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Real-world data on the clinical use of angiogenic factors in pregnancies with placental dysfunction

Anne Dathan-Stumpf, MD; Victoria Czarnowsky, MD; Vicky Hein; Theresa Andraczek; Holger Stepan, MD

BACKGROUND: In routine clinical practice, angiogenic factor measurement can facilitate prediction and diagnosis of preeclampsia and other manifestations of placental dysfunction (eg, intrauterine growth restriction).

OBJECTIVE: This real-world data analysis investigated the utility of soluble fms-like tyrosine kinase-1 and placental growth factor for preeclampsia and placental dysfunction.

STUDY DESIGN: Blood serum soluble fms-like tyrosine kinase-1 and placental growth factor were measured using Elecsys soluble fms-like tyrosine kinase-1 and placental growth factor immunoassays (cobas e analyzer; Roche Diagnostics). Overall, 283 unselected singleton pregnancies with ≥1 determination of soluble fms-like tyrosine kinase-1—to—placental growth factor ratio were included. Distribution of the ratio at admission was normal (<38 [58.7%]), intermediate (38—85/110 [19.1%]), or pathologic (>85/110 [22.3%]). Overall, 15.5% had preeclampsia or hemolysis, elevated liver enzyme levels, and low platelet count, and 15.5% of women had intrauterine growth restriction.

RESULTS: Increasing soluble fms-like tyrosine kinase-1—to—placental growth factor ratio was associated with an increase in priority of delivery (r=0.38; $P<.001$). The percentage of patients who developed preeclampsia by soluble fms-like tyrosine kinase-1—to—placental growth factor ratio at admission was 5.4% (normal), 7.4% (intermediate), and 49.2% (pathologic). The greatest difference in soluble fms-like tyrosine kinase-1—to—placental growth factor ratio from admission to birth occurred in pathologic pregnancies (171.12 vs 39.84 for normal pregnancies). Soluble fms-like tyrosine kinase-1—to—placental growth factor ratio correlated inversely with gestational age at delivery, birthweight, and prolongation time. There was no significant relation between the prolongation period or the gestational age at first determination to the increase of soluble fms-like tyrosine kinase-1 and placental growth factor between admission and delivery (ΔQ). This analysis used a real-world approach to investigate the clinical utility of the soluble fms-like tyrosine kinase-1—to—placental growth factor ratio in placental dysfunction.

CONCLUSIONS: Confirming the results of prospective studies, we observed a positive correlation between soluble fms-like tyrosine kinase-1—to—placental growth factor ratio and severity of placental dysfunction and a negative association with time to delivery. In a real-world setting, the soluble fms-like tyrosine kinase-1—placental growth factor ratio stratifies patients with normal outcome and outcome complicated by placental dysfunction.

Key words: placental dysfunction, preeclampsia, real-world data, soluble fms-like tyrosine kinase-1—to—placental growth factor ratio

Pregnancies with Placental Dysfunction

Preeclampsia (PE) is defined as a recent or preexisting hypertension (>140/90 mm Hg) during pregnancy with ≥1 other organ manifestation that cannot be attributed to other causes.[1] PE is a leading cause of maternal and fetal morbidities and mortalities.[2,3] In Europe, the incidence of this serious multisystem disorder is reported at 2%.[4] The exact pathogenesis of PE is still unclear, but laboratory tests show an imbalance of pro- and antiangiogenic factors.[5]

Because of detectable laboratory changes even before the manifestation of clinical symptoms, the expression of angiogenic proteins, such as soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) and their ratio are widely used in the prediction and diagnosis of PE.[6–8] Regardless of gestational age, a sFlt-1—to—PlGF ratio of <38 indicates a high sensitivity and specificity that PE is unlikely in the subsequent week,[6] whereas a ratio of >85 indicates that PE or another form of placental dysfunction is very probable. Women with a sFlt-1—to—PlGF ratio of 38 to 85 (≤34 weeks of pregnancy [wop]) or 38 to 110 (>34 wop) have an increased risk of developing a placental dysfunction within the next 4 weeks.[9,10]

Numerous studies have shown that the sFlt-1—to—PlGF ratio can be used as a diagnostic aid and predictor of PE, but to our knowledge, there are currently no data from routine clinical practice without the control of a study protocol. The aim of this real-world data (RWD) analysis was to investigate the distribution of sFlt-1 and PlGF and their ratio in routine clinical practice and to determine the clinical utility of these angiogenic factors in pregnancies with placental dysfunction.

Study Design

This was a retrospective single-center study conducted at the Department of Obstetrics, University Hospital Leipzig, Leipzig, Germany. From 2009 onward, the sFlt-1—to—PlGF ratio was determined as part of routine clinical practice at this hospital. In the current analysis, all patients with ≥1 determination of the sFlt-1—to—PlGF ratio (indicated by the treating physician) between January 2017 and December 2017 were included. Placental dysfunction describes all subjects with PE; hemolysis, elevated liver

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AJOG at a Glance

Why was this study conducted?

This study was conducted to investigate the utility of the sFlt-1/PlGF ratio in daily clinical practice with a real-world approach.

Key findings

- sFlt-1/PlGF ratio is a supplemental tool to stratifies patients outcome in placental dysfunction.
- Positive correlation between sFlt-1/PlGF ratio and placental dysfunction.
- Negative correlation between sFlt-1/PlGF ratio and time to delivery.

What does this add to what is known?

- Real world data confirm results of previous prospective studies regarding the use of angiogenic factors.
- In routine use, there is a robust relation between angiogenic factors and outcome in pregnancies with placental dysfunction.

enzyme levels, and low platelet count (HELLP) syndrome; and intrauterine growth restriction (IUGR). All main diagnoses were extracted retrospectively from patient files and were not corrected. In clinical practice, PE was defined, according to the recent International Society for the Study of Hypertension in Pregnancy definition of 2019, as recent or preexisting hypertension (>140/90 mm Hg) in pregnancy with ≥1 other organ manifestations that cannot be attributed to other causes. Although the new definition of PE was not published when the data were collected in 2017, patients with high blood pressure and at least 1 other organ manifestation were given this diagnosis. No explicit distinction between a superimposed PE or a PE without previous risk factors was conducted. Patients with isolated chronic hypertension without any other manifestations were collected for the main diagnosis of "others." IUGR was defined as a restricted growth with a pathologic Doppler sonography of the umbilical artery or the uterine arteries or an oligohydramnion.

