

# Prenatal Clinical Assessment of sFlt-1 (Soluble fms-like Tyrosine Kinase-1)/PIGF (Placental Growth Factor) Ratio as a Diagnostic Tool for Preeclampsia, Pregnancy-induced Hypertension, and Proteinuria

Pränatale klinische Beurteilung der sFlt-1 (soluble fms-like tyrosine kinase-1)/PIGF (placental growth factor) Ratio als diagnostisches Instrument für Präeklampsie, schwangerschaftsinduzierten Hochdruck und Proteinurie

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## Key words

- preeclampsia
- pregnancy-induced hypertension
- sFlt-1
- PIGF
- IUGR
- proteinuria

## Schlüsselwörter

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## Abstract



**Background:** Aim of the study was a critical assessment of the clinical validity of the prenatal determination of sFlt-1/PIGF for preeclampsia (PE), pregnancy-induced hypertension (PIH), and proteinuria. Our analysis was based on a specificity of 95% and a sensitivity of 82% for the prediction of preeclampsia, as described by Elecsys (Roche).

**Methods:** In this retrospective study the ratio of the prenatal antiangiogenic factor sFlt-1 (soluble fms-like tyrosine kinase-1) to the proangiogenic factor PIGF (placental growth factor) was analyzed using the electrochemiluminescence immunoassay of Elecsys (Roche Diagnostics, Mannheim, Germany) in 173 pregnant women. Sixty-three women with PE, 34 women with PIH and 6 women with proteinuria were compared to 72 controls. On average, the sFlt-1/PIGF ratio was determined 8 (controls), 2.4 (PE), 3.2 (PIH) and 4.1 (proteinuria) weeks before delivery. The PE and PIH cases were further subdivided into early (< 34 weeks of gestation) and late (≥ 34 weeks of gestation) onset groups. Statistical data analysis was done using the usual descriptive statistics and logistic regression analysis. ROC curves were calculated, and the sensitivity, specificity, and negative and positive predictive value (NPV, PPV) were estimated for a threshold of 85.

**Results:** Although the specificity of the sFlt-1/PIGF ratio was high for PE, the sensitivity was low (only 59.4%), thus giving unsatisfying results for PE. The sensitivity only increased to 62.5% for the early-onset PE group. Intriguingly, a high ratio was detected for the combination of IUGR (intrauterine growth restriction) and PE in the early-onset PE group (8 cases). In the control group, 4 cases exceeded the cut-off value of 85 but showed no clinical signs of PE and the birth was unremarkable. In summary, we found that the sFlt-1/PIGF ratio could not be used as a predictive

## Zusammenfassung



**Fragestellung:** Kritische Begutachtung der klinischen Validität der vorgeburtlichen Bestimmung der sFlt-1/PIGF-Ratio bei Präeklampsie, schwangerschaftsinduzierter Hypertonie (SIH) und Proteinurie. Zugrunde gelegt wurde die von Elecsys (Roche) publizierte Spezifität von 95% und Sensitivität von 82% für die Vorhersage einer Präeklampsie.

**Material und Methodik:** Durchgeführt wurde eine retrospektive Analyse der sFlt-1/PIGF-Ratio mittels Electrochemiluminescence Immunoassay von Elecsys (Roche Diagnostics, Mannheim, Deutschland) bei 173 Schwangeren. 63 Frauen mit Präeklampsie, 34 Frauen mit SIH und 6 Frauen mit Proteinurie wurden mit 72 Kontrollen verglichen. Im Mittel wurde die Ratio bei den Kontrollen 8, bei den Präeklampsien 2,4, bei SIH 3,2 und bei Proteinurien 4,1 Wochen vor Geburt bestimmt. Die Präeklampsien sowie die SIH-Fälle wurden nochmals in Early-Onset- (< 34 SSW) und Late-Onset-Gruppen (≥ 34 SSW) unterteilt. Zur statistischen Auswertung wurde der Fisher-Exact- und Wilcoxon-Rangsummen-Test durchgeführt, zudem erfolgte eine logistische Regressionsanalyse, die Kalkulation von ROC-Kurven und bei einem Cut-off-Wert von 85 eine Abschätzung von Sensitivität, Spezifität, PPV („positive predictive value“) und NPV („negative predictive value“).

