Atellica IM and ADVIA Centaur sFlt-1 and PlGF Assays

Analytical and Clinical Performance Evaluation of Siemens Healthineers Atellica IM and ADVIA Centaur sFlt-1 and PlGF Assays*

Agostino Palladino, Dr. Xiaochun Zhang, Margarita Hunter-Panzica
Siemens Healthineers, Tarrytown, NY, U.S.

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Clinical Utility

Preeclampsia (PE) is a hypertensive disorder of pregnancy that develops after 20 weeks of gestation and is characterized by high blood pressure and proteinuria. When proteinuria is absent in new-onset hypertensive PE patients, other findings can be present such as thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and headache. It has been estimated that preeclampsia occurs in 2–8% of pregnancies worldwide, which can have a severe impact on both the mother and the child.[1] Fetal complications include low birth weight, prematurity, and death. Maternal complications include renal failure, hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, liver failure, cerebral edema with seizure, and death.

Although hypertension and proteinuria are diagnostic criteria for PE, the traditional tools to measure these conditions have low sensitivity and specificity regarding the prediction of severe maternal and perinatal outcome. Moreover, preeclampsia can be mimicked and thereby confused with many other diseases, such as chronic hypertension, chronic renal disease, and autoimmune disorders. Thus, there is a critical need for a method to reliably help identify high-risk PE patients.

There is no known cure for preeclampsia. Its management focuses on early detection, caring for preexisting conditions, and risk reduction. Antihypertensive therapy, aspirin, and intravenous or intramuscular magnesium sulfate may help with managing the disease. However, the complete resolution of the maternal signs and symptoms of the disease only occurs in the postpartum period, with some symptoms disappearing in a matter of hours, while others may take weeks or months.[2]

Preeclampsia is a costly disease, and most of its expenses are associated with the care of premature babies, especially those born before 28 weeks. Hence, extending time in the womb is key to reducing PE costs, and the best way to ensure this is through a rapid and accurate assessment of the disorder. The etiology and pathophysiology of preeclampsia are not clearly understood. There is growing evidence suggesting that PE is the result of an imbalance of circulating pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and/or placental growth factor (PlGF), and anti-angiogenic factors such as soluble fms-like tyrosine kinase receptor-1 (sFlt-1, also known as soluble VEGF receptor 1).

PlGF is a growth hormone belonging to the VEGF family located on chromosome 14 of the genome. PlGF refers to the placenta because it was first cloned from a human placenta cDNA library, and it was characterized as being highly homologous to VEGF. PlGF is necessary for placentation and placental growth that occurs throughout most of the pregnancy to support the growing fetus.[3,4] It is directly responsible for stimulating and maintaining cytotrophoblast invasion by causing these epithelial cells to take on endothelial characteristics that result in spiral artery remodeling. It also supports angiogenesis of the fetal blood supply and the pseudovasculogenesis that creates the placental lacunae.

The free PlGF in circulation gradually increases during pregnancy starting around week 10 (mean value 36 pg/mL) and peaks around week 30 (mean value 525 pg/mL), where it decreases while pregnancy progresses to term.[5] While VEGF homodimer exerts its biological activities through activation of both of its receptors, Flt-1 and Flk-1 (a receptor for VEGF), PlGF promotes angiogenesis by only binding and inducing auto-phosphorylation of transmembrane receptors through sFlt-1. This will subsequently activate its downstream signal transduction pathway which involves an array of second messengers. Besides its angiogenic effect on its own, it is speculated that the increased concentration of PlGF during pregnancy also leads to the displacement of VEGF from Flt-1. As a result, there is more VEGF available to bind and activate Flk-1, which is more crucial for vascular development than Flt-1. In PE patients, including those who develop the condition later in pregnancy, the level of PlGF is significantly low compared to pregnant individuals without preeclampsia.