Causes for presentation at the clinic included referral from other clinics or settled colleagues, clinical complaints, conspicuous ultrasound findings, conspicuous medical history, or for prediction.

Data on pregnancy, parity, maternal age, gestational age at delivery, birthweight, mode of delivery, indication for determination of sFlt-1—to—PlGF ratio, priority of delivery, indication for delivery, main diagnosis at birth, and number of days of hospitalization before and after delivery were extracted from birth registers, electronic medical records, and ultrasound findings. Maternal indications for delivery included uncontrollable hypertension, severe clinical symptoms, severe right-sided upper abdominal pain, platelets of <100,000/μl, severe increase in liver enzymes with concurrent hemolysis (HELLP syndrome) or imminent eclampsia. Uncontrollable hypertension was defined as blood pressure that could not be reduced to <150/90 mm Hg despite exhausted medication or recurrent hypertensive crises despite high blood pressure medication. Severe clinical symptoms was defined as severe headache, double vision, or neurologic symptoms. Fetal indications for delivery were defined by a lack of fetal weight gain in a 14-day period, a pathologic Doppler sonography of the umbilical artery (zero or reverse flow) or the ductus venosus, or persistent pathologic heart rates (silent, late decelerations, etc.). If neither category clearly applied, a combined delivery indication was recorded.

In addition to the fetal and maternal delivery indications because of placental dysfunction, there were a number of other indications. Fetal delivery indications independent of placental dysfunction included premature rupture of membranes with suspected amniotic infection syndrome, fetal infections (cytomegalovirus, parvovirus B19), positional abnormalities (nonvertex, transverse presentation), cardiotocography abnormalities independent of an IUGR, transmission, and fetal malformation and chromosomal abnormalities (esophageal atresia, trisomy 21). Maternal indications included gestational diabetes or preexisting diabetes, maternal preexisting diseases or malformations (eg, cardiac), and others.

Written informed consent for the scientific use of anonymized data was obtained as an institutional standard procedure in each patient. The study was submitted to and approved by the Institutional Ethical Committee of the University of Leipzig (IRB00001750; registration number 180/18-ek). All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 (in its most recently amended version).

Determination of the Soluble fms-like Tyrosine Kinase-1—to—Placental Growth Factor Ratio

Here, sFlt-1 and PlGF levels in serum were determined using Elecsys sFlt-1 and PlGF electrochemiluminescence immunoassay on a cobas e analyzer (Roche Diagnostics, Basel, Switzerland).[11,12] The sFlt-1—to—PlGF ratio at admission and before delivery and the number of follow-up measurements and the prolongation period between the first admission and delivery were calculated. Follow-up measurements were defined as the number of additional measurements of sFlt-1 and PlGF after the first determination at admission. ΔQ was defined as the difference between the sFlt-1—to—PlGF ratio at admission and at birth. Some subjects received only 1 determination of the sFlt-1—to—PlGF ratio; therefore, in these patients, ΔQ could not be determined. The sFlt-1—to—PlGF ratio at admission was defined as normal (<38), intermediate (38—85 for <34 wop; 38—110 for ≥34 wop), or pathologic (>85 for <34 wop; >110 for ≥34 wop).[9] Ratio cutoffs of >85 (<34.0

wop) and >110 (≥34.0 wop) were used to confirm the diagnosis of PE.

Real-World Data

Often, RWD are defined as data collection beyond a randomized controlled trial.[13] In this investigation, RWD were defined according to the Association of the British Pharmaceutical Industry and the RAND Corporation: "For the purposes of this guidance, RWD will refer to data obtained by any noninterventional methodology that describe what is happening in normal clinical practice."[14] RWD is an umbrella term for different types of healthcare data that are not collected in conventional randomized controlled trials. RWD in the healthcare sector come from various sources, such as patient, hospital, and social data and data from clinicians and payers.[15]