**Ergebnisse:** Wenngleich bei PE eine hohe Spezifität für sFlt-1/PIGF vorliegt, konnte eine Sensitivität von nur 59,4% und somit nicht zufriedenstellende Ergebnisse für PE ermittelt werden. Lediglich beim „Early Onset“-PE-Kollektiv (< 34. SSW) steigt die Sensibilität auf 62,5% an. Auffällig war die hohe Ratio bei der Kombination intrauterine Wachstumsretardierung und Präeklampsie im „Early Onset“-Kollektiv (8 Fälle). Im Kontrollkollektiv überschritten 4 Fälle den Cut-off-Wert von 85, die klinisch keine Präeklampsie bis zur Geburt

test for preeclampsia but rather as an indicator for the development and estimation of the severity of PE. Thus, the test is less suitable for the reliable exclusion of PE in routine clinical practice. **Recommendation:** The determination of the sFlt-1/PlGF ratio is only one element for PE diagnosis in addition to the measurement of blood pressure, proteinuria, ultrasound and Doppler.

## Introduction

Preeclampsia refers to a syndrome characterized by the onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman (systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg, and proteinuria of 0.3 grams or more in a 24-hour urine sample) [1]. Worldwide, preeclampsia occurs in about 3–14% of all pregnancies, in 5–8% of pregnancies in the United States and in 2% of pregnancies in Germany. It constitutes a major cause of maternal and perinatal mortality. 10% of preeclampsia cases occur in pregnancies prior to 34 weeks of gestation [2]. Preeclampsia at 36 weeks or more of gestation is usually managed by delivery. Preeclampsia before 36 weeks of gestation creates a clinical dilemma [3]. If preeclampsia occurs at less than 24 weeks of gestation, perinatal mortality is  $>80\%$  [4].

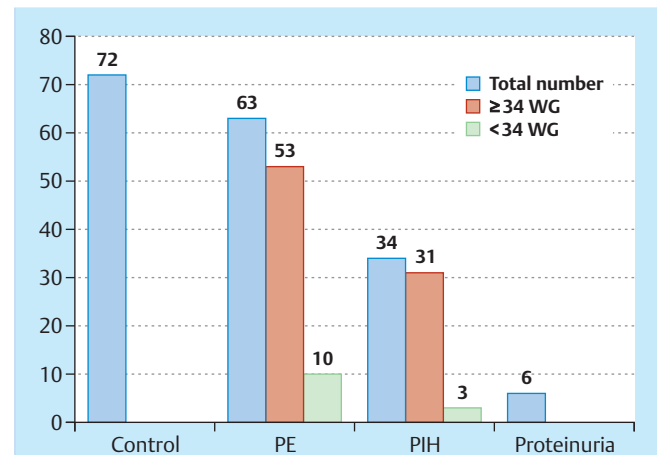
Antiangiogenic soluble fms-like tyrosine kinase-1 (sFlt-1 or sVEGFR-1) is a naturally occurring, circulating antagonist to vascular endothelial growth factor (VEGF). VEGF promotes angiogenesis as a highly specific mitogen which interacts with VEGFR-1 (VEGF receptor-1 or fms-like tyrosine kinase-1 [flt-1]) and VEGFR-2 (kinase-insert domain region [KDR]/Flk-1) [5]. VEGFR-1 and VEGFR-2 are responsible for selective expression on the vascular endothelial cell surface. Proangiogenic placental growth factor (PlGF) belongs to the VEGF family and is predominantly expressed in the placenta. Increased placental expression and secretion of sFlt-1 appears to play an important role in the pathogenesis of preeclampsia [6,7]. PlGF increases in the first and the second trimester and decreases in the third trimester. sFlt-1 increases at the end of pregnancy. These two well-known biomarkers are recommended by Elecsys as useful for the detection and early diagnosis of preeclampsia. The purpose of this study was to assess the validity of the sFlt-1/PlGF ratio for detecting the development of preeclampsia after admission and to evaluate its use as an indicator of the severity of preeclampsia. In addition this study also investigated the utility of the ratio with respect to pregnancy-induced hypertension and proteinuria. We also examined whether a pregnancy complicated by preeclampsia, pregnancy-induced hypertension or proteinuria could be extended while avoiding adverse maternal or perinatal outcomes.

