# Pre-eclampsia screening with PIGF 1-2-3™ kit

revvity

Prenatal screening solutions from the global leader in maternal fetal health

# A new era in pre-eclampsia care with the PlGF 1-2-3™ kit

## The next step in screening and treatment for pre-eclampsia

**Pre-eclampsia is a complication of pregnancy marked by high blood pressure and protein in the urine and/or maternal organ failure. Left untreated, pre-eclampsia can lead to eclampsia, a serious condition that can, in some cases, lead to death. Pre-eclampsia affects blood flow to the placenta, often leading to growth-restric ted or prematurely born babies. Avoiding this condition would bring substantial improve-ments to maternal and fetal health.**

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, 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.

### PlGF 1-2-3™ – the 2nd-generation PlGF assay

Revvity's PlGF 1-2-3 assay is the most sensitive first-trimester screening kit for pre-eclampsia to date.[2] When used in combination with a comprehensive first trimester screening program that includes maternal medical history and mean arterial blood pressure, women at high risk for pre-eclampsia can be identified long before symptoms appear. The PlGF 1-2-3™ assay can also be used in the second and third trimester of pregnancy for effective reassessment, monitoring or diagnosis.[3]

**PIGF**

Low PIGF levels indicate high risk of pre-eclampsia

**1st trimester**

Screen all women
PIGF **1**-2-3

**2nd trimester**

Reassess high risk women
PIGF 1-**2**-3

**3rd trimester**

Prepare birth plan
PIGF 1-2-**3**

## The global burden of pre-eclampsia

### Mothers at risk

- **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.

### Babies at risk

- 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.

## Understanding pre-eclampsia – cause and effect

### Early and preterm pre-eclampsia – poor placentation

While the direct cause of pre-eclampsia is unknown, research-ers 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.

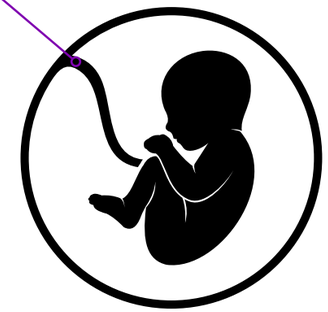
The good news is that aspirin treatment is highly effective in the prevention of early and preterm pre-eclampsia.[4, 5]

### 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.[6,7] 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.[8, 9]

### Placental insufficiency can cause

- Pre-eclampsia
- Fetal Growth Restriction
- Preterm birth
- Stillbirth

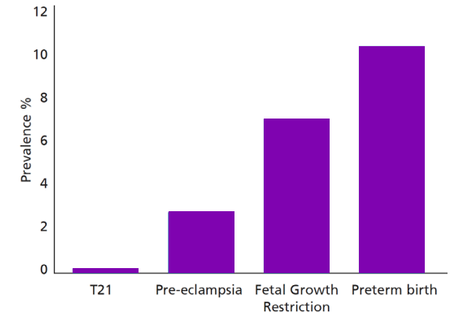


> **"Placental insufficiency is present in virtually every major obstetrical syndrome"**
>
> Romero, Am J Obstet Gynecol. 2011.

## The global burden of pre-eclampsia

### Placental insufficiencies are much more common than Down syndrome.

- Both mother and baby are affected
- Pre-eclampsia is much more common than all aneuploidies combined
- Prevalence of Down syndrome is 1:700 and prevalence of pre-term pre-eclampsia is 1:145




**Very early pre-eclampsia**
- Delivery needed <32 weeks
- Prevalence 0.2%

**Early onset pre-eclampsia**
- Delivery needed <34 weeks
- Prevalence 0.4%

**Preterm pre-eclampsia**
- Delivery needed <37 weeks
- Prevalence 0.7%

**Preterm pre-eclampsia**
- Delivery needed >37 weeks
- Prevalence 2%

### Timeline of pre-eclampsia screening, aspirin treatment and onset of different pre-eclampsia types.


* Revvity 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.

# The combined screening protocol

## From maternal factors to effective combined screening

### The right combination

The combined screening program for pre-eclampsia is the most effective way to identify women at high risk of pre-eclampsia in the early stages of pregnancy. The 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. To achieve maximum effectiveness, aspirin therapy should be started before 16 weeks of gestation among women at high risk of pre-eclampsia.[10]

### Four simple steps

The combined screening program is made up of four simple steps that require short training and minimal additional investment in equipment for screening programs.