Statistical Analysis

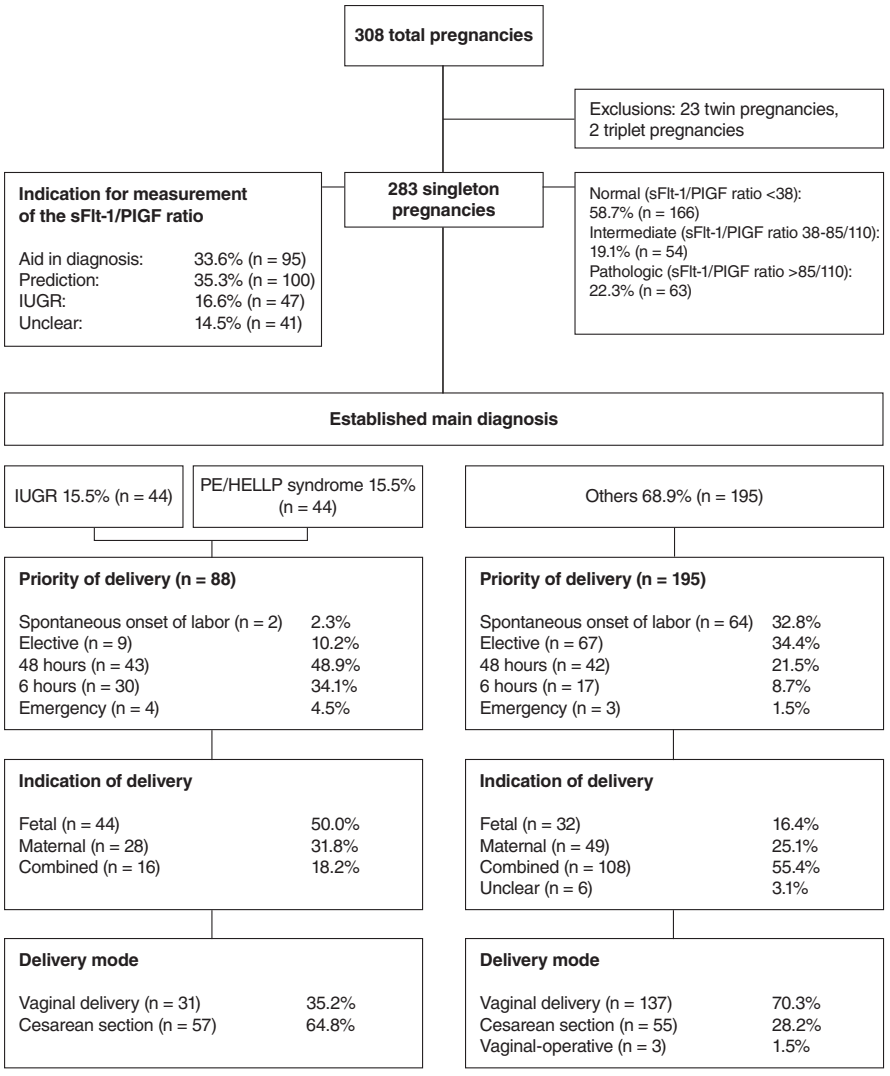
Statistical evaluations were conducted with the IBM Statistical Package for Social Sciences (version 21; Armonk, NY). Standardized statistical methods were used. The significance level was 5% (α=0.05) for all tests. Nonnormally distributed metric values and ordinal data were evaluated using the Kruskal-Wallis test (H test). Because of the large range of sFlt-1−to−PlGF ratios within the groups, both the mean and median values were listed. Because of the wide range of confidence intervals, the interquartile range (IQR) between the first and third quartile is given. Thus, the IQR was composed of the middle 50% of the data. Significant differences between the subgroups were identified by the posthoc test and their Z values reported. The Pearson χ^2 test was used to investigate the relationship between 2 features. A regression analysis was applied to Spearman correlation. To relativize the large range of variation of the sFlt-1−to−PlGF ratio in the investigated categories, a 10-fold logarithm of the ratio was attempted, but this method showed no added value.

Population Characteristics

Because of the lack of validation of the sFlt-1−to−PlGF ratio for multiple pregnancies, and the increased independent risk of preterm delivery, all multiple gestations (23 twins and 2 triplets) were excluded from the analysis. Altogether, 283 singleton pregnancies with ≥1 determination of the sFlt-1−to−PlGF ratio were included (Figure 1). The distribution of the sFlt-1−to−PlGF ratio at admission was normal (<38 [58.7%]), intermediate (38−85/110 [19.1%]), and pathologic (>85/110 [22.3%]). The main diagnoses were IUGR (n=44 [15.5%]), PE or HELLP syndrome (n=44 [15.5%]), and "others" (n=195 [68.9%]) (Figure 1). Furthermore, 11 of 44 women (24%) with a main diagnosis of PE had concurrent fetal growth restriction according to the definition above. To avoid multiple counts of 1 patient, these women were included with a main diagnosis of PE or HELLP syndrome for the data analysis.

The sFlt-1−to−PlGF ratio was used to confirm PE diagnosis in 33.6% of women, for predicting PE in 35.3% of women, and for suspected IUGR in 16.6% of women. The patients in the

FIGURE 1
Flowchart of the total population analysis (N=283)



HELLP, hemolysis, elevated liver enzyme levels, and low platelet count; *IUGR*, intrauterine growth restriction; *PE*, preeclampsia; *PlGF*, placental growth restriction; *sFlt-1*, soluble fms-like tyrosine kinase-1.

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TABLE 1
Characteristics of the total population analysis and subgroups according to the main diagnosis

Total population analysis (N=283)		Mean	SE	Median	Min	Max
Maternal age at delivery (y)		30.30	0.30	30.00	15.00	45.00
Gestational age at delivery (wop)		37.00	0.25	38.50	23.00	41.50
Gestational age at first determination (wop)		33.20	0.34	34.10	11.10	41.40
sFlt-1—to—PlGF ratio at first determination		95.41	13.09	22.65	0.48	2430.70
sFlt-1—to—PlGF ratio at delivery		220.10	28.58	104.84	1.47	1431.70
⊿Q		89.68	17.95	26.40	−270.27	871.25
Prolongation (d)		26.30	2.00	15.00	0	196.00
Follow-up measurements by sFlt-1—to—PlGF ratio (n)	Normal	1.00	1.20	—	0	13.00
	Intermediate	1.10	0.20	—	0	7.00
	Pathologic	2.70	0.40	—	0	13.00
⊿Q by sFlt-1—to—PlGF ratio	Normal (n=49)	39.84	8.77	12.29	−5.34	233.50
	Intermediate (n=18)	51.05	18.10	27.78	−23.06	254.46
	Pathologic (n=40)	171.12	44.64	106.85	−270.27	871.25
Gestational age at delivery by sFlt-1—to—PlGF ratio (wop)	Normal	38.40	0.20	39.10	24.40	41.40
	Intermediate	38.00	0.50	38.30	23.00	41.40
	Pathologic	33.60	0.60	32.30	23.10	41.50
Clinical outcome	Normal	PE, 5.4% (9/166)		IUGR, 9.6% (16/166)		Others, 84.9% (141/166)
	Intermediate	PE, 7.4% (4/54)		IUGR, 18.5% (10/54)		Others, 74.1% (40/54)
	Pathologic	PE, 49.2% (31/63)		IUGR, 28.6% (18/63)		Others, 22.2% (14/63)
First determination of sFlt-1 and PlGF at <34 w (wop)	Prolongation at ≤14 d	PE, 38.9% (14/36)		IUGR, 41.7% (15/36)		Others, 19.4% (7/36)
	Prolongation at >14 d	PE, 16.9% (15/89)		IUGR, 18.0% (16/89)		Others, 65.2% (58/89)
First determination of sFlt-1 and PlGF at <34 w (wop)	Prolongation at ≤14 d	Pathologic, 75.0% (27/36)		Intermediate, 11.1% (4/36)		Normal, 13.9% (5/36)
	Prolongation at >14 d	Pathologic, 15.7% (14/89)		Intermediate, 7.9% (7/89)		Normal, 76.4% (68/89)
Prolongation by priority of delivery (d)	Spontaneous labor	33.0	4.7	21.0	0	196
	Elective delivery	35.3	4.3	22.5	0	173
	48 h	19.5	2.6	8.0	0	112

