

Added Value in Low-Risk Pregnancies of Longitudinal Changes in Uterine Doppler and Circulating Angiogenic Factors during the Third Trimester in Predicting Term Preeclampsia

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Keywords

Preeclampsia · Angiogenic factors · Uterine Doppler · Term pregnancy

Abstract

Introduction: The objective of this study was to assess the relationship between longitudinal changes in the uterine Doppler velocimetry and the maternal profile of angiogenic factors in the third trimester and to assess their ability to predict term preeclampsia (PE). **Methods:** A cohort of low-risk pregnant women was scheduled for a uterine Doppler evaluation and measurement of the circulating levels of angiogenic factors at ~30 and ~36 weeks. The performance of both parameters and their change over time in predicting term PE was evaluated. **Results:** A total of 1,191 women were analyzed, of which 28 (2.4%) women developed term PE. At ~30 weeks, a model including the sFlt-1/PlGF (fms-like tyrosine kinase-1/placental growth factor) ratio and the uterine Doppler explained 16.2% of the uncertainty of developing term PE, while at ~36 weeks, the same variables explained 25.2% [$p < 0.001$]. The longitudinal changes of both predictors had an R^2 of 26.8%, which was not different from that of the ~36 weeks evaluation [$p = 0.45$]. The

area under the curve (AUC) of the ~36 weeks ratio was significantly higher than at ~30 weeks (0.86 [0.77–0.94] vs. 0.81 [0.73–0.9]; $p = 0.043$). The AUC of the longitudinal change of the ratio (0.85 [0.77–0.94]) did not differ from that of at ~36 weeks ($p = 0.82$). At ~36 weeks, for a 10% of false positives, the ratio had a detection rate of 71.4%. **Conclusion:** A cross-sectional measurement of the sFlt-1/PlGF ratio outperforms uterine Doppler in predicting term PE. The combination of both markers does not improve such prediction, nor the evaluation of the longitudinal changes between weeks.

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Introduction

Preeclampsia (PE) is a serious disease complicating pregnancy, which is characterized by predominantly cardiovascular manifestations attributable to systemic inflammation, endothelial dysfunction, and generalized vasoconstriction, resulting in hypertension and multiorgan hypoperfusion [1]. It is the leading cause of maternal and perinatal mortality and morbidity worldwide. It is estimated that more than 50,000 women and 500,000 children die each year because of PE [2].

PE manifests in two different phenotypes: preterm and term PE. Preterm PE is associated with defective deep placentation early in pregnancy [3–5], making it detectable in early pregnancy using biophysical (uterine Doppler [6]) and biochemical (angiogenic factors [7]) markers of placenta insufficiency. On the other hand, term PE, though presenting similar clinical symptoms, is less related to a poorly developed placenta, as indicated by a lower prevalence of Doppler abnormalities [3, 6]. Term PE is believed to result from a mismatch between the metabolic requirements of the growing fetus and the maternal cardiovascular adaptation in the late stages of pregnancy [7]. This cardiovascular insufficiency leading to placental malperfusion and hypoxia becomes evident only in the late stages of pregnancy [1, 8], posing a clinical challenge for prediction.

Several studies have evaluated the performance of both markers of placental insufficiency (uterine Doppler and angiogenic factors [9–11]) at different gestational ages during the third trimester in predicting term PE, overall showing that the angiogenic factors outperform uterine Doppler in predictive capacity. However, the additional predictive value of longitudinal changes across the third trimester has not been explored in low-risk pregnancies. This study aimed to assess the relationship between longitudinal changes in the uterine Doppler velocimetry and the maternal profile of circulating angiogenic factors in the third trimester of pregnancy and to assess their ability, individually or in combination, to predict term PE.

Methods

Population

This study was performed in the subcohort of the Ratio 37 trial recruited in the Hospital Olomouc, Czech Republic, between July 2016 and December 2020. The Ratio 37 trial was a randomized, open-label, multicenter controlled study in which low-risk pregnancies were recruited, and umbilical and middle cerebral artery Doppler measurements were performed at 36–37 weeks in a concealed versus revealed design [12]. Inclusion criteria were singleton, low-risk (absence of any medical and obstetrical pathological condition) pregnancies. For this study, we excluded cases with an estimated fetal weight <10th [13, 14] at the 30-week evaluation and those that developed PE before the 37-week evaluation. Additional exclusion criteria were an abnormal karyotype, structural abnormalities, and congenital infections. All pregnancies were dated by ultrasound, using the crown-rump length measurement before 14 weeks [15]. All women gave their signed consent, and the Ethical

Committee of University hospital Olomouc and Palacky University Olomouc approved the study protocol (number 161/16).