1. Record medical history, weight and height.
2. Take blood sample for measuring PlGF 1-2-3™.
3. Measure blood pressure 2 times from both arms simultaneously.
4. If accessible, measure uterine artery Doppler pulsatility index.

| Record medical history | Blood test PIGF 1-2-3 | Measure blood pressure | Measure uterine artery pulsatility index |
|---|---|---|---|
| ▪ First pregnancy?<br>▪ Previous or family history with pre-eclampsia?<br>▪ Ethnicity?<br>▪ Chronic hypertension?<br>▪ Smoking?<br>▪ Weight and height? |  | Take 2 measurements from both arms simultaneously.<br>  | If ultrasound is accessible, measure uterine artery Doppler pulsatility index. |

### 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 Revvity 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 standar d-ised 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]

### How to measure MAP

- Arms supported at the level of the heart
- Right cuff size: S, M, L
- Take 2 measurements in both arms
- Both feet on the floor

**Approved blood pressure monitors for pre-eclampsia screening**

| Manufacturer | Model |
|---|---|
| Microlife® | WatchBP Home |
| Microlife® | BP A200 |
| Microlife® | 3AS1-2 |
| Microlife® | CRADLE VSA |
| Omron® | MIT-Elite |

Monitors that are not listed here can also be used if they have been validated for pre-eclampsia, or declared identical with a validated model.

## Uterine artery Doppler pulsatility index (UTPI) ultrasound

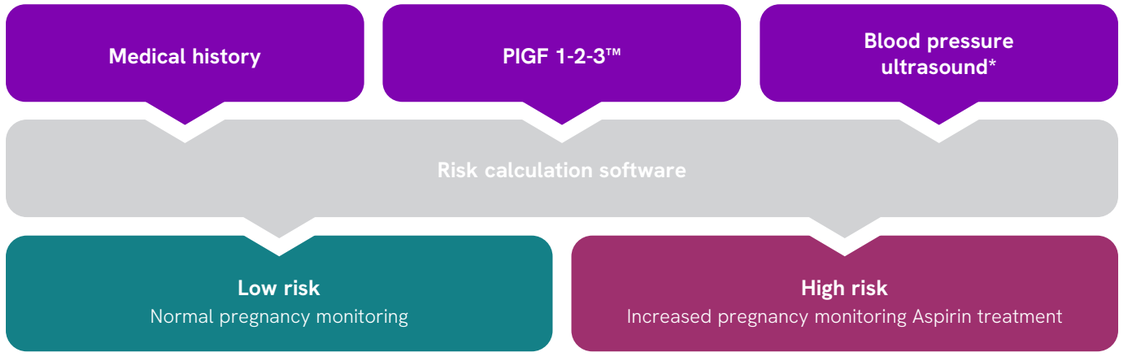
The uterine artery Doppler pulsatility index (UTPI) can be measured between 11–13+6 weeks via a transvaginal or transabdominal ultrasound. Please refer to the Fetal Medicine Foundation's guidelines for the detailed protocol and certificates of competence.[15]

**Procedure for 1T transabdominal UTPI measurement:**

1. Identify uterine arteries.
2. Obtain sagittal section of the cervix and use colour flow Doppler ultrasound.
3. Rotate the transducer from side to side to identify uterine arteries at the level of the internal cervical os.

## Automatic risk assessment

Specialised software generates a unique patient risk profile and report based on maternal risk factors, PlGF 1-2-3™ test results and biophysical information. Depending on access and availability, other marker combinations can also be used to screen for pre-eclampsia.




*Risk calculation can be performed without ultrasound if access is limited as in example below.

## Combined pre-eclampsia screening – the first step to better detection

When it comes to effectively predicting pre-eclampsia, the combined screening program outperforms screening methods that rely only on maternal history. The effectiveness of pre-eclampsia screening also depends on marker combination.[13]

| Parameters | Very Early PE | Preterm PE |
|---|---|---|
| Medical history with: | Detection rate | Detection rate |
| PlGF + PAPP-A | 88 % | 66 % |
| PlGF + MAP | 88 % | 69 % |
| PlGF + MAP + UTPI | 100 % | 75 % |
| PlGF + PAPP-A + MAP + UTPI | 100 % | 80 % |

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, PlGF 1-2-3™ and MAP. If 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) = 10% in this example.



# Information for doctors

## 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. Why? The benefit of detecting and treating pre-eclampsia early in the pregnancy always outweighs the conventional wait-and-see approach to pre-eclampsia management.

