COMPREHENSIVE PRE-ECLAMPSIA MANAGEMENT

PRE-ECLAMPSIA CARE
FOR ALL TRIMESTERS & DIFFERENT NEEDS

Brochure not for distribution in the USA and Canada
Pre-eclampsia is a complication of pregnancy marked by high blood pressure and protein in the urine. Left untreated, pre-eclampsia can lead to eclampsia, a serious condition that can, in some cases, lead to death. Pre-eclampsia also affects blood flow to the placenta, often leading to growth-restricted or prematurely born babies. Avoiding this condition would bring substantial improvements to maternal and fetal health. In fact, according to some researchers, term pre-eclampsia is a completely different pregnancy complication than early and pre-term pre-eclampsia. The alternative view is that pre-eclampsia is a spectrum disorder in which all women eventually develop the condition if the pregnancy is continued indefinitely.

Early and preterm pre-eclampsia – poor placentation

While the direct cause of pre-eclampsia is unknown, researchers agree that if symptoms such as high blood pressure and proteinuria occur between 20 and 37 weeks, there is a high risk that the placenta will be adversely affected. Early onset pre-eclampsia is also associated with preterm birth and fetal growth restriction, with prematurity accounting for most pre-eclampsia-related healthcare costs. If HELLP syndrome or eclampsia occur alongside pre-eclampsia, ICU care is inevitable.

The good news is that aspirin treatment is highly effective in the prevention of early and preterm pre-eclampsia.

Term pre-eclampsia – maternal origin and cardiac dysfunction

New evidence suggests that if pre-eclampsia develops after 37 weeks (term pre-eclampsia), the resulting condition is more closely related to cardiac and metabolic dysfunction in the mother than poor placentation per se.

In fact, according to some researchers, term pre-eclampsia is much more common than all aneuploidies combined. Both mother and baby are affected.

Pre-eclampsia is much more common than Down syndrome.

Prevalence %

Pre-eclampsia Fetal Growth Restriction Preterm birth

Mothers at risk

Babies at risk

Placental insufficiencies are much more common than Down syndrome.

> Pre-eclampsia is much more common than all aneuploidies combined.

> Both mother and baby are affected.

The global burden of pre-eclampsia

>10 million around the world develop pre-eclampsia annually.

At the same time

76,000 pregnant women die each year from pre-eclampsia and related hypertensive disorders globally.

This means about

19 women develop pre-eclampsia every minute and more than one woman every seven minutes loses her life due to these relatively common and often preventable conditions.

The impact of hypertension disorders on global infant mortality is enormous, with an estimated

500,000 babies dying from these pregnancy complications each year.

In fact, pre-eclampsia alone is responsible for up to 20% of the total

13 million preterm births each year globally.
Today women expect doctors to offer effective prenatal care based on the latest research evidence and screening solutions. They want the best care possible throughout pregnancy.

When it comes to pre-eclampsia prevention, the growing consensus among caregivers and researchers is that timing matters more than ever. The earlier you identify women as having a high risk for pre-eclampsia, the better the outcome for mother and child.

What is the role of angiogenic factors?

PlGF and sFlt-1 are found to be key factors in the pathophysiology of pre-eclampsia. [33]

In pregnancies that develop pre-eclampsia, maternal serum placental growth factor (PlGF) levels decrease significantly, while soluble fms-like tyrosine kinase 1 (sFlt-1) levels increase several weeks prior to clinical symptom onset. Serum levels of PlGF and sFlt-1 are altered in women with pre-eclampsia compared to those with uncomplicated pregnancies. In pre-eclampsia, there is an imbalance between PlGF and sFlt-1. [34]

Thus, PlGF and sFlt-1 are important biomarkers used to identify high-risk women that are likely to develop preterm pre-eclampsia later in their pregnancy and to predict the onset of pre-eclampsia. Biomarker levels are also found to be correlating with severity of disease. [34]

THE NEXT STEP IN SCREENING AND TREATMENT FOR PRE-ECLAMPSIA

1T: screening and prevention of preterm pre-eclampsia

Traditional methods (Blood pressure and Proteinuria) have poor sensitivity and specificity to predict pre-eclampsia. Decreased PlGF levels predict future development of PE, especially early-onset and preterm pre-eclampsia, severe PE requiring delivery <34 gestational weeks and <37 gestational weeks, respectively. [13,27]