## Material and Methods

This study was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects before the start of the study. In this retrospective study 63 women with preeclampsia, 6 women with proteinuria of other origin, and 34 women with pregnancy-induced hypertension (PIH) were analyzed and compared to 72 controls (Fig. 1). All women admitted to our hospital during a one-year time frame with a suspicion

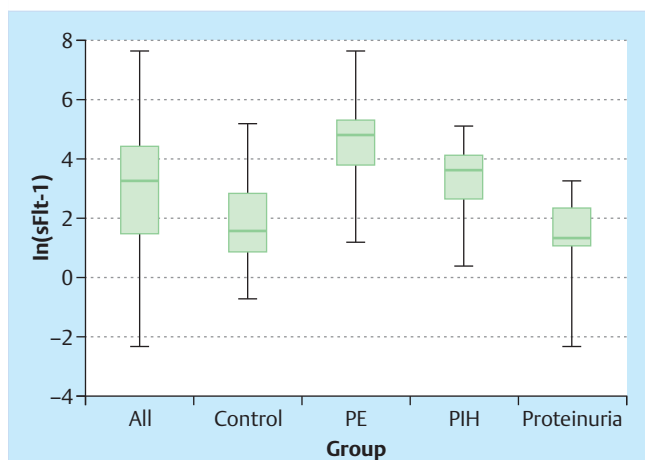
entwickelten. Insgesamt konnte die sFlt-1/PlGF-Ratio nicht zur Prädiktion, sondern eher zur Entwicklung und Schweregradeinschätzung einer Präeklampsie verwendet werden. Der Test ist daher weniger zum sicheren Ausschluss einer Präeklampsie im klinischen Alltag geeignet.

**Empfehlung:** Die Bestimmung der sFlt-1/PlGF-Ratio ist ein Mosaikbaustein bei der PE-Diagnostik neben Messung von Blutdruck und Eiweißausscheidung sowie Ultraschall und Dopplermessung.

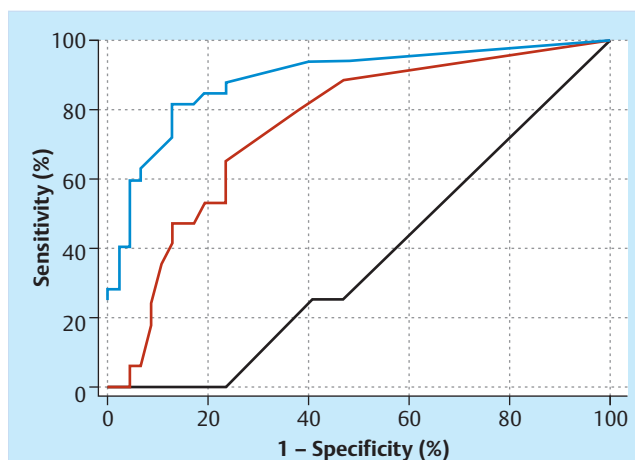


**Fig. 1** Vertical bars in different colors (blue, red, green) represent the investigated groups. The number of investigated women is shown above the bars. Blue: total number of women in the respective group; controls  $n = 72$ , PE (preeclampsia)  $n = 63$ , PIH (pregnancy-induced hypertension)  $n = 34$ , proteinuria  $n = 6$ . Red: late onset of either PE or PIH at  $\geq 34$  WG (weeks of gestation). Green: early onset of either PE or PIH at  $<34$  WG (weeks of gestation).

