Preeclampsia and angiogenic factors
sFlt-1/PlGF ratio in the diagnosis of preeclampsia
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 cause of preeclampsia is not fully understood, but there is growing evidence that angiogenic factors such as placental growth factor (PIGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) play a major role in the development of the disease.

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 PIGF, a pro-angiogenic protein, predict subsequent development of preeclampsia.

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.
During normal pregnancy, sFlt-1 and PIGF are involved in placental vascular remodelling

During fetal development, the human placenta undergoes high levels of both angiogenesis and vasculogenesis. The initiation, maturation, and maintenance of the placental vasculature are of critical importance. Failure to do so can lead to adverse obstetric outcomes such as preeclampsia and/or intrauterine growth restriction (IUGR).

Studies show that the first step in the building of the vascular network is mediated by the vascular endothelial growth factor (VEGF) family, which includes PIGF and the VEGF family receptor sFlt-1. PIGF is expressed in the placenta and is proangiogenic; sFlt-1 binds PIGF and can inhibit its activity.

In preeclampsia patients:
- sFlt-1 and soluble endoglin (sEng) levels are increased prior to clinical symptoms and also correlate with the severity of the disease
- PIGF levels are significantly decreased

Several recent clinical studies suggest that angiogenic biomarkers such as sFlt-1 and PIGF may serve to diagnose and predict preeclampsia and its related complications. In addition, depleting or antagonizing sFlt-1 and sEng in the maternal circulation may prove to be a valuable approach for preeclampsia treatment.

The angiogenic and antiangiogenic factors soluble fms-like tyrosine kinase (sFlt-1) and placental growth factor (PIGF) have been implicated in the mechanisms of disease responsible for preeclampsia. Moreover, it has been proposed that the concentrations of these markers in maternal serum/plasma may have predictive value.

This study evaluates the Elecsys ® assay for sFlt-1 and PIGF and tests the value of the sFlt-1/PIGF ratio in the assessment of preeclampsia.

Elecsys automated assays allow fast and easy assessment of sFlt-1, PIGF and the sFlt-1/PIGF ratio in a clinical context. The sFlt-1/PIGF ratio has a superior diagnostic ability compared to either of the biomarkers alone. Calculation of the sFlt-1/PIGF ratio can assess preeclampsia with high sensitivity and specificity.

The sFlt-1/PIGF ratio may be of value in the prediction of PE and in the differential diagnosis of patients with atypical presentations of preeclampsia, and in the differential diagnosis of women with chronic hypertension suspected to develop superimposed preeclampsia.
Second trimester sFlt-1/PIGF is particularly useful in the prediction and diagnosis of preeclampsia

The clinical impact of preeclampsia on the mother and child can be severe and the cost to society is immense.

The pathogenesis of the disease is not well understood:
• Hypoxia caused by defective placentation is a key event in preeclampsia. Placental ischemia/hypoxia probably triggers the altered angiogenic balance, promoting the anti-angiogenic state
• Dysregulation of angiogenesis is not only implicated in inducing the maternal syndrome, but is also involved in the altered placentation

Prediction and diagnosis: Studies have shown that sFlt-1, sEng and PIGF could be suitable biomarkers for preeclampsia prior to the development of the disease. Second trimester sFlt-1/PIGF ratio was found to be useful as an aid in the prediction and diagnosis of preeclampsia. The addition of sFlt-1/PIGF to Doppler ultrasound was found to improve the sensitivity and specificity of Doppler ultrasound alone.

Importance of risk assessment: Intensified monitoring and referral to a specialized center could reduce maternal and fetal morbidity. Therefore the identification of a reliable identifier could be of particular importance.
An imbalance of angiogenic markers correlates with the severity of preeclampsia symptoms and can be detected well before clinical signs and symptoms appear.

Recent studies on the use of angiogenic markers in preeclampsia prediction have shown that:

- the sFlt-1/PlGF ratio is a better predictor than either of these parameters alone
- sequential changes in the concentrations of sFlt-1, PlGF and sEng may be more informative than single measurements
- the addition of angiogenic marker measurements can improve the predictive value of Doppler ultrasound alone

There is a more pronounced alteration of angiogenic factors in early-onset compared with late-onset preeclampsia. In the second trimester the sFlt-1/PlGF ratio may be ideal parameter to diagnose early-onset preeclampsia (< 34 weeks) or preterm preeclampsia (< 37 weeks).

Angiogenic markers, in particular sFlt-1/PIGF, have been shown to be useful in the differential diagnosis of hypertensive disorder of pregnancy and in predicting the development of adverse outcomes and preterm delivery.

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- sequential changes in the concentrations of Flt-1, PlGF and sEng may be more informative than single measurements
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Angiogenic markers, in particular sFlt-1/PlGF, have been shown to be useful in the differential diagnosis of hypertensive disorder of pregnancy and in predicting the development of adverse outcomes and preterm delivery.

sFlt-1 and PlGF were measured in 388 singleton pregnancies with normal pregnancy outcome, 164 with preeclampsia, 36 with gestational hypertension and 42 with chronic hypertension. Patients with preeclampsia had a significantly increased sFlt-1/PlGF ratio as compared with controls and with patients with chronic and gestational hypertension in <34 weeks and >34 weeks (P < .001). Time to delivery was significantly reduced in women with preeclampsia in the highest quartile of the sFlt-1/PlGF ratio (P < .001).

