Advances in the management of suspected preeclampsia with Elecsys® sFlt-1/PlGF ratio

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Life needs answers

"Preeclampsia is a common and potentially serious condition that presents a continuing challenge to clinicians due to the variable features and lack of diagnostic tests."

Prof. Andrew Shennan, King's College London, London, UK

Preeclampsia
A serious pregnancy complication

Introduction to preeclampsia[1]
Preeclampsia is a serious complication in pregnancy which affects both the mother and the unborn child. Women with preeclampsia develop high blood pressure and high protein in their urine.

Preeclampsia is defined by the new onset of elevated blood pressure and proteinuria after 20 weeks of gestation. It is considered severe if blood pressure and proteinuria are increased substantially or symptoms of end-organ damage (including fetal growth restriction) occur. There is no single reliable, cost-effective screening test for preeclampsia, and there are no well-established measures for primary prevention. Management before the onset of labour includes close monitoring of maternal and fetal status.[2]

The majority of cases develop in healthy women bearing their first child. In addition several medical conditions are associated with an increased preeclampsia risk such as chronic hypertension, diabetes and renal disease. The cause of preeclampsia is not fully understood, but there is growing evidence that angiogenic factors such as placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) play a major role in the development of preeclampsia.

Preeclampsia may develop from 20 weeks of gestation until 48 hours after delivery. It is most commonly diagnosed after 32 weeks of gestation. Early-onset disease (20 – 33 + 6 weeks) is associated with particularly serious threats for the mother and fetus.

Complications
Preeclampsia is associated with increased mortality and morbidity. Women are often unaware that they have preeclampsia, even when it is life-threatening.

Amongst others, the most common complications of preeclampsia include:

For the mother:
- Eclampsia – preeclampsia in combination with generalized seizures
- Convulsions
- Kidney damage / Kidney failure
- Abruptio placentae
- Antepartum hemorrhage
- Cerebrovascular bleeding

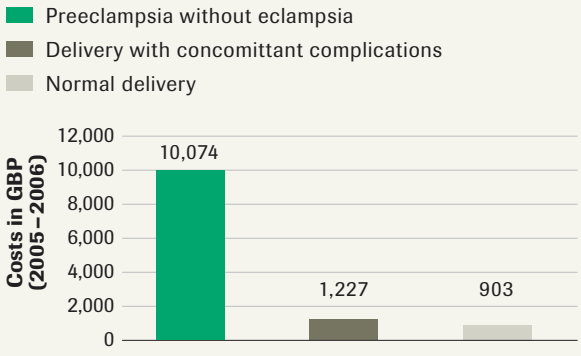
For the fetus:
- Fetal growth retardation
- Low birth weight
- Kidney damage / Kidney failure
- Premature birth
- Antepartum hemorrhage
- Stillbirth
- Respiratory distress syndrome
- Necrotizing enterocolitis

Incidence

Preeclampsia is the most common hypertensive disorder during pregnancy. It occurs in 3 – 5 % of pregnancies and is defined by maternal hypertension with proteinuria.[3]

Preeclampsia has the greatest effect on maternal and infant outcome; it is a leading cause of preterm birth and consequent neonatal morbidity and mortality.

Hospital costs for both mother and baby[4]



Health Economics impact of Preeclampsia

Preeclampsia puts a major financial burden on the health care cost for pregnancies. In 2005 the average cost estimate for preeclampsia alone (excluding normal delivery costs) was GBP 9,009 per pregnancy.[4]

With an estimated 8.5 million women affected by preeclampsia every year, the estimated annual cost of preeclampsia worldwide is GBP 76.6 billion (based on the 2005 estimate). Costs might still be an underestimation due to the lack of proper diagnosis.[5]

