Women's Health Newsletter No. 01/2016
Preeclampsia updates: PROGNOSIS study and literature review

FAQ on the PROGNOSIS Study

Why the PPV and NPV reported in the publication are different from the data in the Method Sheet?

In the Method Sheets for sFlt-1 and PlGF we reported the following PPV and NPV for the cut-off 38 calculated using the **entire patient population of the PROGNOSIS Study (1,050 women).**

Short-term prediction of preeclampsia – RULE-OUT for 1 week	
sFlt-1/PlGF ratio	<38
NPV	**99.1%**

Short-term prediction of preeclampsia – RULE-IN for 4 weeks	
sFlt-1/PlGF ratio	**>38**
PPV	**38.6 %**

In the publication process, the reviewers from the New England Journal of Medicine required a separate analysis for NPV and PPV separating the 2 cohorts of patients: development cohort (500 women) and validation cohort (550 women). The PPV and NPV reported in the publication abstract are referring **only to the validation cohort**

Short-term prediction of preeclampsia – RULE-OUT for 1 week	
sFlt-1/PlGF ratio	<38
NPV	**99.3%**

Short-term prediction of preeclampsia – RULE-IN for 4 weeks	
sFlt-1/PlGF ratio	**>38**
PPV	**36.7%**

Are these data valid for all ethnicities?

The PROGNOSIS study recruited patients in Europe, Latin America, Australia, New Zealand and Canada. Most of the women were Caucasians so the performance data are validated in this patient group. Limited data are available for other ethnicity.
Currently the PROGNOSIS Asia study is ongoing with the objective to validate the PROGNOSIS cut-off in the Asian population.

Are this cut-off and performance data valid for multiple pregnancies?

No, multiple pregnancies were excluded from the anylisis and therefore the cut-off and performance data are valid for singleton pregnancies.
78 women with multiple pregnacies were included in the PROGNOSIS study and their data will be analysed in the next future and will probably be the content for a new publication.

Do we have data for the cut-off 38 and time to delivery?

In the supplementary Appendix of the study (available on line: **link**) the data for time to delivery from the time of testing according to the sFlt-1/PlGF ratio cut-off of 38 are reported - Supplementary Figure S7.
This analysis shows that women with a higher sFlt-1/PlGF ratio have a shorter time to delivery compared with women with a ratio <38. Time to delivery will be the focus of a second publication from the PROGNOSIS study that is currently in submission.

Can the ratio predict maternal or fetal adverse outcomes even without preeclampsia?

Yes, this is one of the interesting data from the PROGNOSIS analysis. An sFlt-1/PlGF ratio cutoff point of 38 or lower also had value in predicting the absence of fetal adverse outcomes within 1 week, as well as the absence of the combined end point of preeclampsia or adverse maternal or fetal outcomes within 1 week. In the supplementary Appendix of the study (available on line: **link**) the data for the prediction of the combined endpoint (Preeclampsia / eclampsia / HELLP syndrome, maternal adverse outcomes and/or fetal adverse outcomes)are reported - Supplementary Figure S8 and S9. The data are showing that the ratio is higher in pregnancies developing adverse outcomes. This is the case even in patients that sis not develop preeclampsia but had adverse outcomes.

Can the ratio exclude preeclampsia for more than 1 week?

The study wa spowered to validate the exclusion of preeclampsia for 1 week and the NPV reported is referring to the prediction for one week. We calculated NPV also for the exclusion of preeclampsia for longer periods but these data are not reported in the PROGNOSIS publication. Extending the prediction period reduced the NPV that remains however >95% up to 4 weeks.

PPV of 36.7% seems low: how can we explain this result?

It is very important that this result is considered in the right context. Today the only available tools for prediction of preeclampsia in suspected patients are measurements of blood pressure and proteinuria. The observed positive predictive value of the sFlt-1/PlGF ratio represents an improvement in prediction, as compared with clinical variables in post hoc analyses. Assessment for proteinuria and measurement of blood pressure have a reported positive predictive value of only 20% in detecting preeclampsia-related adverse outcomes. This means that with the sFlt-1/PlGF ratio the predictive performance is almost double the current standard.

What happened to the 0.7% of patients with a ratio <38 that did develop preeclampsia in the next week?

In the study a small group of patients had a sFlt-1/PlGF ratio below 38 but developed preeclampsia in the next 1 week. These cases were reviewed in details by the investigators and all these patients developed preeclampsia (as defined with blood pressure and proteinuria) but they didn't develop any adverse outcome requiring emergency actions in this period. Therefore, even if ruled-out based on the ratio, there was no risk for these patients.

