



Advances in diagnostics through Elecsys® Preeclampsia Immunoassays





“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

Preeclampsia

A serious pregnancy complication

Introduction to preeclampsia¹⁶

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.

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 growth 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.

PlGF is responsible for normal placental function and thereby maintenance of a healthy pregnancy, whereas sFlt-1 is associated with termination of pregnancy in the last weeks of gestation.

Circulating levels of sFlt-1 and PlGF are altered in women who develop preeclampsia.

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.¹

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

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



“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, St. Thomas Hospital, London, UK

Status quo in diagnostic testing

A need for improved diagnosis of preeclampsia

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.^{2,3}

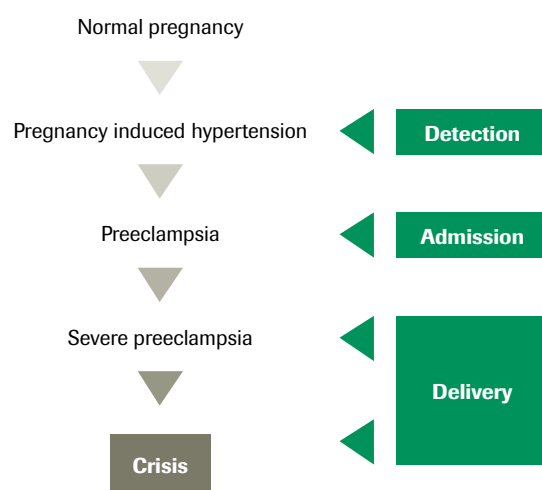
Aid in diagnosis

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.⁴

There is a need for a rapid and accurate aid in diagnosing preeclampsia for this common and potentially serious condition to facilitate effective clinical management and to improve outcome for mother and fetus.^{3,5}

Preeclampsia landmarks



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

In preeclampsia pregnancies sFlt-1 levels are raised (▲) and PlGF levels are decreased (▼)^{6,7}



Today's challenge - differentiation between PIH and preeclampsia

Preeclampsia can mimic and be confused with many other diseases, especially pregnancy-induced hypertension (PIH), which is a form of high blood pressure in pregnancy. It occurs in about 5 to 8 percent of all pregnancies.

It is particularly difficult to differentiate and diagnose between PIH and preeclampsia when preexisting diseases such as hypertension are present.

Current standard of diagnosing preeclampsia⁴

Diagnosis of preeclampsia is not always easy.

For the diagnosis of preeclampsia, both hypertension and proteinuria must be present.

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.

**Preeclampsia**

- Blood pressure: 140 mm Hg or higher systolic or 90 mm Hg or higher diastolic after 20 weeks of gestation in a woman with previously normal blood pressure. Systolic increased > 30 mm Hg or diastolic increased > 15 mm Hg 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 mm Hg or higher systolic or 110 mm Hg 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

Complications

Preeclampsia is associated with increased mortality and morbidity. Women are often unaware 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

Elecsys sFlt-1/PlGF

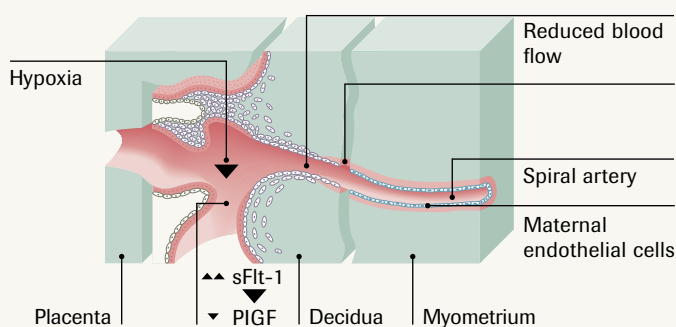
The first available automated diagnostic tests