PlGF values are used together with other relevant clinical information (Maternal history, Mean Arterial blood pressure and uterine artery pulsatility index). The risk is calculated by using a software with a risk calculation algorithm (e.g. LifeCycle). During 1T sFlt-1 levels are not predictive for the onset of preterm pre-eclampsia. [34]

2T and 3T: Short term prediction and aid in diagnosis

During 2T and 3T sFlt-1 and PlGF are both predictive and diagnostic for pre-eclampsia. It has been shown that increased levels of sFlt-1 and decreased levels of PlGF in maternal serum can predict the subsequent onset of pre-eclampsia. Determining serum sFlt-1 and PlGF levels improves the clinical management and decision-making (risk stratification) with women showing signs and symptoms of pre-eclampsia. [34]
A combined screening program for pre-eclampsia is recommended by international guidelines.[22, 23] to identify women at high risk of pre-eclampsia in the early stages of pregnancy. The combined screening program consists of the PlGF 1-2-3™ blood test, maternal medical history assessment, mean arterial blood pressure measurement and, if available, uterine artery Doppler ultrasonography.

1st trimester – perfect timing
The timeframe for pre-eclampsia screening is the first trimester, when low-dose aspirin therapy shows the best results in the prevention of pre-eclampsia.[10] To achieve maximum effectiveness, aspirin therapy should be started before 16 weeks of gestation among women at high risk of pre-eclampsia.[22, 23]

Medical history – a priori risk
The traditional method of screening for pre-eclampsia has been based on asking women a series of questions during their first pregnancy visit.[11, 12] This method considers each risk factor as an independent and unrelated event. The more effective approach to defining maternal a priori risk uses an algorithm that determines the relative importance of each risk factor and their interrelationship.[13]

PlGF 1-2-3 blood test
The high-sensitivity PlGF 1-2-3™ assay can be performed as early as the first trimester, at 11–13+6 weeks. The blood sample is analysed using the same PerkinElmer instrument that is used for aneuploidy screening. No additional blood sample is required as the same sample can be used both to screen for pre-eclampsia and for aneuploidy screening. Women with an elevated risk of pre-eclampsia show a lower maternal serum level of placental growth factor (PlGF).

Mean arterial blood pressure – MAP
When mean arterial blood pressure (MAP) is used as a pre-eclampsia screening marker, it is important to use the standardised protocol for MAP measurement. The blood pressure (BP) should be measured two times from both arms simultaneously using two blood pressure monitors. The blood pressure should be recorded from both arms because of significant non-pathological inter-arm variations.[14]

Uterine artery Doppler pulsatility index (UTPI) ultrasound
The uterine artery Doppler pulsatility index (UTPI) can be measured between 11–13+6 weeks via a transvaginal or transabdominal ultrasound. Please refer to the Fetal Medicine Foundation’s guidelines for the detailed protocol and certificates of competence.[15]
Specialised software generates a unique patient risk profile and report based on combination of risk factors. Depending on access and availability, other marker combinations can also be used to screen for pre-eclampsia.

What do the results mean?

Low risk
Low risk means that there is minimal risk of developing pre-eclampsia later in pregnancy. While it is possible to develop pre-eclampsia regardless of low risk status, the pregnancy can continue as normal and the mother can rest assured that there is little or no reason for concern.

High risk
If the risk of developing pre-eclampsia later in pregnancy is high, the doctor may start treatment at the optimum time and monitor the pregnancy more closely. While not all women in the high-risk group develop pre-eclampsia, doctors can now consider whether preventive treatment is appropriate.

Who should be screened for pre-eclampsia?
All pregnant women should be assessed early on in their pregnancy to prevent the development of pre-eclampsia. All pregnant women should be assessed early on in their pregnancy to prevent the development of pre-eclampsia.

Why should women be screened for pre-eclampsia?
While pre-eclampsia screening is critical to protecting the health of mother and child, many women are unaware of pre-eclampsia and that pre-eclampsia can affect any pregnancy. Some pregnancies are more at risk of developing pre-eclampsia than others. Combined pre-eclampsia screening with the PlGF 1-2-3™ assay is an effective way to assess this risk of this preventable condition.