TABLE 1
Characteristics of the total population analysis and subgroups according to the main diagnosis *(continued)*

	Urgent (6 h)			16.0	3.3	4.0	0	108	
	Emergency (immediately)			24.2	14.8	11.0	0	93	
Diagnostic subgroups	Mean	SE	Min	Max	Mean	SE	Min	Max	
	Placental dysfunction (n=88)				"Others" (n=195)				
Gestational age at delivery (wop)	33.60	0.50	23.10	40.60	38.60	0.20	23.00	41.50	
sFlt-1—to—PlGF ratio at admission	231.49	37.32	0.66	2430.70	34.00	4.11	0.48	465.94	
sFlt-1—to—PlGF ratio at delivery	354.05	47.39	−0.66	1431.70	81.00	16.09	1.47	569.54	
ΔQ (n=55/52)	137.69	32.64	−270.27	871.25	38.9	9.32	−38.68	254.46	
Follow-up measurements (n)	2.80	0.30	0	13.00	0.80	0.10	0	9.00	
Prolongation (d)	20.90	2.90	0	100.00	28.70	2.50	0	196.00	

ΔQ, soluble fms-like tyrosine kinase-1 and placental growth factor between admission and delivery; *Max*, maximum; *Min*, minimum; *PlGF*, placental growth factor; *PE*, preeclampsia; *SE*, standard error; *sFlt-1*, soluble fms-like tyrosine kinase-1; *wop*, week of pregnancy.

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subgroup prediction followed the inclusion criteria of the PROGNOSIS study. The indication for the determination of the ratio was indeterminate in 41 cases (14.5%) (Supplemental Table 1); thereof, 5 patients (12.5%) developed PE.

The mean maternal age was 30.25 years (±0.34), and the mean gestational age at delivery was 37.0 wop (±0.25) (Table 1). The percentage of patients who developed PE or IUGR using sFlt-1—to—PlGF ratio at admission was as follows: normal, 5.4% (PE) and 9.6% (IUGR); intermediate, 7.4% (PE) and 18.5% (IUGR); and pathologic, 49.2% (PE) and 28.6% (IUGR) (Table 1).

Priority of Delivery

Mean and median sFlt-1—to—PlGF ratios for the total population analysis at admission and at delivery are shown in Supplemental Table 2. Because of the large range of the sFlt-1—to—PlGF ratio, only the median values are referred to here. The delivery priority was primarily divided into elective (without time pressure), intermediate (within 48 hours), urgent (within 6 hours), and emergency (without any time delay). Increasing median sFlt-1—to—PlGF ratios were associated with an increasing priority of delivery (χ^2=43.99; P<.001); this relationship was significant (r=0.38; P<.001). In addition, 66 of 283 (23.3%) subjects had a spontaneous onset of labor.

The highest median sFlt-1—to—PlGF ratios were measured in women with a main diagnosis of PE or HELLP syndrome, with median increases of >120 in some cases between the determination at first admission and at delivery (Supplemental Table 2). Significant differences were also seen in the sFlt-1—to—PlGF ratio among the diagnoses (χ^2=65.76; P<.001) of IUGR (Z score=4.23; P<.001), PE (Z score=7.58; P<.001), and "others." Similar proportions were shown for the indication for delivery (χ^2=11.58; P=.009).

The median sFlt-1—to—PlGF ratios at admission and at delivery for women with a main diagnosis of IUGR or PE or HELLP syndrome (n=88) are shown in Table 2. Because of the small number of women in the priority of delivery group "spontaneous labor" (n=2), these results

TABLE 2
sFlt-1—to—PlGF ratios at admission and at delivery for women with a main diagnosis of IUGR or PE or HELLP syndrome

sFlt-1—to—PlGF ratio at admission (n=88)		Median	Mean	IQR	Min	Max
Priority of delivery	Elective delivery (n=9)	15.08	49.82	73.35	0.66	214.69
	48 h (n=43)	77.76	180.35	141.69	1.46	1065.33
	Urgent (6 h) (n=30)	249.60	370.12	434.21	4.04	2430.70
	Emergency (immediately) (n=4)	203.39	202.06	311.38	4.82	396.64
Indication for delivery	Fetal (n=44)	62.64	186.04	148.67	0.66	2430.70
	Maternal (n=28)	143.90	238.59	330.73	4.50	933.23
	Combined (n=16)	213.02	344.06	543.04	1.70	1058.63
Prolongation (d)	≤2 (n=30)	253.15	401.07	530.38	4.04	2430.70
	3—7 (n=14)	160.13	288.85	359.69	46.35	792.06
	>7 (n=44)	51.40	100.35	114.26	0.66	625.32
Prolongation by priority of delivery (d)	Spontaneous labor (n=2)	38.00	38.00	—	0	76.00
	Elective delivery (n=9)	34.00	43.30	52.00	16.00	98.00
	48 h (n=43)	8.00	21.10	29.00	0	100.00
	Urgent (6 h) (n=30)	3.00	11.80	20.80	0	52.00
sFlt-1—to—PlGF ratio at delivery (n=54)		**Median**	**Mean**	**IQR**	**Min**	**Max**
Priority of delivery	Elective delivery (n=7)	100.60	103.62	188.17	0.66	208.14
	48 h (n=29)	189.33	316.01	290.24	19.62	1187.82
	Urgent (6 h) (n=16)	515.37	559.44	597.37	102.45	1431.70
Indication for delivery	Fetal (n=21)	135.10	266.32	273.92	0.66	1065.33
	Maternal (n=23)	212.74	382.33	414.56	72.73	1431.70
	Combined (n=10)	317.15	473.27	746.31	17.75	1187.82
Delivery mode	Vaginal delivery	164.96	259.94	149.35	0.66	1065.33
	Cesarean delivery	301.12	397.30	467.20	12.13	1431.70

HELLP, hemolysis, elevated liver enzyme levels, low platelet count; *IQR*, interquartile range ($Q1_{25\%}$—$Q3_{75\%}$); *IUGR*, intrauterine growth retardation; *PE*, preeclampsia; *PlGF*, placental growth factor; *sFlt-1*, soluble fms-like tyrosine kinase-1.

