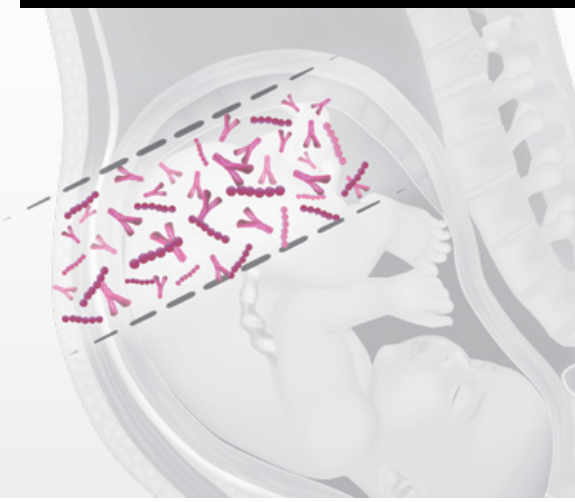

## Angiogenic Factors

# Key Biomarkers for Pregnancy Management in Women at Risk of Preeclampsia

## Background

Bringing a child safely into the world is one of life's most profound moments, yet preeclampsia (PE) remains a serious threat to mothers and babies worldwide. PE is a complex, life-threatening pregnancy disorder that typically develops after 20 weeks of gestation, marked by new-onset hypertension and organ dysfunction (See table 1 for detailed diagnostic criteria for PE). For mothers, complications can include eclampsia, stroke, HELLP syndrome, organ failure, and even death. For the fetus, risks include growth restriction, prematurity, and loss. Women with a history of PE face a 15–20% chance of recurrence[1] and an increased long-term risk of cardiovascular disease[2] and diabetes.[3]

PE has also a significant public health impact globally. It has been estimated that it affects approximately 2–8% of pregnancies worldwide. Globally, there are around 46,000 maternal deaths per year and 0.5 million fetal or newborn deaths per year due to PE.[4] The incidence varies by region with higher rates in low and middle-income countries at around 10% of maternal deaths in Asia and Africa and 25% in Latin America due to preeclampsia and eclampsia.[4] In the United States, Canada and Western Europe, the incidence of PE is reported to be between 2% and 5%.[5] In France, Olié et al. reported that PE complicates around 2% of pregnancies.[6]

**Table 1. Definition of preeclampsia (de novo) by the International Society for the Study of Hypertension in Pregnancy[1]**

Gestational hypertension (sBP ≥140 mm Hg and/or dBP ≥90 mm Hg) accompanied by one or more of the following new-onset conditions at ≥20 weeks' gestation:

1. Proteinuria: 24-h urine protein ≥300 mg/d or spot urine protein/creatinine ratio ≥0.30 mg/mg or urine dipstick testing ≥2+
2. Other maternal end-organ dysfunction, including:
   - Neurological complications (e.g., eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, or persistent visual scotomata)
   - Pulmonary oedema
   - Hematological complications (e.g., platelet count <150,000/µL, Disseminated Intravascular Coagulation, hemolysis)
   - Acute kidney injury (creatinine ≥90 µmol/L; 1 mg/dL)
   - Liver involvement (e.g., elevated transaminases such as ALT or AST >40 IU/L) with or without right upper quadrant or epigastric abdominal pain)
3. Uteroplacental dysfunction (e.g., placental abruption, angiogenic imbalance, fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or intrauterine fetal death)



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Furthermore, PE has a significant impact on healthcare systems. In the United States, where the incidence of PE has increased in the past years,[7,33] Stevens et al. estimated at $2.18 billion in the United States the economic burden of PE during the first 12 months after delivery, comprising $1.03 billion in excess maternal health care expenditures and $1.15 billion in additional infant-related costs.[8]