of hypertension, proteinuria, a history of adverse maternal or perinatal outcome in previous pregnancies complicated by preeclampsia, acute or chronic hypertension, proteinuria, HELLP (hemolysis, elevated liver enzymes, low platelet counts) syndrome or other clinical symptoms indicating possible preeclampsia in any week of gestation prior to delivery were included in the study. Both singleton and twin pregnancies were included. Preterm premature rupture of membranes, intra-amniotic infection, bleeding caused by abruptio placentae or placenta previa were primarily excluded from the study. The purpose of this study was to assess the validity of the sFlt-1/PlGF ratio for the detection of preeclampsia in a general clinical setting. Control for possible biases was not the primary focus and all suitable patients were therefore included in the study. The sFlt-1/PlGF ratio was determined prenatally using maternal venous blood. Serum samples were stored at  $-20^{\circ}\text{C}$  before analysis. The biochemical values were determined by electrochemiluminescence immunoassay using a Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany) and the ROC curves were calculated (Fig. 3). In the control group ( $n = 72$ ) the ratio was determined on average 8 weeks prior to delivery (mean: at 31.6 weeks of gestation; range: 21–40 weeks of gestation). For the other groups, samples were taken 2.4 weeks before delivery in the preeclampsia group ( $n = 63$ ) (mean: at 34.7 weeks of gestation; range: 24–41 weeks of gestation), 3.2 weeks before delivery in the PIH group ( $n = 34$ )



**Fig. 2** Box plots for the logarithm of sFlt-1 in all investigated groups. The plots show the minimum, 25%-quantile, median, 75%-quantile and maximum values.



**Fig. 3** ROC curves. Blue line: preeclampsia (PE) vs. controls. Red line: pregnancy-induced hypertension (PIH) vs. controls. Black line: proteinuria vs. controls.

(mean: at 35.4 weeks of gestation; range: 24–41 weeks of gestation) and 4.1 weeks before delivery in the proteinuria group ( $n=6$ ) (mean: at 33 weeks of gestation; range: 30–38 weeks of gestation) (Table 1, Fig. 2). Previous studies have discussed the use of the ratio as a possible predictive value to detect the development of preeclampsia, and a cut-off value of 85 had been determined [8,9]. For a cut-off value of 85, Roche Diagnostics gives a specificity of 95% and a sensitivity of 82% for their immunoassay [9]. All the women in our study were enrolled based on this specificity and sensitivity.

Statistical analysis of data consisted of the usual descriptive statistics and the calculation of ROC curves. The sensitivity, specificity, negative and positive predictive values (NPV, PPV) were estimated for a threshold of 85. Logistic regression analysis was performed to reassess the ROC results.

## Results

(See Figs. 1, 2 and 3, Tables 1 and 2)

### Control group

The control group consisted of women with typical problems of prematurity such as cervical insufficiency, placental insufficiency, premature contractions, headache, mild edema, serious problems in previous pregnancies, and uncoordinated contractions near term. The mean sFlt-1/PIGF ratio for this group was 18.52 (min 0.50 – max 192.70) and the standard deviation (SD)

was 32.74. In 4 cases, a ratio higher than the cut-off value of 85 was calculated, but no preeclampsia, proteinuria or PIH could be detected clinically. These 4 cases included one singleton case with a known angiotensin-converting-enzyme deficiency (ratio: 192.7, determined at 35 weeks of gestation; delivered vaginally at 39 weeks of gestation); one twin pregnancy (ratio: 100.3, determined at 34 weeks of gestation; delivered vaginally at 37 weeks of gestation), one singleton pregnancy (ratio: 89.1, determined at 39 weeks of gestation; delivered vaginally at 41 weeks of gestation) and one singleton (ratio: 137.0, determined at 36 weeks of gestation; delivered vaginally at 39 weeks of gestation).

