Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 23 (2021) 116–122

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

Angiogenic markers during preeclampsia: Are they associated with hypertension 1 year postpartum?

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ARTICLE INFO

Keywords:
Preeclampsia
Angiogenic biomarkers
Postpartum
Hypertension
Pregnancy

ABSTRACT

Objectives: Preeclampsia is associated with hypertension in later life, but the underlying pathophysiological mechanisms remain uncertain. We aimed to explore whether the angiogenic markers soluble Fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) measured in women with preeclampsia could be associated with hypertension 1 year after delivery.

Methods: This is a secondary analysis of a prospective cohort study, originally aimed to evaluate the use of sFlt-1/PlGF ratio to predict adverse outcome in women with (suspected) preeclampsia. Office blood pressure (BP) was evaluated at 1 year postpartum in women who had a confirmed diagnosis of preeclampsia within one week of biomarker measurement.

Results: Eighty women were included with a median (interquartile range) gestational age (GA) at biomarker measurement of 30 (27–33) weeks. Twenty-three (29%) women had hypertension 1 year postpartum. These women showed higher median SBP during their pregnancy and lower GA at PE diagnosis compared to women without hypertension. Median PlGF levels were lower in women with hypertension 1 year postpartum compared to women without hypertension (23 vs. 48 pg/mL, $p = 0.017$), while no differences in sFlt-1 or sFlt-1/PlGF ratio were observed. Multivariable analysis adjusted for GA did not show significant association between PlGF (nor sFlt-1, sFlt-1/PlGF ratio) and hypertension 1 year postpartum (OR [95% CI] 0.9 [0.2–4.4], $p = 0.97$).

Conclusion: Our data indicate that sFlt-1, PlGF or their ratio measured during pregnancy are not suitable for the prediction of hypertension 1 year postpartum and hence guiding follow-up of women with previous preeclampsia.

1. Introduction

Preeclampsia is a severe hypertensive disorder affecting 5–7% of all pregnancies. It is characterized by the new onset of hypertension accompanied by either proteinuria, utero-placental dysfunction such as intrauterine growth restriction and/or other maternal organ dysfunction at or after 20 weeks gestation [1]. Preeclampsia not only has significant impact on maternal and fetal health during pregnancy [2], but has also been established as a risk factor of cardiovascular disease for both mother and offspring [1]. A recent study reported that about 42% of women with severe preeclampsia already show some form of hypertension 1 year after pregnancy [3]. Unfortunately, our knowledge of factors that could predict the development of hypertension (or other cardiovascular disease) or not, is limited. Identification of these factors could enable clinicians to determine which women with previous preeclampsia require earlier follow-up after delivery.

Although the underlying pathophysiology of preeclampsia is not completely elucidated, an imbalance between circulating pro- and antiangiogenic factors, reflected by elevated soluble Fms-like tyrosine kinase-1 (sFlt-1) and low placental growth factor (PlGF) levels has been well established [1]. This high antiangiogenic state inducing a pro-inflammatory state and endothelial dysfunction is thought to play a key role in the disorder. In fact, endothelial dysfunction has been reported to persist up to 15 years after preeclampsia [4].

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https://doi.org/10.1016/j.preghy.2020.11.011
Received 19 September 2020; Received in revised form 10 November 2020; Accepted 27 November 2020
Available online 3 December 2020

We have reported that plasma PlGF levels were independently associated with mean arterial pressure during pregnancy [5] whereas the severity of hypertension itself is a predictor for the development of future hypertension [6]. Although sFlt-1, PlGF and their ratio have been investigated widely for the prediction of preeclampsia [7] and preeclampsia-related pregnancy outcomes [8], their role in prediction of postpartum hypertension or cardiovascular disease in later life has not yet been determined.

Therefore, we aimed to evaluate whether the angiogenic imbalance during preeclampsia could predict hypertension 1 year after pregnancies complicated by preeclampsia.

2. Methods

2.1. Study design and participants

This was a secondary analysis of a prospective observational cohort study conducted from 2012 to 2016 at the Erasmus Medical Center, Rotterdam, the Netherlands, originally aimed to evaluate the usefulness of the sFlt-1/PlGF ratio to predict adverse pregnancy outcome in 408 women with suspected or confirmed preeclampsia. Written informed consent to participate in the study, which was approved by the local research ethics committee (MEC-2013-202), was obtained from all participants. For the current analysis, women with pre-existing hypertension and/or proteinuria were excluded (n = 117). In order to assess the biomarker values at the time of confirmed preeclampsia, we excluded women who did not have confirmed preeclampsia within one week of study entry (time of biomarker measurement) (n = 136). Women who had a follow-up appointment at the Internal Medicine clinician and/or at the Follow-Up Pre-Eclampsia (FUPEC) Outpatient Clinic at the Erasmus Medical Center, Rotterdam, within 9 to 15 months postpartum were included in the analysis.