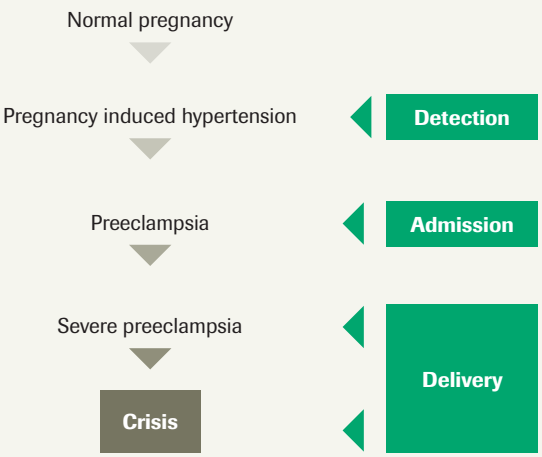
Preeclampsia diagnosis and care is not optimal even in developed countries. Between 2006 and 2008 in the UK, 20 out of 22 deaths linked to preeclampsia involved substandard care. The substandard care in 63 % of these deaths was categorized as major and they were described as “undoubtedly avoidable”.[6]

Pathogenesis
Hypertension and proteinuria are the diagnostic criteria for preeclampsia but they are only symptoms of the pathophysiologic changes that occur in the disorder. sFlt-1 and PlGF are indicators of the endothelial dysfunction associated with preeclampsia.[7,8]

Aid in diagnosis
Diagnosis of preeclampsia is currently based on variable clinical parameters. Complications of the disease may be serious even when hypertension and/or proteinuria are mild.

Currently there is no single, objective laboratory test for the diagnosis of preeclampsia.[2] There is a need for a rapid and accurate aid in diagnosing this common and potentially serious condition to facilitate effective clinical management and to improve outcome for mother and fetus.[8,9]

Preeclampsia landmarks



Each landmark demands a change in place and pace of care (frequency of screening)

Diagnosis of preeclampsia

Current standard of diagnosing preeclampsia[2]

Diagnosis of preeclampsia is not always easy. For the diagnosis of preeclampsia, both hypertension and proteinuria must be present.

Preeclampsia

- Blood pressure: 140 mmHg or higher systolic or 90 mmHg or higher diastolic after 20 weeks of gestation in a woman with previously normal blood pressure. Systolic increased > 30 mmHg or diastolic increased > 15 mmHg in a patient with preexisting chronic hypertension
- Proteinuria: 0.3 g or more of protein in a 24-hour urine collection

Severe preeclampsia

- Blood pressure: 160 mmHg or higher systolic or 110 mmHg or higher diastolic on two occasions at least six hours apart in a woman on bed rest
- Proteinuria: 5 g or more of protein in a 24-hour urine collection or 3+ or greater on urine dipstick testing of two random urine samples collected at least four hours apart
- Other features: oliguria (less than 500 mL of urine in 24 hours), cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia, intrauterine growth restriction

NICE Antenatal Care Guideline 2008[9]

The NICE guidelines recommend that the following risk factors for preeclampsia should be sought at the first visit: age 40+ years, nulliparity, pregnancy interval of more than 10 years, family history of preeclampsia, BMI 30+ kg/m^2, pre-existing vascular disease such as hypertension, pre-existing renal disease and multiple pregnancy. According to NICE, more frequent blood pressure measurements should be considered for any women who have any of the above risk factors.

The preeclampsia community guideline (PRECOG)[10]

Refinements to the NICE guidelines, recommending that specialist referral is offered if **any risk factor** from the following list is present:

- **Previous preeclampsia**
- **Multiple pregnancy**
- **Long term medical condition**
  - **Hypertension**
  - **Renal disease**
  - **Diabetes**
  - **Antiphospholipid antibodies**

Refinements to the NICE guidelines, recommending that specialist referral is offered if **any two risk factors** from the following list are present:

- **First pregnancy**
- **≥ 10 years since the last baby**
- **Age ≥ 40 years**
- **BMI ≥ 35**
- **Family history of preeclampsia (mother or sister)**
- **Booking diastolic blood pressure ≥ 80 mmHg**
- **Proteinuria at booking ≥ 0.3 g / 24 hours**

Today's challenges in the clinical management of preeclampsia

The management of preeclampsia is troublesome

Clinical management of Preeclampsia can be challenging due to:

