Angiogenic factors in preeclampsia: diagnosis, prediction and impact on clinical management
20th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI)
New clinical trial data showing how the Elecsys® immunoassay sFlt-1*/PIGF# ratio can be used to improve clinical management of women with suspected preeclampsia were presented for the first time at the 20th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI) in Paris (December 4–7, 2014).

Underlining the predictive power of the sFlt-1/PIGF ratio in preeclampsia management, Professor Shaun Brennecke, co-chair of the Roche-sponsored symposium, Angiogenic factors in preeclampsia: diagnosis, prediction and impact on clinical management, highlighted the careful design and meticulous performance of the new preeclampsia studies – PROGNOSIS** and PreOS^:

“PROGNOSIS has an excellent negative predictive value that allows us to rule out preeclampsia and its complications in the heterogeneous group of patients who present to us, and the positive predictive value gives us the best available data to help us pick out high risk patients who need close surveillance,” said Professor Brennecke, from the Royal Women’s Hospital, Victoria, Australia.

“PreOS has given us information about the clinical utility of knowledge of this ratio which enables us to intervene less in patients who do not need interventions and focus on those who most need them, so we can move forward in our clinical practice,” he added.

“Results from the PROGNOSIS study mark a significant step forward in the prediction of preeclampsia,” said Professor Harald Zeisler, Department of Obstetrics and Gynecology at Medical University Vienna, Austria. “The Elecsys preeclampsia test allows physicians to predict the short term absence and manifestation of preeclampsia. Its application in clinical practice has the potential to reduce fetal and maternal morbidity and mortality as well as to avoid unnecessary hospitalizations.”

Footnotes:
* sFlt-1: soluble fms-like tyrosine kinase-1
# PIGF: placental growth factor
**: PRediction of short-term Outcome in preGNant wOmen with Suspected preeclampsia Study
^: Preeclampsia Open Study
sFlt-1/PIGF thresholds indicate preeclampsia risk

Angiogenic factors play a key role in the pathogenesis of preeclampsia, and a high sFlt-1/PIGF ratio can be used to confirm the diagnosis of preeclampsia and predict adverse outcomes in women with the condition.

Summing up nearly 15 years of research showing the importance of the sFlt-1/PIGF ratio, Dr Elisa Llurba, from the Hospital Universitari Vall d'Hebron, Barcelona, Spain, suggested that preeclampsia may need to be redefined in the light of current knowledge about the link with angiogenic factors.

Dr Llurba described the pathophysiological features of endothelial dysfunction that can lead to preeclampsia (Figure 1), and presented results of placental research which demonstrated that rising levels of sFlt-1 and decreasing levels of PIGF are associated with increasing severity of preeclampsia. She also discussed research suggesting that the rise in sFlt-1 and the fall in PIGF are more pronounced in early-onset (<34 weeks) than in late-onset preeclampsia. In addition, the natural rise in sFlt-1/PIGF ratio which occurs in the last weeks of pregnancy means there is greater overlap, at this stage, between ratios seen in healthy pregnancies and those with preeclampsia.

Results of a recently published study showed that, in earlier gestation (20+0-33+6 weeks) an Elecsys® immunoassay sFlt-1/PIGF ratio <33 helped rule out the possibility of preeclampsia or HELLP syndrome while a ratio >85 could confirm the diagnosis. During late gestation, the threshold Elecsys® immunoassay sFlt-1/PIGF ratios to rule out and rule in preeclampsia were <33 and >110 respectively.

Dr Llurba explained that sFlt-1/PIGF ratio is a much better predictor of adverse pregnancy outcome than traditional indicators such as blood pressure or proteinuria. She presented data showing that in women presenting before 34 weeks of pregnancy, the Elecsys® immunoassay sFlt-1/PIGF ratio was a better predictor of adverse outcomes than alanine aminotransferase (ALT), uric acid, systolic blood pressure or creatinine (Figure 2). Delivery occurred within 2 weeks of presentation in 86% of women with a sFlt-1/PIGF ratio > 85 compared with 15.8% of women with a sFlt-1/PIGF ratio < 85.

"We now know that the ratio can be used in the management of established preeclampsia because it enables us to select those women who need more surveillance," concluded Dr Llurba. "Only about 14% of women with a ratio above 85 remained pregnant after 2 weeks, whereas nearly all women with a ratio below 85 remained pregnant for 2 weeks and most of them for 1 month, so this is an important message to take home."

