The role of sFlt-1/PlGF in preeclampsia

Alex Lefèvre
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- sFlt-1 and PlGF in testing for PE

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Pregnancies in Belgium

Complications of pregnancy in Belgium.

Data about Belgium*

128,000 single deliveries in Belgium (2011)

19 of the 106 maternity hospitals have MIC (Maternal Intensive Care) beds (7 are imbedded in a university setting).

In Belgium, 27.8% of all deliveries occur in MIC services.

Complications of pregnancy in Belgium.

A maternal death rate of 4.5 to 6.0 /100,000

50% of all obstetric ICU admissions are related either to preeclampsia or to haemorrhage (2006)

Mild or unspecified pre-eclampsia: 1.5% (data IMA 2004).

Source: *KCE 2008 & 2014, Zeeman et al. 2006
Patient flow

Total number of pregnancies

At risk of PE

Not at risk

Symptomatic

Asymptomatic

Patient has PE/HELLP syndrome

Patient does not have PE/HELLP syndrome

Patient has PE/HELLP syndrome

Patient does not have PE/HELLP syndrome

SCREENING

EARLY-ONSET PREDICTION

1st trimester

100% of pregnancies

EARLY-ONSET PREDICTION

At risk

25% of pregnancies

SHORT-TERM PREDICTION

Symptomatic

20% of pregnancies *

DIAGNOSIS

PREDICTION OF ADVERSE OUTCOMES

5% of pregnancies **

CONTINUUM OF CARE

Source: Adapted from market research 2011 by UBC

* Aid in short-term prediction: 60% x 25% + 7% x 75% = 20.3% of pregnancies

** Aid in diagnosis and prediction of adverse outcomes: 25% x 60% x 27% + 75% x 7% x 20% = 5.1% of pregnancies
## Preeclampsia overview: current situation

### Pregnancy timelines & preeclampsia indications

<table>
<thead>
<tr>
<th>Trimesters</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; trimester</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; trimester</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; trimester</th>
</tr>
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<tbody>
<tr>
<td><strong>Preeclampsia</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
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<td><strong>Markers</strong></td>
<td>PlGF &amp; PAPP-A</td>
<td>sFlt-1/PlGF ratio</td>
<td></td>
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<tr>
<td><strong>Indications</strong></td>
<td>Screening for early-onset PE (in combination with Down's Syndrome)</td>
<td>1) Aid in diagnosis of PE in suspected patients 2) Short-term prediction of PE (1 week rule-out &amp; 4 weeks rule-in)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment options</strong></td>
<td>Low-dose aspirin</td>
<td>Closer follow-up and monitoring; MgSO₄ or corticosteroid treatment; induction of birth; apheresis (pregnancy extended through sFlt-1 removal)*</td>
<td></td>
</tr>
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MgSO₄: Magnesium sulfate; PAPP-A: Pregnancy-associated plasma protein A

*all under development*
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Biomarkers in preeclampsia diagnosis

Improving diagnostic ability

The *angiogenic* (placental growth factor) **PlGF** and *anti-angiogenic* (soluble fms-like tyrosine kinase receptor-1) **sFlt-1** are biomarkers closely related to placental dysfunction\(^1,2,3\)

\(^3\) Chaiworapongsa, T., et al. (2014). *Nat Rev Nephrol* 10, 466–480

VEGF: Vascular endothelial growth factor
Imbalance in the concentrations of sFlt-1 and PlGF

Detectable prior to the onset of preeclampsia

sFlt-1 concentrations increase approx. 5 weeks before the onset of PE

PlGF concentrations decrease 11-9 weeks prior to onset, with a substantial decrease 5 weeks before onset of PE

PlGF levels are decreased in affected individuals

The data as obtained for all samples of cases (■) and controls (□) are shown in the scatter plots below.
sFlt-1 levels are elevated in affected individuals