On the other hand, sFlt-1, a shortened splice variant of Flt-1 that lacks the transmembrane and cytoplasmic domain, counteracts the angiogenic effects of circulating VEGF and PlGF by adhering to and preventing their binding to the functional transmembrane receptors, Flt-1, on the cell surface. During pregnancy, sFlt-1 is made by the placenta and used to tightly regulate the availability of PlGF and VEGF throughout pregnancy to prevent placental overgrowth. In PE patients, there is a significant increase in sFlt-1 in both the placenta and blood circulation during early pregnancy, which can lead to reduced placental vascularization and termination of pregnancy. If the sFlt-1 level is >1000 pg/mL from 10 to 28 weeks of gestation, it is considered abnormal.[5]

The clinical importance of sFlt-1 and PlGF production in preeclampsia is crucial to understanding and managing this condition. Levine et al.,[6] demonstrate that from 13 to 16 weeks onward, PlGF is significantly lower in women who developed PE relative to their healthy counterparts. Furthermore, PlGF is substantially lower in women with clinically diagnosed preeclamspia.

In contrast, levels of sFlt-1 remain low during most of a normal pregnancy, whereas in PE patients, sFlt-1 increases at a greater rate in circulation in later stages of pregnancy and remains elevated.[6]

As a result of these changes, the sFlt-1/PlGF ratio, also known as the PE ratio, increases significantly in preeclampsia patients. Therefore, combined with clinical symptoms, the sFlt-1/PlGF ratio could be used in the risk assessment of PE. Using the sFlt-1/PlGF ratio along with clinical judgment also shows a trend toward earlier diagnosis and reduction in maternal costs of care: Combining the standard of care with the sFlt-1/PlGF ratio performed better than either standard of care alone or use of the ratio alone.[7-9]

Numerous other studies support the use of the sFlt-1/PlGF ratio to improve clinical decision making. One consistent outcome from these studies is that the sFlt-1/PlGF ratio is significantly increased in preeclampsia patients compared to the control groups as well as to chronic and gestational hypertension groups. These findings indicate that the sFlt-1/PlGF ratio combined with the clinical symptoms could be used as risk assessment to improve outcomes of the mother and the fetus.[10]

Assay Methodology

The Atellica® IM and ADVIA Centaur® sFlt-1 assays are two-site sandwich immunoassays employing direct chemiluminometric technology, which uses constant amounts of two anti-human sFlt-1 antibodies (see Figure 1 for details). The first antibody in the Lite Reagent is a mouse monoclonal anti-human sFlt-1 antibody labeled with acridinium ester. The second antibody is a biotinylated monoclonal mouse anti-human sFlt-1 antibody that is preformed to streptavidin-coated paramagnetic latex particles in the Solid Phase. The Atellica IM and ADVIA Centaur PlGF assays are two-site sandwich immunoassays using direct chemiluminometric technology, which uses two anti-human PlGF antibodies. The first antibody in the Lite Reagent, is a rat monoclonal anti-human PlGF antibody labeled with acridinium ester. The second antibody is a biotinylated mouse monoclonal anti-human PlGF antibody that is preformed to streptavidin coated paramagnetic latex particles in the Solid Phase.

The Atellica IM and ADVIA Centaur analyzers automatically perform the steps shown in Figure 1. A direct relationship exists between the amount of analyte present in the patient sample and the amount of relative light units (RLUs) detected by the system.