- A lack of effective treatment options other than delivery[1]
- The necessity of a reliable tests for assessing disease severity and progression[1], and for predicting preeclampsia related complications[11]
- The necessity to balance maternal and fetal risks[12], which may be in opposition
- The need for a reliable identification of high-risk preeclampsia patients to be referred to a specialized perinatal care center[13]

Diagnostic gold standard is not perfect

Current 'gold standard' for the diagnostic assessments include the determination of blood pressure and proteinuria.[14,15,16]

However, **the current gold standard measurements have low sensitivity and specificity for predicting the disease and maternal and perinatal outcomes.**[1] Prediction and prognosis of preeclampsia remains an important unmet medical needs that is particularly critical given the unpredictable nature of this condition.

Also diagnosis of preeclampsia may be challenging when the clinical picture is not straightforward.

"Our understanding of the pathophysiology of preeclampsia, including the role of the placental factors sFlt-1 and PlGF, has improved. With this better understanding comes the opportunity to improve the way we diagnose this common and sometimes serious condition."

Dr. Nadia Berkane, Hôpital Tenon, Paris, France

Elecsys® sFlt-1/PlGF

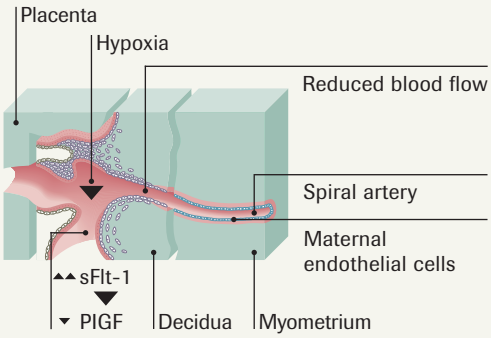
The first fully automated tests for preeclampsia

Improved understanding leads to diagnostic advances: sFlt-1 and PlGF

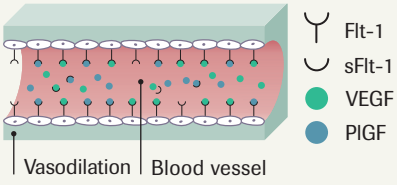
Preeclampsia may be caused by an imbalance of angiogenic factors. It has been demonstrated that high serum levels of sFlt-1, an anti-angiogenic protein, and low levels of PlGF, a pro-angiogenic protein, predict subsequent development of preeclampsia. In the absence of glomerular disease leading to proteinuria, sFlt-1 is too large a molecule to be filtered into the urine, while PlGF is readily filtered. The hypoxic placenta, which is commonly found in preeclampsia, produces sFlt-1.[7,17,18,19,20]

These pathological changes lead to a vasospasm which is responsible for reduced perfusion of the placenta.