The data as obtained for all samples of cases (■) and controls (□) are shown in the scatter plots below.
The ratio of sFlt-1/PlGF

The data as obtained for all samples of cases (■) and controls (□) are shown in the scatter plots below.
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Patient flow

CONTINUUM OF CARE

SCREENING

EARLY-ONSET PREDICTION
1st trimester
100% of pregnancies

EARLY-ONSET PREDICTION
At risk
25% of pregnancies

SHORT-TERM PREDICTION
Symptomatic
20% of pregnancies *

DIAGNOSIS

PREDICTION OF ADVERSE OUTCOMES

5% of pregnancies **

PIGF & PAPP-A

Gestational week
12
Early screening with PIGF measurement weeks 11-13+
Aspirin therapy must be started by week 16

20
Development of maternal blood supply to placenta complete
PE symptoms start to appear

34
Pre-eclampsia and premature delivery delayed or prevented

sFlt-1/PIGF

CURRENT CLAIMS
UNDER ASSESSMENT

Roche

29 November 2015  page 13  © 2014 Roche
The Elecsys®® sFlt-1/PlGF assay

Aid in the differential diagnosis of preeclampsia

- The sFlt-1/PlGF ratio can aid in the differentiation between different forms of hypertensive disorders

- **Women with PE or HELLP syndrome had significantly higher sFlt-1/PlGF ratios (p < 0.001)** than women with:
  - Gestational hypertension (GH),
  - Chronic hypertension (chrHTN) or
  - No hypertensive disorder at all (controls)

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The Elecsys® sFlt-1/PlGF assay

Aid in prediction of preeclampsia

- sFlt-1/PlGF better than the markers alone for the prediction of PE\(^1\)

- sFlt-1/PlGF significantly higher in PE patients weeks prior to PE onset, particularly in early-onset PE\(^2,3\)
  - In particular, sFlt-1/PlGF was found to be higher 4 weeks prior to diagnosis in PE patients\(^3\)
  - When observed in the 2\(^{nd}\) trimester, this was found to be a high-risk marker for early-onset PE\(^4\)

- Several studies have been investigating the use of cut-offs to predict PE\(^5\)

Studies supporting evidence-based strategy

Roche-sponsored studies

PROGNOSIS study (>1,200 patients)

- **Objective:** To evaluate the use of sFlt-1/PlGF for the short-term prediction of PE/eclampsia/HELLP syndrome in pregnant women with suspected PE

PROGNOSIS Health Economics study (>1,200 patients)

- **Objective:** To evaluate the cost-effectiveness of using information from the sFlt-1/PlGF ratio for short-term prediction of PE

PROGNOSIS ASIA (> 500 patients)

- **Objectives**
  - To validate the sFlt-1/PlGF ratio of 38 as a cut-off for the short-term prediction of PE/eclampsia/HELLP syndrome in pregnant women with suspected PE

PreOS study (150 patients)

- **Objective:** To evaluate the impact/influence of the sFlt-1/PlGF ratio on the decision-making of treating physicians in pregnant women with suspicion of PE

Spanish early-onset PE (800 patients)

- **Objective:** To determine whether the sFlt-1/PlGF ratio is a marker for the prediction of early-onset PE
The Elecsys® sFlt-1/PlGF assay

Aid in prediction of preeclampsia

• sFlt-1/PlGF ratio aids short-term prediction of PE using selected cut-offs

- It may be used to **rule-out PE within 1 week**
  in pregnant women with signs and symptoms of PE
  (clinical suspicion)\(^1,3\)

- It may be used to **rule-in PE within 4 weeks**
  in pregnant women with signs and symptoms of PE
  (clinical suspicion)\(^1,3\)

• Roche supporting studies:

  - **PROGNOSIS** (Roche sponsored study): Evaluating the Elecsys® sFlt-1/PlGF ratio for short-term prediction of PE/eclampsia/HELLP syndrome in pregnant women with suspected PE\(^3,4\)
  