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are not listed. An increasing delivery priority was associated with a higher median sFlt-1—to—PlGF ratio; the median sFlt-1—to—PlGF ratio was more than 3-fold higher among women requiring urgent (6 hours [249.6]) vs intermediate (48 hours [77.76]) delivery. Maternal indications for delivery included uncontrollable hypertension, severe clinical symptoms, or apprehension of an epileptic fit. Maternal indications for delivery were associated with a median sFlt-1—to—PlGF ratio more than twice that observed with fetal indications for delivery (143.9 vs 62.6). For women with a main diagnosis of "others" (n=195), no relevant difference in the median sFlt-1—to—PlGF ratios for priority of delivery was observed (Table 3). Any urgent or emergency deliveries in this population were because of other obstetrical complications, such as fetal bradycardia or anomalies of position.

Across the total population analysis, the sFlt-1—to—PlGF ratio showed a mean increase of 89.68 from first admission to delivery (Table 1). The percentage distribution of the delivery priorities was skewed to a less urgent priority of delivery among women with a main diagnosis of "others," whereas the distribution was skewed to a more urgent priority of delivery in those with a main diagnosis of IUGR or PE or HELLP syndrome (Figure 1).

Delivery Mode

The rate of cesarean delivery in the total population analysis was 39.6%, approximately 13.5% higher than the rate recorded during the same year at the University Hospital Leipzig (26.1%). For women with IUGR or PE or HELLP syndrome, the rate of cesarean delivery was 64.8% (57 of 88; primary, 52.3%; secondary, 9.1%; emergency, 3.4%). The mean sFlt-1—to—PlGF ratio among women requiring a cesarean delivery (mean, 397.30; median, 301.12) was

TABLE 3
sFlt-1—to—PlGF ratios at admission and delivery for women with a main diagnosis of "others"

sFlt-1—to—PlGF ratio at admission (n=195)		Median	Mean	IQR	Min	Max
Priority of delivery	Spontaneous labor (n=64)	10.43	29.89	29.43	0.64	465.94
	Elective delivery (n=67)	11.48	29.24	42.36	0.48	232.68
	48 h (n=42)	19.82	37.54	45.70	1.20	153.30
	Urgent (6 h) (n=17)	10.72	28.32	42.25	0.95	101.84
	Emergency (immediately) (n=3)	36.71	60.90	—	8.15	137.83
Indication for delivery	Fetal (n=32)	18.20	33.79	35.33	0.95	146.63
	Maternal (n=49)	14.19	41.27	63.28	0.48	393.49
	Combined (n=108)	12.72	30.63	29.76	0.64	465.94
	Unclear (n=6)	22.69	36.64	68.15	1.84	101.26
Prolongation period	≤2 d (n=43)	43.31	78.09	81.95	0.95	465.94
	3—7 d (n=27)	33.73	51.79	58.92	2.27	232.68
	>7 d (n=125)	5.93	15.00	16.28	0.48	104.84
sFlt-1—to—PlGF ratio at delivery (n=52)		**Median**	**Mean**	**IQR**	**Min**	**Max**
Priority of delivery	Spontaneous labor (n=8)	23.46	39.87	69.05	1.47	154.54
	Elective delivery (n=23)	50.43	86.73	63.72	0.48	455.27
	48 h (n=12)	95.69	99.30	131.95	6.04	308.45
	Urgent (6 h) (n=8)	18.91	17.12	27.30	0.52	33.26
Indication for delivery	Fetal (n=8)	18.91	44.02	81.86	0.52	174.36
	Maternal (n=19)	77.57	108.23	132.10	0.48	569.54
	Combined (n=23)	30.93	65.45	58.54	1.47	455.27
Delivery mode	Vaginal delivery	57.52	109.03	126.35	1.47	569.54
	Cesarean delivery	22.79	48.52	28.93	0.48	455.27

IQR, interquartile range ($Q1_{25\%}$—$Q3_{75\%}$); *PlGF*, placental growth factor; *sFlt-1*, soluble fms-like tyrosine kinase-1.

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noticeably higher than that for those who underwent vaginal deliveries (mean, 259.94; median, 164.96) (Table 2), but this difference was not statistically significant (χ^2=2.72; *P*=.1). The cesarean delivery rate for women with a main diagnosis of "others" was 28.2% (55 of 195; primary, 13.3%; secondary, 12.3%; emergency, 2.6%); there was no statistically significant difference in the mean or median sFlt-1—to—PlGF ratio by delivery mode in this subgroup (χ^2=0.51; *P*=.48). The results of vacuum extraction were not shown because of the small number of subjects in this subgroup (n=3).

