Preeclampsia and angiogenic factors

sFlt-1/PlGF ratio in the diagnosis of preeclampsia

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Life needs answers

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 (PlGF) 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 PlGF, a pro-angiogenic protein, predict subsequent development of preeclampsia.

The sFlt-1 and PlGF 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 PlGF 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 PlGF and the VEGF family receptor sFlt-1. PlGF is expressed in the placenta and is proangiogenic; sFlt-1 binds PlGF 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
- PlGF levels are significantly decreased

Several recent clinical studies suggest that angiogenic biomarkers such as sFlt-1 and PlGF 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.

Cerdeira, A.S. & Karumanchi, S.A. (2012). Angiogenic factors in preeclampsia and related disorders. Cold Spring Harb Perspect Med; 2(11): pii:a006585.

The sFlt-1/PlGF ratio can be used as an additional diagnostic tool for preeclampsia

Verlohren, S. et al. (2010). An automated method for the determination of the sFlt-1/PlGF ratio in the assessment of preeclampsia. Am J Obstes Gynecol; 202:161.e1-11.

The angiogenic and antiangiogenic factors soluble fms-like tyrosine kinase (sFlt-1) and placental growth factor (PlGF) 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 PlGF and tests the value of the sFlt-1/PlGF ratio in the assessment of preeclampsia.

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

The sFlt-1/PlGF 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/ PlGF 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 PlGF could be suitable biomarkers for preeclampsia prior to the development of the disease. Second trimester sFlt-1/PlGF ratio was found to be useful as an aid in the prediction and diagnosis of preeclampsia. The addition of sFlt-1/PlGF 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.

Verlohren, S., Stepan, H., Dechend, R. (2012). Angiogenic growth factors in the diagnosis and prediction of pre-eclampsia. Clin Sci (Lond); 122(2),43-52.

Angiogenic markers may be useful in the prediction, diagnosis and prognosis of preeclampsia

Hagmann, H. et al. (2012). The promise of angiogenic markers for the early diagnosis and prediction of preeclampsia. Clin Chem; 58(5), 837-45.

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/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.

In preeclampsia/HELPP the sFlt-1/PlGF ratio is significantly higher than in other Hypertensive Disorders in pregnancy and controls and indicates an increased risk of imminent 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/PlGF ratio might help to reduce morbidity and mortality by enabling early individualized risk stratification.

Verlohren, S. et al. (2012). The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. Am J Obstet Gynecol; 206, 58.e1-8.

Addition of sFlt-1/PlGF ratio to a clinical multi-variate model improves its performance for predicting complications

Moore, A.G. et al. (2012). Angiogenic biomarkers for prediction of maternal and neonatal complications in suspected preeclampsia. J Matern Fetal Neonatal Med; 25(12), 2651-2657.

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 (PlGF), 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, PlGF, 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/PlGF ratio were associated with an increased odds of complications among women presenting prior to 37 weeks.

A multivariable model combining the sFlt1/PlGF 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).

The sFlt-1/PlGF ratio correlates with a higher risk of adverse outcomes and imminent delivery

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/PlGF was measured at presentation in 616 women who were evaluated for suspected preeclampsia. Women with preeclampsia had a higher sFlt-1/PlGF 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/PlGF 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/PlGF 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.

Rana, S. et al. (2012). Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. Circulation; 125(7), 911-9.

Removing sFlt-1 may benefit women with very preterm (<32 weeks) preeclampsia

Thadhani, R. et al. (2011). Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. Circulation; 124(8), 940-50.

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

Technical assay features of Elecsys® sFlt-1 and PlGF

	sFlt-1	PlGF
Total duration	18 minutes	
Assay principle	Immunoassay based on ECLIA	
Sample volume	20 µL	50 µL
Sample material	serum	
Measuring range	6 – 85,000 pg/mL	2 – 10,000 pg/mL
Analytical sensitivity	Approx. 6 pg/mL	< 2pg/mL
Kit size	100 determinations	

Elecsys® sFlt-1 package insert (2013), Roche Diagnostics Documentation, Basel
Elecsys® PlGF package insert (2013), Roche Diagnostics Documentation, Basel

Roche Diagnostics International Ltd
CH-6343 Rotkreuz
Switzerland
www.cobas.com