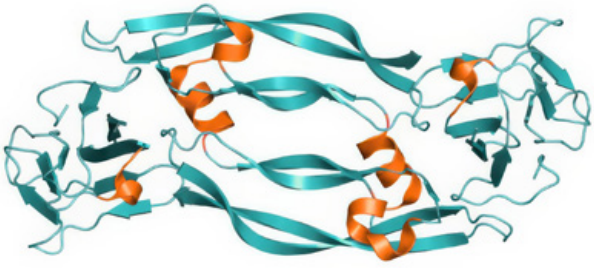

Currently, starting preventive treatment with low-dose aspirin before 16 weeks of gestation is recommended to reduce the risk of preeclampsia in high-risk pregnant women (such as those with a history of PE).[1] Delivery, however, remains the only definitive treatment. Management prior to delivery depends on disease severity and gestational age, which is why PE is often classified based on the timing of gestation: early-onset (before 34 weeks of gestation) and late-onset (at or after 34 weeks).[9] Identifying those at risk for early-onset PE is critical not only to inform expectant mothers, but also to personalize antenatal care and reduce the likelihood of severe complications.

## The key role of angiogenic factors

The physiopathology of PE is not completely known but involves placental dysfunction and angiogenic imbalance.[10-12] This imbalance is characterized by abnormal concentrations of angiogenic factors in maternal circulation with a decrease of the pro-angiogenic placental growth factor (PlGF) and an increase in the anti-angiogenic soluble fms-like tyrosine kinase-1 (sFlt-1).

### Placental Growth Factor (PlGF)

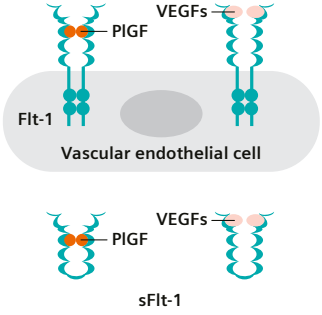
PlGF is a key member of the vascular endothelial growth factor (VEGF) family, predominantly expressed by placental cells. It plays a central role in placental development by promoting cytotrophoblast invasion, spiral artery remodeling, and angiogenesis, which are essential for fetal vascularization.[10,11] PlGF concentrations increase progressively from around week 10, peak at week 30, and decline toward term.[12]



Its dynamic expression is critical for maintaining proper placental function and supporting fetal growth. It has been reported that from 13 to 16 weeks onward, PlGF is significantly lower in women who developed PE compared to those with normal and healthy pregnancies.[12] (See figures 1 and 2)

### Soluble fms-like tyrosine kinase receptor-1 (sFlt-1)

sFlt-1 is a splice variant of the VEGF receptor Flt-1 and lacks membrane-binding domains, allowing it to act as a decoy receptor. It binds circulating VEGF and PlGF, preventing their interaction with cell surface receptors and thereby inhibiting angiogenesis.




Produced by the placenta, sFlt-1 regulates vascular growth during pregnancy.[11] In PE, elevated sFlt-1 concentrations—especially early in gestation—are associated with impaired placental vascularization. Concentrations of sFlt-1 increased earlier in gestation and to higher concentrations in individuals who later developed PE. (See figures 1 and 2)

**Figure 1. PlGF and sFlt-1 production during normal pregnancy. Adapted from reference 12.**

Free PlGF concentrations begin rising around week 11, peak between weeks 29–32 and supports placental development. sFlt-1 concentrations remain stable until weeks 33–36, then increase by approximately 145 pg/mL per week until delivery.