The case control group also included 4 cases with HELLP syndrome, 4 twin pregnancies, 2 IUGR (intrauterine growth restriction) cases, and one case of severe preeclampsia in previous pregnancies. One of the IUGR cases with an sFlt-1/PIGF ratio of 14.9 determined at 31 weeks of gestation (WG) was delivered at 38 WG; the other IUGR was delivered at the end of 38 WG and had an sFlt-1/PIGF ratio of 15.0 determined at the beginning of 38 WG. There were also 4 cases with gestational diabetes mellitus (sFlt-1/PIGF ratios: 5.5/36 WG, 2.3/29 WG, 3.5/31 WG; 10.2/35 WG; delivery was in 39/39/38/39 WG).

### Preeclampsia

In the preeclampsia group, 37 of 63 sFlt-1/PIGF ratios were higher than 85. The mean sFlt-1/PIGF ratio was 186.01 (min 3.40 – max 2267.50) with an SD of 302.68. The highest protein excretion in a 24 h-urine specimen was 16.7 g/24 h which concurred with a

**Table 1** Calculation of sFlt-1/PIGF ratios for all gestations ( $n$ ), the control group, preeclampsia (PE) group, pregnancy-induced hypertension (PIH) group and proteinuria group, showing the mean, standard deviation (SD), minimum, median and maximum values.

Groups	n	Mean	SD	Minimum	Median	Maximum
All gestations	175	83.76	199.61	0.10	27.20	2267.50
Control	72	18.52	32.74	0.50	5.00	192.70
Preeclampsia	63	186.01	302.68	3.40	127.50	2267.50
Proteinuria	6	8.10	9.98	0.10	3.90	27.20
Pregnancy-induced hypertension	34	43.46	38.17	1.50	38.25	173.80

**Table 2** Sensitivity and specificity of the immunoassay from Roche Diagnostics for the diagnosis of preeclampsia, pregnancy-induced hypertension, proteinuria as well as early-onset and late-onset preeclampsia/PIH using a cut-off value of 85 as proposed by Roche as an indicator of a positive test result. PE: preeclampsia, PIH: pregnancy-induced hypertension, early onset: < 34 weeks of gestation, late onset: ≥ 34 weeks of gestation.

Elecsys ratio (cut-off 85)	Sensitivity (%)	Specificity (%)	Positive predictive value (PPV) (%)	Negative predictive value (NPV) (%)	p-Value	OR	95% CI
PE vs. controls	59.38	93.62	86.36	77.19	< 0.0001*	1.034	1.021–1.047
PIH vs. controls	5.88	93.62	25.00	73.33	0.0042	1.020	1.006–1.033
Proteinuria vs. controls	0.00	93.62	0.00	91.67	0.4579	0.975	0.911–1.043
Proteinuria vs. PE	0.00	40.63	0.00	76.47	0.0236	0.884	0.795–0.984
PIH vs. PE	5.88	40.63	5.00	44.83	0.0003	0.981	0.970–0.991
PIH vs. proteinuria	5.88	100.00	100.00	20.00	0.0706	1.097	0.992–1.213
Early-onset PE vs. controls	62.50	100.00	100.00	40.00	< 0.0001*	1.028	1.016–1.041
Late-onset PE vs. controls	58.33	93.33	82.35	80.77	0.4211	1.131	0.838–1.527
Early-onset PIH vs. controls	100.00	100.00	100.00	100.00	0.5001	1.016	0.970–1.065
Late-onset PIH vs. controls	0.00	93.33	0.00	72.41	0.0386	1.016	1.001–1.031

sFlt-1/PIGF-ratio of 2267.50 and a maximum blood pressure (BP) of 155/105 mmHg.

As mentioned above, the average interval between taking the blood samples and delivery was 2.4 weeks in the PE group compared to 8 weeks in the control group. The highest systolic BP was 220 mmHg and the highest diastolic BP was 130 mmHg. The PE group included 5 twin pregnancies, 8 IUGR cases, and one eclamptic woman. There were also two cases with gestational diabetes mellitus who had preeclampsia at delivery (sFlt-1/PIGF ratio: 127.4, BP: pressure 150/110 mmHg, proteinuria 9.4 g/24 h [33 WG]; sFlt-1/PIGF ratio: 32.5, BP: 160/100 mmHg, proteinuria 0.6 g/24 h [38 WG]). Interestingly, the women with severe preeclampsia gave birth within 1–14 days after admission.

