Thieme

Significance of the sFlt-1/PlGF Ratio in Certain Cohorts – What Needs to be Considered?

Wertigkeit des sFlt-1/PlGF-Quotienten in bestimmten Kollektiven – was gibt es zu beachten?

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ABSTRACT

The sFlt-1/PlGF ratio is an established tool in clinical practice, where it is part of a diagnostic algorithm and informs the prognosis of preeclampsia (PE). Maternal and gestational comorbidities can affect the performance of the sFlt-1/PlGF ratio and its constituent elements, and a good understanding of the potential pitfalls is required. The objective of this paper was to provide a current narrative review of the literature on the diagnostic and predictive performance of the sFlt-1/PlGF ratio in specific patient cohorts. Potential factors which can negatively affect the clinical interpretability and applicability of the sFlt-1/PlGF ratio include chronic kidney disease, twin pregnancy, and maternal obesity. Pathophysiological mechanisms related to these factors and disorders can result in different concentrations of sFlt-1 and/or PlGF in maternal blood, meaning that the use of standard cut-off values in specific cohorts can lead to errors. To what extent the cut-off values should be adapted in certain patient cohorts can only be clarified in large prospective cohort studies. This applies to the use of the ratio both for diagnosis and prognosis.

ZUSAMMENFASSUNG

Der sFlt-1/PlGF-Quotient hat sich bezogen auf den diagnostischen Algorithmus und die Prognoseabschätzung der Präeklampsie (PE) im klinischen Alltag etabliert. Mütterliche und gestationsbedingte Komorbiditäten können die Performance des sFlt-1/PlGF-Quotienten und seiner Bestandteile beeinflus-

sen und erfordern ein entsprechendes Wissen über mögliche Fallstricke. Ziel dieser Arbeit ist es, eine aktuelle, narrative Literaturübersicht im Kontext der diagnostischen und prädiktiven Performance des sFlt-1/PlGF-Quotienten in speziellen Patientinnenkollektiven zu geben. Zu potenziellen Störfaktoren der klinischen Interpretier- und Anwendbarkeit des sFlt-1/PlGF-Quotienten zählen hier u. a. eine chronische Nierenerkrankung, Zwillingsschwangerschaften und eine mütterliche Adipositas. Dabei kommt es auf Basis von pathophysiologischen Mechanismen zu unterschiedlichen Konzentrationen von sFlt-1 und/oder PlGF im Blut der Mutter, wodurch eine Übertragung der gängigen Cut-off-Werte fehleranfällig sein kann. Inwieweit bei diesen Patientinnengruppen eine Anpassung der Cut-off-Werte erfolgen sollte, kann nur in großen prospektiven Kohortenstudien geklärt werden. Dies gilt sowohl für die Frage der Diagnose als auch Prognose.

Introduction

The sFlt-1 (soluble fms-like tyrosine kinase 1)/PlGF (placental growth factor) ratio has been found to be useful in routine clinical practice as it provides information that feeds into the diagnostic algorithm for hypertensive disorders of pregnancy (HDPs) [1].

The pathophysiological consequences of an angiogenic imbalance (in favor of sFlt-1 and at the expense of PlGF – expressed by an increased sFlt-1/PlGF ratio) is endothelial dysfunction. The resulting vascular leakage and consequent intravascular lack of volume and the reduced perfusion of organs such as the kidneys, liver, or placenta leads to the well-known symptoms of preeclampsia (PE) [2]. It is important to emphasize at this point that in patients with endothelial disease, sFlt-1 and/or PlGF may be increased or decreased even outside of pregnancy [3, 4, 5, 6, 7]. The cut-off values for the sFlt-1/PlGF ratio to estimate the risk of PE and the degree of placental dysfunction but also to predict an unfavorable neonatal or maternal outcome and the associated short time to delivery have been published with a high level of evidence [8, 9, 10, 11, 12] (▶ **Table 1**).

Overview

The use of the sFlt-1/PlGF ratio and its constituent elements in special patient cohorts is described in more detail below. The focus is on diagnosing PE and on the predictive value of angiogenic factors with regards to adverse perinatal outcomes (APOs).