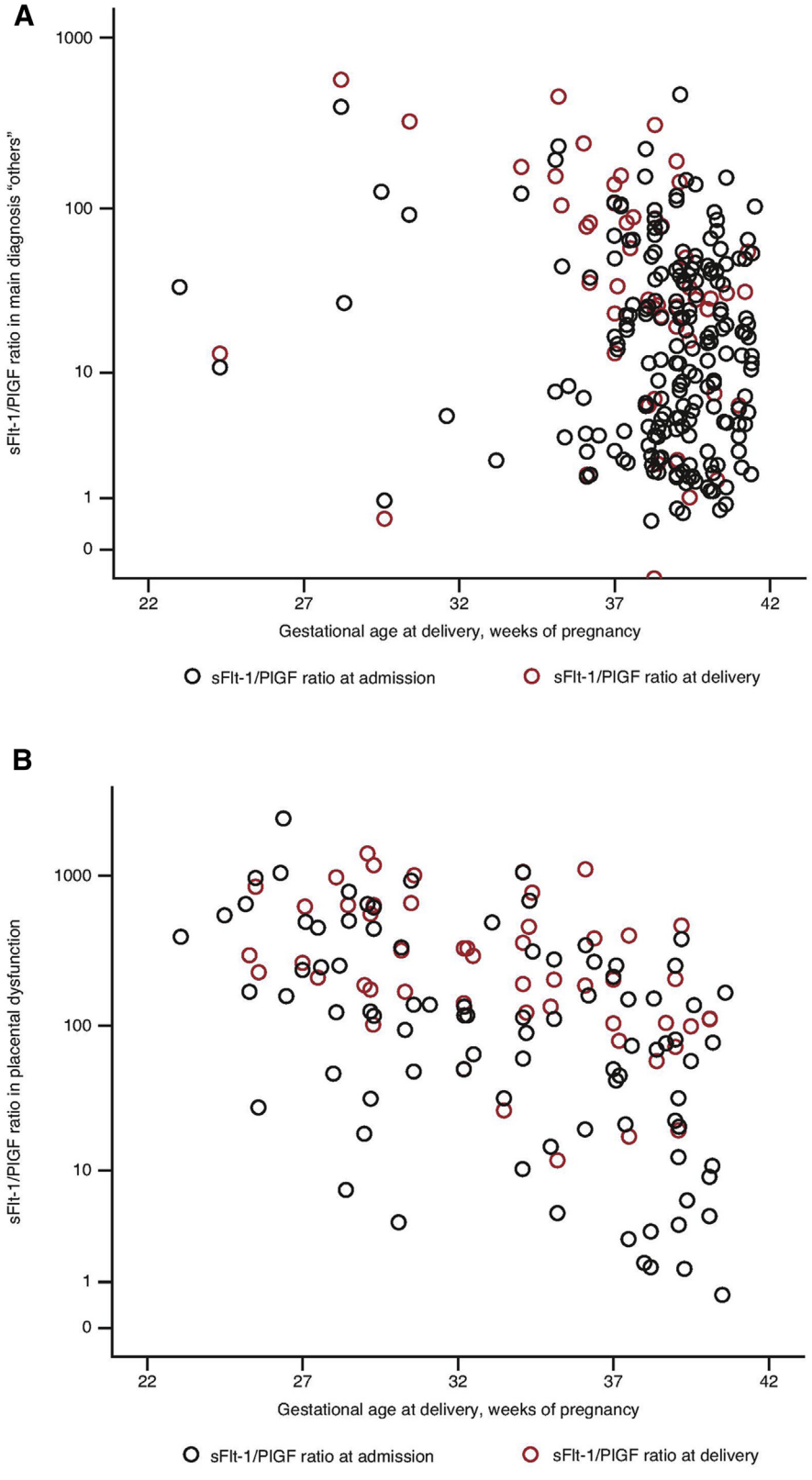
Follow-up Measurements

Only 107 of 283 subjects (37.8%) received multiple measurements of the sFlt-1—to—PlGF ratio. The number of follow-up measurements varied greatly. Even in the group with an initially normal sFlt-1—to—PlGF ratio (<38), 1 patient had 13 follow-up measurements (Table 1). The mean number of controls was 1.43 (±0.14) across the total population analysis: 2.83 (±0.34) for women with PE or HELLP syndrome and 0.81 (±0.11) for women with a main diagnosis of "others." Principally, patients with only 1 determination of the ratio had the main diagnosis of "others" (143 of 195 [73.3%]), followed by IUGR (23 of 44 [52.3%]) and PE or HELLP syndrome (11 of 44 [25%]). However, women with higher sFlt-1—to—PlGF ratios at admission were controlled more frequently (r=0.24; *P*<.001). As expected, the greatest difference between the sFlt-1—to—PlGF ratio at admission and at birth (ΔQ) was observed in women with a pathologic ratio (>85/110) at first admission. The mean increase in this group was 171.12 (±44.64) compared with 39.84 (±8.77) in women with an initial normal ratio (Table 1). The mean ΔQ in patients with placental dysfunction was 137.69 (±32.64) and 38.90 (±9.32) for women with a main diagnosis of "others."

Gestational Age

Women with an initial pathologic sFlt-1—to—PlGF ratio had a statistically significant lower mean gestational age at delivery of 33.6 wop (±0.6) compared with those who had a normal ratio (38.4 wop ±0.2) or an intermediate ratio (38.0 wop ±0.5; r=−0.62; *P*<.001) (Table 1)

FIGURE 2
sFlt-1/PlGF ratio at admission and before delivery by gestational age



and therefore had a significantly higher risk of prematurity. The mean gestational age for women with IUGR or PE or HELLP syndrome was 33.6 wop (±0.52). A lower gestational age at delivery was inversely correlated with a significantly higher sFlt-1—to—PlGF ratio at delivery. This was true for the whole population (r=−0.62; $P<.001$) and for patients with placental dysfunction (r=−0.52; $P<.001$). The mean 5-minute Apgar score in patients with placental dysfunction was 8.20 (±0.15). The 5-minute Apgar score in women with a main diagnosis of "others" was 9.07 (±0.11). There was no significant difference between the 2 groups concerning umbilical pH value.

Figure 2 shows the distribution of measurements of the sFlt-1—to—PlGF ratio at admission and at delivery. The highest ratios (maximum, 2430.7) were found before 30 wop and illustrate the risk of premature birth associated with early-onset PE (≤34.0 wop). The largest density of measurements was evident beyond 35 wop. Thus, there was a significant inverse relationship between the sFlt-1—to—PlGF ratio and birthweight (r=−0.58; $P<.001$).

A lower gestational age at first determination was inversely correlated with a significantly longer prolongation period. This was true for the whole population (r=−0.6; $P<.001$) and for women with placental dysfunction (r=−0.43; $P<.001$). A higher sFlt—to—PlGF ratio at delivery was associated with a lower gestational age

Presentation of the sFlt-1—to—PlGF ratio at admission (*black circles*) and before delivery (*red circles*) by gestational age (weeks of pregnancy) in women with a main diagnosis of "others" (n=195/52) (**A**) and placental dysfunction (n=88/55) (**B**). In both groups, the highest measurements were documented before 30 week of pregnancy and demonstrate the associated significant risk of a premature birth. In women with a main diagnosis of "others," the largest density of measurements was documented beyond 35 week of pregnancy.