### Pregnancy-induced hypertension (PIH)

Only 2 of 34 women in the PIH group had an sFlt-1/PIGF ratio > 85. The mean sFlt-1/PIGF ratio was 43.46 (min 1.50 – max 173.80) with an SD of 38.17. The highest systolic BP was 190 mmHg and the highest diastolic BP was 130 mmHg. Five IUGR cases were included in the group with an sFlt-1/PIGF ratio, respectively, of 0.1, 2.7, 258.4, 120.6, and 173.8. Two of the women (sFlt-1/PIGF ratio 27.2 and 120.6, respectively) were delivered in 33 WG. There was no case of gestational diabetes mellitus in this group. The interval between the first blood sample and delivery was about 4 weeks.

### Proteinuria

The mean sFlt-1/PIGF ratio was 8.10 with an SD of 9.98 (range: 0.10–27.20). Protein excretion was below 0.6 g/24 h. There were no cases of IUGR or gestational diabetes mellitus in this group. One woman had previously had HELLP syndrome, another woman had previously had preeclampsia. Neither of them had any specific underlying disease in this pregnancy.

### Preeclampsia vs. controls

There was a significant difference between the preeclampsia group and the control group ( $p < 0.0001$ ). Logistic regression yielded an odds ratio (OR) of 1.034 with a 95% confidence interval (CI) of 1.021–1.047. At a cut-off value of 85, the sensitivity was 59.4%, the specificity was 93.6%, PPV was 86.4% and NPV was 77.2%.

Gestational diabetes mellitus can influence preeclampsia under clinical conditions. But in this study the sFlt-1/PIGF ratio was not help in estimating the development or severity of preeclampsia. The decision to deliver the baby was based on severe hyperten-

sion and severe proteinuria and aimed to avoid an adverse maternal and/or perinatal outcome.

### Pregnancy-induced hypertension (PIH) vs. controls

There was a significant difference between the PIH group and controls ( $p = 0.0042$ , OR 1.020, 95% CI 1.006–1.033). The specificity was 93.6%, the sensitivity was 5.9%, PPV was 25.0% and NPV was 73.3% at a cut-off value of 85.

### Proteinuria vs. controls

There was no statistical difference between the proteinuria group and the control group ( $p < 0.4579$ , OR 0.975, 95% CI 0.911–1.043). The sensitivity was 0.0%, the specificity was 93.6%, PPV was 0.0% and NPV was 91.7%. The ROC curves in **Fig. 3** show the association between sensitivity and specificity for the sFlt-1/PIGF ratio (based on the convention of 100% minus specificity) for the comparisons between the PE, PIH and proteinuria groups and the control group; the values for a threshold of 85 are presented in **Table 2**. The diagram clearly shows that the prognostic ability of the sFlt-1/PIGF ratio is best for PE and poor for proteinuria.

### Early-onset/late-onset preeclampsia vs. controls

This comparison showed some interesting results. 10 women (16.4%) < 34 weeks of gestation developed early-onset preeclampsia. At a cut-off value of 85, the sensitivity was 62.5%, the specificity was 100.0%, PPV was 100.0% and NPV was 40.0%. In 8 of these 10 early-onset preeclamptic women there was an association with IUGR. One woman had gestational diabetes mellitus, and one had a twin pregnancy. One of the 8 IUGR cases had a previous history of preeclampsia during pregnancy and one IUGR case had an association with HELLP syndrome.

Only one case with IUGR and inherited thrombophilia did not pass the cut-off value of 85. Thus, not all cases of early-onset preeclampsia could be detected using the sFlt-1/PIGF ratio.

In the group of women with late-onset preeclampsia ( $n = 53$ , ≥ 34 weeks of gestation), the sensitivity was 58.3%, the specificity was 93.3%, PPV was 82.4% and NPV was 80.8% for a cut-off value of 85.