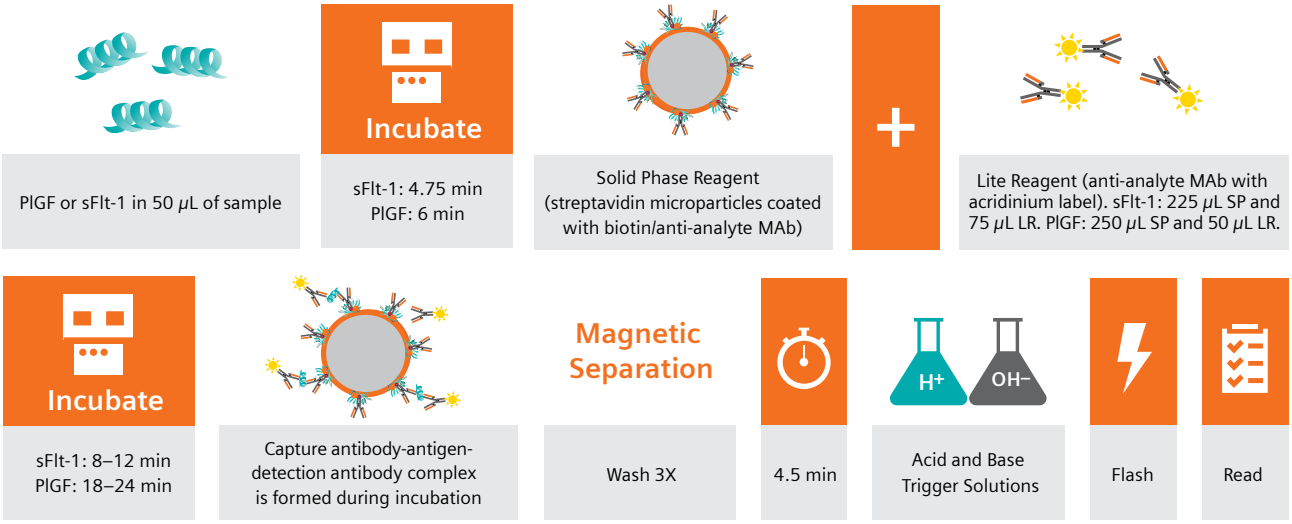

Figure 1. Atellica IM and ADVIA Centaur sFlt-1 and PlGF assay format.

Performance of sFlt-1 and PlGF Assays on Atellica IM and ADVIA Centaur Analyzers

Analytical performance

Siemens Healthineers conducted analytical studies to evaluate the performance of the sFlt-1 and PlGF assays. The evaluation included detection capabilities, precision, linearity, interferences, and stability studies.

The sFlt-1 assay has a measuring range of 15–85,000 pg/mL and the PlGF assay has a measuring range of 9–10,000 pg/mL. Illustrated in Table 1 is the detection capabilities for each of the assays.[11-16]

Table 1. Atellica IM and ADVIA Centaur assay detection capabilities.

	ADVIA Centaur XP/XPT	ADVIA Centaur CP	Atellica IM
sFlt-1			
Limit of Blank (LoB)	4 pg/mL	2 pg/mL	2 pg/mL
Limit of Detection (LoD)	10 pg/mL	5 pg/mL	10 pg/mL
Limit of Quantitation (LoQ)	13 pg/mL	20 pg/mL	13 pg/mL
PlGF			
Limit of Blank (LoB)	5 pg/mL	3 pg/mL	3 pg/mL
Limit of Detection (LoD)	9 pg/mL	6 pg/mL	6 pg/mL
Limit of Quantitation (LoQ)	9 pg/mL	14 pg/mL	9 pg/mL

Figure 2 uses a Deming regression model to show the relationship between the ADVIA Centaur XP sFlt-1 assay (y) and COBAS e 411 ELECSYS sFlt-1 assay (x) in 338 samples ranging from 451–35061 pg/mL: ADVIA Centaur XP sFlt-1 = 1.44 x – 822 pg/mL, r = 0.944

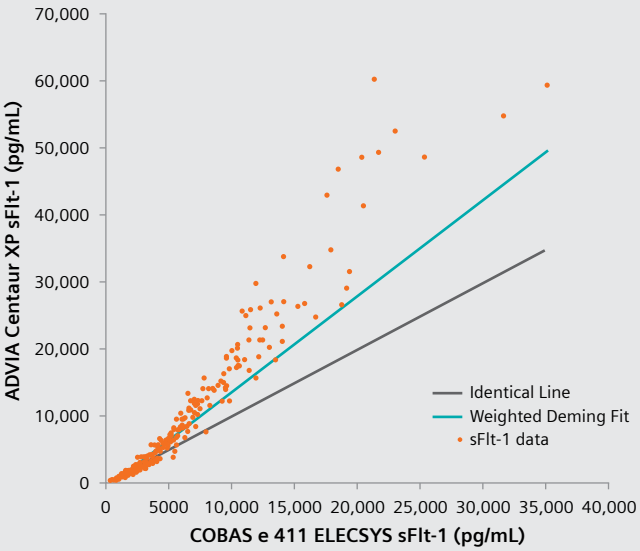

Figure 2. Correlation of ADVIA Centaur XP sFlt-1 assay vs. COBAS e 411 ELECSYS sFlt-1 assay.