  - **PreOS** (Roche sponsored study): Assessment of the impact or influence of the Elecsys® sFlt-1/PlGF ratio on decision-making of the physician in patients with suspected PE\(^5\)

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\(^3\) Hund, M., et al. (2014) *BMC Pregnancy and Childbirth* 14, 324;  
\(^4\) Zeisler, H., et al. (2014) XX COGI World Congress 2014;  
\(^5\) Klein, E., et al. (2014) XX COGI World Congress 2014;
The Elecsys® sFlt-1/PIGF assay

Results from the PROGNOSIS study

sFlt-1/PIGF ratio cut-offs for prediction and diagnosis of pre-eclampsia in singleton pregnancy
The Elecsys® sFlt-1/PlGF assay

Aiding physician decision-making

- Data obtained from the PreOS study:
  - Multicentre, prospective, open, non-interventional study
  - 118 of 209 enrolled patients comprised the per-protocol population.
  - sFlt-1/PlGF ratio was found to influence decision-making for hospitalisation in suspected PE
  - Changed decisions were in concordance with the incidence of major clinical outcomes (e.g. PE) as assessed by an adjudication committee

<table>
<thead>
<tr>
<th>Hospitalisation before knowledge of sFlt-1/PlGF results ratio</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation after knowledge of sFlt-1/PlGF results ratio</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Cost-effectiveness of the sFlt-1/PlGF ratio for short-term prediction of preeclampsia

**PROGNOSIS study - HECON objective**

- Patient data population was taken from the PROGNOSIS study
- The study shows that the **initial decision to hospitalise** patients prior to the diagnosis of PE can be **better focused with the test information**
- The cost-effectiveness study shows that the **sFlt-1/PlGF assay offers an opportunity to reduce costs** by reducing the number of women who are hospitalised due to suspected PE
- In the **base case scenario**:
  - The **reduction of hospitalisation is almost 50%**
  - The cost reduction for the cohort is £418,927
  - The **cost reduction per patient is £399**

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**Base case scenario**

<table>
<thead>
<tr>
<th>Cohort cost (in million £)</th>
<th>Cost per patient (£)</th>
<th>Cost per cohort (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No test</td>
<td>3,750</td>
<td>4,250</td>
</tr>
<tr>
<td>With test</td>
<td>3,500</td>
<td>4,000</td>
</tr>
</tbody>
</table>

**Strunz-McKendry, T., et al. (2014). XX COGI World Congress 2014**
Multicenter evaluation of the first automated Elecsys® sFlt-1 and PlGF assays in normal pregnancies and preeclampsia

Within-run imprecision CVs were between 0.5 and 6.8% for sFlt-1 and between 0.6 and 2.6% for PlGF.

The sFlt-1 and PlGF concentrations of the inter-laboratory samples were within the expected target range and the inter-laboratory CVs were below 5% for sFlt-1 and below 4% for PlGF.

Between-run CVs were below 4% for sFlt-1 concentrations between 45 and 64,800 pg/mL and PlGF concentrations between 20 and 8200 pg/mL.

The total imprecision CVs were between 2.3 and 4.3% for sFlt-1 (range: 60–80,000 pg/mL) and between 2.0 and 4.1% for PlGF (range: 100–9500 pg/mL).

Elecsys® sFlt-1/PlGF ratio in function of the week of gestation in serum samples from pregnant women. Classification as either apparently normal (n=267) or PE/HELLP (n=15) reflects the status at time of blood taking.