### Early-onset/late-onset PIH vs. controls

Two women with PIH and associated IUGR were < 34 weeks of gestation. Only 1 of the 2 early-onset PIH women passed the cut-off value of 85. In the late-onset (> 34 weeks of gestation) PIH group ( $n = 31$ ), the sensitivity was 0% and the specificity was



93.3%. The late-onset PIH group included three cases with associated IUGR.

## Discussion

Studies by Levine et al. and Maynard et al. showed that sFlt-1 and PIGF levels display opposing tendencies in the last two months of pregnancy with sFlt-1 levels increasing and PIGF levels declining. The increase in sFlt-1 levels occurs in the last 5 weeks of pregnancy and PIGF levels are significantly lower in women who develop preeclampsia [7, 10].

Chaiworupsonga et al. confirmed these findings for early-onset preeclampsia [11].

Exposing cultured human term placental villous tissue explants to cigarette smoke extracts was found to reduce sFlt-1 and increase PIGF levels. Accordingly, a reduced incidence of preeclampsia was reported in smoking women [12]. A systematic review consistently reported varying levels of sFlt-1 and PIGF in the normal group and the group that developed preeclampsia after the 25th week of gestation [13].

Verlohren et al. emphasized the high detection rate of preeclampsia in a multicenter study of 5 centers [8]. The study examined 71 women with preeclampsia and compared them to 280 age-matched controls. The best result was achieved for the identification of early-onset PE (area under the receiver operating characteristic curve of 0.97). Our ROC curve is comparable for PE (Fig. 3). Tallarek et al. reported a sensitivity of 89% and a specificity of 97% at < 34 weeks of gestation with the test [14]. A prospective study by Verlohren et al. examined sFlt-1/PIGF ratios determined before 34 weeks of gestation. Ratios were divided into quartiles for the prediction of an adverse outcome with the diagnosis 'suspicion of preeclampsia'. An sFlt-1/PIGF ratio above the 3rd quartile indicated the highest risk of impending delivery [15]. Rana et al. reported a ratio of > 85 in twin pregnancies with suspected preeclampsia for pregnant women who gave birth within 2 weeks due to complications or clinical necessity. In comparison, only 15.8% of women with ratios of < 85 gave birth within 2 weeks [16]. In another study of 616 women with suspected preeclampsia at < 34 weeks of gestation, the sFlt-1/PIGF ratio predicted adverse outcomes within 2 weeks [17].

In our study, a cut-off value of 85 for the sFlt-1/PIGF ratio was used, as previously recommended by Roche Diagnostics. The sensitivity for PE and early-onset PE was only approximately 60%, with a specificity of 93% and 100%, respectively. The positive predictive value was 86% and the negative predictive value was 77% when the preeclampsia group was compared with the control group. However, in the group of women who were < 34 weeks of gestation, the sensitivity for early-onset preeclampsia was 62.5% and the specificity was 100%. In our study, the decision to deliver the baby depended on typical parameters such as blood pressure, proteinuria, pathological Doppler velocity waveforms, scan (IUGR), a fetal recording indicating a pathological condition or HELLP syndrome. The sFlt-1/PIGF ratio was used to endorse the decision to deliver the baby to avoid an adverse maternal and/or perinatal outcome. However, in all cases with preeclampsia the decision to deliver a baby prematurely was not taken based on a high sFlt-1/PIGF ratio. The ratio only served as additional confirmation.

One study group examined the combination of abnormal uterine artery Doppler velocity (UADV) waveforms and high plasma PIGF

concentrations (< 280 pg/ml) in the second trimester as indicators for a high risk for developing preeclampsia, early-onset and/or severe preeclampsia. Among women with abnormal UADV findings, a maternal plasma PIGF of < 280 pg/ml identified most patients who went on to develop early-onset and/or severe preeclampsia [18].

Benton et al. published similar data using the same test from Roche Diagnostics. The overall sensitivity reported in this study was 59%: 64% for early-onset preeclampsia and 53% for late-onset preeclampsia with a specificity and PPV of 100% [19]. The NPV for any gestation was 82%; it was 84% for early-onset preeclampsia and 80% for late-onset preeclampsia. Thus, our data confirm the previous findings of Benton et al. and demonstrate that the expected and stated sensitivity of 82% cannot be reached.