Pre-eclampsia affects both the mother and the child also later in life. In fact, women with a history of pre-eclampsia have a three to four times greater risk of developing chronic hypertension than mothers with no history of pre-eclampsia and double the risk of ischemic heart disease, venous thromboembolism and stroke.[16] Pre-eclampsia can cause prematurity, which in turn subjects babies to additional risks, as well as cardiovascular diseases and diabetes later in life. [25, 26, 27]

Aspirin treatment according to ASPRE study design[5]

- A dose response effect of aspirin is demonstrated. A high proportion (1/3) of the population is non-responsive to aspirin at lower doses.[18,19]
- Aspirin is effective if given to high risk women before 16 weeks of gestation.[4,10]
- Avoid potential hemorrhage for neonate.[20]
- Lower incidence of PE when taken at bedtime compared to morning or afternoon.[21]

Aspirin treatment according to ASPRE study design[5]

Medical history and blood test can help to identify 88% of very early pre-eclampsia cases and 66% of preterm pre-eclampsia cases. Similar detection rates can be achieved with medical history. If the UTPI is available, the detection rate is close to 100% for very early PE and between 75%-80% for preterm PE.[13] These are examples and other combinations are possible. FPR (False Positive Rate) is 10% in this example.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Very Early PE</th>
<th>Preterm PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history with:</td>
<td>Detection rate</td>
<td>Detection rate</td>
</tr>
<tr>
<td>PIGF + PAPP-A</td>
<td>88 %</td>
<td>66 %</td>
</tr>
<tr>
<td>PIGF + MAP</td>
<td>88 %</td>
<td>69 %</td>
</tr>
<tr>
<td>PIGF + MAP + UTPI</td>
<td>100 %</td>
<td>75 %</td>
</tr>
<tr>
<td>PIGF + PAPP-A + MAP + UTPI</td>
<td>100 %</td>
<td>80 %</td>
</tr>
</tbody>
</table>

Who should be screened for pre-eclampsia?
All pregnant women should be assessed early on in their pregnancy to prevent the development of pre-eclampsia. They should also have access to screening even if there are no maternal risk factors or history of pre-eclampsia. The benefit of detecting and treating pre-eclampsia early in the pregnancy always outweighs the conventional wait-and-see approach to pre-eclampsia management.[14]

Why should women be screened for pre-eclampsia?
While pre-eclampsia screening is critical to protecting the health of mother and child, many women are unaware of pre-eclampsia and that pre-eclampsia can affect any pregnancy. Some pregnancies are more at risk of developing pre-eclampsia than others. Combined pre-eclampsia screening with the PlGF 1-2-3™ assay is an effective way to assess this risk of this preventable condition.

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While aspirin treatment is not a cure for pre-eclampsia, fewer women need to suffer from this serious disease if low-dose aspirin is administered early in the pregnancy. [30]

Low-dose aspirin in the prevention of pre-eclampsia

| Dose | 150 mg | A dose response effect of aspirin is demonstrated. A high proportion (1/3) of the population is non-responsive to aspirin at lower doses.[18,19] |
| Start | 12 weeks | Aspirin is effective if given to high risk women before 16 weeks of gestation.[4,10] |
| Finish | 36 weeks | Avoid potential hemorrhage for neonate.[20] |
| Time Bedtime | Lower incidence of PE when taken at bedtime compared to morning or afternoon.[21] |

PerkinElmer does not endorse or make recommendations with respect to research, medication, or treatments. All information presented is for informational purposes only and is not intended as medical advice. For country-specific recommendations please consult your local health care professional.
sFlt-1/PlGF ratio - Short term prediction and aid in diagnosis

During 2T and 3T, sFlt-1 and PlGF are both predictive and diagnostic for PE. It has been shown that increased levels of sFlt-1 and decreased levels of PlGF in maternal serum can predict the subsequent onset of pre-eclampsia. [33, 34]

Determining serum sFlt-1 and PlGF levels, used as a ratio, improves the clinical management and decision making (risk stratification) with women showing signs and symptoms of pre-eclampsia. [33, 34]

