Pre-eclampsia: background

- Pre-eclampsia (PE) is defined as recent onset hypertension (artificial pressure ≥ 140/90 mmHg for 2 measurements at 4hr interval) and proteinuria (≥ 300 mg/24hr) after 20 weeks amenorrhea (WA) in a priori normotensive women.

- Early onset (between 20 and 34 WA) is associated with a less favourable prognosis with higher fetal and maternal risks.

- Pre-eclampsia is still a leading cause of maternal and perinatal mortality and morbidity in Ireland.

- In Ireland PE affects from 2 to 3% of all pregnancies, and 5 to 7% of nulliparous women. It accounts for 20% per cent of all neonatal intensive care unit (NICU) admissions. [1]

- In severe forms (10% of cases), maternal, fetal and/or neonatal complications can develop rapidly with serious complications and a potentially fatal prognosis.

- Induced delivery may be proposed by the clinician based on the clinical signs of the patient and the impact on the fetus.

Every year 2,000 pregnant women in Ireland are affected by PE.

Screening in 1st trimester (11+0 to 13+6 WA) [3-5]

Benefits
- Establish close obstetric monitoring
- Initiate aspirin therapy at low doses before 16 WA

Risk calculation

“PE risk” patients can be screened for the presence of risk factors with the Doppler measurement of the pulsatility index (PI) of the uterine arteries (UAD), mean arterial pressure (MAP) and the assay of PAPP-A and PIGF biomarkers.

Risk factors incorporated in the calculation
- BMI
- Geographical origin
- Parity
- Personal or family history of PE
- Chronic high blood pressure, treated or not
- Smoking

Risk calculation

In 2013, the Nicolaides team (Akolekar et al, 2013) has published a study with 58,884 single pregnancies, 2.4% of which with PE. The detection rate is better for early PEs and, compared to purely clinical information, the combination of biophysical and biochemical data significantly improves the detection rate.

PE detection rate by risk analysis (after Akolekar, 2013)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PE with birth &lt;34 weeks</th>
<th>PE with birth &lt;37 weeks</th>
<th>PE with birth &gt;37 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP 5%</td>
<td>FP 10%</td>
<td>FP 5%</td>
<td>FP 10%</td>
</tr>
<tr>
<td>Clinical data with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIGF, PAPP-A, UAD &amp; MAP</td>
<td>93.4%</td>
<td>96.3%</td>
<td>61.1%</td>
</tr>
</tbody>
</table>

The same team published a new study at the start of 2016 of 35,948 pregnancies (O’Gorman et al, 2016), 2.9% of which with PE, using a new calculation method. The combination of clinical information with PIGF, PAPP-A, UAD and MAP enables screening, with 5% false positives, of 82% of PEs before 32 WA (42% with only maternal risk factors); the detection rate is 59% for PEs between 32+0 and 36+6 WA and 37% between 37+0 and 39+6 WA (34% and 31% respectively with only maternal risk factors).
**SFlt-1** (soluble PlGF receptor) is an antiangiogenic factor. It captures the circulating PlGF that cannot be attached to its membrane receptor, thereby decreasing its pro-angiogenic activity.

- The PlGF concentration is abnormally elevated around **5 weeks before the occurrence of PE**.

- The imbalance in sFlt-1 and PlGF concentrations is detectable **several weeks before** the clinical onset of pre-eclampsia.

The sFlt-1/PlGF ratio has a better positive predictive value (PPV) than the measurement of sFlt-1 by itself.
**PROGNOSIS study** [8]

The PROGNOSIS study is a multicentre, prospective, non-interventional, randomized, double-blind study that evaluated the short-term prediction of pre-eclampsia in pregnant women at risk of pre-eclampsia. Between December 2010 and January 2014, 1270 patients were enrolled and 30 centres located in 14 countries participated. The results were published at the start of 2016.

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**sFlt-1/PIGF ratio: a decision-making aid for the clinician**

A ratio <38 is the basis for referring women to **outpatient care** with a negative predictive value (NPV) of 99.3% at one week. A ratio ≥ 38 flags the **need for care and hospitalization of patients** at high risk with a positive predictive value (PPV) of 36.7% at 4 weeks of developing a PE.

In the presence of a warning sign, the sFlt-1/PIGF ratio alerts the clinician to possible development of pre-eclampsia.