Figure 3 uses a Deming regression model to show the relationship between the ADVIA Centaur XP PlGF assay (y) and COBAS e 411 ELECSYS PlGF assay (x) in 338 samples ranging from 8–2187 pg/mL: ADVIA Centaur XP PlGF = 1.30 x – 2.7 pg/mL, r = 0.980

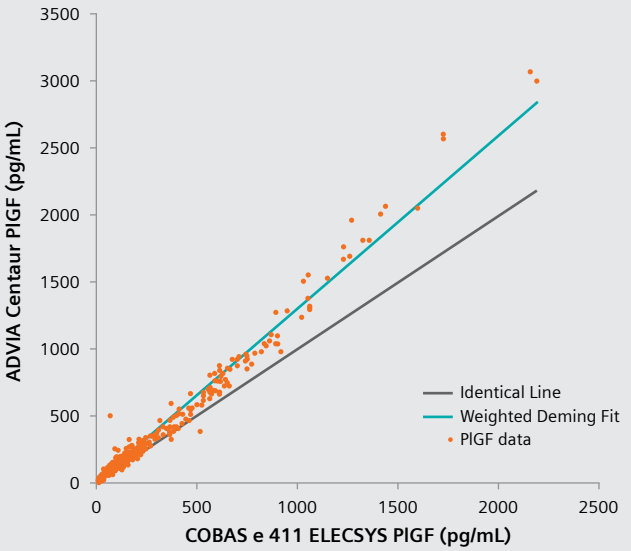

Figure 3. Correlation of ADVIA Centaur XP PlGF assay vs. COBAS e 411 ELECSYS PlGF assay.

Representative data, results obtained at individual laboratories may vary from the data presented.

The sFlt-1 and PlGF assays were designed to provide repeatability of less than 7% CV and within-lab precision of less than 8% CV. Assay precision achieved was well below the design requirements. Both assays have less than 10% interference up to 3510 ng/mL of biotin and less than 10% interference from other common endogenous interferents.

Method comparison†

Individual assays and PE ratio results were also compared to results of the Roche COBAS e 411 ELECSYS immunoassay.

Method comparison studies to Roche COBAS e 411 ELECSYS preeclampsia assays show that ADVIA Centaur sFlt-1 and PlGF individual assay results are generally higher at the upper end of the measuring range.

†The method comparison study is based on internal research and development testing that are not commercially available.

However, individual assay results are not used to make a clinical assessment. Comparison of the ADVIA Centaur PE ratio to the COBAS e 411 ELECSYS PE ratio shows close alignment.

In clinical practice, the PE ratio (sFlt-1/PlGF) is used in the prognosis of adverse outcomes and preterm deliveries. The data below (Figures 4 and 5)[17] shows PE ratios for the ADVIA Centaur and COBAS e 411 ELECSYS assays where there is a high correlation between the two methods, especially below a ratio of 100, where the ratio is clinically significant.

Figure 4 uses a Deming regression model to show the relationship between the ADVIA Centaur XP PE ratio (y) and COBAS e 411 ELECSYS PE ratio (x) from 336 ratio results ranging from 1–2348: ADVIA Centaur PE ratio = 0.98 x – 0.62, r = 0.930

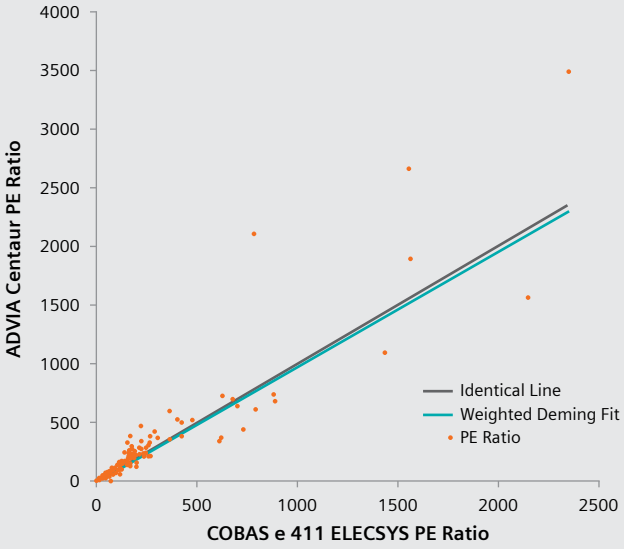

Figure 4. Correlation of ADVIA Centaur PE ratio vs. COBAS e 411 ELECSYS PE ratio.

