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Full length article

Decoding placental dysfunction with a new angiogenic classification of PlGF and sFlt-1

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ABSTRACT

Objective: The ratio between sFlt-1 (soluble fms-like tyrosine kinase-1) and PlGF (Placental Growth Factor) was recently introduced to aid in the management of hypertensive disorders of pregnancy and fetal growth restriction, but it has limitations. This study proposes a new angiogenic classification of PlGF and sFlt-1 to enhance maternal and fetal risk assessment in pregnancies with suspected placental dysfunction.
Study design: A retrospective analysis was conducted on hospitalized singleton pregnancies beyond the 20th week complicated by hypertensive disorders of pregnancy and/or fetal growth restriction. Patients were classified based on sFlt-1/PlGF (low, medium, high, very high) and into the nine possible combinations using PlGF and sFlt-1 gestational age-specific levels: (1) PlGF and sFlt-1 within range; (2) PlGF in range, sFlt-1 < range; (3) PlGF in range, sFlt-1 > range; (4) PlGF < range, sFlt-1 in range; (5) PlGF and sFlt-1 < range; (6) PlGF < range, sFlt-1 > range; (7) PlGF > range, sFlt-1 in range; (8) PlGF > range, sFlt-1 < range; (9) PlGF and sFlt-1 > range.
Results: The cohort included 227 patients. The most common categories were 1, 3, 4, and 6. Categories 4 and 6 had a higher proportion of fetal growth restriction, whereas categories 3 and 6, presented a greater risk of severe maternal complications. Category 6 exhibited the highest risk of adverse maternal-fetal outcomes; conversely, category 1 was the category at the lowest risk for complications. Notably, 40 % of patients classified as low or medium risk by the sFlt-1/PlGF were high-risk by our classification.
Conclusion: Evaluation of actual PlGF and sFlt-1 levels rather than set cut-off ratios can improve the risk stratification of clinical manifestations of placental pathology.

Introduction

Diagnosis and management of hypertensive disorders of pregnancy and fetal growth restriction, major causes of maternal and perinatal morbidity, remain challenging [1–3]. Common diagnostic methods have predictive limitations [4], and despite guidelines, there is no clear consensus on criteria or management [5,6]. This uncertainty leads to diagnostic inconsistencies, adverse outcomes, and increased costs [7]. The discovery of angiogenic markers in the 2000s improved our understanding of placental dysfunction [8].

Angiogenesis, essential for placental function, is regulated by pro- and anti-angiogenic factors [9]. An imbalance in these factors can signal placental dysfunction, leading to conditions like hypertensive disorders of pregnancy and fetal growth restriction [10]. Currently, two angiogenic markers, PlGF (Placental Growth Factor) and sFlt-1 (soluble fms-like tyrosine kinase 1), are used in clinical practice. PlGF, produced by the syncytiotrophoblast, promotes angiogenesis and vascular homeostasis, while sFlt-1, an antiangiogenic protein, antagonizes PlGF and vascular endothelial growth factor in circulation, leading to endothelial dysfunction. sFlt-1 is released from the trophoblast in response to various triggers such as hypoxia and oxidative stress. In healthy pregnancy, PlGF rises until week 32 and then declines, while sFlt-1 levels increase later. Lower PlGF and/or higher sFlt-1 levels are observed in placental dysfunction [11], and elevated sFlt-1 has been linked to