Measurements

Women were recruited at the time of second trimester routine scan and scheduled for a Doppler evaluation and blood sampling at 30⁺⁰–32⁺⁶ weeks and at 36⁺⁰–36⁺⁶ weeks. Ultrasound examinations were performed by qualified sonographers with a GE Voluson E10 (GE Medical Systems, Zipf, Austria) ultrasound device equipped with a 2–8 MHz convex probe. Uterine artery (UtA) was evaluated by Doppler using a transabdominal approach adhering to the International Society of Ultrasound in Obstetrics and Gynecology [16]. The mean pulsatility index (PI) was calculated as the average of right and left arterial values.

Blood was collected in clot tubes (VACUETTE, Greiner). Samples were analyzed at the Department of Clinical Biochemistry, University Hospital Olomouc, immediately after centrifugation. Assessment of sFlt-1 and PlGF was performed using an automated analyzer B R A H M S Kryptor Compact (Thermo Fisher Scientific, B R A H M S GmbH, Germany). The B-R-A-H-M-S PlGF plus Kryptor and B-R-A-H-M-S sFlt-1 Kryptor kits were used according to manufacturer instruction. It is a technology based on TRACE (Time-Resolved Amplified Cryptate Emission) homogenous immunoassay.

Outcomes

The main outcome of this study was term PE (onset >37⁺⁰ weeks), defined according to the ISSHP [17], as de novo hypertension (systolic pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg at least 4 h apart plus any of the following: (i) proteinuria (>300 mg/24 h or a urine protein/creatinine ratio >0.3 mg/mmol); (ii) end-organ dysfunction: systolic blood pressure >160 mm Hg, diastolic blood pressure >110 mm Hg, platelet count <100 × 10⁹/L, blood concentrations of alanine and aspartate transaminase >70 IU/L, serum creatinine concentration >1.1 mg/dL, lactate dehydrogenase >700 IU/L, presence of right upper quadrant or epigastric pain, dyspnea, and/or cerebral/visual disturbances; or (iii) utero-placental dysfunction (estimated fetal weight <3rd centile or <10th centile with abnormal uterine or umbilical Doppler [pulsatility index >95th centile]). Severe PE was defined as PE with end-organ dysfunction criteria. The measurements of angiogenic factors were not considered for the clinical management.

Statistical Analysis

UtA-PIs were transformed into z-values by gestational age according to published references [18]. Changes between the first and second measurements were

Table 1. Baseline characteristics by the occurrence of term PE

	No term PE (n = 1,163)	Term PE (n = 28)	p value
Maternal age at recruitment, mean (SD), years	30.8 (4.9)	30.6 (5.6)	0.791
BMI at booking, mean (SD), kg/m ²	24.4 (4.8)	25.2 (5.8)	0.361
Smoking at recruitment, n (%)	27 (2.3)	0	0.375
Use of recreational drugs during pregnancy, n (%)	0	2 (7.1)	0.001*
Education level, n (%)			0.365
Primary	67 (5.8)	0	
Secondary	651 (56)	18 (64.3)	
High education	445 (38.3)	10 (35.7)	
Low maternal class, n (%)	10 (0.9)	0	1*
Nulliparity, n (%)	524 (45.1)	21 (75)	0.002
Assisted reproductive technique, n (%)	60 (5.2)	4 (14.3)	0.059*

AC, abdominal circumference; BMI, body mass index; SD, standard deviation. *Exact Fisher test.

calculated as delta values [measurement at ~30 weeks – measurement at ~36 weeks].

Univariate analysis of delta values between women with and without term PE was performed by *t*-test without assumption of equal variances. Multivariate analysis by logistic regression was additionally performed.

ROC curve analyses were performed and areas under the curve (AUC) calculated. Pairwise areas were compared by the DeLong method [19]. Analyses were performed using SPSS 23.0 (IBM Corp.) and R v3.1.2 (The R Foundation for Statistical Computing) packages.

Results

A total of 1,206 pregnancies were included, at a median gestational age of 30.0 weeks (range: 30⁺⁰–32⁺⁶ weeks). A total of 17 women delivered before the second measurement (including 5 women who developed PE before the second measurement) and were excluded from the analysis, leaving 1,191 women for the analysis.