## What should women know?

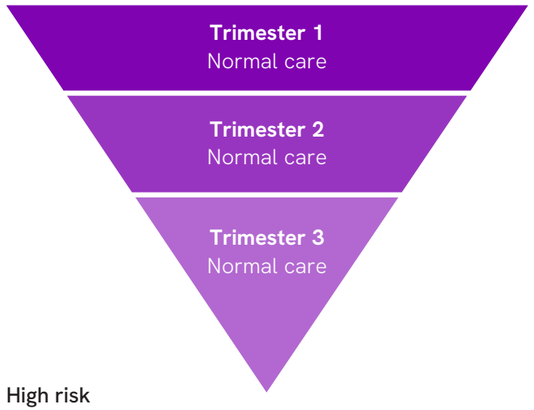
While pre-eclampsia screening is critical to protecting the health of mother and child, many women are unaware of  pre-eclampsia or combined pre-eclampsia screening with the PlGF 1-2-3™ assay. They need to know that pre-eclampsia can affect any pregnancy. They should also be informed that some pregnancies 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.

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]

## What do the results mean?

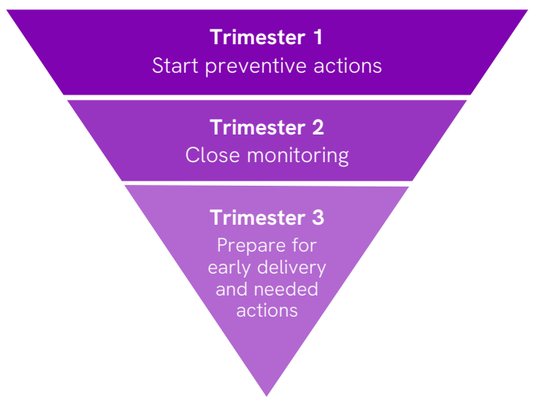
**Low risk**

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 can 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 offer the best possible care early in the pregnancy and significantly improve the outcome for mother and child.






## ASPRE – low-dose aspirin in the prevention of pre-eclampsia

Low-dose aspirin is effective in reducing the risk of pre-eclampsia – especially the early forms of the disease. The best results are achieved with a dose of 150 mg aspirin per day.[17] In the ASPRE trial, aspirin treatment was started after pre-eclampsia screening at around 12 weeks and finished at 36 weeks. The trial results showed that the rate of developing early onset pre-eclampsia dropped by 82% and preterm pre-eclampsia by 62% among those women who received aspirin treatment and were at high risk of risk of developing the disease. To identify women in the high risk group, ASPRE employed a first-trimester combined screening program that included Revvity's PlGF 1-2-3™ assay.

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.[5]

| Dose | Start | Finish | Time |
|---|---|---|---|
| 150 mg | 12 weeks | 36 weeks | Bed time |
| 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 pre-eclampsia when taken at bedtime compared to morning or afternoon.[21] |

Aspirin treatment according to ASPRE study design[5]

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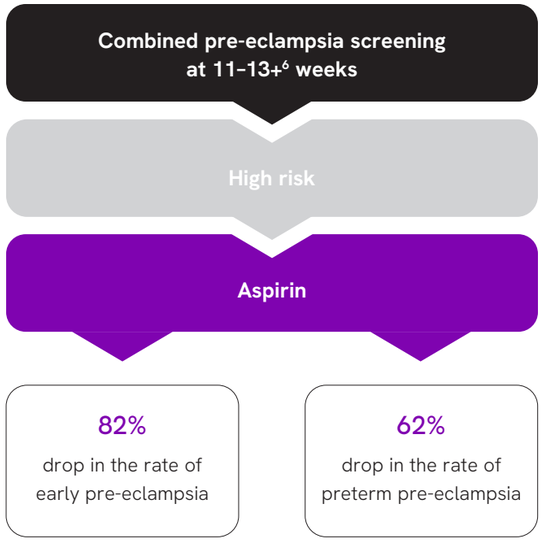
## What makes ASPRE special?

ASPRE was the biggest prospective, randomized, placebo-controlled trial ever  on the prophylactic use of aspirin in women at increased risk of pre-eclampsia. Funded by the European Union and administered by the Fetal Medicine Foundation, more than 30,000 pregnancies were studied in the UK, Belgium, Italy, Spain, Greece and Israel. No other clinical study on low-dose aspirin and pre-eclampisa matches the scale and and scope of ASPRE.