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hypertensive disorders [12] as well as their severity [13]. High sFlt-1 levels have also been found in conditions like COVID-19, causing preeclampsia-like syndrome [14]. Low PlGF is associated with hypertensive disorders of pregnancy and fetal growth restriction [15]. Despite reflecting placental function [16], the routine clinical use of these markers remains inconsistent, with ongoing questions about interpretation, cut-offs, and performance in conditions such as multiple pregnancies or infections [17]. Current methods, like measuring PlGF alone or using the sFlt-1/PlGF ratio, have limitations, particularly in guiding delivery timing, and may lead to unnecessary interventions [18]. While extensive research has focused on low PlGF levels and elevated sFlt-1/PlGF ratios, which are linked to shorter gestational duration and increased adverse outcomes [19–25], including efforts to define cut-offs, the role of sFlt-1 alone has been less explored [26]. Furthermore, not all ratios are equivalent, and a fixed ratio may overlook significant biomarker variations, as PlGF and sFlt-1 have distinct roles and provide different insights into placental disorders [27]. To address these issues, this study proposes a new angiogenic classification that categorizes pregnancies into nine combinations of PlGF and sFlt-1 levels adjusted for gestational age-specific ranges (within, above, or below range). By applying this classification to a cohort of pregnancies complicated by hypertensive disorders and/or fetal growth restriction, we aim to improve the assessment of maternal and fetal risk in cases of suspected placental dysfunction.

Materials and methods

We conducted a retrospective cohort analysis at the San Gerardo Hospital Obstetrics Unit in Monza, Italy, from May 2018 to December 2020, including singleton pregnancies beyond the 20th week, hospitalized for hypertensive disorders and/or fetal growth restriction, and with at least one assay for PlGF and sFlt-1 performed during their hospitalization. Preeclampsia was defined according to ACOG criteria [28], while fetal growth restriction was defined as an estimated fetal weight or abdominal circumference below the 10th percentile, or as a deflection or arrest in fetal growth. Among these, cases fulfilling the Delphi consensus criteria were classified as Delphi-defined fetal growth restriction (D-FGR) [29]. Neonatal birth weight distribution was assessed using Italian birth weight charts [30]. All patients provided informed consent for biological material collection. Serum samples were analyzed for sFlt-1 and PlGF levels using the Cobas e601 platform (Roche Diagnostics), with the electrochemiluminescence immunoassay principle (REF 05109523190 and 05144671190, respectively). According to the EP05-A3-CLSI protocol, both intra-assay variability and inter-assay variability were assessed for serum PlGF and sFlt-1 levels at various concentration levels (6.8–9,219 pg/mL and 53.2–70,552 pg/mL, respectively), with an overall variability of <5 %. In cases of multiple assays during the same or different hospitalizations, only the first test result was included in the analysis.

Both sFlt-1/PlGF ratios and individual levels of PlGF and sFlt-1 adjusted for gestational age (within range, above, or below range) were evaluated. The sFlt-1/PlGF was categorized into four groups based on the 34th week of gestation [17]: low (<38), medium (38–85 or 38–110 after 34 weeks), high (>85 or >110 after 34 weeks), and very high (>655 or >201 after 34 weeks) – Supplementary materials Table S1 [20]. PlGF and sFlt-1 levels were adjusted for gestational age and classified as within range (10th-90th percentile), above range (>90th percentile), or below range (<10th percentile) using data from a prospective study on uncomplicated singleton pregnancies (Supplementary materials Table S2) [31]. This resulted in nine distinct categories (Supplementary materials Table S3):

Both PlGF and sFlt-1 within range
PlGF within range, sFlt-1 below range
PlGF within range, sFlt-1 above range
PlGF below range, sFlt-1 within range
Both PlGF and sFlt-1 below range
PlGF below range, sFlt-1 above range
PlGF above range, sFlt-1 within range
PlGF above range, sFlt-1 below range
Both PlGF and sFlt-1 above range

The primary outcome of the study was to apply the new classification to a cohort of patients with suspected placental dysfunction due to hypertensive disorders of pregnancy and/or fetal growth restriction and to evaluate the advantages of this new method in terms of maternal-fetal risk stratification compared to the current method, the sFlt-1/PlGF ratio.

Anamnestic details were collected for each patient, and pregnancy outcomes were analyzed according to the above classifications. Medical decisions were based on maternal-fetal clinical assessments, ultrasound findings, and traditional laboratory parameters; biochemical angiogenic markers were not used clinically, given the absence of specific guidelines at the time.