A total of 28 (2.4%) women developed PE. Tables 1 and 2 show the baseline characteristics and the perinatal outcomes of the included population by the occurrence of term PE. Of the 28 women that developed PE, 7 (25%) severity criteria were met: 3 cases with severe hypertension, 1 case with neurological manifestations, 1 with persistent epigastric pain, and one with signs of hemolysis.

Table 3 details the Doppler and biochemical parameters at each measurement (~30 and ~36 weeks) and the change between both measurements, by the occurrence of

term PE. The uterine Doppler z-scores were not significantly different between term PE and control group in the first, second, and delta measurements. While no significant differences were found in PlGF delta values between groups, women that developed term PE had significant higher sFlt-1 delta values.

Figures 1 and 2 show the longitudinal changes of the sFlt-1/PlGF ratio and UtA-PI z-value in women with and without term PE. Table 4 shows the results of the multivariate analysis. While at ~30 weeks, a model including ratio sFlt-1/PlGF and UtA-PI explained a 16.2% of the uncertainty of developing term PE, at ~36 weeks, the same variables explained 25.2% (*R*² Nagelkerke) [*p* < 0.001]. A model including the longitudinal changes between the first and second measurements of both predictors had an *R*² of 26.8%, which was not significantly different from that of the ~36-week evaluation [*p* = 0.45].

At ~30 weeks, the model including the z-UTA-PI and the log-log sFlt-1/PlGF ratio had an AUC of 0.82 [95% CI: 0.74–0.9], which did not significantly differ from a model including only the sFlt-1/PlGF ratio (0.81 [0.73–0.9]) [*p* = 0.108]. At ~36 weeks, the model including the z-UtA-PI and the log-sFlt-1/PlGF ratio had an AUC of 0.86 [95% CI: 0.77–0.94], which did not significantly differ from that including only the sFlt-1/PlGF ratio (0.86 [0.77–0.94]) [*p* = 0.829]. Regarding the models evaluating the 30 to 36 changes, a model including both parameters had an AUC of 0.86 [0.77–0.94], which was not significantly different from a model including only the log-sFlt-1/PlGF ratio change (0.85 [0.77–0.94]) [*p* = 0.85].

Table 2. Perinatal outcomes by the occurrence of term PE

	No term PE (n = 1,163)	Term PE (n = 28)	p value
Gestational age at delivery, mean (SD), weeks	39.5 (1.2)	38.7 (1.3)	0.002
Birthweight, mean (SD), g	3,356 (451)	3,165 (568)	0.002
Neonatal sex, n (%)			
Male	581 (50)	17 (60.7)	0.261
Female	582 (50)	11 (39.3)	
Labor onset, n (%)			
Spontaneous	744 (64)	9 (32.1)	0.002
Labor induction	250 (21.5)	12 (42.9)	
Elective cesarean section	169 (14.5)	7 (25)	
Method of induction ¹ , n (%)			
No induction	908 (78.4)	16 (57.1)	0.008
Prostaglandins	169 (14.6)	10 (35.7)	
Mechanical methods	81 (7)	2 (7.1)	
Mode of delivery ² , n (%)			
Spontaneous	835 (72)	15 (53.6)	0.067
Instrumental	72 (6.2)	4 (14.3)	
Cesarean section	253 (21.8)	9 (32.1)	
Instrumental delivery for non-reassuring fetal status ³ , n (%)	68 (5.9)	4 (14.3)	0.095
Cesarean section for non-reassuring fetal status ³ , n (%)	62 (5.4)	2 (7.1)	
5-min Apgar score <7, n (%)	14 (1.2)	0	1*
Neonatal acidosis ⁴ , n (%)	17 (1.5)	0	1*
Hypoglycemia ⁴ , n (%)	5 (0.4)	0	1*
Neonatal morbidity, n (%)	48 (4.1)	1 (3.6)	1*

SD, standard deviation. ¹Missing values = 5. ²Missing values = 3. ³Missing values = 7. ⁴Missing values = 2. *Exact Fisher test.