Footnotes:
º: haemolysis, elevated liver enzymes, low platelets
**Figure 1** Pathophysiological features of preeclampsia

**Stage 1**
**DECIDUA**
- Deficient pro-angiogenic factor expression (VEGF, PlGF)
- Low HO1 activity

**Stage 2**
**PLACENTA**
- Abnormal remodelling spiral arteries and trophoblast invasion
- Hypoxia-reoxygenation
- Oxidative damage
- Apoptosis
- sFlt-1
- sEng
- Cytokines

**Stage 3**
**PERIPHERAL VASCULATURE**
- Endothelial dysfunction
- Preeclampsia

HO1, heme oxygenase-1; PlGF, placental growth factor; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase 1; VEGF, vascular endothelial growth factor

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**Figure 2** sFlt-1/PlGF ratio as a predictor of prognosis in established preeclampsia

- sFlt-1/PlGF ratio (0.89)
- ALT (0.62)
- Uric acid (0.79)
- Systolic blood pressure (0.76)
- Creatinine (0.68)
- Reference

ALT, alanine aminotransferase
Angiogenic factors in preeclampsia

PROGNOSIS shows predictive power of sFlt-1/PIGF ratio

The global preeclampsia trial, PROGNOSIS, has shown that an Elecsys® immunoassay sFlt-1/PIGF ratio > 38 is a reliable short-term predictor of preeclampsia/eclampsia/HELLP syndrome in women clinically suspected to be at risk. Results of the study showed that an Elecsys® immunoassay sFlt-1/PIGF ratio > 38 could rule out preeclampsia within 1 week, with a negative predictive value (NPV) of 99.1% and could rule in preeclampsia within 4 weeks with a positive predictive value (PPV) of 38.6%.

"PROGNOSIS provides the missing piece to the preeclampsia research of recent years. Numerous case control studies have shown that sFlt-1/PIGF ratio can diagnose preeclampsia but this is the first to show that the addition of this clinical marker, with its negative predictive value of 99.1%, can give us clinical certainty," said PROGNOSIS investigator, Dr Stefan Verlohren, from the Charité – Universitätsmedizin, Berlin, Germany.

PROGNOSIS was a multicentre, prospective, double-blind, non-interventional clinical trial carried out in 32 centres in North and South America, Europe and Australasia.

Primary objectives of PROGNOSIS were to investigate whether:\n
• Low ratios of sFlt-1/PIGF predict absence of preeclampsia/eclampsia/HELLP syndrome for 1 week after the baseline visit ("rule-out")
• High ratios of sFlt-1/PIGF predict diagnosis of preeclampsia/eclampsia/HELLP syndrome within 4 weeks after the baseline visit ("rule-in")

The secondary objective of PROGNOSIS was to:\n
• Collect evidence that low ratios of sFlt-1/PIGF correlate with absence (within 1 week of baseline visit), and high ratios correlate with presence (within 4 weeks) of maternal preeclampsia-related adverse outcomes (other than preeclampsia/eclampsia/HELLP syndrome, which is included in the primary objective) or fetal preeclampsia-related adverse outcomes

Dr Verlohren presented outcomes on 1050 women (gestational age 24 weeks+0 days to 36 weeks+6 days) recruited to PROGNOSIS on the basis of clinical suspicion of preeclampsia (blood pressure or proteinuria or other symptoms or preeclampsia related findings). The overall prevalence of preeclampsia at any stage during the study was 19%.

Patients who developed preeclampsia within 1 or 4 weeks after sFlt-1/PIGF testing had a higher ratio than those who did not develop the condition.
Elecsys® sFlt-1/PIGF test results impact on clinical decisions

Knowing the Elecsys® immunoassay sFlt-1/PIGF ratio of a woman with suspected preeclampsia does affect a clinician’s decision whether to hospitalize her or send her home, according to results of PreOS, a multicentre, prospective, open label study, reported by Professor Holger Stepan, from the University Hospital, Leipzig, Germany.

Clinical decisions on 118 patients with suspicion of preeclampsia were analysed before and after determination of the sFlt-1/PIGF ratio to identify the impact of results on chosen interventions, such as induction of delivery or fetal lung maturation, and requests for further diagnostic and therapeutic procedures. Test results were also used to assess the ability of the sFlt-1/PIGF ratio to predict adverse outcomes of preeclampsia, eclampsia and HELLP syndrome, and other preeclampsia-related adverse outcomes in mothers and neonates.