Chi-square or parametric/non-parametric tests were applied, with a two-sided p-value <0.05 considered significant.

Results

The study included 227 patients hospitalized for hypertensive disorders of pregnancy and/or fetal growth restriction and delivered at our institution. The cohort was distributed across the four published sFlt-1/PlGF categories as follows: low (32 %), medium (30 %), high (28 %), and very high (10 %) (Supplementary materials Table S4).

Patients were also classified into nine angiogenic categories based on the possible combinations of PlGF and sFlt-1 levels adjusted for gestational age. The most frequent categories were category 1 (35 %), in which both markers were normal, and category 6 (34 %), characterized by low PlGF and high sFlt-1. Category 3 (16 %), with normal PlGF and high sFlt-1, and category 4 (11 %), with low PlGF and normal sFlt-1, were less common. Categories 2, 5, 7, 8, and 9 were rare in this population, each comprising only 0 % to 3 % of cases (Supplementary materials – Table S5 – Description of patients in categories 2, 7, and 8).

For this reason, the subsequent analysis focused on categories 1, 3, 4, and 6. Future research will further explore the application of this classification to all pregnancies, and not only to those complicated by hypertensive disorders and/or fetal growth restriction.

No significant demographic differences were observed between the sFlt-1/PlGF categories (Table 1A), except for the absence of pre-existing conditions in the very high category. Table 1B shows the same characteristics for the assigned combinations of sFlt-1 and PlGF levels. Tables 2A and 2B report obstetric outcomes according to published and new classifications, respectively. Gestational age at testing was lower in higher ratio groups and in category 6.

Obstetric outcomes showed significant differences across categories. Hypertensive disorders of pregnancy, especially preeclampsia, and severe preeclampsia, were prevalent in the high and very high ratio categories, with no significant difference between them. Categories 3 and 6 (high sFlt-1) also showed elevated rates of these conditions (up to 92 %), while preeclampsia associated with Delphi-defined fetal growth restriction (D-FGR) was present in 51 % of category 6. D-FGR was mainly observed in category 6 (62 %), as well as in high and very high ratio categories (57–54 %).

Category 6 patients had the highest risk of severe conditions (32 %), such as HELLP syndrome, eclampsia, placental abruption, liver rupture, and acute heart failure post-partum. In contrast, no complications were noted in category 1. In the reference classification, no events were observed in the low sFlt-1/PlGF, while the highest complications occurred in the high and very high ratios. HELLP syndrome and atypical preeclampsia were more frequent in categories 3 and 6 (14–16 %), placental abruption occurred only in category 6 (13 %), and eclampsia was observed in categories 3–6. This stratification was less clear in the reference classification, where placental abruption also occurred in the

Table 1A
Population characteristics according to the published angiogenic classification of sFlt-1/PlGF ratio [Mean ± standard deviation; n; (%)].

Anamnestic details	sFlt-1/PlGF = 227								
	low		medium		high		very high		p value
	n 72	% 32	n 68	% 30	n 63	% 28	n 24	% 10	
Age (years)	32 ± 6		33 ± 5		34 ± 5		32 ± 7		0.164
Caucasian	55	76	56	82	49	78	17	71	0.664
Primigravid	32	44	32	47	32	51	15	63	0.470
Primiparous	47	65	51	75	41	65	17	71	0.555
ART	3	4	5	7	9	14	3	13	0.182
Obesity (pregestational BMI ≥ 30 kg/m^2)	17	24	15	22	14	22	3	13	0.379
Documented pre-pregnancy medical condition	20	28	17	25	9	14	0	0	**0.012**
Previous HDP/SGA/SB	15	21	12	18	10	16	4	17	0.893
GDM	17	24	16	24	8	13	4	17	0.334
LDA < 16th week	20	28	18	26	11	17	4	17	0.395
LMWH therapy during pregnancy	1	1	2	3	1	2	0	0	0.790
LDA + LMWH therapy during pregnancy	1	1	0	0	2	3	1	4	0.423

Table 1B
Population characteristics according to the combinations of actual sFlt-1 and PlGF levels [Mean ± standard deviation; n; (%)].