The sFlt-1/PlGF ratio may therefore have clinical value for clinical management, counseling and risk anticipation. A timely referral to a perinatal care center alone is able to reduce perinatal morbidity and mortality by 20%. Using the sFlt-1/PIGF ratio might help to reduce morbidity and mortality by enabling early individualized risk stratification.

In preeclampsia/HELP the sFlt-1/PIGF ratio is significantly higher than in other Hypertensive Disorders in pregnancy and controls and indicates an increased risk of imminent delivery.

The diagnosis of preeclampsia is based on the non-specific signs of hypertension and proteinuria, but the presence and severity of these features are poorly predictive of complications. A disease-specific biomarker accurately predicting maternal/neonatal complications in suspected preeclampsia would facilitate the decision-making of clinicians regarding monitoring/treatment.

Soluble fms-like tyrosine kinase-1 (sFlt1), placental growth factor (PIGF), and soluble endoglin (sEng) were measured in maternal serum samples prospectively collected from 276 women with suspected preeclampsia at the time of initial presentation to hospital triage with signs or symptoms of preeclampsia. sFlt1, PIGF, and sEng were significantly different in women who developed maternal and neonatal complications as compared to women without complications. Higher levels of sFlt1, sEng, and the sFlt1/PIGF ratio were associated with an increased odds of complications among women presenting prior to 37 weeks.

A multivariable model combining the sFlt1/PIGF ratio with clinical variables was more predictive of complications (AUC 0.91, 95% CI 0.85 – 0.97) than a model using clinical variables alone (AUC 0.82, 95% CI 0.79 – 0.90).

Addition of sFlt-1/PIGF ratio to a clinical multivariate model improves its performance for predicting complications

Preeclampsia is the leading indication for premature delivery of a fetus and is therefore associated with substantial neonatal morbidity and mortality, as well as considerable healthcare expenditure.

sFlt-1/PIGF was measured at presentation in 616 women who were evaluated for suspected preeclampsia. Women with preeclampsia had a higher sFlt-1/PIGF ratio than women with other hypertensive disorders and significantly more so than controls, particularly when presenting at < 34 weeks. Women with any subsequent adverse outcome had a significantly higher sFlt-1/PIGF ratio than those who did not (median [25th – 75th centile]: 47.0 15.5 – 112.2], n = 268 versus 10.8 [4.1 – 28.6 ], n = 348; p < 0.001). This relationship was even stronger in women presenting at < 34 weeks.

In women with suspected preeclampsia presenting at 34 weeks, circulating sFlt1/PIGF ratio predicts adverse outcomes occurring within 2 weeks. The accuracy of this test is substantially better than that of current approaches and may be useful in risk stratification and management.

Preeclampsia is a devastating medical complication of pregnancy associated with significant maternal and fetal morbidity and mortality. The risk is highest in very preterm (<32 weeks) preeclampsia when the infant mortality rate is 70 times higher than at term. Delivery of the placenta remains the only effective means to treat preeclampsia. Targeted therapies to stabilize the clinical manifestations and prolong pregnancy in preeclampsia do not exist.

In this pilot study, it was demonstrated that a single dextran sulfate cellulose apheresis treatment reduces circulating sFlt-1 levels in a dose-dependent fashion. 3 women with very preterm preeclampsia (gestational age at admission 28, 30 and 27+4 weeks) and elevated circulating sFlt-1 levels were treated with multiple apheresis. Dextran sulfate apheresis lowered circulating sFlt-1, reduced proteinuria and stabilized blood pressure without apparent adverse events to mother and fetus. Pregnancy lasted for 15 and 19 days in women treated twice and 23 days in a woman treated 4 times. In each, there was evidence of fetal growth.

Elecsys® sFlt-1 and Elecsys® PlGF from Roche

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. 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.

<table>
<thead>
<tr>
<th>Technical assay features of Elecsys® sFlt-1 and PIGF</th>
<th>sFlt-1</th>
<th>PIGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total duration</td>
<td>18 minutes</td>
<td></td>
</tr>
<tr>
<td>Assay principle</td>
<td>Immunoassay based on ECLIA</td>
<td></td>
</tr>
<tr>
<td>Sample volume</td>
<td>20 μL</td>
<td>50 μL</td>
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<tr>
<td>Measuring range</td>
<td>serum</td>
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<tr>
<td>Measuring range</td>
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<td>2 – 10,000 pg/mL</td>
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<tr>
<td>Analytical sensitivity</td>
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<td>&lt; 2pg/mL</td>
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<tr>
<td>Kit size</td>
<td>100 determinations</td>
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Elecsys® sFlt-1 package insert (2013), Roche Diagnostics Documentation, Basel
Elecsys® PlGF package insert (2013), Roche Diagnostics Documentation, Basel
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