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

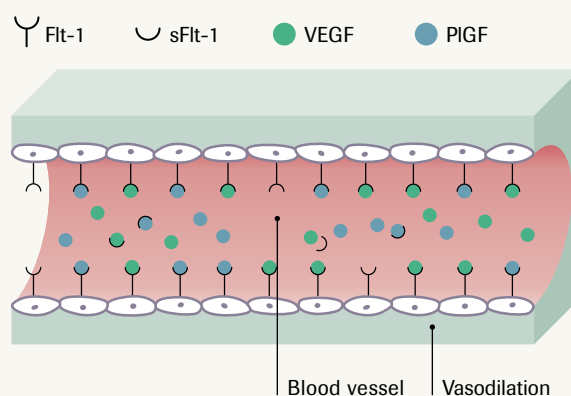
Preeclampsia may be caused by an imbalance of angiogenic factors. It has been demonstrated that high serum levels of sFlt-1, an anti-angiogenic protein, and low levels of PlGF, a pro-angiogenic protein, predict subsequent development of preeclampsia. In the absence of glomerular disease leading to proteinuria, 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.^{2,7,9,10,11}

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

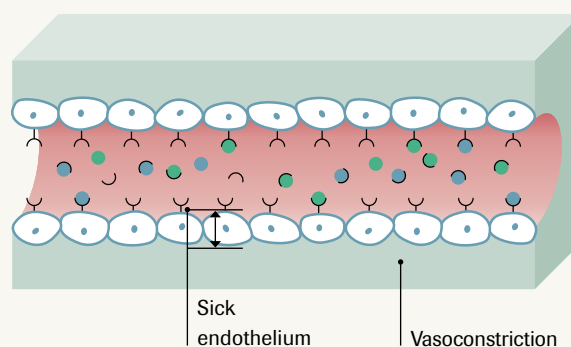
Hypoxic placenta



Normal pregnancy



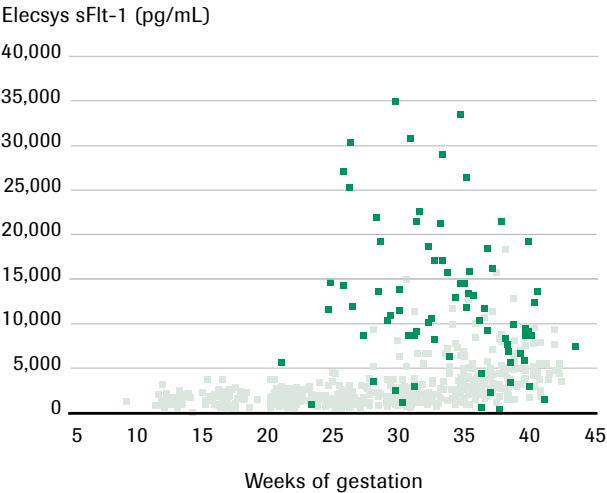
Preeclampsia



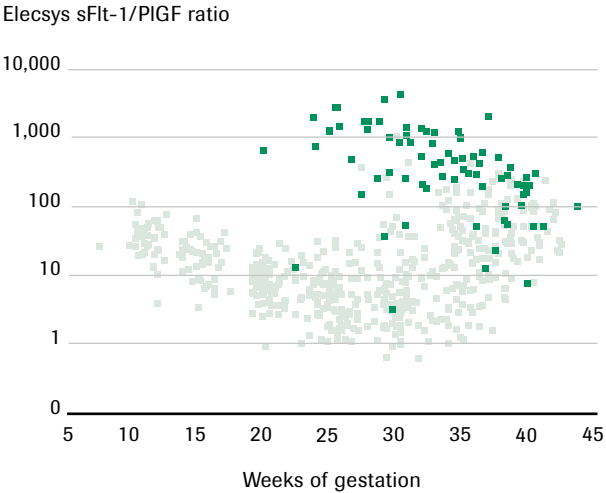
In a multicenter case-control study including 351 pregnant women sFlt-1 levels have been found to be higher and PIGF levels have been found to be lower than in normal pregnancies.¹²