Anamnestic details	Categories n = 227								
	Cat. 1 PlGF and sFlt-1 in range		Cat. 3 PlGF in range, sFlt-1 > range		Cat. 4 PlGF < range, sFlt-1 in range		Cat. 6 PlGF < range, sFlt-1 > range		p value
	n 79	% 35	n 37	% 16	n 24	% 11	n 77	% 34	
Age (years)	33 ± 5		34 ± 5		33 ± 6		33 ± 6		0.696
Caucasian	67	85	30	81	19	79	55	71	0.228
Primigravid	40	51	20	54	8	33	40	52	0.386
Primiparous	57	72	30	81	14	58	50	65	0.189
ART	5	6	3	8	2	8	10	13	0.537
Obesity (pregestational BMI ≥ 30 kg/m^2)	17	22	4	11	8	33	17	22	0.608
Documented pre-pregnancy medical condition	20	25	6	16	8	33	10	13	0.083
Previous HDP/SGA/SB	11	14	6	16	7	29	13	17	0.383
GDM	18	23	7	19	8	33	10	13	0.140
LDA < 16th week	22	28	5	14	6	25	17	22	0.389
LMWH therapy during pregnancy	2	3	0	0	0	0	1	1	0.654
LDA + LMWH therapy during pregnancy	1	1	1	3	0	0	2	3	0.804

Legend: ART – assisted reproductive technology, BMI – body mass index.
Documented pre-pregnancy medical condition: diabetes mellitus type 1–2, chronic hypertension, autoimmune disease, nephropathy, thrombophilia.
HDP – hypertensive disorder in pregnancy.
SGA – small for gestational age baby
SB – stillbirth.
GDM – gestational diabetes mellitus.
LDA < 16th week – prophylaxis with Low-Dose Aspirin – 150 mg/day started by the 16th week of pregnancy.
LMWH – low-molecular-weight heparin
LDA + LMWH – combined therapy of both.

medium ratio category, with more cases in the high category than in the very high one. Similarly, the case of liver rupture, which also belonged to category 6, had a high sFlt-1/PlGF, but not a very high one. Antihypertensive therapy and other treatments were most common in the high-very high ratio categories, but without a significant difference, and in category 6. Intensive care unit (ICU) admission (n = 3) was reported in patients with a high/very high sFlt-1/PlGF and categories 3 and 6.

Deliveries occurred earlier in high/very-high ratio categories and category 6 (75 %). Vaginal birth rates were lower in high/very high categories, with urgent cesarean sections for hypertensive disorders of pregnancy and/or fetal growth restriction reasons in 40–42 % of cases. In the new classification, only 32 % of category 6 patients had vaginal births, while urgent cesarean sections for for these conditions were performed in 14 % of category 3 and 44 % of category 6 cases (high sFlt-1 categories).

The traditional classification showed no significant differences in neonate birth weight distribution across categories. Conversely, the new classification showed more small-for-gestational-age babies in categories 4 and 6 (50–52 %) with low PlGF and more large-for-gestational-age babies in categories 1 and 3 (11–5 %) with normal PlGF.

Furthermore, results showed that low sFlt-1/PlGF ratios were most common in category 1 (67 %), medium ratios in categories 3 and 4, while high ratios increased progressively in categories 4, 3, and 6. Very high ratios were linked to categories with higher sFlt-1 levels, especially category 6 (27 %). Notably, 40 % of patients with low/medium ratios were in categories 3, 4, and 6, which are associated with maternal/fetal/neonatal risks according to the new algorithm (Fig. 1).

Comment

Angiogenic markers are increasingly used in obstetric practice for screening, diagnosis, and monitoring placental dysfunction disorders, particularly preeclampsia and fetal growth restriction [27]. A standardized interpretation of these markers is urgently needed.

