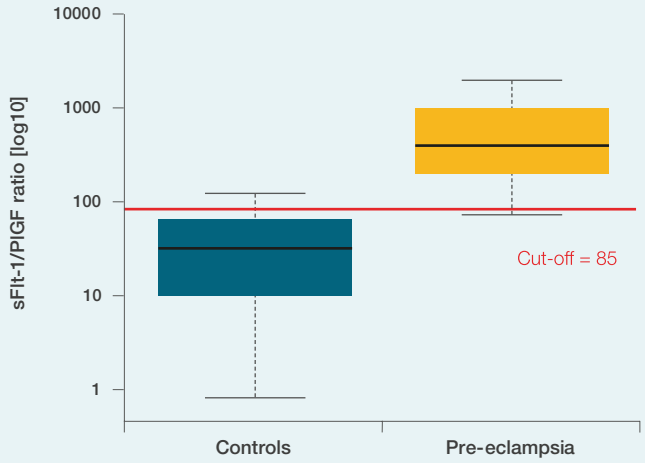
Easy interpretation for better clinical decisions

Ease of use for better clinical management

Reduced cost for unnecessary hospitalizations

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.[18]

Clinically validated sFlt-1/PlGF ratio cut-off at 85 for diagnosis and prognosis of adverse outcome



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

PlGF and sFlt-1 were measured on B·R·A·H·M·S KRYPTOR Analyzers 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.[26]

The latest studies show highly accurate performances in diagnosing pre-eclampsia by using the sFlt-1/PlGF ratio on B·R·A·H·M·S KRYPTOR Analyzers.[25,29,30]

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

sFlt-1/PlGF, as a marker of uteroplacental dysfunction, is now part of the criteria recommended by the **International Society for the Study of Hypertension in Pregnancy (ISSHP)** in the assessment of women suspected of having pre-eclampsia (<37 weeks).[31]

Prognosis of adverse outcome with sFlt-1/PlGF ratio

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.[20]

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.[20]

KRYPTOR assays accurately assess the risk of pre-eclampsia associated short-term adverse outcomes at the time of initial evaluation of pre-eclampsia.

With ratios >85 it is difficult to remain undelivered after 5 days.[25]

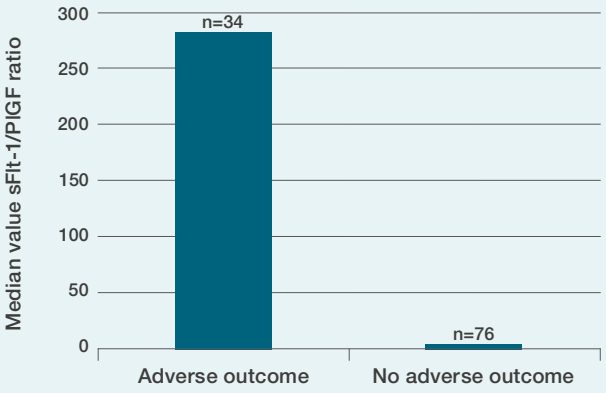
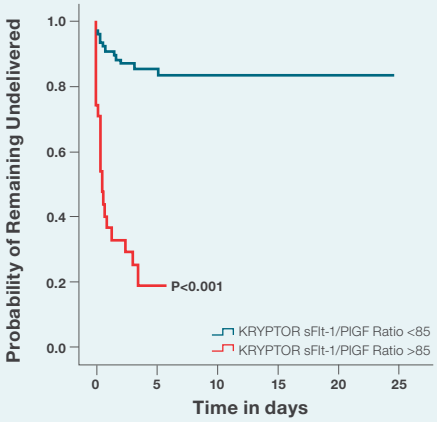


Figure 2. Prediction of adverse outcomes with sFlt-1/PlGF ratio in women presenting < 34 weeks' gestation[20]



Kaplan–Meier survival function for time to delivery in participants presenting at <34 weeks of gestation.[25]

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.[25]

Click here to learn more

Publication on B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR assays all over the world showing great reliability of results.

- Validated studies for B·R·A·H·M·S PlGF plus KRYPTOR assay in first trimester pre-eclampsia screening
- Validated studies for B·R·A·H·M·S PlGF plus and B·R·A·H·M·S sFlt-1 KRYPTOR assays in second and third trimester pre-eclampsia management

Click here to learn more

Intended uses[15,16,32]

	T1	T2 (from week 20)	T3	Cut-off
Screening	PlGF PAPP-A	PlGF sFlt-1	PlGF sFlt-1	It is the responsibility of the user to choose the cut-off which will apply for further procedures
Aid for Diagnosis		sFlt-1/PlGF	sFlt-1/PlGF	85
Short-term prediction		sFlt-1/PlGF	sFlt-1/PlGF	66

Ease of handling[15,16,32]

	PAPP-A	PlGF plus	sFlt-1
Sample volume	50 µl	70 µL	8 µL
Sample type	Serum	Serum, plasma (K2 EDTA)	Serum, plasma (K2 EDTA)
Incubation time	19 min	29 min	9 min
Linear direct measuring range	0.010 - 6 IU/L	7.7- 7,000 pg/mL	39.5 - 90,000 pg/mL
Limit of Detection	0.0054 IU/L	4.91 pg/mL	28.5 pg/mL
Limit of Quantitation	0.01 IU/L	7.7 pg/mL	39.5 pg/mL
Kit stability on board	29 days	29 days	29 days
Calibrator	1 point	1 point	2 points
Calibration stability	15 days	15 days	15 days

- IVDR Compliant
- 24/7 with KRYPTOR analyzers and assays
- Result in < 30 min

Exceptionally precise, fast and easy
B·R·A·H·M·S KRYPTOR Analyzers

B·R·A·H·M·S KRYPTOR GOLD

B·R·A·H·M·S KRYPTOR compact PLUS

The Fetal Medicine Foundation

- All B·R·A·H·M·S KRYPTOR analyzers are FMF-approved
- Excellent precision and proven median stability
- One-stop clinic for assessment of risks (OSCAR) compatible

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