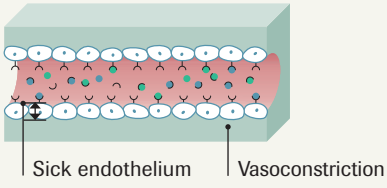
Hypoxic placenta



Normal pregnancy

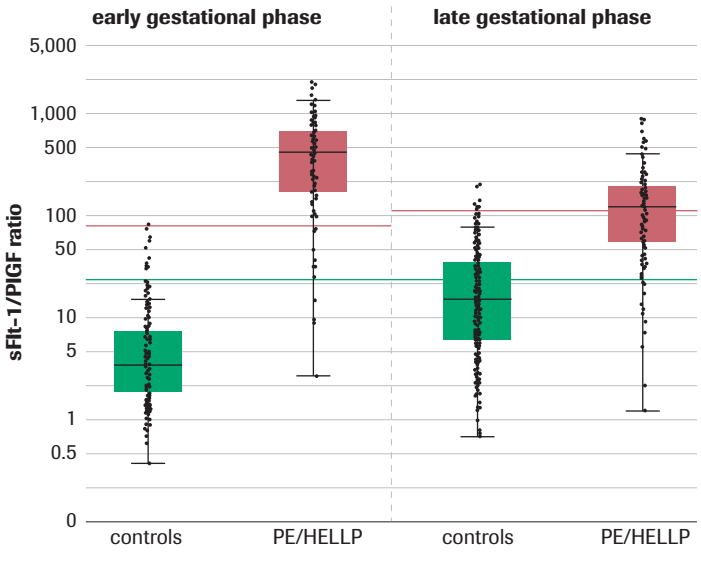


Preeclampsia



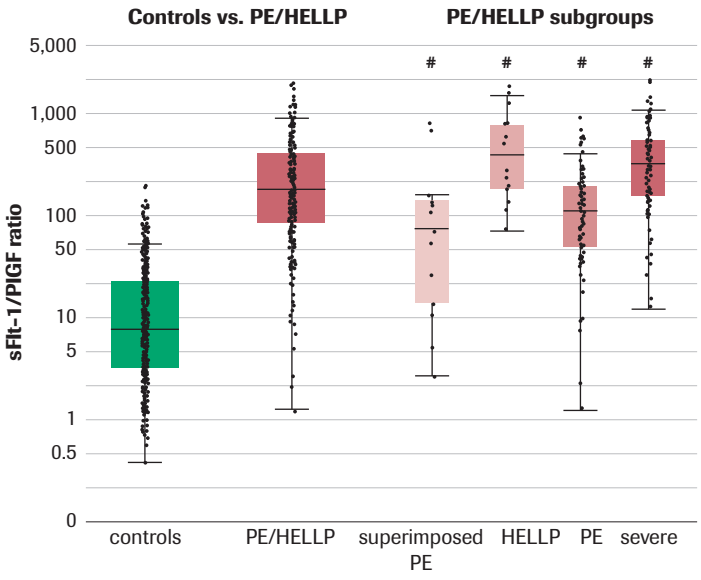
In a multicenter case-control study the Elecsys sFlt-1 and Elecsys PlGF assays were tested in parallel on samples from 468 pregnant women with normal pregnancy outcome (no preeclampsia, no HELLP syndrome, no intrauterine growth restriction) and 234 patients with preeclampsia / HELLP syndrome. All pregnancies were singleton pregnancies.[23,33] Different sets of cut-offs are suggested for early-onset and late-onset preeclampsia for use as an aid in the diagnosis of preeclampsia.

sFlt-1/PlGF ratio for aid in diagnosis of preeclampsia[33]



PE/HELLP = preeclampsia / HELLP syndrome; sFlt-1/ PlGF ratio cut-offs for early gestational phase: 33 / 85; sFlt-1/PlGF ratio cut-offs for late gestational phase: 33 / 110

sFlt-1/PlGF ratio for aid in diagnosis of preeclampsia[33]



 # P < 0.001 multigroup comparison PE subgroups

"Preeclampsia by itself cannot be treated, but the clear stratification of risk can trigger concrete actions, such as the close monitoring of the mother and fetus as well as the referral to a specialist delivery unit offering intensive care."

Prof. Holger Stepan, University of Leipzig, Germany

Improve the management of suspected preeclampsia patients

Patients with signs and/or symptoms of preeclampsia are sometimes difficult to be managed. Often, a suspicion of preeclampsia triggers escalation to a higher level of care. In fact, appropriate and timely referral to specialized centers reduces perinatal morbidity and mortality by 20%.[13]

The prognostic performance of the current diagnostic standard in determining which women will develop preeclampsia and how the disease will progress is quite poor.[1] As a consequence, many pregnant women with signs and/or symptoms of preeclampsia are often unnecessarily hospitalized for observation, resulting in stress for the expectant woman and significant additional costs to pregnancy care.

The measurement of the Elecsys® sFlt-1/PlGF ratio is a reliable tool to identify the patients that are at high risk to develop preeclampsia requiring a closer monitoring. On the other hand, the Elecsys sFlt-1/PlGF test allows you to confidently send home patients for one week that are not going to develop the disease.[22,23]

Improve outcome for mother & child through effective clinical management

In addition to supporting the prediction of preeclampsia Elecsys immunoassays help to optimise the clinical management. Following the diagnosis of preeclampsia an assessment is needed to grade the severity of the disease to determine whether conservative or active management is appropriate.