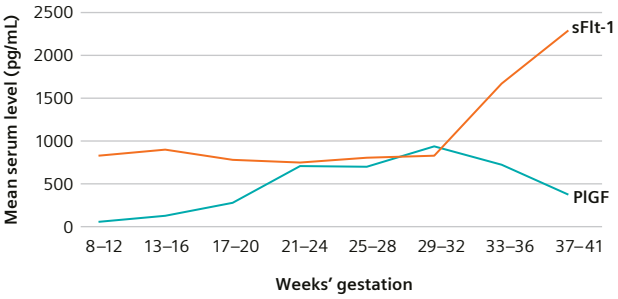
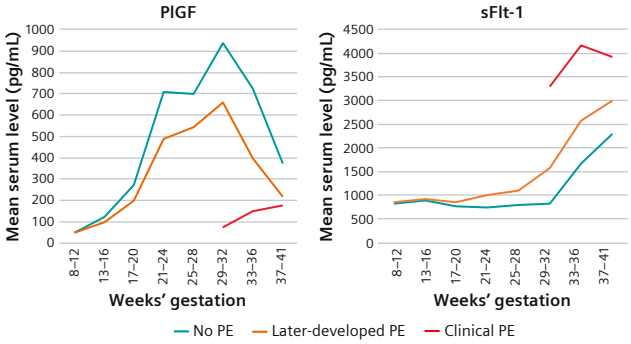



**Figure 2. PlGF and sFlt-1 production in PE. Adapted from reference 12.**

PlGF concentrations follow a similar pattern in all three groups but are significantly lower in pregnant women who develop PE (orange/red lines) compared to controls (green line). sFlt-1 concentrations are elevated in PE groups, with the highest concentrations observed in women with established PE (red line).




Elevated sFlt-1 and lower PlGF concentrations leading to an elevated sFlt-1/PlGF ratio is observed in cases of placental dysfunction and is associated with pregnancies complicated by PE. (Figures 3 and 4)

**Figure 3. sFlt-1/PlGF ratio in women who develop PE later in pregnancy. Adapted from reference 12.**

Representation of both PlGF and sFlt-1 concentrations over time reveals a significantly higher sFlt-1/PlGF ratio in women who develop PE compared to controls.

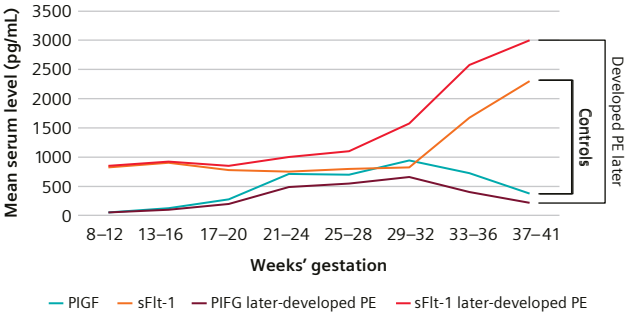
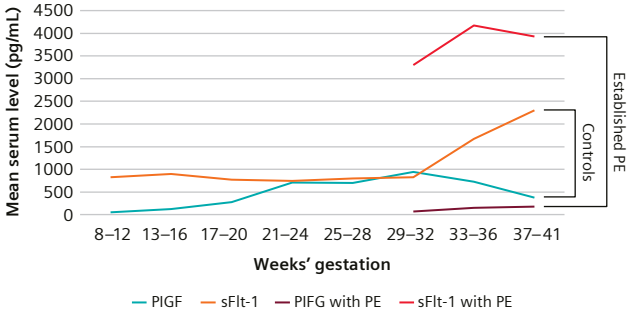



**Figure 4. sFlt-1/PlGF ratio in women with established PE. Adapted from reference 12.**

The sFlt-1/PlGF ratio is markedly elevated in women with established PE compared to controls, supporting its potential use in predicting disease onset




## Clinical and cost-effectiveness evidence supporting the value of using the sFlt-1/PlGF ratio in clinical practice

Once the role of angiogenic factors in the pathophysiology of PE was uncovered, researchers sought to better define the clinical utility of the measurements of those biomarkers and how they could support clinicians in accurately diagnosing the disease and improving patient care. Extensive research has explored the interest of measuring the sFlt-1/PlGF ratio in three key areas: to improve diagnostic accuracy,[13] to predict short-term development of PE,[14-16] and to assess the prognosis of adverse maternal and fetal outcomes.[17] This section highlights a selection of studies supporting the clinical and economic value of measuring the sFlt-1/PlGF ratio.[18-20] While not exhaustive, these examples illustrate the growing evidence supporting the use of the sFlt-1/PlGF ratio.