Professor Stepan reported that, after clinicians had the results of Elecsys® immunoassay sFlt-1/PIGF ratio, the most likely changes in decisions related to requests for additional laboratory tests, ultrasound examination, patient monitoring and hospitalisation. Clinicians were more likely to ‘step down’ their earlier decisions for more interventions or procedures than to ‘step up’ their plans for patient management.

“This means that if we implement the ratio in clinical decision making, it can help us concentrate our actions and resources on the patients at greatest risk of preeclampsia,” pointed out Professor Stepan.

When decisions about hospitalisation were related to sFlt-1/PIGF ratios, it was shown that clinicians were more likely to hospitalise patients with a high ratio and to send them home if the ratio was low.

“It was particularly important to see that when physicians changed their decision to hospitalise from ‘yes’ to ‘no’, this was in patients with a low ratio, so the change was made in the right patients,” said Professor Stepan.

He concluded that the test results changed decision making in almost 17% of patients and high sFlt-1/PIGF ratios were associated with increased admission to hospital:

“The test guides appropriate hospitalisation and enables us to focus our activities on those patients who need them most, and to save our resources and costs.”
Introducing sFlt-1/PlGF testing in clinical practice has potential for considerable cost savings, according to results of cost effectiveness analyses carried out in the UK and Spain, presented at COGI 2014.

Data from the UK cost effectiveness analysis based on PROGNOSIS data showed a likely 50% reduction in hospitalisation prior to preeclampsia diagnosis and suggested a cost saving of £399 per patient (not including neonatal intensive care [NICU] costs) if Elecsys® immunoassay sFlt-1/PlGF testing is used in clinical practice.

The study predicted that 41% of women hospitalised for suspected preeclampsia on the basis of a sFlt-1/PlGF test would go on to develop the condition, compared to 26% of untested women.

In the Spanish analysis, also using PROGNOSIS data, researchers predicted a 34% reduction in hospitalisation prior to preeclampsia diagnosis, leading to a cost saving of €228 per patient (not including NICU costs).

The model predicted that 64% of women hospitalised following a sFlt-1/PlGF test would develop preeclampsia, compared with 26.9% hospitalised without a test.

In calculating costs, both the UK and Spanish analyses took account of the potential for more emergency and neonatal intensive care unit (NICU) admissions if routine hospitalisation for suspected preeclampsia was reduced. But the potential costs of such admissions were outweighed by the lower costs related to fewer routine admissions.
In clinical practice

A woman with a high Elecsys® immunoassay sFlt-1/PIGF ratio in the absence of maternal or fetal indications should not automatically be sent for immediate delivery, but the test result can guide management decisions over subsequent days and weeks.

At a ‘Meet the Expert’ session at the conference, preeclampsia specialists presented a series of case studies illustrating the dilemmas faced in daily clinical practice. Contributors focused on the need to take account of maternal, gestational and practical factors when deciding how to respond to sFlt-1/PIGF test results.

For example, serial sFlt-1/PIGF measurements may be needed before deciding whether to send some patients home, and clinicians also need to take account of access to emergency treatment if a woman does deteriorate after being sent home. Thus, on a Friday afternoon, an obstetrician may prefer to deliver a woman with a very high sFlt-1/PIGF ratio, but few or no other indications, rather than risk her needing an emergency C-section on a Sunday carried out by a non-specialist physician.

Gestational age may also affect decisions, as prompt delivery may be more appropriate for a fetus at late stage gestation than at an earlier stage of pregnancy.

Meet the Expert panel: Prof Holger Stepan, University of Leipzig, Hospitals and Clinics, Germany; Dr Elisa Llurba, Vall d’Hebron University Hospital, Barcelona, Spain; Dr Stefan Verlohren, Charité University Medicine, Berlin, Germany; Prof Sean Brennecke, Royal Women’s Hospital, Melbourne, Australia; and Prof Harald Zeisler, Medical University, Vienna, Austria.

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References


Legend

Figure 1. Pathophysiological features of preeclampsia Adapted from Chaiworapongsa, T. et al. Nat. Rev. Nephrol. 10, 466–480 (2014)

Figure 2. sFlt-1/PlGF ratio as a predictor of prognosis in established preeclampsia. Adapted from Rana S, et al. Circulation 2012:125:911–9.