PlGF and sFlt-1: unveiling diverse roles in pregnancy risk stratification

This article proposes a new classification of angiogenic markers with nine distinct classes. Current risk categories for the sFlt-1/PlGF may not ensure optimal obstetric management [27]. Identifying abnormal markers (sFlt-1 or PlGF) relative to gestational age can help tailor care, focusing on the fetus in cases of low PlGF, the mother with high sFlt-1, or both. This approach can enhances pregnancy management, optimizes delivery timing, and aids in complication prevention. Low PlGF effectively distinguishes constitutionally small fetuses from those with growth restriction due to placental pathology [32,33]. This association is evident in the new classification, where categories 4 and 6, characterized by lower PlGF levels, had increased rates of fetal growth restriction based on the Delphi consensus criteria (33 % and 62 %, respectively; $p < 0.0001$), higher proportions of small for gestational age babies (50 % and 52 %, respectively; $p = 0.004$), and no large for gestational age infants. Specific fetal growth restriction cut-offs are undefined, but this study uses PlGF percentiles from Verlohren's research on uncomplicated pregnancies [31]. A PlGF value lower than expected for gestational age can signal current or potential future fetal growth restriction, prompting fetal biometry and Doppler flowmetry.

Excessive sFlt-1 production causes maternal endothelial injury, contributing to the clinical manifestations of preeclampsia [12], and serves as a strong predictor of disease severity and adverse outcomes. There appears to be a threshold beyond which high sFlt-1 levels become toxic to the mother. Our group showed that elevated sFlt-1 levels (≥15,802 pg/mL) are linked to severe obstetric complications in multiple pregnancies with hypertensive disorders of pregnancy and/or fetal growth restriction, regardless of gestational age and chorionicity [26]. These findings highlight the importance of monitoring sFlt-1 levels in predicting adverse outcomes, as patients in categories 3 and 6 with

Table 2A
Obstetric outcomes according to the published angiogenic classification of sFlt-1/PlGF ratios.

Variables	sFlt-1/PlGF = 227									
	low		medium		high		very high			p value
	n	%	n	%	n	%	n	%		
	72	32	68	30	63	28	24	10		high – very high
Mean GA at blood test (weeks.days)	35.2 ± 4		37.3 ± 2,6		33.3 ± 3.4		34.5 ± 5.0		<0.001	0.030
Pregnancy complications at blood test										
HDP	43	60	47	69	31	49	12	50	0.104	0.948
FGR	24	33	13	19	6	10	2	8	0.002	0.864
HDP + FGR	5	7	8	12	26	41	10	42	<0.0001	0.973
Obstetric outcomes										
HDP	48	67	55	81	57	90	22	92	0.002	0.864
pregestational CH	14	19	8	12	5	8	0	0	0.044	0.158
CH (pregestational – diagnosis in pregnancy)	19	26	14	21	11	17	0	0	0.041	0.031
preE	20	28	32	47	51	81	22	92	<0.0001	0.227
Severe preE	5	7	10	15	37	59	15	63	<0.0001	0.750
D-FGR	21	29	19	28	36	57	13	54	0.001	0.804
preE + D-FGR	3	4	7	10	28	44	11	46	<0.0001	0.908
Severe clinical pictures	0	0	4	6	22	35	8	33	<0.0001	0.890
HELLP S./HELLP like S./atypical preE	0	0	3	4	12	19	4	17	0.0002	0.799
Placental abruption	0	0	1	1	8	13	2	8	0.002	0.571
Eclampsia	0	0	0	0	1	2	1	4	0.206	0.476
Liver rupture	0	0	0	0	1	2	0	0	0.404	0.537
Acute heart failure	0	0	0	0	0	0	1	4	0.065	0.105
Treatments										
Antihypertensive drugs before delivery	16	22	19	28	34	54	14	58	0.0001	0.716
Usual therapy in CH patients	5	7	3	4	0	0	0	0	0.121	/
Antihypertensive drugs after delivery	17	24	16	24	38	60	11	46	<0.0001	0.226
Antihypertensive therapy at postpartum discharge	16	22	16	24	30	48	11	46	0.002	0.882
Additional treatments	2	3	2	3	11	17	5	21	0.001	0.718
ICU admission	0	0	0	0	2	3	1	4	0.042	0.822
Mean GA at delivery (weeks.days)	38.0 ± 2.5		38.3 ± 2.0		35.0 ± 3.1		35.4 ± 4.3		<0.001	0.095
<37th week	9	13	7	10	43	68	12	50	<0.0001	0.117
<34th week	2	3	1	1	23	37	6	25	<0.0001	0.312
Latency time – blood test and delivery median days [IQR]	10 [3–23]		4 [2–9]		7 [3–14]		3 [2–6]		0.00002	0.995
Latency time – blood test and delivery > 14 days	29	40	10	15	14	22	3	13	0.002	0.310
Delivery mode										
Induced labor	41	57	53	78	22	35	12	50	<0.0001	0.200
Spontaneous labor	16	22	8	12	5	8	2	8	0.072	0.952
Vaginal delivery	50	69	47	69	24	38	10	42	0.0002	0.762
Cesarean section	22	31	21	31	39	62	14	58	0.0002	0.762
Elective cesarean section	12	17	5	7	10	16	1	4	0.170	0.144
Urgent cesarean section for HDP/FGR	1	1	4	6	25	40	10	42	<0.0001	0.867
Newborn										
AGA	44	61	39	57	36	57	10	42	0.424	0.199
SGA	23	32	24	35	26	41	14	58	0.122	0.156
LGA	5	7	5	7	1	2	0	0	0.232	0.537