Chronic Kidney Disease

The prevalence of PE in women with chronic kidney disease (CKD) can be up to 40 % [18, 19], in women with advanced CKD it may be as high as 70 % [19, 20, 21]. In a CKD cohort, the overlapping clinical presentations of the two pathologies, both of which usually include pre-existing hypertension and proteinuria, can make it more difficult to identify the underlying cause [22]. Moreover, renal dysfunction disorders such as systemic lupus erythematosus (SLE), thrombocytopenic purpura (TTP) or atypical hemolytic uremic syndrome (aHUS) may first appear during pregnancy or be exacerbated by pregnancy, which makes differentiating placental complications as difficult as predicting the pregnancy outcome [23, 24]. Rolfo et al. were able to show that, despite overlapping characteristics (hypertension and proteinuria), it is possible to differentiate between PE and CKD using the sFlt-1/PlGF ratio. In their prospective cohort study, patients with CKD (n = 23) had significantly lower sFlt-1/PlGF values (4.00 [interquartile range {IQR}: 0.51–136.59] vs. 435.79 [IQR: 160.90–1153.53]; p < 0.001) compared to patients without CKD (n = 34) but with PE (based on the diagnostic criteria hypertension and proteinuria before 20 + 0 weeks of gestation) [13]. Moreover, a higher APO rate and a shorter mean time to delivery in the CKD cohort (n = 171) was observed, which correlated with the level of anti-angiogenic imbalance indicated by the sFlt-1/PlGF ratio [25]. The usefulness of the sFlt-1/PlGF ratio to diagnose PE in a CKD cohort was emphasized in the S2 k-guideline "Chronic Kidney Disease and Pregnancy" [26]: "PlGF and sFlt-1 should be used as additional diagnostic parameters if preeclampsia is suspected in patients with CKD." The special pathophysiological features of the circulating PlGF levels in CKD patients need to be considered as the figures can be misleading. Outside pregnancy, increased PlGF production and decreased sFlt-1 concentrations have been demonstrated in CKD cohorts [27, 28]. PlGF is filtered in the kidney and excreted in urine [29]. Progressive impairment of kidney function in pregnancy can therefore result in higher PlGF levels due to reduced renal clearance. In a "normal" population, a PlGF of less than 100 pg/ml is suspicious or associated with a higher risk of placental complications. To achieve the same sensitivity and specificity, the recommendation is that the threshold value should be increased for women with CKD [14]. Wiles et al. therefore recommended that the monitoring of CKD patients with a PlGF serum level of less than 150 pg/ml after 20 + 0 weeks of gestation should be increased, although it must be noted that the value of PlGF serum levels for predicting PE decreases as the impairment of kidney function increases [14].

Obesity

As with pre-existing diabetes mellitus, obesity is a risk factor for developing PE and, like PE, it is characterized by a pro-inflammatory micromilieu [30, 31]. The PROGNOSIS study, which evaluated and established gestational age-specific cut-off values for the sFlt-1/PlGF ratio, did not differentiate between obese (BMI > 30 kg/m^2) and normal-weight (BMI < 25 kg/m^2) women based on BMI [32] and it therefore also did not investigate whether different threshold values would be necessary for obese pregnant women [8]. Zera et al. observed an inverse correlation between sFlt-1 and maternal BMI, i.e., the higher the BMI, the lower the sFlt-1 level [15]. A recently published prospective observational study (n = 1450 PE vs. n = 1065 controls) showed that women with PE and obesity had significantly lower sFlt-1 concentrations in the

▶**Table 1** Overview of established cut-off values [8, 10] for the sFlt-1/PlGF ratio and its constituent elements for the reference cohort, and the special pathophysiological features associated with specific maternal or gestational comorbidities.

	Reference cohort [8, 10]	Chronic kidney disease [13, 14]	Obesity [15, 16]	Twin pregnancy [17]
sFlt-1	Stable in 1 st and 2 nd trimester, increased in 3 rd trimester	Changes in sFlt-1 values the same as for the reference cohort	Significantly lower sFlt-1 values when BMI is > 30	Increase in sFlt-1 in the 3 rd trimester is more pronounced compared to singleton pregnancies
PlGF	Continuous increase, followed by a decrease from week 34 of gestation	In principle, higher PlGF values	Similar PlGF course	Similar PlGF course
sFlt-1/PlGF	Values decrease until the 3 rd trimester when the ratio increases again	Lower GFR correlates with lower informative value of the ratio	Ratio significantly lower in the 3 rd trimester if BMI is > 30	Ratio higher from 29 + 0 weeks of gestation
Possible cause of change	–	PlGF is eliminated renally and PlGF accumulates if GFR is reduced	Higher plasma volume TNF-α inhibits endogenous sFlt-1 production	Higher placental mass
sFlt-1/PlGF				
< 38	PE unlikely in the next 4 weeks	A ratio of less than 38 does not rule out PE	Data unclear	Established cut-off values after 29 + 0 weeks of gestation cannot be transferred
38–85 or 110	Development of PE over the course of pregnancy is possible, control within 7 days is recommended	–		
> 85 or 110	PE very probable	PE very probable		
PlGF < 100	Placental dysfunction is probable	A value of more than 100 does not rule out placental dysfunction		
MTTD	Ratio > 655: delivery within 48 h or 7 days probable	PlGF > 150 does not rule out high probability of delivery within the next 14 days	Data unclear	Ratio < 38: delivery within next 2 weeks unlikely
APO/AMO	Ratio < 38: unlikely Ratio > 655: probable	Data unclear	Ratio < 38 does not rule out an APO	Ratio < 38 does not rule out an APO