- Case sample
- Control group

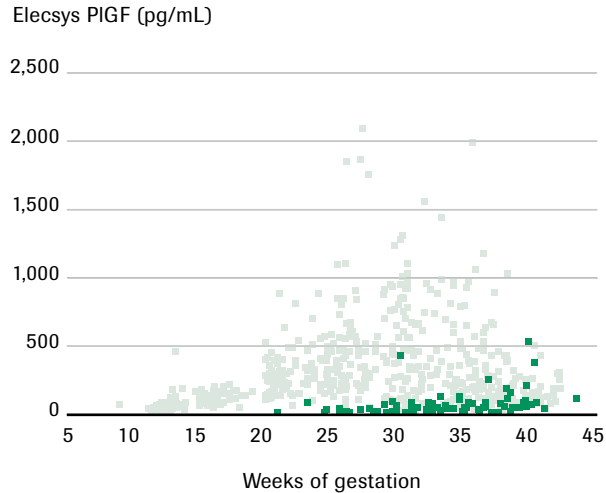
Elecsys sFlt-1 assay



Elecsys sFlt-1/PIGF ratio



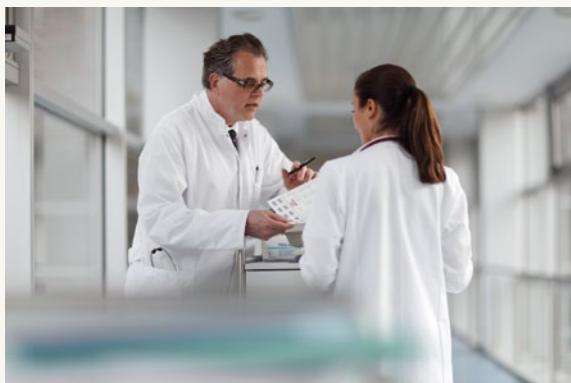
Elecsys PIGF assay



Diagnosis of preeclampsia

NICE Antenatal Care Guideline 2008¹³

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/m², 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)⁸

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**

“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

Currently there is no single, objective laboratory test for the diagnosis of preeclampsia. The diagnosis is dependent on clinical features, which are variable, like hypertension and proteinuria.

None of these tests are specific for preeclampsia.

The new Elecsys immunoassays could bring a major advance in preeclampsia diagnosis which has remained virtually unchanged for decades.

Improve outcome for mother & child through effective clinical management

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.⁴

With the Elecsys immunoassays the physician does not just have to rely on the basis of the degree of hypertension, the degree of proteinuria and the presence or absence of symptoms.



Facing unmet medical needs

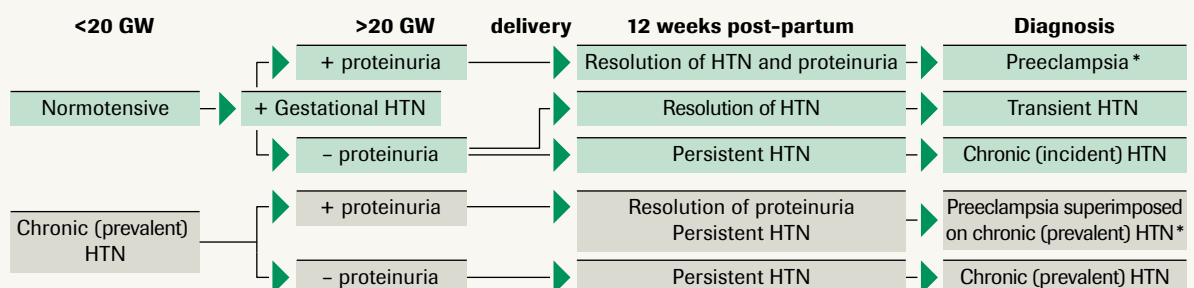
Medical value of Elecsys Preeclampsia immunoassays

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 PE 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.¹⁶

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 PE than normotensive women.^{16,17,18}