elevated sFlt-1 levels faced a higher risk of severe conditions and ICU admission.

Category 6: the highest obstetric risk category

Category 6, characterized by abnormal PlGF (below range) and sFlt-1 (above range), had the highest risk of severe outcomes, including premature birth, urgent cesarean sections, the need for antihypertensive and other therapies, and conditions like HELLP syndrome, eclampsia, placental abruption (which occurred only in this category), liver rupture, and heart failure. Elevated sFlt-1 may indicate increased long-term cardiovascular risk, suggesting the need for ongoing cardiological follow-up [34]. In contrast, category 1, with normal PlGF and sFlt-1 levels, showed no complications.

Advantages of an angiogenic classification in obstetric care

The new classification aims to standardize obstetric care based on angiogenic profiles, potentially reducing maternal and perinatal morbidity and mortality, as well as unnecessary interventions like hospitalizations, labor inductions, and additional ultrasounds. This approach could lower healthcare costs and stress for both patients and providers. It can improve risk stratification by identifying high-risk cases among those with low/medium ratios and refining the categorization of high and very high ratio patients. For example, 40 % of patients with low/medium ratios were classified into categories 3, 4, and 6, including a case of placental abruption, and more severe clinical scenarios occurred in the high-ratio category compared to the very high category. Furthermore, the wide range for high ratios (85–655 before 34 weeks)

Table 2B
Obstetric outcomes according to the four most frequent angiogenic categories based on combinations of actual PlGF and sFlt-1 levels.