Table 3. Biochemical and Doppler parameters at ~30 and ~36 weeks and change between both measurements

	No term PE (n = 1,163)	Term PE (n = 28)	p value
First measurement, mean (SD)			
Gestational age (weeks)	30.3 (0.5)	30.1 (0.3)	0.117
PlGF (pg/mL)	470 (288.4)	242.8 (187.3)	<0.001
sFlt-1 (pg/mL)	1,424.1 (900.9)	2,152.7 (1,049.5)	<0.001
Ratio sFlt-1/PlGF	5.1 (11.1)	17 (17)	<0.001
z-UtA-PI	-0.35	-0.78	0.055
Second measurement, mean (SD)			
Gestational age (weeks)	36.1 (0.2)	36.1 (0.3)	0.646
PlGF (pg/mL)	275.9 (237.9)	93.5 (76.7)	<0.001
sFlt-1 (pg/mL)	2,818.8 (1,923.2)	6,620.8 (3,607.5)	<0.001
Ratio sFlt-1/PlGF	24 (40.8)	146.8 (160.9)	<0.001
z-UtA-PI	-0.42	-0.64	0.302
Change from first to second measurement			
PlGF (pg/mL)	-194.1 (220.9)	-149.3 (129.8)	0.286
sFlt-1 (pg/mL)	1,394.7 (1,397.9)	4,468.1 (3,071.8)	<0.0001
Ratio sFlt-1/PlGF	18.9 (33.4)	129.8 (151.5)	<0.0001
z-UtA-PI	0.14	-0.06	0.159

PlGF, placental growth factor; sFlt-1, Fms-like tyrosine kinase 1; UtA-PI, uterine artery pulsatility index.