Figure 5 uses a Deming regression model to show the relationship between the ADVIA Centaur XP PE ratio (y) and COBAS e 411 ELECSYS PE ratio (x) from 225 ratio results ranging from 1–97, at the low end of the ratio range: ADVIA Centaur PE ratio = 0.90 x – 0.48, r = 0.924

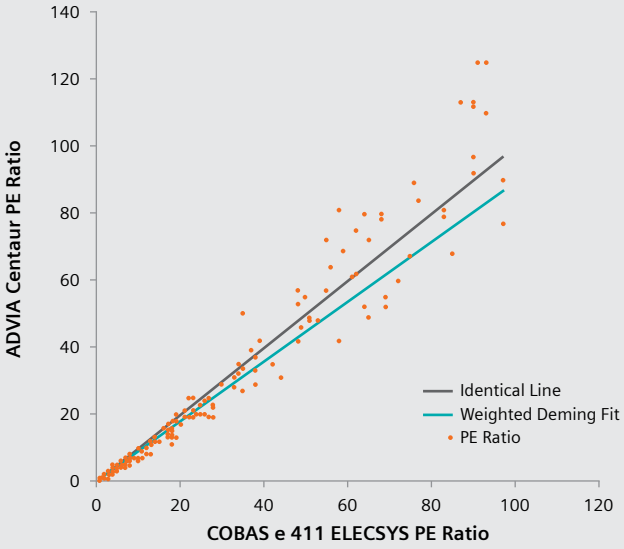

Figure 5. Correlation of ADVIA Centaur PE ratio vs. COBAS e 411 ELESYS PE ratio at the low end.

Representative data, results obtained at individual laboratories may vary from the data presented.

Concordance analysis

Individual assays and PE ratio results were also compared to results from COBAS e 411 ELECSYS immunoassays. A total of 338 samples were compared using a cutoff of 38. The concordance results shown in Table 2 demonstrate high agreement between the two systems.

Table 2. Concordance of PE ratio results compared to Roche COBAS e 411 ELECSYS immunoassays.

		COBAS e 411 ELECSYS PE Ratio	
		Positive ≥38	Negative <38
ADVIA Centaur PE Ratio	Positive	126	2
	Negative	6	204
	% Agreement	97.6%	
	PPA	95.5%	
	NPA	99.0%	

Positive Percent Agreement (PPA)
Negative Percent Agreement (NPA)

Conclusions

The Atellica IM and ADVIA Centaur sFlt-1 and PlGF assays used in this evaluation study demonstrate analytical and clinical performance competitive with commercially available assays on the market:

- The sFlt-1 and PlGF assays have measuring ranges of 15–85,000 pg/mL and 9–10,000 pg/mL, respectively.
- Within-laboratory and repeatability precision studies demonstrated % CVs ≤5 across the measuring range for both assays.
- Minimal interference from biotin and other endogenous interferents was observed for both assays.
- Overall agreement of the ADVIA Centaur PE ratio vs. the COBAS e 411 ELECSYS PE ratio is 97.6% when using a cutoff of 38 for prognosis of preterm delivery and adverse outcomes,[11-16,18-19] showing a positive correlation between methods.†

This evaluation shows that the Atellica IM and ADVIA Centaur PE assays are precise and sensitive for measuring sFlt-1 and PlGF across a wide range of concentrations. The data demonstrated high concordance with Roche COBAS e 411 ELECSYS PE assays.

The Atellica IM and ADVIA Centaur sFlt-1 and PlGF assays are rapid and accurate tools to help physicians identify and manage patients with preeclampsia at risk for preterm delivery and adverse outcomes.

†The method comparison study is based on internal research and development testing that are not commercially available.

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Siemens Healthineers Headquarters
Siemens Healthcare GmbH
Henkestr. 127
91052 Erlangen, Germany
Phone: +49 9131 84-0
siemens-healthineers.com

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Siemens Healthcare Diagnostics Inc.
Laboratory Diagnostics
511 Benedict Avenue
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USA
Phone: +1 914-631-8000

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