Decisions are needed as to whether urgent admission, hospital assessments or monitoring are appropriate.[2]

With the Elecsys sFlt-1/PlGF ratio the physician does not just have to rely on the degree of hypertension, the degree of proteinuria and the presence or absence of symptoms.

Addressing unmet medical needs

Medical value of Elecsys® preeclampsia immunoassays

Aid in short-term prediction of preeclampsia[22,23]

A recent multicenter prospective study – PROGNOSIS (**Pr**ediction of short-term **o**utcome in pre**gn**ant w**o**men with suspected preeclamp**si**a **s**tudy) – evaluated the use of the Elecsys sFlt-1/PlGF ratio in the short-term prediction of preeclampsia / eclampsia / HELLP syndrome in pregnant women with suspected preeclampsia. The PROGNOSIS Study collected samples and clinical data from 1,273 pregnant women with clinical suspicion of preeclampsia between gestational weeks 24 + 0 days – 36 + 6 days at 30 study sites in different global regions.

One single cut-off of 38 for sFlt-1/PlGF ratio was identified in the PROGNOSIS Study:[23]

- **sFlt-1/PlGF ratio < 38: Rule-out preeclampsia for 1 week**
- **sFlt-1/PlGF ratio ≥ 38: Rule-in preeclampsia within 4 weeks**

Short-term prediction of preeclampsia Rule-out within 1 week (n = 1,050)[23]

sFlt-1/PlGF ratio	< 38
NPV (95 % CI)	**99.1 % (98.2 – 99.6)**
Sensitivity (95 % CI)	85.7 % (72.8 – 94.1)
Specificity (95 % CI)	79.1 % (76.5 – 81.6)

Short-term prediction of preeclampsia Rule-in within 4 weeks (n = 1,050)[23]

sFlt-1/PlGF ratio	≥ 38
PPV (95 % CI)	**38.6 % (32.6 – 45.0)**
Sensitivity (95 % CI)	70.3 % (61.9 – 77.8)
Specificity (95 % CI)	83.1 % (80.5 – 85.5)

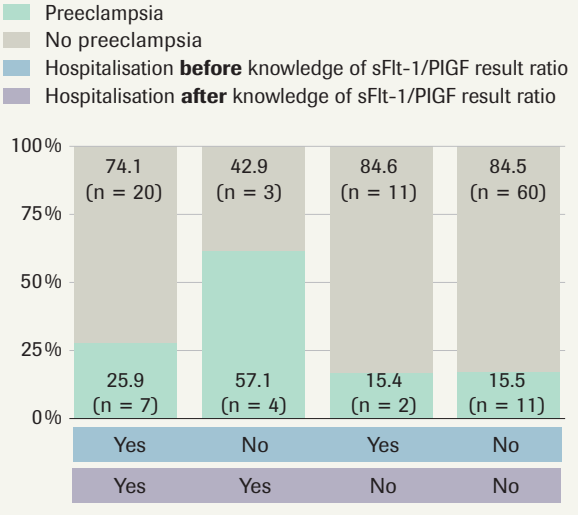
CI = Confidence Interval
NPV = Negative Predictive Value
PPV = Positive Predictive Value

Elecsys® sFlt-1/PlGF ratio as tool to support physician decision-making

When a pregnant woman presents with signs and symptoms of preeclampsia, the physicians often face a challenging decision making process. There are different components to be considered: the necessity to balance maternal and fetal risks[12], the need to best allocate healthcare resources to the patients at the highest risk but also the desire to avoid unnecessary stress for the patients.

The Preeclampsia Open Study (PreOS) assessed the influence of the Elecsys sFlt-1/PlGF test on the decision making of the physicians to hospitalize patients with suspicion of preeclampsia. PreOS collected data from 209 patients in a multicenter, prospective and non-interventional setting.[24,25] The Elecsys sFlt-1/PlGF ratio was found to influence decision-making for hospitalisation in suspected preeclampsia and the changed decisions were in concordance with the incidence of major clinical outcomes (e.g. preeclampsia).