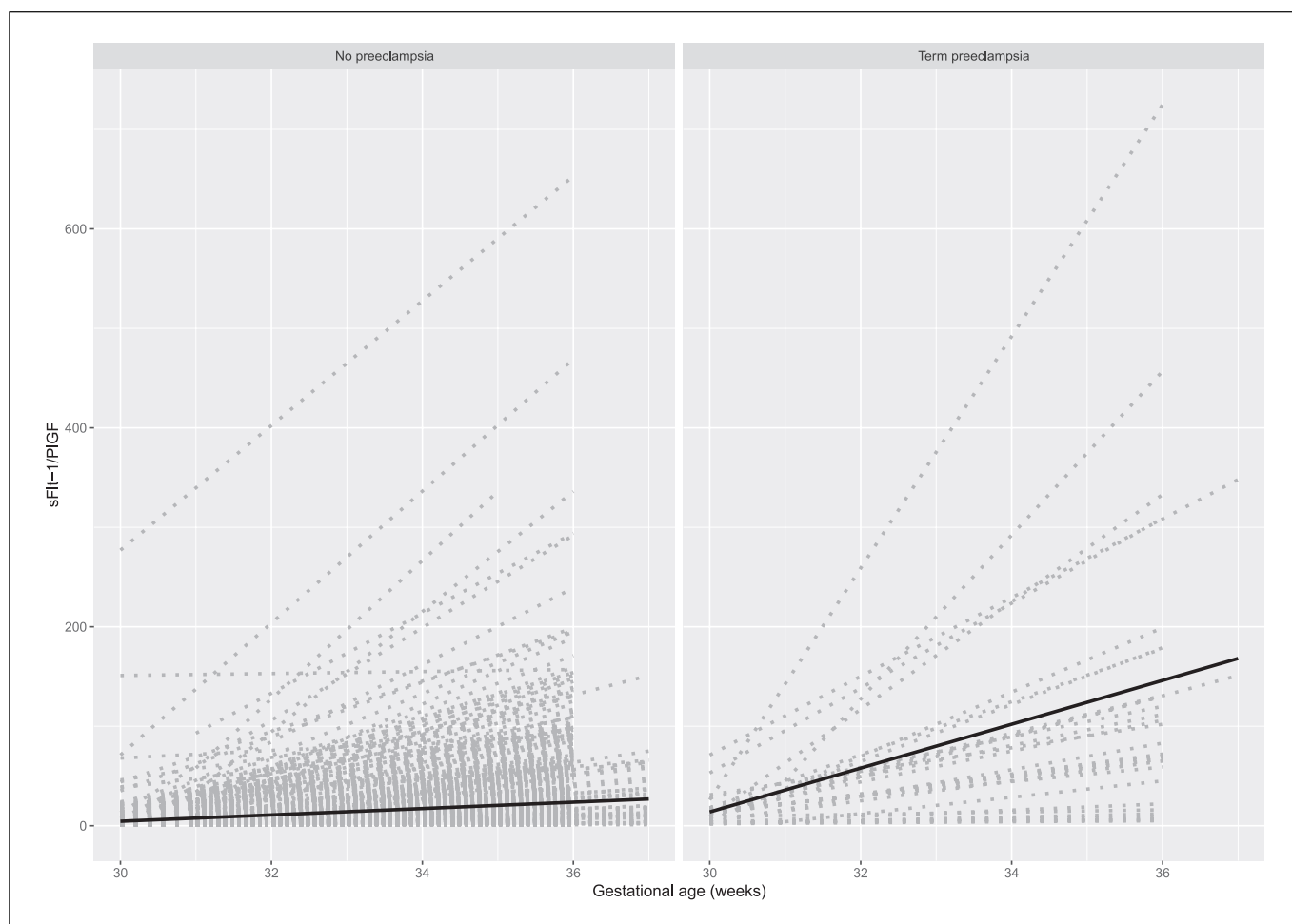


Fig. 1. Longitudinal changes in sFlt-1/PlGF ratio between 30 and 36 weeks by the occurrence of term PE. PlGF, placental growth factor; sFlt-1, Fms-like tyrosine kinase 1.

Table 5 and Figure 3 show the diagnostic performance for term PE of 30-week and 36-week sFlt-1/PlGF ratio and of the 30- to 36-week change. Of note, the AUC of the ~36-week sFlt-1/PlGF ratio was significantly higher than at ~30 weeks (0.86 [0.77–0.94] vs. 0.81 [0.73–0.9]; $p = 0.043$). The AUC of the 30- to 36-week change of the sFlt-1/PlGF ratio (0.85 [0.77–0.94]) did not significantly differ from that at ~36 weeks ($p = 0.82$).

Online supplementary Figure 1 (available at <https://doi.org/10.1159/000541731>) shows the performance of the ~30-week and ~36-week sFlt-1/PlGF ratio for severe PE. For 5%, 10%, and 15% of false positives, the detection rate of ~36-week sFlt-1/PlGF ratio were 57%, 85.7%, and 100%, respectively. At ~30 weeks, the detection rates were 14%, 71%, and 85%, respectively. Overall, the AUC of that parameter was 95% (92%–98%) versus 86% (74%–99%).

Discussion

Our cohort shows that (i) a cross-sectional measurement of the angiogenic factors near term outperforms uterine Doppler in predicting term PE; (ii) the combination of both markers does not improve the prediction; and (iii) the longitudinal changes between ~30 and ~36 weeks does not increase the prediction of a ~36-week cross-sectional evaluation.

In our series 2.4% of women developed term PE which is consistent with a prospective study by Sovio et al. [20]. Their reported incidence was 2.8%. Mac Donald et al. [21] described 39 cases of PE after 36 weeks from a cohort of 1,000 pregnant women, corresponding to an incidence of 3.9%. The higher incidence may have been due to using the ratio (≥ 38) as a criterion for the diagnosis of PE.

We failed to find predictive capacity of the uterine Doppler measured at third trimester for term PE. We also