Variables	Categories n = 227								p value
	Cat. 1 PlGF and sFlt-1 in range		Cat. 3 PlGF in range, sFlt-1 > range		Cat. 4 PlGF < range, sFlt-1 in range		Cat. 6 PlGF < range, sFlt-1 > range		
	n	%	n	%	n	%	n	%	
	79	35	37	16	24	11	77	34	
Mean GA at blood test (weeks.days)	36.5 ± 3.5		37.4 ± 2.2		36.3 ± 3.1		32.6 ± 3.4		<0.001
Pregnancy complications at blood test									
HDP	50	63	28	76	15	63	34	44	0.008
FGR	25	32	3	8	5	21	8	10	0.002
HDP + FGR	4	5	6	16	4	17	35	45	<0.0001
Obstetric outcomes									
HDP	54	68	34	92	19	79	69	90	0.002
pregestational CH	13	16	2	5	4	17	6	8	0.178
CH (pregestational – diagnosis in pregnancy)	18	23	5	14	8	33	11	14	0.129
preE	24	30	23	62	10	42	64	83	<0.0001
Severe preE	6	8	13	35	2	8	45	58	<0.0001
D-FGR	23	29	8	22	8	33	48	62	<0.0001
preE + D-FGR	2	3	4	11	4	17	39	51	<0.0001
Severe clinical pictures	0	0	6	16	2	8	25	32	<0.0001
HELLP S./HELLP like S./atypical preE	0	0	5	14	2	8	12	16	0.004
Placental abruption	0	0	0	0	0	0	10	13	0.0003
Eclampsia	0	0	1	3	0	0	1	1	0.501
Liver rupture	0	0	0	0	0	0	1	1	0.233
Acute heart failure	0	0	0	0	0	0	1	1	0.233
Treatments									
Antihypertensive drugs before delivery	17	22	13	35	6	25	44	57	<0.0001
Usual therapy in CH patients	3	4	1	3	2	8	0	0	0.153
Antihypertensive drugs after delivery	15	19	11	30	6	25	46	60	<0.0001
Antihypertensive therapy at postpartum discharge	14	18	10	27	6	25	39	51	0.0001
Additional treatments	1	1	4	11	1	4	13	17	0.005
ICU admission	0	0	1	3	0	0	2	3	0.239
Mean GA at delivery (weeks.days)	38.3 ± 2.4		38.3 ± 1.6		38.0 ± 2.0		34.3 ± 3.2		<0.001
<37th week	6	8	6	16	3	13	56	73	<0.0001
<34th week	2	3	1	3	0	0	29	38	<0.0001
Latency time – blood test and delivery median days [IQR]	4 [2–15]		3 [2–10]		8 [2–12]		7 [3–15]		0.298
Latency time – blood test and delivery > 14 days	20	25	6	16	6	25	20	26	0.686
Delivery mode									
Induced labor	50	63	28	76	18	75	26	34	<0.0001
Spontaneous labor	16	20	4	11	2	8	7	9	0.159
Vaginal delivery	59	75	25	68	16	67	25	32	<0.0001
Cesarean section	20	25	12	32	8	33	52	68	<0.0001
Elective cesarean section	10	13	2	5	4	17	10	13	0.547
Urgent cesarean section for HDP/FGR	1	1	5	14	0	0	34	44	<0.0001
Newborn									
AGA	47	59	26	70	12	50	37	48	0.123
SGA	23	29	9	24	12	50	40	52	0.004
LGA	9	11	2	5	0	0	0	0	0.008

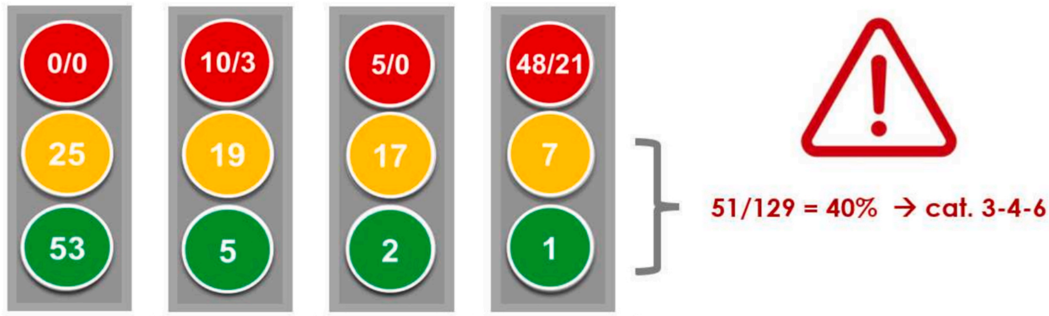
Legend Tables 2A and 2B: GA – gestational age, HDP – hypertensive disorder in pregnancy, FGR – fetal growth restriction, preE – preeclampsia (ACOG criteria), D-FGR – fetal growth restriction according to the Delphi consensus definition, IQR – interquartile range, AGA – appropriate for gestational age, SGA – small for gestational age, LGA – large for gestational age, CH – chronic hypertension, HELLP syndrome – hemolysis, elevated liver enzymes, and low platelets syndrome, ICU – intensive care unit.