Preeclampsia outcome by hospital admission[25]

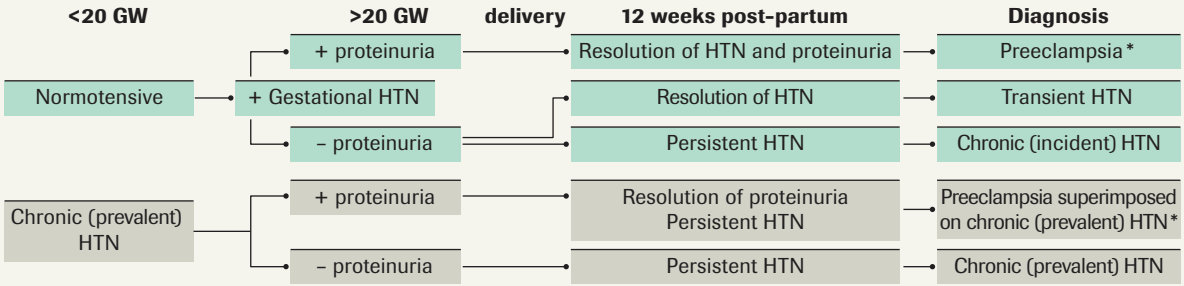


Differential diagnosis of preeclampsia is often complicated

The clinical presentation of preeclampsia and subsequent clinical course of the disease can vary tremendously. The tools currently available to diagnose preeclampsia include measuring blood pressure and assessing proteinuria. However, these have low sensitivity and specificity in terms of assessing disease severity or predicting the course of the disease.[1]

Underlying chronic disorders, such as renal diseases or autoimmune disorders can mimic the preeclampsia phenotype, making diagnosis difficult. Other hypertensive disorders in pregnancy include gestational hypertension and chronic hypertension. Pregnant women with chronic hypertension are at higher risk of developing superimposed preeclampsia than normotensive women.[1,13,25]

Hypertensive pregnancy disorders: classification and diagnostic criteria[19]



** The diagnosis of eclampsia, a convulsive form of preeclampsia, is based on new-onset seizures, in the absence of a previous history of a seizure disorder. (GW = gestational weeks; HTN = hypertension)*

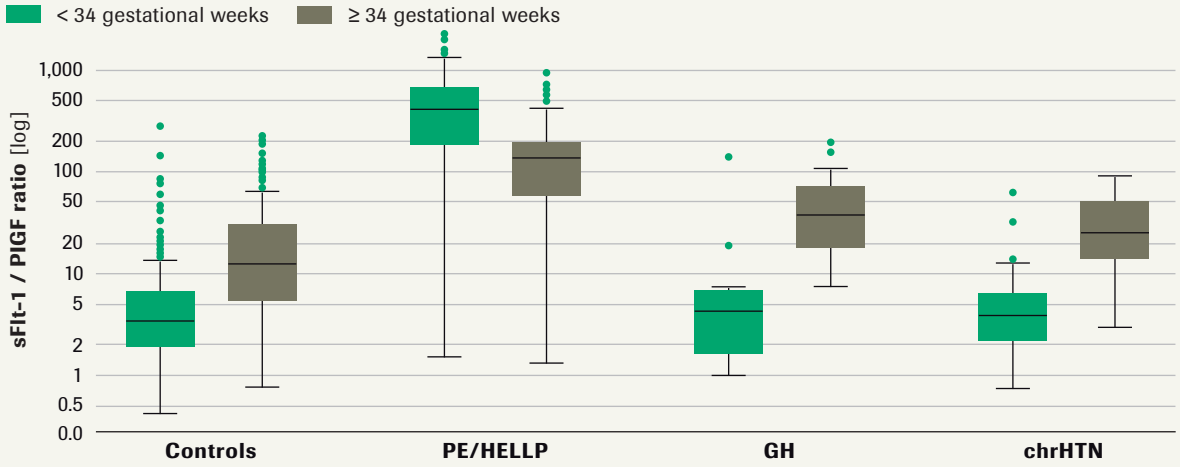
"We hope that early identification of women at high risk of developing preeclampsia will allow healthcare professionals to prevent the most serious effects of the disease and avoid unnecessary expenditure by healthcare systems on excessive medical treatment or unnecessary hospital admission prompted by inadvertently positive diagnoses based on current standard of clinical practice"