Benton et al. also looked at another test, the Triage PIGF by Alere which focuses only on PIGF. The specificity for this test was 95%; the sensitivity was 77% for the overall collective, 100% for the early-onset group but only 47% for the late-onset group. This appears to indicate that measurement of PIGF alone in pregnant women < 34 weeks of gestation might be sufficient as an indicator for the development of preeclampsia [19]. Oliviera et al. came to similar conclusions in their study, as did Knudsen et al., who pointed out that the determination of PIGF levels using the rapid point-of-care Triage test could serve as additional confirmation in the diagnosis of preterm preeclampsia [20, 21]. Ghosh et al. carried out a prospective study of maternal serum PIGF levels at 20–22 weeks of gestation to determine whether maternal PIGF levels could predict the occurrence of IUGR and/or early-onset preeclampsia. They reported a strong association of serum PIGF levels < 155 pg/ml with early-onset preeclampsia and early-onset IUGR, with a sensitivity for predicting early-onset preeclampsia and early-onset IUGR of 82 and 84, respectively [22].

## Points to consider

1. The Elecsys test can be used in routine clinic practice to confirm the diagnosis in women with established preeclampsia. In women with PIH and proteinuria alone, it can only be used to exclude preeclampsia if the ratio is < 85. We would like to point out, however, that in our study 3 women in the PIH group had ratios > 85. There was no false positive value in the proteinuria group, but 4 women in the control group had values > 85.
2. Data collection proved to be difficult in our tertiary intensive care center since the only women referred to this center are women believed to have developed preeclampsia or with a previous history suspicious for preeclampsia or with the clinical signs of edema, headache, and upper abdominal pain, thrombophilia. Thus, most of the women in the preeclampsia group had mild hypertension and proteinuria. The sFlt-1/PIGF ratio was used to predict the expected severity of preeclampsia, but the decision to deliver a baby was not based on the sFlt-1/PIGF ratio. The assessment was independently completed by ultrasound and Doppler velocity measurements. The time frame of 3.2 weeks in the PIH group and 4.1 weeks in the proteinuria group is used to improve the possibility of excluding preeclampsia 2–5 weeks before delivery, as mentioned above.
3. Finally, the pathologically high mean sFlt-1/PIGF ratio of 186.01 can be used as a confirmation of the development or onset of preeclampsia. However, it should be noted that in our preeclampsia group only 37 of 63 women had a ratio > 85.

4. The sFLT-1/PIGF ratio is only useful for the early-onset preeclampsia group as an indicator of the severity of preeclampsia, especially in combination with IUGR (specificity 100%, sensitivity 62.5%).
5. The specificity of 93.62% for the PE group compared to controls determined in our retrospective study is that same as that given by Roche Diagnostics (95%). However, the sensitivity in our study was 59.38% and thus much lower than the figure stated by the company (82%) for a cut-off ratio of > 85.
6. Monitoring for preeclampsia will continue to focus on typical signs such as high blood pressure, high protein levels in urine, a fetal recording indicating a pathological condition, a suspicious scan or pathological Doppler velocity measurement; a suspicious sFLT-1/PIGF ratio can be used to support these findings.
7. While an sFLT-1/PIGF ratio < 85 cannot exclude the possibility of developing preeclampsia, it can indicate a decreased risk of unexpectedly developing preeclampsia.

## Conclusion

Our data suggest a targeted use of the test as an indicator for the combination of early-onset preeclampsia and associated IUGR. Determination of the sFLT-1/PIGF ratio could be helpful to detect incipient preeclampsia prior to its clinical manifestation and prior to possible suspicious ultrasound or pathological Doppler measurements. However, the ratio < 85 is not an exclusion criterion for preeclampsia. For the purposes of routine screening, additional data and larger study groups will be necessary to determine whether the Elecsys test (Roche) is useful in further clinical applications.

## Conflict of Interest

None.

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