AMO = adverse maternal outcome; APO = adverse perinatal outcome; GFR = glomerular filtration rate; MTTD = medium time to delivery

2 nd and 3 rd trimester of pregnancy compared to overweight (BMI 25–30 kg/m^2) and normal-weight patients with PE. The sFlt-1/PlGF ratio itself did not show any significant differences between groups [16]. Possible explanations for the decreased sFlt-1 levels in obese PE patients could be the generally higher plasma volumes as well as a higher extracellular matrix mass with heparan sulfate proteoglycans which can degrade sFlt-1 [33, 34]. TNF-α (TNF-α: tumor necrosis factor α) could also play a role, as it is a pro-inflammatory factor which is elevated in obese women while endogenous sFlt-1 expression is reduced in adipose tissue [35]. While it appears that BMI does affect sFlt-1, currently no studies have developed alternative threshold values with sufficient evidence. The sFlt-1/PlGF ratio should and can be used for the diagnostic workup of PE in obese pregnant women. But caution is advised when the risk of a potential APO is being estimated based on the ratio. A retrospective analysis was able to show that an APO could not be ruled out despite an sFlt-1/PlGF ratio of less than 38 in the obese PE cohort [36].

Twin Pregnancies

The incidence of PE in twin pregnancies is double that reported for singleton pregnancies [37]. In twin pregnancies, the sFlt-1/PlGF ratio provides verifiable prognostic and diagnostic information [38, 39], although how chorionicity can affect test accuracy has not yet been conclusively determined [1]. Dröge et al. were able to show that the concentration levels of sFlt-1 and PlGF differ between singleton and twin pregnancies, with higher levels of sFlt-1 and PlGF observed in the twin cohort [40]. A gestational age-related reference value for normal twin pregnancies (n = 269) was recently published [17]: the data shows that sFlt-1/PlGF ratios in women with twin and singleton pregnancies are similar up until week 29 + 0 of gestation. From week 29 + 0 of gestation, however,

significantly higher sFlt-1/PlGF levels (caused by a significant increase in sFlt-1) were observed in twin pregnancies, which is why the ratio after 29 + 0 weeks of gestation appears to be less discerning when predicting PE in twin pregnancies; results should therefore be interpreted with caution [1]. One suggested explanation for the higher sFlt-1/PlGF concentrations in twin pregnancies currently being discussed is the larger placental mass [41]. Although retrospective studies with small case numbers have shown a clear correlation between the ratio and shorter times to delivery [39, 42], they did not show that the sFlt-1/PlGF ratio had an additional diagnostic value with regards to predicting an APO [39, 42, 43].

Chronic and Gestational Hypertension

Compared to patients with chronic or gestational hypertension, patients with PE have a significantly higher sFlt-1/PlGF ratio [44]. The term generally used when the sFlt-1/PlGF ratio is higher than 85 before 34 + 0 weeks of gestation or higher than 110 in or after 34 + 0 weeks of gestation is "angiogenic PE" [45]. Chronic hypertension (and gestational hypertension) is not associated per se with higher sFlt-1/PlGF levels and this allows them to be safely differentiated from superimposed PE [46]. Binder et al. showed that in pregnant women with chronic hypertension and suspected superimposed PE, adding the sFlt-1/PlGF ratio to the standard diagnostic criteria proposed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) [47] significantly improved the detection rate of adverse perinatal and maternal outcomes (AMO) [48]. Accordingly, angiogenic markers can be routinely used in patients with chronic hypertension of pregnancy and gestational hypertension.