Are these data only valid for the Elecsys® sFlt-1/PlGF ratio?

Yes, the study clearly states that the data are based on the Elecsys® sFlt-1/PlGF ratio. Also in the Editorial by Ellen W. Seely and Caren G. Solomon "Improving the Prediction of Preeclampsia" **(link)** they clearly state that the study was performed using the Elecsy® sFlt-1/PlGF assays.
Competitors cannot propose the same cut-off unless they run a similar study to validate that this cut-off can achieve the same performance (this would require years).

Preeclampsia literature review Q3-Q4 2015

This new Preeclampsia Literature review covers the key scientific papers on Preeclampsia published between May and November 2015. In this review you will find the summary of 7 original research publications and 1 review. The slides are available on the Preeclampsia intranet page **link**
For a quick overview, before each article you will find the "Key points for Roche" box with the key take-away from the paper.

Prediction of Preeclampsia

- Pregnant women with systemic lupus erythematosus (SLE) who later develop PE (early- or late-onset) have significantly higher sFlt-1/PlGF ratios compared to normal SLE pregnancies from week 12 onwards[1]
- The risk to develop PE in SLE pregnancies progressively increases with the increase of serum sFlt-1/PlGF ratio[1]
- Serum sFlt-1/PlGF ratio measured from week 12 onwards can be used to predict the onset of PE in SLE pregnancies[1]
- Angiogenic-related factors measured between 24 and 34 weeks can identify the majority of mothers diagnosed with sSGA who subsequently develop PE or those who require preterm delivery ≤ 34 weeks[2]
- Use of angiogenic-related factors in addition to clinical and Doppler parameters significantly improves PE and preterm delivery risk assessment[2]
- For preterm PE screening, PlGF is a useful marker from the 1st trimester and sFlt-1 from the 2nd trimester[3]
- Repeat measurements of sFlt-1, PlGF and sFlt-1/PLGF ratio are likely to be better predictors of PE than measurement at a single time point in pregnancy[3]

[1]Leaños-Miranda, A., Campos-Galicia, I., et al. (2015) *J Rheumatol* 42(7):1141-1149
[2]Chaiworapongsa, T., Romero, R., et al. (2015) *J Matern Fetal Neonatal Med.* [Epub ahead of print]
[3]Khalil, A., Maiz, N., et al. (2015) *Ultrasound Obstet Gynecol.* [Epub ahead of print]

Prognosis of Preeclampsia

- In pregnant Haitian women, PE-related adverse outcomes are significantly increased in pregnancies with early-onset PE compared to those with late-onset PE[1]
- Increased sFlt-1/PlGF ratio is associated with
  - Incidence of early- and late-onset PE[1]
  - PE-related adverse outcomes[1]
- A combination of biophysical and biochemical markers (serum sFlt-1 and PlGF) tested at 30-34 and 35-37 weeks can be used to predict the occurrence of PE, small for gestational age (SGA), and the need for Caesarean sections due to fetal stress before birth[2,3]
- In pregnancies without PE or SGA, adverse events during labour or after birth (including stillbirth) are poorly predicted by this combination of biomarkers[2,3]

[1]March, M.I., Geahchan C., et al. (2015) *PLoS One* 10(5):e0126815
[2]Valiño, N., Giunta, G., et al. (2015) *Ultrasound Obstet Gynecol*. [Epub ahead of print] doi: 10.1002/uog.14928
[3]Valiño, N., Giunta, G., et al. (2015) *Ultrasound Obstet Gynecol*. [Epub ahead of print] doi: 10.1002/uog.15663

Treatment of Preeclampsia

- Therapeutic apheresis reduced circulating sFlt-1 and proteinuria in women with very preterm PE (23-32 weeks)
- Therapeutic apheresis appeared to prolong pregnancy in women with very preterm PE without major adverse maternal or fetal outcomes

Thadhani, R., Hagmann, H., et al. (2015) *J Am Soc Nephrol*. [Epub ahead of print]

Review

- sFlt-1/PlGF supports diagnosis and prognosis of placental-dysfunction (PD) related diseases
- Using risk factors, uterine artery Doppler and sFlt-1/PlGF can improve selection of PD patients for intensive care
- The use of sFlt-1/PlGF for the early diagnosis and management of PD patients might be cost-effective and beneficial for the mother and fetus

Herraiz, I., Simón, E., Gómez-Arriaga, P.I., et al. (2015) *Int J Mol Sci 16*(8),19009-19026.

We hope the information in this Newsletter is useful for your local activities and we remain at your disposal to support you!

Please let us know if additional colleagues should be included in the distribution list. Any feedback on how to improve this Newsletter is very welcome!

Kind Regards

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