When should I determine the sFlt-1/PlGF ratio?
- Testing is applicable to women with signs and symptoms of pre-eclampsia after week 20 of gestation
- To confirm clinical suspicion of pre-eclampsia with symptomatic women and/or to confirm unclear diagnosis of pre-eclampsia
- To monitor women that are at high risk for pre-eclampsia

What is the sFlt-1/PlGF ratio used for?
- Confirming or excluding diagnosis of pre-eclampsia:
  - Measuring maternal serum concentrations of sFlt-1 and PlGF can differentiate healthy women from women with pre-eclampsia. Changes in sFlt-1 and PlGF levels reflect the severity of the disease. [33, 34]
  - To avoid unnecessary hospitalization
  - For improved diagnosis and prognosis

Decisions regarding delivery are not based solely on the sFlt-1/PlGF ratio, but are always made in context of other clinical signs and symptoms

sFlt-1/PlGF Ratio calculation with LifeCycle™ software*

With LifeCycle™ software you can follow up the patient from 1T pre-eclampsia risk assessment to 2T/3T pre-eclampsia management. sFlt-1 and PlGF concentrations are transferred automatically from the DELFIA® Xpress platform to the LifeCycle™ software, so there is no need for manual typing.

LifeCycle™ software enables monitoring pre-eclampsia status with the sFlt-1/PlGF ratio and the ratio results can be linked to the same patients’ other results in LifeCycle™Software. For ratio calculations the cut-offs for PE management are adjustable.

FOR LABORATORY: Short term prediction and aid in diagnosis

2T/3T when symptoms appear

sFlt-1/PlGF ratio

Low ratio
Intermediate ratio
Increased ratio

Short term prediction:
Rule Out
Monitoring
Rule In

Aid in diagnosis:

PRE-ECLAMPSIA MANAGEMENT
PerkinElmer’s high-sensitivity PlGF 1-2-3™ kit is the only assay that can offer the level of accuracy and precision that was required by the ground-breaking ASPRE trial. The kit is used as an aid in screening pregnant women for pre-eclampsia in all pregnancy trimesters. The kit is available in two package sizes for three different platforms to accommodate different throughput needs.

**Native Serum Controls**

Lyophilized human serum controls are intended for use as an assayed quality control serum to monitor precision of laboratory measurement procedures for the DELFIA® assays. Two levels of controls are sold as separate products for both PlGF and SFlt-1 assays to allow performance monitoring within the clinical range.

**DELFIA® Xpress sFlt-1 kit**

This kit is intended for the quantitative determination of soluble Fms-like tyrosine kinase-1 (sFlt-1) in maternal serum using the 6000 DELFIA® Xpress random access immunanalyzer. The ratio of sFlt-1/PlGF may be used as an aid in diagnosis of pre-eclampsia and for short term prediction of suspected pre-eclampsia together with other biochemical and clinical information. The kit is available in two package sizes.

**COMPREHENSIVE OFFERING COVERING ALL TRIMESTERS**

**COMBINED SCREENING PROTOCOL**

**LIFECYCLE® RISK CALCULATION SOFTWARE**

**AID IN DIAGNOSIS**

**LOW RISK**

**HIGH RISK: Preventive actions**

**SHORT-TERM PREDICTION & AID IN DIAGNOSIS**

**TRIMESTER 1**

Start preventive actions

**TRIMESTER 2**

Close monitoring

**TRIMESTER 3**

Prepare for early delivery and needed actions

**PRE-ECLAMPSIA OFFERING**

**Sample collection**

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Sample collection</th>
<th>Analysis and measurement</th>
<th>Reagents</th>
<th>Result and interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum samples</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Instrumentation for different laboratory needs**

**1st trimester assays**

- Small Victor2D
  - PlGF 1-2-3™
- Medium DELFIA® Xpress
  - PlGF 1-2-3™
  - sFlt-1
- High AutoDELFIA®
  - PlGF 1-2-3™
  - sFlt-1 controls

**2nd/3rd trimester assays**

- High AutoDELFIA®
  - PlGF controls
  - LifeCycle™
  - Statistical Services™
  - Astraia® link, ViewPoint® link

For more information about our prenatal screening offering including aneuploidy screening with biochemical markers and NIPT, please visit [www.prenataltesting.perkinelmer.com](http://www.prenataltesting.perkinelmer.com)