Hypertensive pregnancy disorders: classification and diagnostic criteria¹⁹



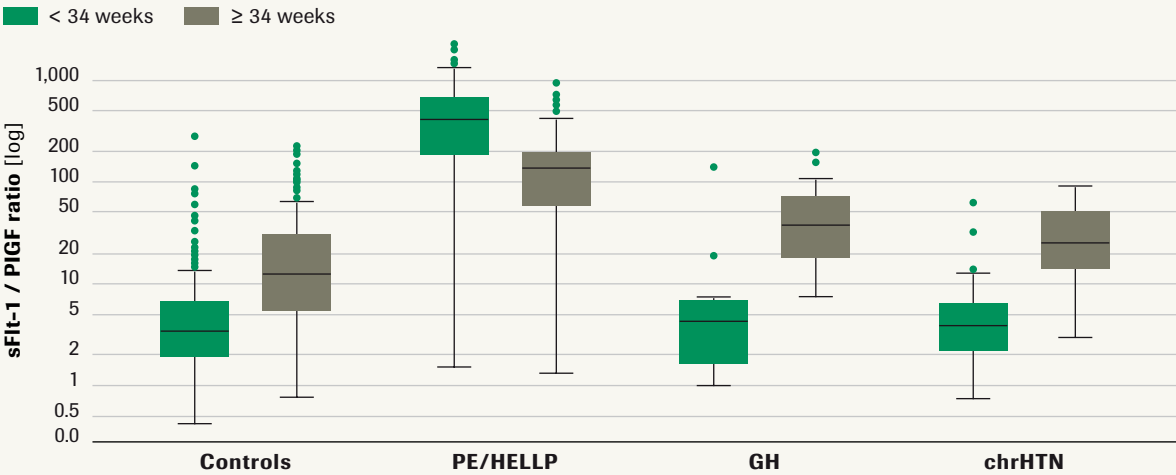
* The diagnosis of eclampsia, a convulsive form of preeclampsia, is based on new-onset seizures, in the absence of a previous history of a seizure disorder. (GW = gestational weeks; HTN = hypertension)



Angiogenic factors can support in the differential diagnosis of preeclampsia

A study showed that the measurement of the sFlt-1/PIGF ratio can differentiate between different forms of hypertensive disorders. Women with preeclampsia or HELLP had significantly higher sFlt-1/PIGF ratios than women with gestational hypertension, chronic hypertension or no hypertensive disorder at all ($p < 0.001$).¹⁷

Another study showed that the sFlt-1/PIGF ratio may facilitate the diagnosis of superimposed PE in women with chronic hypertension.¹⁸



*sFlt-1/PIGF ratio in PE/HELLP, GH, chrHTN, and healthy controls¹⁷
(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 PE, however, it has limited predictive value.²⁰

Combining Doppler sonography and biomarkers can improve the positive predictive value (PPV) for pre-eclampsia. Combination with biomarkers has been shown to improve the predictive performance of Doppler sonography.²¹

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 required²²

Use of angiogenic biomarkers in the clinical management of PE

PE is associated with a number of serious adverse events, including:²³

- 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/PIGF ratio and a more rapid elevation in the sFlt-1/PIGF ratio are associated with a significantly increased risk for an immediate delivery.^{17,24}

Early-onset PE is associated with a faster shift in the angiogenic balance, resulting in a more rapid elevation in the sFlt-1/PIGF ratio.²⁴

Novel innovative biomarkers

Precise, consistent, reliable

Preeclampsia is a progressive and unpredictable disease that can only be resolved by delivery.

Elecsys sFlt-1 and PIGF immunoassays are the first available and approved automated diagnostic tests for use as an aid in the diagnosis of preeclampsia.

A simple blood test can now deliver clear, reliable results with a specificity of 95 % and a sensitivity of 82 % to help identifying patients at risk for potentially life threatening complications.¹²

This is particularly important to pregnant women but also has implications for the unborn child.

The Elecsys immunoassays allow for objective aid in diagnosis of preeclampsia. They represent another important milestone for women's health.

The sFlt-1 and PIGF biomarkers have the potential to offer major advances in the diagnosis and management of this common and potentially life-threatening condition.

The ratio of sFlt-1 to PIGF has been shown to be a better predictor of preeclampsia than either measure alone.¹⁵

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