PlGF, placental growth restriction; *sFlt-1*, soluble fms-like tyrosine kinase-1.

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(placental dysfunction, r=−0.52; $P<.001$; "others," r=−0.38; $P=.01$).

Prolongation Period

For the total population analysis, the mean prolongation period from first determination of the sFlt-1−to−PlGF ratio to delivery was 26.3 days compared with 20.9 days in the subgroup of women diagnosed with IUGR or PE or HELLP syndrome (Table 1). As the sFlt-1−to−PlGF ratio increased, the prolongation period decreased significantly (placental dysfunction, r=−0.51; $P<.001$; "others," r=−0.63; $P<.001$). The proportion of women with their first determination of sFlt-1−to−PlGF ratio of <34.0 wop and a prolongation period of ≤14 days was 38.9% for those with PE or HELLP syndrome, 41.7% for those with IUGR, and 19.4% for those with "others." By ratio at admission, the distribution of first-time determination of sFlt-1−to−PlGF ratio of <34.0 wop and a prolongation period of ≤14 days was 13.9% (normal), 11.1% (intermediate), and 75.0% (pathologic) (Table 1). For women with a placental dysfunction and a maximum prolongation of 2 days, the mean sFlt-1−to−PlGF ratio was 401.07 compared with 288.85 for a prolongation of 3 to 7 days and 100.35 for a prolongation of >7 days (Table 2). Even for a prolongation period of >7 days, a maximum sFlt-1−to−PlGF ratio of 625.32 at admission was measured. The difference among the mean sFlt-1−to−PlGF ratios for the 3 prolongation intervals was significant ($P<.001$). The same correlation was found for women with a main diagnosis of "others." However, a mean sFlt-1−to−PlGF ratio of >85 was not observed for any of the 3 prolongation intervals (Table 3). No significant relation between the prolongation period and ΔQ was observed (total r=0.06; $P=.51$; placental dysfunction r=0.19; $P=.17$). There was also no significant relation between the gestational age at the first determination and ΔQ. This was true for women with placental dysfunction (r=−0.24; $P=.08$) and women with a main diagnosis of "others" (r=−0.25; $P=.08$).

A significant inverse relationship between prolongation time and priority of delivery was also seen. For the total population analysis, median prolongation time before an urgent delivery (6 hours) was 4.0 days (mean, 16.0 days) vs 22.5 days (mean, 35.3 days) for an elective delivery (Table 1). The median prolongation period for placental dysfunction and an intermediate delivery (48 hours) was 8.0 days (mean, 21.05 days); for urgent deliveries (6 hours), the median was 3.0 days (mean, 11.83 days) (Table 2). Thus, for women with a diagnosis of placental dysfunction and urgent delivery (6 hours), with a median sFlt-1−to−PlGF ratio of 249.6 at first admission and 515.37 at delivery, a median prolongation period of ≥3.0 days was realized (Table 2). The median prolongation period before an emergency delivery was not analyzed because of the small number of subjects (n=3).

Clinical Utility of the Soluble fms-like Tyrosine Kinase-1−to−Placental Growth Factor Ratio

Our retrospective analysis shows that the main findings of a number of prospective and case control studies, assessing the clinical utility of sFlt-1 and PlGF, can be reproduced in a real-world setting. Approximately 30% of women with ≥1 determination of the sFlt-1−to−PlGF ratio developed placental dysfunction (15.5% IUGR and 15.5% PE or HELLP syndrome). This was approximately 10% higher than the reported in the PROGNOSIS study,[16] in which approximately 20% of women with suspected PE developed PE or HELLP syndrome.[6] The divergence between these 2 results may be explained by the inclusion criteria: in the PROGNOSIS study, women with a manifested PE respectively confirmed diagnosis were excluded, whereas all women in this study who fulfilled the inclusion criteria were investigated unselectively. Generally, a routine determination of the angiogenic factors in everyday clinical practice does not provide any additional benefit concerning the prediction of an adverse peripartal outcome.[17] In our data set, the determination of the sFlt-1−to−PlGF ratio was indicated by the treating physician. Thus, our cohort is representative of the unselective use of the ratio in daily clinical practice. In approximately 15% of cases, the indication for the determination of the sFlt-1−to−PlGF ratio was unclear. In addition, it was found that even patients with a normal ratio and no indication for the determination had multiple follow-up measurements. This is precisely the characteristic of a real-world analysis and shows that medical resources are not always used meaningfully and purposefully in clinical practice. Normally, increased clinical experience of the physician results in a more economical use of medical resources.[18] Thus, it should be investigated whether clinical experience also affects the use and frequency of follow-ups of the sFlt-1−to−PlGF ratio. A consistent recommendation on the time interval of follow-up measurements does not exist but rather depends on the individual clinical situation. In patients with normal sFlt-1 and PlGF measurements, a 2-week follow-up interval may be justified, although there is no guarantee for occurrence of progression. For a confirmed PE, with a sFlt-1−to−PlGF ratio of >85/110, repeat measurements after 2 to 4 days are recommended.[9] Multiple repeat measurements within 1 day, as observed occasionally in our analysis, are not meaningful.

For patients without placental dysfunction, the cesarean delivery rate of 28.2% was slightly higher than the 26.1% total rate of cesarean deliveries at University Hospital Leipzig in 2017 and approximately 3.0% below the national average of 30.5%.[19] For the diagnosis of PE, the cesarean delivery rate was twice as high and therefore significantly lower than the international rates.[20,21] In women with placental dysfunction, the median and mean of the sFlt-1−to−PlGF ratio were noticeably, but not significantly, higher with cesarean delivery compared with vaginal delivery. However, this does not mean that delivery mode is dependent on the value of the ratio but rather is determined by the overall clinical situation. Our data demonstrated that even with a maximal value of sFlt-1−to−PlGF ratio, more than 1000 women had a vaginal delivery. Therefore, the cesarean delivery rate is

not triggered by the magnitude of the ratio but by the severity of placental dysfunction, the correlated prematurity, and adverse maternal and fetal morbidities.