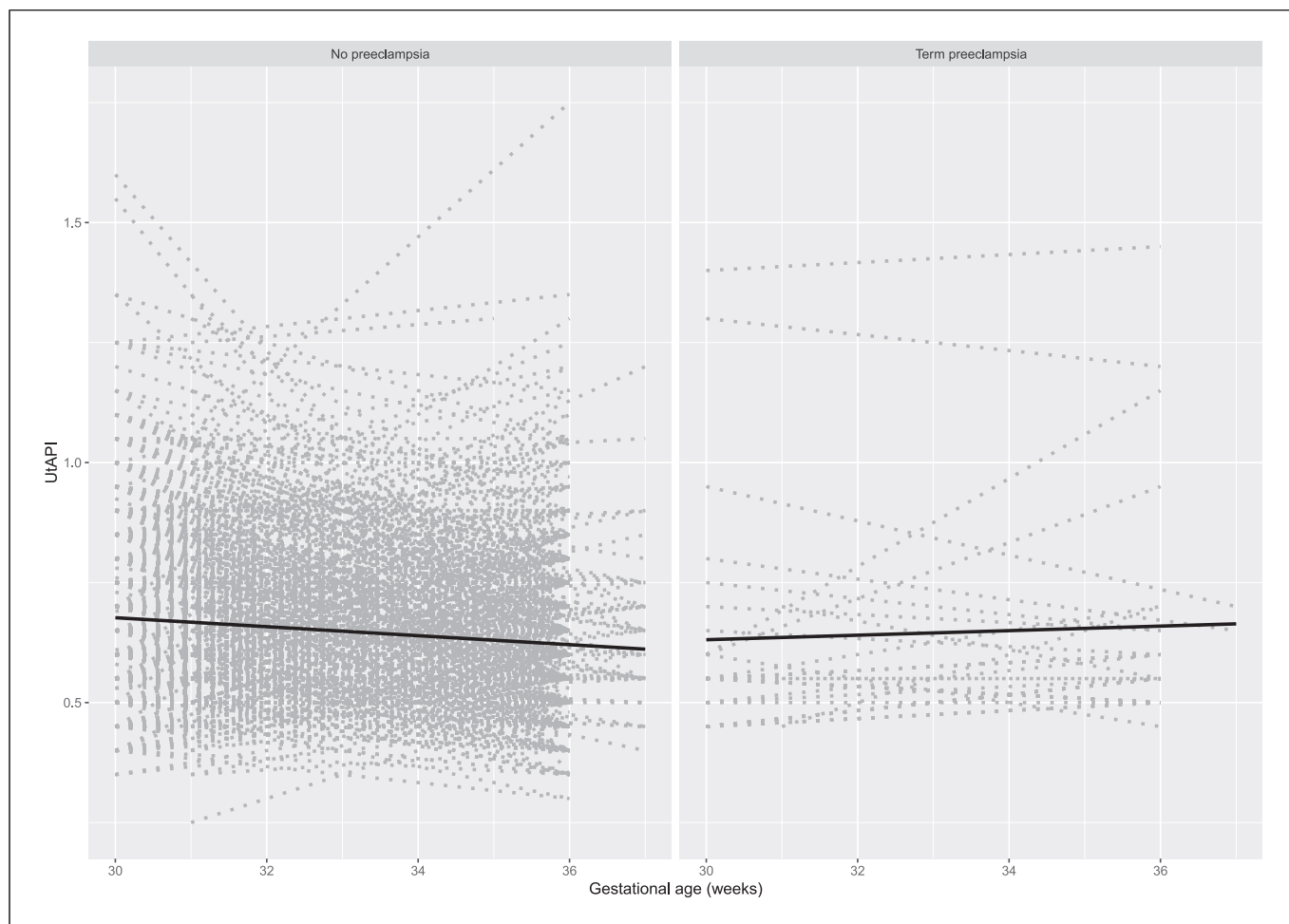


Fig. 2. Longitudinal changes in uterine artery pulsatility index (UtA-PI) between 30 and 36 weeks by the occurrence of term PE.

Table 4. Multivariate association of biochemical and Doppler parameters with the occurrence of term PE

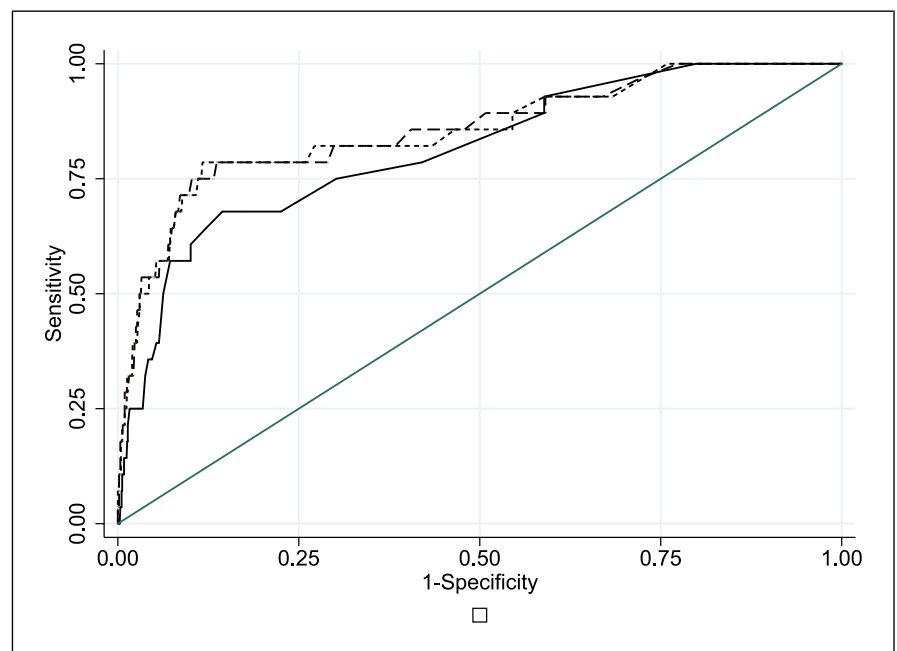
	R^2 Nagelkerke	OR	95% CI		<i>p</i> value
			lower	upper	
30 weeks					
Log-sFlt-1/PlGF ratio	16.2%	3.12	2.12	4.61	<0.001
z-UtA-PI		1.17	0.87	1.57	0.306
36 weeks					
Log-sFlt-1/PlGF ratio	25.2%	4	2.46	6.48	<0.001
z-UtA-PI		0.92	0.68	1.25	0.601
30- to 36-week change					
Log-sFlt-1/PlGF ratio	26.8%	6.25	3.9	10.02	<0.001
z-UtA-PI		0.79	0.61	1.03	0.086