## Diagnostic accuracy across gestational ages

Verlohren et al.[13] conducted a multicenter case–control study involving 1149 patients to define gestational age–specific sFlt-1/PlGF cutoffs for the diagnosis of PE. Their results showed that using two cutoffs, one focusing on high sensitivity and the other on high specificity, improved the diagnostic precision across gestational ages:

**Early gestation** (20+0 – 33+6 weeks)

| | | |
|---|---|---|
| Low-risk cutoff ≤33 | Sensitivity 95% | Specificity 94% |
| High-risk cutoff ≥85 | Specificity 99.5% | Sensitivity 88% |

**Late gestation** (≥34 weeks)

| | | |
|---|---|---|
| Low-risk cutoff ≤33 | Sensitivity 89.6% | Specificity 73.1% |
| High-risk cutoff ≥110 | Specificity 95.5% | Sensitivity 58.2% |

The authors also indicate that sFlt-1/PlGF ratio values falling between these cutoffs for the early and late gestational phases are considered equivocal and should help identifying patients at intermediate risk.[13]

## Short-term prediction of PE

The PROGNOSIS study[14] aimed to determine whether the sFlt-1/PlGF ratio could predict the absence of PE within 1 week and the presence of PE within 4 weeks. The study was conducted as an international prospective, multicenter observational trial involving 1273 pregnant women (aged 18 years and older) at 24 to 36+6 weeks of gestation with singleton pregnancies in whom PE was suspected. The results demonstrated that an sFlt-1/PlGF ratio ≤38 helped to rule out PE within one week (NPV 99.3%), while a ratio >38 helped to predict PE within four weeks (PPV 36.7%). These findings were confirmed by PROGNOSIS Asia[15] (2019; n = 764), reporting similar performance (NPV 98.6%, PPV 30.3%). The INSPIRE trial[16] included 370 women (18 years old or older) with singleton pregnancy between 24+0 and 37+0 weeks of gestation and a clinical suspicion of PE. This study further validated that using the sFlt-1/PlGF ratio improved clinical precision showing 100% sensitivity and NPV for PE within one week when the ratio was ≤38. However, the use of the sFlt-1/PlGF ratio didn't contribute to a significant reduction of hospitalizations (26% vs. 32%; p = 0.192).

## Prediction of adverse outcomes

Rana et al.[17] measured the sFlt-1/PLGF ratio at presentation in 616 women with singleton pregnancies (28.6% before gestational week 34) with signs and symptoms of preeclampsia. They reported that the individuals who developed adverse events had a significantly higher sFlt-1/PLGF ratio, with a difference being especially pronounced before 34 weeks of gestation. They concluded that adding the sFlt-1/PlGF ratio to hypertension and proteinuria for women presenting before 34 weeks gestation could predict adverse outcomes, with an area under the curve (AUC) of 0.93 (vs. 0.84 for hypertension and proteinuria alone; P=0.001).

A sFlt-1/PlGF ratio ≥85 before 34 weeks was associated with an 86% of delivery within two weeks, compared to only 15.8% when the ratio was <85.

In addition to clinical utility and benefits, several other studies have employed economic models to evaluate the impact of implementing the sFlt-1/PlGF ratio in terms of reduction of unnecessary hospitalizations and overall healthcare expenditures. Such studies concluded that the implementation of the sFlt-1/PlGF ratio could result in cost savings per patient, estimated at £344 (UK),[18] €361 (Germany)[19] and €670 (Italy).[20] Those potential cost-savings would be driven primarily by enabling earlier intervention and avoiding unnecessary hospitalizations.