limits detailed risk assessment.

Considerations and insights into the new angiogenic classification in obstetric care

Interpreting angiogenic markers requires caution in patients undergoing pharmacological treatments, with uncontrolled diabetes, or infections, as these factors can affect placental angiogenesis [17,35,36]. This analysis focuses on the most common categories associated with hypertensive disorders of pregnancy and/or fetal growth restriction (1, 3, 4, and 6), while categories 2, 5, 7, 8, and 9 were less prevalent, with no complications observed in categories 5 and 9, all of which resulted in term deliveries. Future research will further explore the application of this classification to all pregnancies. This classification could improve our understanding of placental angiogenesis and guide therapeutic strategies aimed at correcting imbalances and extending pregnancy, especially in early gestation [36].

The latency period between blood testing and delivery is influenced by various biases, primarily gestational age. In early gestation, the focus is on prolonging pregnancy, while labor induction is common at term.



	Cat. 1		Cat. 3		Cat. 4		Cat. 6	
	PlGF and sFlt-1 in range		PlGF in range sFlt-1 > range		PlGF < range sFlt-1 in range		PlGF < range sFlt-1 > range	
	n	%	n	%	n	%	n	%
	79	35	37	16	24	11	77	34
sFlt-1/ PlGF								
Low	53	67	5	14	2	8	1	1
Medium	25	32	19	51	17	71	7	9
High	0	0	10	27	5	21	48	62
Very high	0	0	3	8	0	0	21	27

Fig. 1. Distribution of the classic categories of the sFlt-1/PlGF ratio within the new categories 1-3-4-6. Green light for low ratio – yellow for medium ratio – red for high/very high ratio %, n). 40% of patients with low/medium ratio, 51 out of 129, were in categories 3-4-6. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

For tests before 37 weeks, it's crucial to assess how angiogenic marker levels differ from those expected in full-term pregnancies. We suggest a threshold limit for both PlGF (important for fetal growth) and sFlt-1 (which affects maternal endothelial function). In this regard, we recently proposed a new index, Mtp (Multiples of a normal term placenta), to predict delivery timing based on how angiogenic markers deviate from normal term values [37]. The Mtp index helps assess placental aging and delivery risk. Incorporating these markers into clinical practice may improve personalized delivery timing and enhance neonatal care, facilitating the identification of newborns who need closer monitoring in both the short and long term [38].

Our study has several limitations, including its retrospective, single-center design and small sample size of hospitalized singleton pregnancies with hypertensive disorders of pregnancy and/or fetal growth restriction after the 20th week. Larger prospective studies are needed.

Conclusion

The clinical integration of angiogenic markers is crucial for obstetrics. This new approach can improve surveillance and risk stratification. Further research on placental angiogenesis and associated conditions is needed, especially for less represented cases. Outdated definitions of hypertensive disorders of pregnancy and fetal growth restriction highlight the need for an 'angiogenic revolution' in obstetrics, along with proper education for obstetricians.

CRediT authorship contribution statement

Valentina Giardini: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alice AF Santagati:** Data curation. **Elisabetta Marelli:** Data curation. **Marco Casati:** Writing – review & editing, Investigation, Data curation. **Patrizia Vergani:** Writing – review & editing, Supervision. **Anna Cantarutti:** Writing – review & editing. **Anna Locatelli:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2025.114539.

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