CI, confident interval; OR, odds ratio; PlGF, placental growth factor; sFlt-1, Fms-like tyrosine kinase 1; UtA-PI, uterine artery pulsatility index.

Table 5. Predictive performance of sFlt-1/PlGF ratio for term PE

AUC (95% CI)	FPR, %	Cutoff, pg:mL/pg:mL	DR, %	+LHR	–LHR	DOR
30 weeks						
0.81 (0.73–0.9)	15	7.5	67.9	4.7	0.38	12.4
	10	9	57.1	5.7	0.48	11.9
	5	14.4	35.7	7.6	0.67	11.3
36 weeks						
0.86 (0.77–0.94)	15	39.6	78.6	5.2	0.25	20.8
	10	58.6	71.4	7.29	0.32	22.8
	5	89.1	53.6	10.7	0.49	21.8
30- to 36-week change						
0.85 (0.77–0.94)	15	72.8+	78.6	5.28	0.25	21.1
	10	49.6+	71.4	7.35	0.32	23.0
	5	34.5+	53.6	10.6	0.49	21.6

AUC, area under the curve; DOR, diagnostic odds ratio; DR, detection rate; FPR, false-positive rate; LHR, likelihood ratio; PlGF, placental growth factor; sFlt-1, Fms-like tyrosine kinase 1; +, increase from 30 to 36 weeks.

**Fig. 3.** Predictive performance of sFlt-1/PlGF ratio for term PE of sFlt-1/PlGF ratio at ~30 weeks (solid line), ~36 weeks (short-dashed line), and 30- to 36-week change (long-dashed line). PlGF, placental growth factor; sFlt-1, Fms-like tyrosine kinase 1.

found that the uterine Doppler does not add predictiveness to the sFlt-1/PlGF ratio. These findings agree with previous reports [22, 23]. This parameter reflects a shallow cytotrophoblast interstitial invasion and decreased placental perfusion. In term PE, these pathophysiological mechanisms have little involvement.

We found a better performance for sFlt-1 than for PlGF, when measured at third trimester. Many studies show that sFlt-1 plays an important role in vasoconstriction, increasing endothelial stress and thus increasing blood pressure

[24–26]. Other studies confirm that low PlGF levels are a more strongly correlated to placental stress and hypoxia [27–29]. Regarding these findings, it is not surprising that sFlt-1 is a stronger predictor than PlGF of term PE.

Several studies have evaluated the performance of the sFlt-1, PlGF or their ratio measured near term for term PE in unselected populations [20, 21, 30–33]. Overall, their reported AUC (from 73% to 90%), is in line with the performance of our series (86%). All the previous series were performed in unselected pregnancies, one of them

excluding multiparas [20], while we only included low-risk women. Similarly, Park et al. [23] in a series of 262 low-risk women evaluated at 34–37 weeks (of which 8 [3%] subsequently developed PE). They reported that sFlt-1/PlGF ratio had an AUC of 94% (95% CI: 87%–100%) for late PE. Our study provides evidence extending the good performance of the ratio at 35–37 weeks for term PE. In their series, they reported a pronounced difference of change of the ratio from second to third trimester. Although predictive capacity of the slope of the ratio was not used formally tested, they concluded that this value might be useful. In our cohort, we found no added value of the 30- to 36-week change of the ratio in predicting term PE over the cross-sectional evaluation at ~36 weeks. Of note, even the best performing model had a moderate capacity to rule in (+LHR) and rule out (–LHR) term PE.