Prof. Harald Zeisler, University of Vienna, Austria

Angiogenic factors can support in the differential diagnosis of preeclampsia

A study showed that the measurement of the sFlt-1/PlGF ratio can differentiate between different forms of hypertensive disorders. Women with preeclampsia or HELLP syndrome had significantly higher sFlt-1/PlGF ratios than women with gestational hypertension, chronic hypertension or no hypertensive disorder at all ($p < 0.001$).[13]

Another study showed that the sFlt-1/PlGF ratio may facilitate the diagnosis of superimposed preeclampsia in women with chronic hypertension.[26]



sFlt-1/PlGF ratio in PE/HELLP, GH, chrHTN, and healthy controls[13]
(PE = preeclampsia; HELLP = Hemolysis, Elevated Liver Enzymes, Low Platelets; GH = gestational hypertension; chrHTN = chronic hypertension)

Combination of angiogenic factors with Doppler sonography

Preeclampsia is characterised by an abnormal perfusion of the uterine arteries. Doppler sonography is often used as part of the clinical examination for patients with suspected preeclampsia, however, it has limited predictive value.[27]

Combining Doppler sonography and biomarkers can improve the positive predictive value (PPV) for preeclampsia. Combination with biomarkers has been shown to improve the predictive performance of Doppler sonography.[20,27]

For example, 2nd trimester sFlt-1 measurements improve the PPV for Doppler sonography from:

- 33 % to 50 % for all cases of Preeclampsia
- 31 % to 56 % for cases of Preeclampsia where delivery before 34 weeks was required[28]

Use of angiogenic biomarkers in the clinical management of preeclampsia

Preeclampsia is associated with a number of serious adverse events, including:[11]

- Maternal acute renal failure, liver dysfunction, seizures and cerebral accidents
- Fetal growth restriction
- Maternal or fetal mortality

Clinical criteria alone (blood pressure and proteinuria) may be inadequate to predict adverse outcomes. Recent studies showed that a high sFlt-1/PlGF ratio and a more rapid elevation in the sFlt-1/PlGF ratio are associated with a significantly increased risk for an immediate delivery.[11,13,20,29]

Health Economic impact of preeclampsia testing

Clinical use of the sFlt-1/PlGF ratio at triage could enable reductions in direct hospital costs and resource use

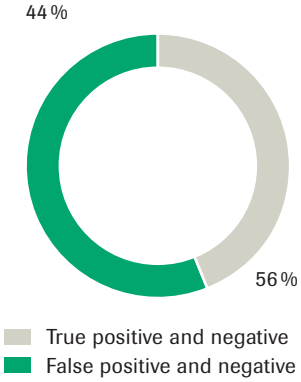
The use of the sFlt-1/PIGF assays could allow cost-savings
A correct short-term prediction and diagnosis of preeclampsia might allow a reduction of maternal and fetal morbidity as well as mortality. Timely referral of the patients at highest risk to a perinatal care centre reduces perinatal morbidity and mortality by 20 %.[13] In addition, quick and reliable detection of preeclampsia facilitates prompt intervention with steroids for fetal lung maturation, magnesium sulphate for seizure prophylaxis and antihypertensive therapy.