# Information for laboratories

## Choose PlGF 1-2-3™ and enter a new era

Revvity's high-sensitivity PlGF 1-2-3™ kit is the only assay that can offer the level of accuracy and precision required by the ground-breaking ASPRE trial.

PlGF 1-2-3™ is also the first assay optimized for first-trimester screening of pre-eclampsia, which makes it the logical choice in the new era of improved pre-eclampsia management.

## PlGF 1-2-3™ – the ASPRE assay

- Options for 48 and 96 test kits
- Sensitivity 1.9 pg/mL
- 20 min incubation time with DELFIA® Xpress
- Native pregnancy serum CE-IVD controls
- Clinical validity demonstrated in the ASPRE study
- Same CE-IVD assay kit is applicable in 1st, 2nd and 3rd trimesters
- Proven DELFIA® technology

| | Revvity PlGF 1-2-3™ | Company A | Company B |
|---|---|---|---|
| LoD | 1.9 pg/mL | 3.0 pg/mL | 3.6 pg/mL |
| LoQ | 3.3 pg/mL | 10 pg/mL | 6.9 pg/mL |

The ASPRE study chose DELFIA®Xpress and PlGF 1-2-3™ assay, because sensitivity and precision matters in screening.[22]

funded by EU FP7 ASPRE project

**Sensitivity** | **Precision**

**Clinical validity** | **Choice of experts ASPRE**

**Accuracy of results can be ensured in 1T when the clinically relevant PlGF level is very low**


PlGF 1-2-3™ assay


DELFIA® Xpress

## Complete panel of prenatal screening and maternal fetal health markers on DELFIA platforms

| |
|---|
| PlGF 1-2-3™ |
| sFlt-1 |
| PAPP-A |
| Free hCGß |
| PAPP-A / Free hCGß dual |
| hAFP |
| hAFP / Free hCGß dual |
| hCG |
| uE3 |
| Inhibin A |
| PlGF controls |
| sFlt-1 Controls |
| Maternal health control early |

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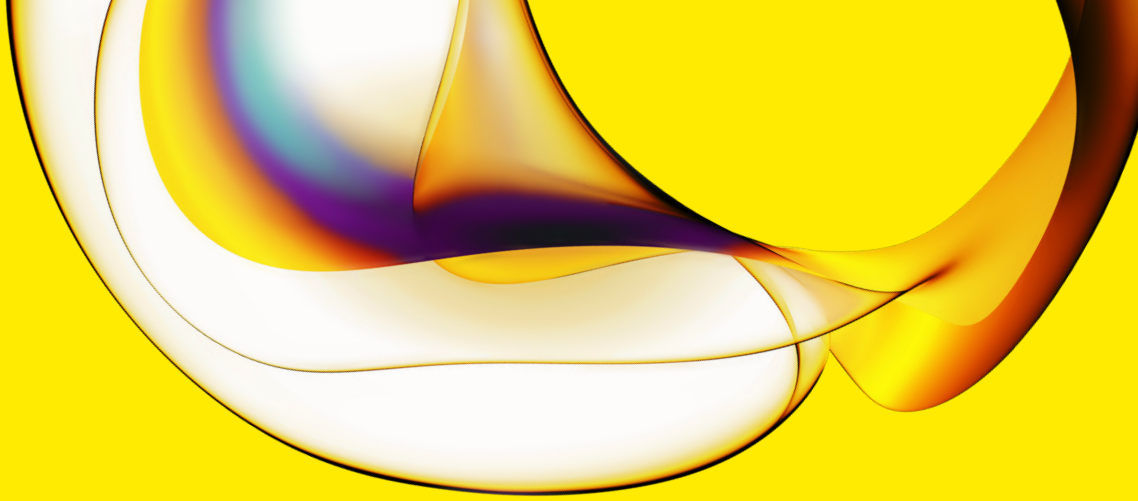
## Revvity is committed to advancing maternal fetal health

With more than 10 million prenatal screens performed annually on our solutions, Revvity is the globally recognized leader in maternal fetal health. Our complete screening and diagnostic solutions, combining clinically proven assays, equipment and informatics, are devoted to supporting the needs of all women worldwide. Revvity is committed to leveraging this know ledge to advance the  science of maternal fetal health and expand the capabilities of laboratory specialists and clinicians now, and in the future.



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