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**PREDICTIVE TEST FOR PRE-ECLAMPSIA 2ND AND 3RD TRIMESTERS (20 TO 37 WA)**

- **Interpretation:**
  - Low risk patients
  - Diagnosis of pre-eclampsia excluded
  - Patients with an sFlt-1/PIGF ratio <38 do not have pre-eclampsia at the time of the test and will not develop it for at least the coming week.

- **Performance:**
  - NPV for pre-eclampsia: 99.3% at week 1
  - More than 80% of patients belong to this low risk group

- **Response:**
  - Outpatient monitoring every 1-4 weeks depending on clinical signs of patient
  - New assay may be performed if pre-eclampsia suspected
  - A return home may be considered if the patient was hospitalized

- **Probability of pre-eclampsia in the next 4 weeks**
  - Diagnosis of pre-eclampsia
  - The higher the ratio, the more adverse is the prognosis

- **Hospitalization and deciding on further treatment on basis of severity and trend.**
  - At very elevated sFlt-1/PIGF ratios (> 655, if <34 weeks or > 201, if ≥ 34 weeks) induction of labour within 48 hours may be considered
  - The care of the patient must be in accordance with the recommendations[^8]
Strategy for use of biomarkers

**SCREENING**
- Patient at risk of PE
  - Risk factors (RFs)

**CLINICAL PATHOLOGY**
- At time of screening of T21:
  - IP + MAP + PIGF + PAPP-A + RF
  - PE screening

**CLINICAL**
- Standard monitoring
- Intensive outpatient monitoring. Preventive measures

**PREDICTIVE**
- 2nd and 3rd trimesters

**Appearance of a 1st warning sign***

**Identification of imminent PEs**
- sFlt-1/PIGF ratio
  - Predictive at weeks 1–4
  - ratio < 38
  - ratio ≥ 38

**NPV 99.3% at week 1**
- Outpatient monitoring

**PPV 36.7% at week 4**
- Intensive monitoring or hospitalization

**DIAGNOSIS**
- Symptoms
  - sFlt-1/PIGF ratio
  - ratio > 85 (if < 34 WA)
  - ratio > 110 (if ≥ 34 WA)

**PE diagnosis and prognosis**
- Management

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**Risk factors (RFs)**
- New onset or exacerbated arterial hypertension
- New onset or exacerbated proteinuria
- Epigastric pain
- Excessive edema
- Headaches
- Visual disorders

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**Symptoms**
- Sudden weight gain
- Thrombopenia (< 100 giga/L)
- Elevated hepatic enzymes
- IUGR (suspected)
- Abnormal ultrasound result for uterine arteries
## In practice

### For pre-eclampsia screening in 1st trimester

**Recommendation**
- PIGF and PAPP-A assay

**Sampling**
- Between 11°0 et 13°6 WA
- Blood sample: use a separate dry tube for PE screening. After removal of clot, centrifuge at high speed to separate serum.

**Storage and transport**
- Refrigerate (+2 °C to +8 °C)

### For the pre-eclampsia predictive test

**Recommendation**
- sFlt-1/PlGF assays

**Sampling**
- Starting from 20 WA
- Blood sample (2 ml): use a separate dry tube for PE screening. After removal of the clot, centrifuge at high speed to separate the serum.

**Storage and transport**
- Freeze (-18 °C)

**Information to be provided**
- It is essential to provide pregnancy dates (date of pregnancy or crown-rump length and date of ultrasound examination between weeks 11°0 and 13°6) and date of sample

## References

1. HSE, The Diagnosis and Management of Pre-eclampsia and eclampsia clinical practice Guideline, 2013, 3.0

## Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAD</td>
<td>Doppler ultrasound of uterine arteries:</td>
</tr>
<tr>
<td>RF</td>
<td>Risk factor</td>
</tr>
<tr>
<td>FP</td>
<td>False positive rate</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>Pregnancy-Associated Plasma Protein-A</td>
</tr>
<tr>
<td>PE</td>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td>PIGF</td>
<td>Placental Growth Factor</td>
</tr>
<tr>
<td>WA</td>
<td>Week of amenorrhea</td>
</tr>
<tr>
<td>sFlt-1</td>
<td>fms-like tyrosine kinase 1 (soluble fraction of type VEGF receptor (VEGF-R1))</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
</tbody>
</table>
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