An improved prediction and diagnosis can allow a reduction of inappropriate discharges as well as a reduction of unnecessary hospitalizations, therefore a reduction of the health care burden.[11]

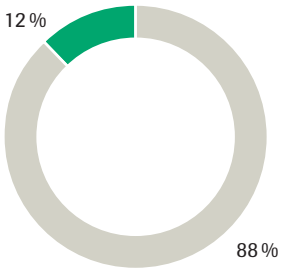
In a recent model, adding the Elecsys® sFlt-1/PIGF ratio to the standard diagnostic method improved risk stratification with a significant reduction of false positive and false negative diagnosis. This could enable reductions in direct hospital costs and resource use with savings of 540 – 1,215 USD per patient.[30]

By using the novel preeclampsia test in the UK, the NHS could save GBP 730 million annually and in Germany, national savings could reach EUR 436 million annually.[31,32]

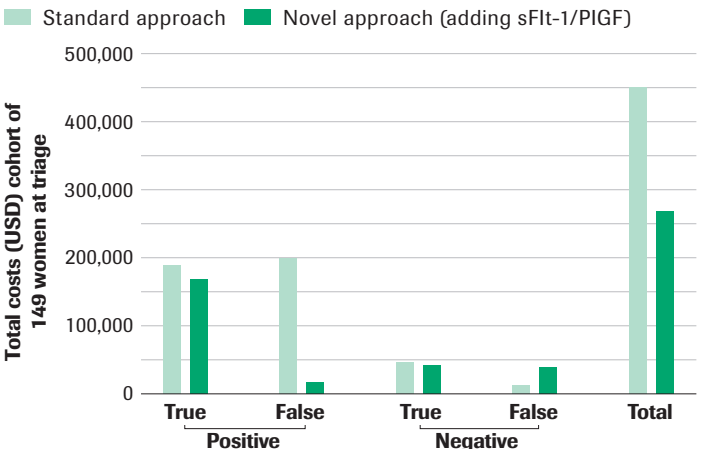
Standart approach[30]



New approach[30] (adding sFlt-1/PIGF ratio)



Ideal case budget impact by implementation of sFlt-1/PIGF[30]



Novel innovative Elecsys sFlt-1/PlGF ratio test

Precise, consistent, reliable

sFlt-1/PlGF ratio cut-offs[23,24,33]

Early-onset preeclampsia – gestational week 20 – 33 + 6 days

sFlt-1/PlGF ≥ 85	Diagnosis	**99.5 % specificity** the woman has preeclampsia Sensitivity: 88.0 %
sFlt-1/PlGF < 85 ≥ 38	Prediction rule-in within next 4 weeks	**38.6 % PPV** the woman is at high risk to develop preeclampsia within the next 4 weeks
sFlt-1/PlGF < 38	Prediction rule-out for the next 1 week	**99.1 % NPV** the woman will not develop preeclampsia for the next 1 week

Late-onset preeclampsia – gestational week 34 to end of pregnancy

sFlt-1/PlGF ≥ 110	Diagnosis	**95.5 % specificity** the woman has preeclampsia Sensitivity: 58.2 %
sFlt-1/PlGF < 110 ≥ 38	Prediction rule-in within next 4 weeks	**38.6 % PPV** the woman is at high risk to develop preeclampsia within the next 4 weeks
sFlt-1/PlGF < 38	Prediction rule-out for the next 1 week	**99.1 % NPV** the woman will not develop preeclampsia for the next 1 week

Make sure you don't miss preeclampsia diagnosis

Roche Elecsys® sFlt-1/PlGF assay helps identifying preeclampsia patients at the highest need of intensified care in daily management and it provides reliable results in critical situations, when only a non-specific clinical picture is available. With the support of the Elecsys sFlt-1/PlGF assay, timely decisions regarding treatment and disease management are possible, thereby reducing danger to mother and fetus.

The sFlt-1/PlGF ratio allows gynaecologists to focus on the high-risk patients and reassure the patients not going to develop pre-eclampsia /eclampsia /HELLP syndrome for one week.[23,24]

Peace of mind for physicians to timely and correctly diagnose preeclampsia

- **a disease where the clinical picture is not always clear**
- **a disease where the onset is unpredictable**
- **a disease where the assessment of the severity/ prognosis is difficult**
- **a disease where timely decision can be critical both for mother and fetus**

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