Mac Donald et al. [21] used an sFlt-1/PlGF ratio value of ≥ 38 to predict late-onset PE at 36 weeks, measured by a Cobas Elecsys Analyzer (Roche). They achieved 66.7% sensitivity and 94.2% specificity. Our cutoff of the ratio for term PE was higher (58 for a FPR of 10%). Stepan et al. [34] reported that cutoffs validated for Elecsys immunoassays are not transferable to Kryptor Compact immunoassays. Cheng et al. [35] making inter-manufacturer comparisons found out that the clinical equivalent of the Kryptor Compact ratio to the Elecsys ratio for PE after 34 week is 188. It is not surprising that when aiming at term PE rather than PE after 34 weeks, we found a lower cutoff. Indeed, Park et al. [23] in low-risk women evaluated at third trimester proposed a cutoff level of 28 for term PE using an Elecsys analyzer, which is also lower than the previously validated cutoffs of 38 [36].

Clinical Implications

Although adverse consequences are more severe in preterm than in term PE, the overall contribution is similar because term PE is 5 times more common [37]. Clinical diagnosis of term PE followed by planned delivery has been shown to reduce the rates of severe maternal complications [38]. However, such a strategy misses a large proportion of cases in the preclinical face of the disease. Unfortunately, most women developing term PE have no baseline risk factors that could rise clinical awareness. So far, no first- or second-trimester predictive model with acceptable performance for term PE has been developed [39, 40]. Strategy of screening closer to the disease onset is an alternative option. Unlike preterm PE, strategies aimed to prevent term PE by low-dose aspirin or statin administration to high-risk women have failed to demonstrate efficacy [41, 42].

A strategy of planned delivery at term of women at high risk for developing PE has the potential to prevent most instances occurring at term and reduce its associated complications. Labor induction at term is well accepted by women [43] and seems a safe strategy for the neonate [44]. We are conducting a multicenter clinical trial (the PE37 study) to establish the efficacy of planned delivery at term in women with abnormal sFlt-1/PlGF values at 36 weeks of pregnancy (ClinicalTrials.gov Identifier: NCT04766866).

Study Limitations

Our sample size did not allow us a robust analysis of the performance for severe PE, as we only had 7 events, which was beyond the study objectives. Although no conclusions could be drawn, in our series, the predictive performance of the sFlt-1/PlGF ratio was even better than for overall PE which is consistent with larger series findings [20].

Several series have combined more factors measured at 35–37 weeks with maternal baseline risk factors or blood pressure aiming to improve the predictive performance. These parameters may have increased the predictive performance of our models. We did not find added value of the UtA, and our low-risk population did not allow us to combine the baseline risk factors with other markers. However, a recent meta-analysis [45] including 14 studies carried out at third trimester found that the predictive capacity for subsequent PE of such combined models was similar to that of the serum sFlt-1/PlGF ratio as a standalone parameter.

Conclusion

A cross-sectional measurement of the sFlt-1/PlGF ratio outperforms uterine Doppler in predicting term PE. The combination of both markers does not improve such prediction, nor the evaluation of the longitudinal changes between ~30 and ~36 weeks.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of University Hospital Olomouc and Palacky University Olomouc, Approval No. (161/16). All participants gave written informed consent to participate in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Lucie Roubalova: substantial contributions to the acquisition, analysis and interpretation of data for the work, drafting the article, and final approval of the version to be published and agreement to be accountable for all aspects of the work. Vladimira Kroutilova: substantial contributions to the acquisition of data for the work and drafting the article. Maria Fernanda Lopez-G. Tinajero and Judit Martinez-Egea: contributions to the analysis and interpretation of data for the work, drafting the article, and final approval of the version to be published. Claudia Pumarola: contributions to the analysis and interpretation of data for the work. Francesc Figueras: substantial contributions to

the conception and design of the work, analysis and interpretation of data for the work, reviewing work critically for important intellectual content, and final approval of the version to be published and agreement to be accountable for all aspects of the work. Marek Lubusky: substantial contributions to the acquisition, conception and design of the work, analysis and interpretation of data for the work, reviewing work critically for important intellectual content, and final approval of the version to be published and agreement to be accountable for all aspects of the work.

Data Availability Statement

The data that support the findings of this study are not publicly available due to General Data Protection Regulation and legislative policy but are available from the corresponding author [Lucie Roubalova].

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