Pregnancy-related Liver Complications

Acute fatty liver of pregnancy (AFLP) and HELLP syndrome are two rare hepatic complications of pregnancy associated with high rates of maternal and fetal morbidity and mortality. In addition to the clinical characteristics, the constellation of laboratory findings is often similar and can include thrombocytopenia, hemolysis, and elevated concentrations of hepatic enzymes [49]. Differentiating HELLP syndrome from AFLP can sometimes be difficult, particularly if hypertension or PE are not additionally present. In patients with AFLP, the serum level of sFlt-1 is dramatically increased (compared to HELLP syndrome) [50, 51, 52, 53]. In addition to the Swansea criteria, an sFlt-1 value > 31 100 pg/ml appears to be an additional parameter which points to AFLP. In contrast, PlGF serum levels are only decreased in patients with HELLP syndrome. This would fit with the characteristic placental dysfunction which occurs in HELLP syndrome (and the normal placental function in AFLP) and underscores the different entities of the two pathologies [53]. Elevated sFlt-1 serum levels have also been reported outside of pregnancy in patients with chronic liver disease [54]. Studies into the role played by sFlt-1 in liver function impairment using a mouse model [55, 56] suggest that high sFlt-1 serum levels in patients with AFLP are not simply an epiphenomenon but a major cause of the disorder [53]. With regards to HELLP syndrome, in the rare case of isolated HELLP syndrome (without PE), the sFlt-1/PlGF ratio is significantly decreased [57].

Rheumatic Diseases

Patients with rheumatoid disorders such as systemic lupus erythematosus (SLE), Sjögren's syndrome, systemic sclerosis, dermatomyositis, and rheumatoid arthritis have a higher risk of PE [58]. Making a differential diagnosis of PE and HELLP syndrome as opposed to lupus nephritis flares, vasculitis, or a renal crisis in the context of systemic sclerosis can often be difficult. In the differential diagnosis of PE, the sFlt1/PlGF ratio can be used as a sure sign of placental involvement [59]. A prospective multicenter observational study showed that in patients with SLE and/or antiphospholipid syndrome, the sFlt1/PlGF ratio in the 2 nd trimester of pregnancy (in addition to other factors such as the necessity for antihypertensive medication) was one of the strongest predictors for an APO [60]. In its position paper "Management of Rheumatic Diseases During Pregnancy and Breastfeeding," the section Maternal Diseases in Pregnancy of the Working Group for Obstetrics and Prenatal Medicine (AGG) noted: "Determination of [...] the sFlt1/PlGF ratio in the second and third trimester of pregnancy can be used as part of the differential diagnosis to determine prognosis when placental involvement is present" [59].

Differential Diagnosis of Thrombotic Microangiopathy/Thrombotic Thrombocytopenic Purpura

Diseases from the family of thrombotic microangiopathies (TMAs) such as aHUS and TTP can manifest in pregnancy and puerperium and present a clinical picture which overlaps with that of the obstetric disorders "severe PE" and (postpartum) "HELLP syndrome." As the potential therapeutic options differ considerably, it would be useful to have biomarkers which are able to differentiate between TMAs and obstetric disorders and able to show whether the primary pathogenetic problem is placental dysfunction. A study published in 2023 investigated whether the sFlt1/PlGF ratio is different in patients with TTP. The study was able to show that the sFlt1/PlGF ratio was elevated in both the congenital and the acquired form of TTP in a relevant percentage of patients but not in all of them (27.3 % – 52.2 %). As regards the outcomes of these pregnancies (maternal and fetal survival), in patients with TTP there was no difference between cases with normal and cases with pathological angiogenesis. As TMA and placental dysfunction may develop in parallel and can mutually influence each other, angiogenic markers are not able to unequivocally identify the primary cause and have no prognostic value with regards to outcomes in cases with TTP [61].

Conclusion

Maternal and gestational comorbidities have the potential to frustrate the clinical interpretability and applicability of the sFlt-1/PlGF ratio and its constituent elements. Recent studies indicate that pregnant women with comorbidities may develop PE with a milder elevation of the sFlt-1/PlGF ratio compared to pregnant women without comorbidities. The presence of pre-existing endothelial dysfunction could be one reason for this as, under certain circum-

stances, this can lower the anti-angiogenic imbalance threshold [62]. Prospective studies with large case numbers are needed to clarify whether adapting established cut-off values would be useful for diagnosing PE and predicting an APO in specific patient cohorts.

Conflict of Interest

HS: lectures and consultancy work for Sanofi, Alexion, Roche Diagnostics and Norgine. SV: Speaker fees: Thermo Fisher Scientific, Roche Diagnostics, Comanche Biopharma, Alexion Advisory Board: Siemens, Beckman Coulter, Comanche Biopharma.

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