## sFlt-1/PlGF Ratio in Practice: Insights from International Societies and Clinical Guidelines

The NICE guidelines,[21] the European Society of Cardiology (ESC) guidelines,[22,23] the combined guidelines on Hypertensive Disorders in Pregnancy[24] (German Society of Gynecology and Obstetrics (DGGG), Austrian Society of Gynecology and Obstetrics (OEGGG), Swiss Society of Gynecology and Obstetrics (SGGG)), the Spanish Society of Gynecology and Obstetrics (SEGO)[25] recommend measuring the sFlt-1/PlGF ratio to help diagnose and/or predict development of PE. In contrast, the French College of Obstetricians and Gynecologists[26] does not recommend routine use of the sFlt-1/PlGF ratio solely to reduce maternal or perinatal morbidity in suspected or confirmed PE, citing moderate to low evidence and limited test availability—as STAT tests available 24/7—in maternity centers across France. Similarly, the Danish Society for Obstetrics and Gynecology[27] excludes angiogenic assays from its guidelines due to limited clinical implementation.

## Conclusion

While limited availability and access to angiogenic assays might remain a challenge in some countries, numerous studies provide evidence supporting the value of measuring the sFlt-1/PlGF ratio for managing pregnant women with signs and symptoms of preeclampsia.

## About Atellica IM sFlt-1 and Atellica IM PlGF assays*

The Atellica IM PlGF and Atellica IM sFlt 1 assays are for in vitro diagnostic use in the quantitative determination of the placental growth factor and of the soluble fms-like tyrosine kinase 1 in human serum and plasma (dipotassium EDTA).[28-31] These two assays are used in combination on Atellica IM and CI Analyzers to determine the sFlt-1/PlGF ratio. The Atellica IM sFlt-1/PlGF ratio is intended for use:

- in the prognosis of preterm delivery and adverse outcomes in women presenting with signs and symptoms of preeclampsia.
- as an aid in the diagnosis of preeclampsia, in conjunction with signs and symptoms of the disease.
- as an aid in short-term prediction of preeclampsia (rule-out and rule-in) in pregnant women with suspicion of preeclampsia in conjunction with other diagnostic and clinical information.

The results of the sFlt-1/PlGF ratio should always be interpreted in conjunction with the patient's medical history, clinical presentation, and other findings.

See Instructions for Use[28-31] and below for detailed information on each intended use of the sFlt-1/PlGF ratio determined on Atellica IM and CI Analyzers.

### Prognosis of preterm delivery and adverse outcomes in women presenting with signs and symptoms of preeclampsia†

**Gestational Age 20+0 – 35+6 (weeks + days)**

PE ratio (sFlt-1/PlGF) → cutoff ≥38 → **Interpretation:** Increased risk for developing adverse maternal/fetal outcomes or preterm delivery within 2 weeks

| Clinical Performance | | |
|---|---|---|
| **PE Ratio (sFlt-1/PlGF) cutoff ≥38** | **Estimate** | **95% CI** |
| Sensitivity | 88.42% (84/95) | 81.99–94.86% |
| Specificity | 87.65% (213/243) | 83.52–91.79% |
| Positive Predictive Value (PPV) | 73.68% (84/114) | 65.60–81.77% |
| Negative Predictive Value (NPV) | 95.09% (213/224) | 92.26–97.92% |

A total of 338 specimens collected from 12 sites across the United States were tested at 1 clinical testing site. Specimens were from individuals with singleton pregnancies between gestational weeks 20+0 days and 35+6 days with signs and symptoms of preeclampsia.[32] The clinical performance of the PE ratio was evaluated for the prognosis of preterm delivery and adverse outcomes within 2 weeks using a cut-off value of 38. Of the 338 subjects, 95 subjects experienced preterm delivery or an adverse outcome within 2 weeks of presentation.[28-31]

## Aid in short-term prediction of preeclampsia in pregnant women with suspicion of preeclampsia in conjunction with other diagnostic and clinical information†

**Gestational Age 24+0 – 36+6/7 (weeks + days)**

sFlt-1/PlGF ratio

- cutoff ≤38 → **Interpretation:** Rule-Out Preeclampsia for 1 week (decreased likelihood for developing preeclampsia in the next week)
- cutoff >38 → **Interpretation:** Rule-In Preeclampsia within 4 weeks (increased likelihood for developing preeclampsia in the next four weeks)