Our results showed that the sFlt-1—to—PlGF ratio is widely used in clinical practice, especially after 35 wop.[22] The ratio was used to exclude a late-onset PE (≥34 wop) and may help to determine whether an immediate delivery is necessary or not. Of course, the sensitivity of cutoffs for the sFlt-1—to—PlGF ratio will not reach 100%.[9] However, the current standard (using blood pressure and proteinuria) has an even lower test performance, with a positive predictive value approximately 20%. The current guidelines of the German Society for Gynecology and Obstetrics on hypertensive gestational disorders[1] state that a sFlt-1—to—PlGF ratio of <38 can safely exclude a PE within the next week (a negative predictive value of 99.3%; value based on PROGNOSIS study[16]).

According to the study by Ciobanu et al,[23] the determination of biomarkers, such as sFlt-1 or PlGF, barely improves the prediction of delivery in small-for-gestational-age (SGA) neonates. In our study, fetuses with growth restriction were summarized with PE as placental dysfunction. In clinical routine, as described by Ciobanu et al,[23] the estimated fetal weight in ultrasound and pulse wave Doppler are used as the primary diagnostic agents in SGA fetuses. However, the sFlt-1—to—PlGF ratio can be used as a supplemental tool because many patients with intrauterine growth restriction will develop symptoms of PE in further gestational age. Thus, sFlt-1—to—PlGF may help predict an exacerbation. Placental dysfunction is associated with prematurity and, thus, with fetal morbidity and mortality.[24,25] Maximum prolongation of pregnancy is therefore key to avoid premature delivery.

In our analysis, placental dysfunction was associated with a significantly lower gestational age at delivery. The lower 5-minute Apgar scores in these patients compared with women with a main diagnosis of "others" probably resulted from preterm birth. Obstetrical management was not determined by the size of the sFlt-1—to—PlGF ratio; even with a maximum ratio of >625 at admission and a confirmed diagnosis of PE, a prolongation time of >7 days could be achieved. Generally, 50% of all pregnancies with placental dysfunction (44/88) were prolonged for >7 days. In addition, a mean prolongation time of 20.9 days was demonstrated despite placental dysfunction (mean sFlt-1—to—PlGF ratio of 231.49 at admission). Even before an urgent delivery (mean sFlt-1—to—PlGF ratio of 559.44), a mean prolongation period of approximately 12 days (median, 3.0) was shown. The relationship between prolongation time and priority of delivery is not linear but rather mediate. Patients with a short prolongation period usually also showed greater pathology, which increased the probability of a prompt delivery. The fact that a lower gestational age at first determination was associated with a longer prolongation period was not surprising because it is the obstetrical aim to prolong the pregnancy as long as possible despite placental dysfunction. By neglecting gestational age, our real-world analyses of the impact of the sFlt-1—to—PlGF ratio on possible prolongation period confirmed the results of the multicenter prospective study by Verlohren et al[26]; mean sFlt-1—to—PlGF ratios for each prolongation period in our analyses vs Verlohren et al,[26] respectively, were as follows:≤2 days, 401.07 vs 403.22; 3 to 7 days, 288.85 vs 346.99; and >7 days, 100.35 vs 143.01. Similarly, the trend in ΔQ was similar to results of the PROGNOSIS study.[7] In some international studies, immediate delivery within 48 hours is recommended in cases where a severely elevated sFlt-1—to—PlGF ratio is measured (655 in early-onset PE; >201 in late-onset PE) to prevent an adverse maternal outcome.[27,28] However, it is clear that the sFlt-1—to—PlGF ratio is not only a diagnostic tool but also could help predict the clinical course and rate of progression of placental dysfunction, when considered in combination with clinical symptoms, laboratory and sonographic findings, and physician experience. This combination of different tools was examined in the study by Ciobanou et al.[29] The working group was able to show that in a combination of a competing risks model, the sFlt-1—to—PlGF ratio and the mean arterial pressure (triple test) were even superior to the isolated measurement of the ratio in the prediction of PE (35—37 wop). Other working groups were also able to show that the combination of angiogenic biomarkers with a baseline model of maternal characteristics may significantly improve the prediction of delivery in hypertensive gestational disorders and PE.[30,31] Nevertheless, it should be noted that nationally and internationally, even the sFlt-1—to—PlGF ratio has not been established in many hospitals, and therefore, triplet tests and combined baseline models are not currently conceivable as daily clinical tools.

A limitation of this analysis is the single determination of the sFlt-1—to—PlGF ratio in a few women (n=107), especially for women with the main diagnosis of "others." Nevertheless, the results of this investigation were representative, because most of the women were probably healthy, and therefore, the indication for the following determinations of the ratio did not exist. Another limitation is that no explicit division between the fetal delivery indication because of a placental or non-placental dysfunction was conducted. However, 44 women in the placental dysfunction group with fetal indication had a cause of placental dysfunction. In women with a main diagnosis of "others," the indication for fetal delivery was heterogenic.

This investigation was a retrospective analysis without blinding the results of the sFlt-1—to—PlGF ratio. Nevertheless, this does not lead to a substantial treatment bias, because the intention of a retrospective data analysis was made years after the data collection. The results were representative of the daily obstetrical management at the University Hospital Leipzig.

Soluble fms-like Tyrosine Kinase-1—to—Placental Growth Factor Ratio as a Supplemental Tool

This investigation used a real-world approach in a diverse collective of daily

clinical practice. Approximately 30% of women had PE or another manifestation of placental dysfunction. Our data show that clinical management of these women is not determined solely by the sFlt-1—to—PlGF ratio; however, the sFlt-1—to—PlGF ratio serves as a supplemental tool that could help to estimate the severity of placental dysfunction and to antedate the progression of pregnancy. A broader use of the sFlt-1—to—PlGF ratio may help improve the obstetrical management of pregnancies with placental dysfunction. ■

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Author and article information

From the Department of Obstetrics, University Hospital Leipzig, Leipzig, Germany.

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Corresponding author: Holger Stepan, MD. holger.stepan@medizin.uni-leipzig.de