Source: J. Schiettecatte et al, 2010
## Assay-specific competitive landscape

### 3 other IVD companies offer preeclampsia assays

<table>
<thead>
<tr>
<th>Assays currently on the market</th>
<th>Roche Elecsys sFlt-1/PlGF</th>
<th>Perkin Elmer PlGF test (3 different systems)</th>
<th>Thermo Fisher sFlt-1 &amp; PlGF</th>
<th>Alere Triage® PlGF Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay type</td>
<td>Fully automated</td>
<td>Manual to fully automated</td>
<td>Fully automated</td>
<td>Automated</td>
</tr>
<tr>
<td>Imprecision (%)</td>
<td>&lt; 4.3 / &lt; 4.1</td>
<td>≤ 5 &amp; ≤ 5.1</td>
<td>&lt; 13.2</td>
<td></td>
</tr>
<tr>
<td>Sample type</td>
<td>Serum</td>
<td>Serum</td>
<td>Serum</td>
<td>EDTA plasma</td>
</tr>
<tr>
<td>Minimum sample volume (µL)</td>
<td>20 / 50</td>
<td>25 - 50</td>
<td>40</td>
<td>8 &amp; 70</td>
</tr>
<tr>
<td>Incubation time (min)</td>
<td>18</td>
<td>2 to 4 h</td>
<td>30</td>
<td>9 &amp; 29</td>
</tr>
<tr>
<td>Limit of detection (pg/mL)</td>
<td>10 / 3</td>
<td>1.9</td>
<td>22 &amp; 3.6</td>
<td></td>
</tr>
<tr>
<td>Limit of quantification (pg/mL)</td>
<td>15 / 10</td>
<td>5.6 - 7</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Measuring range (pg/mL)</td>
<td>10 - 85,000</td>
<td>22 - 90,000 &amp; 3.6 - 7,000</td>
<td>12 - 3,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 - 10,000</td>
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What about guidelines?

To date, the use of sFlt-1, PI GF or the sFlt-1/PI GF ratio has not been incorporated into official guidelines.

But sFlt-1/PI GF were recently incorporated into the German guidelines.

Good clinical practice guidance for implementation of this method into the management algorithm of pregnant women.

Use of the sFlt-1/PI GF ratio may help to optimize care by improving management of women with suspected PE.
A study by Yves Giguère from Laval University in Québec created several PE prediction algorithms based on a priori clinical characteristics, body mass index, mean arterial pressure, placental growth factor, soluble Fms-like tyrosine kinase-1, pregnancy-associated plasma protein A, and inhibit A. The estimated detection rates were 42% for PE and 50% for severe PE at a 10% false-positive rate. The authors conclude that due to the low prevalence of preterm PE, the risk algorithms did not reach a performance justifying clinical implementation as screening test early in pregnancy. (Giguère Y, Massé J, Thériault S, Bujold E, Lafond J, Rousseau F, Forest JC. BJOG. 2015 Feb;122(3):402-10).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is insufficient evidence to recommend additional screening (compared with usual routine assessment based on history and physical exam) for increased risk of pre-eclampsia in low-risk women. Primary screening for risk of pre-eclampsia in low-risk women should only be performed within the framework of research. (new KCE 2016).</td>
<td>NA</td>
<td>No evidence</td>
</tr>
</tbody>
</table>
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### Summary - Conclusions
**Take home messages**

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<th><strong>sFlt-1/PlGF ratio ≠ a screening test</strong></th>
</tr>
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<tr>
<td><strong>sFlt-1/PlGF ratio does not replace other techniques to monitor high-risk patients</strong></td>
</tr>
<tr>
<td>Criteria contributing to suspicion of clinical diagnosis of pre-eclampsia is not only limited to hypertension &amp; proteinuria.</td>
</tr>
<tr>
<td><strong>sFlt-1/PlGF ratio as a test for all pregnant women at risk of developing pre-eclampsia = 20%</strong></td>
</tr>
</tbody>
</table>

**Consensus statement**

- Screening for PE in first trimester do not reach the performance justifying clinical implementation
- sFlt-1/PlGF ratio has an impact on hospitalisation of women with PE
- sFlt-1/PlGF ratio may be used to rule-out PE within 1 week
- sFlt-1/PlGF ratio may be used to rule-in PE within 4 weeks
Doing now what patients need next