**Clinical Performance**

| Parameter | N[a] | Estimate | 95% CI |
|---|---|---|---|
| Positive Percent Agreement | 27 | 100% (27/27) | (87.5%, 100%) |
| Negative Percent Agreement | 105 | 96.2% (101/105) | (90.6%, 98.5%) |

[a]*Number of measurements.*

A study enrolled 132 pregnant women aged 18 years or older with singleton pregnancies between gestational weeks 24+0 days and 36+6 days, all presenting with signs and symptoms of preeclampsia.[32] Specimens were used to evaluate the diagnostic concordance between the sFlt 1/PlGF ratio obtained from the Atellica IM sFlt 1 and Atellica IM PlGF assays and a commercially available sFlt 1/PlGF ratio, using a PE ratio cut-off value of 38 for short-term prediction of preeclampsia. Results were established using the Atellica IM Analyzer.[28-31]

## Aid in the diagnosis of preeclampsia, in conjunction with signs and symptoms of the disease†

**Early Gestation 20+0 – 33+6 (weeks + days)**

sFlt-1/PlGF ratio

- cutoff ≤33 → **Interpretation:** Rule-Out Preeclampsia
- cutoff ≥85 → **Interpretation:** Rule-In Preeclampsia

**Clinical Performance**

| PE Ratio (sFlt-1/PlGF) cutoff | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| ≤33 (Rule-Out) | 91.6% (120/131) | 85.6–95.2% | 97.6% (240/246) | 94.8–98.9% |
| ≥85 (Rule-In) | 81.7% (107/131) | 74.2–87.4% | 99.2% (244/246) | 97.1–99.8% |

**Late Gestation 34+0 – delivery (weeks + days)**

sFlt-1/PlGF ratio

- cutoff ≤33 → **Interpretation:** Rule-Out Preeclampsia
- cutoff ≥110 → **Interpretation:** Rule-In Preeclampsia

**Clinical Performance**

| PE Ratio (sFlt-1/PlGF) cutoff | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| ≤33 (Rule-Out) | 85.3% (81/95) | 76.8–91.0% | 84.5% (212/251) | 79.5–88.4% |
| ≥110 (Rule-In) | 55.8% (53/95) | 45.8–65.4% | 96.8% (243/251) | 93.8–98.4% |

Testing was performed on 723 prospectively collected serum specimens from 18 sites across the United States at 1 site using 1 reagent lot for each assay. The 2:1 case control study included women with singleton pregnancy diagnosed with preeclampsia at the time of enrollment, and women with singleton pregnancy who did not develop preeclampsia/eclampsia/hemolysis, elevated liver enzyme levels, and low platelet count or intrauterine growth restriction during pregnancy. Preeclampsia diagnoses were confirmed by adjudication using the International Society for the Study of Hypertension in Pregnancy (ISSHP) definition for preeclampsia.[1] Separate PE ratio (sFlt 1/PlGF) cut-off values were verified for both early gestational phase (week 20+0 days and week 33+6 days) and late gestational phase (≥34 weeks) using the ruleout and rule-in PE ratio (sFlt 1/PlGF) cut-off values of 33 and 85 for subjects in early gestation and 33 and 110 for subjects in late gestation: Results were established using the Atellica IM Analyzer.[28-31]

Talk to your Siemens Healthineers representative to learn more about the sFlt-1 and PlGF tests available on Atellica Analyzers. Do not miss the opportunity to enhance your lab's clinical value. By adding angiogenic markers to your laboratory's test menu, you can help improve access for obstetricians and gynecologists, supporting them in the timely and effective care of preeclampsia. Click here to explore Siemens Healthineers comprehensive test portfolio for reproductive endocrinology.


† See products' Instructions for Use for detailed information on study design and clinical performance supporting each intended use.[28-31]

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