2.2. Preeclampsia diagnosis

Preeclampsia was defined according to the definition of the International Society for the Study of Hypertension in Pregnancy (ISSHP) of 2018; de novo hypertension (diastolic blood pressure [DBP] of ≥90 mmHg or systolic blood pressure [SBP] of ≥140 mmHg) accompanied by ≥1 of the following new-onset conditions at or after 20 weeks' gestation: proteinuria (urinary protein-to-creatinine ratio [uPCR] ≥ 30 mg/mmol or ≥300 mg/24 h or 2+ dipstick), acute kidney injury (AKI) (creatinine ≥90 μmol/L; 1 mg/dL), neurological complications (e.g. eclampsia), hematological complications (thrombocytopenia-platelet count <150.000/μL, disseminated intravascular coagulation, hemolysis), liver involvement (elevated transaminases, e.g.: alanine aminotransferase [ALAT] or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain, or uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery (UA) Doppler wave form analysis or stillbirth) [9]. HELLP syndrome, defined as hemolysis, elevated liver enzymes and low platelet count, was now also considered as preeclampsia according to the ISSHP 2018 criteria [9].

2.3. Data collection

Serum for the analysis of sFlt-1 and PlGF was collected at inclusion of the original study. Serum was stored at −80 °C after centrifugation, until analysis. All samples were measured postpartum. Measurement of sFlt-1 and PlGF was performed using an automated analyzer (Cobas 6000, e-module; Roche Diagnostics, Mannheim, Germany). Clinical data during and after pregnancy including demographic information, gestational age (GA) at biomarker measurement, diagnosis and delivery, physical examination, laboratory test results and pregnancy outcome were attained from the electronic medical records of the patients and ascertained by two independent researchers (R.I.N and A.M.J.F). Time to delivery was defined as the amount of days between study entry (at time of biomarker measurement) and delivery.

2.4. Outcome measures at 1-year follow-up

A trained nurse or research assistant measured office BP with the participant in the upright sitting position after 5 min of rest. The appropriate arm cuff was placed around the right upper arm to measure BP with a validated oscillometric device. Women were not allowed to speak during BP measurements.

Hypertension based on office BP was defined according to the European Society of Hypertension and European Society of Cardiology: office hypertension (average SBP of ≥140 mmHg and/or an average DBP of ≥90 mmHg) and/or the use of antihypertensive medication.

2.5. Statistical analysis

Data are reported as median (interquartile range) for continuous variables and as number (percentage) for categorical variables. Normal distribution for continuous variables was assessed using the Shapiro-Wilk W test. To investigate the difference between non-parametric continuous data, Mann Whitney *U* test was performed. The Fisher's exact (in the case of a small sample size, ≤5) and Chi-square were used to assess differences between two categorical variables. Spearman rank-order correlation was applied to calculate correlation coefficients. A non-response analysis was performed to evaluate baseline characteristics between women that were included and women lost to follow-up. Logistic regression analysis was performed to study the association between potential predictors (i.e., biomarkers) and postpartum hypertension at 1 year follow-up. Biomarkers evaluated in univariable analysis included sFlt-1, PlGF and sFlt-1/PlGF ratio. Due to the fact that GA at time of biomarker measurement can affect the levels of these biomarkers, multivariable analysis was performed to correct for GA at biomarker measurement. Because of the limited number of events (n = 23), we were unable to adjust for additional confounders. Clinical parameters such as nulliparity, highest SBP during pregnancy, preconceptional BMI, time to delivery, GA at delivery and at preeclampsia diagnosis were evaluated as predictors in univariable analysis. The discriminative ability of the models was assessed using concordance-statistic (C-statistic) which is equivalent to the area under the ROC curve for dichotomous outcomes. To evaluate the added value of sFlt-1, PlGF or their ratio when corrected for GA at measurement, we fitted a logistic regression model containing sFlt-1, PlGF or sFlt-1/PlGF ratio and a logistic regression model containing both GA at measurement and one of the angiogenic markers. sFlt-1, PlGF or sFlt-1/PlGF ratio were considered to have additional value if the likelihood ratio test comparing both models was statistically significant. SPSS Statistics 21 (IBM Corporations) and R Software were used for the statistical analysis.

3. Results

3.1. Patient demographics

The final population for analysis consisted of 80 women (Fig. 1). Patient characteristics during pregnancy and at 1 year follow-up of all participants (aged 20–43) are shown in Table 1. Median (interquartile range) GA at study entry (biomarker measurement) was 30 weeks (27–33). Fifty-nine women (74%) were nulliparous, and eight women (10%) had a previous history of preeclampsia. Preconceptional BMI (kg/m^2) was 23 (22–27). The median highest SBP during pregnancy was 157 (140–165) mmHg, the median highest uPCR was 98 (38–262) g/mol and the median sFlt-1/PlGF ratio was 296 (68–602). GA at delivery was 30 (28–34) weeks. At 1 year follow-up, the overall SBP normalized to 124 (114–135) mmHg, whereas 3 women (4%) still had proteinuria (uPCR ≥ 30 g/mol).

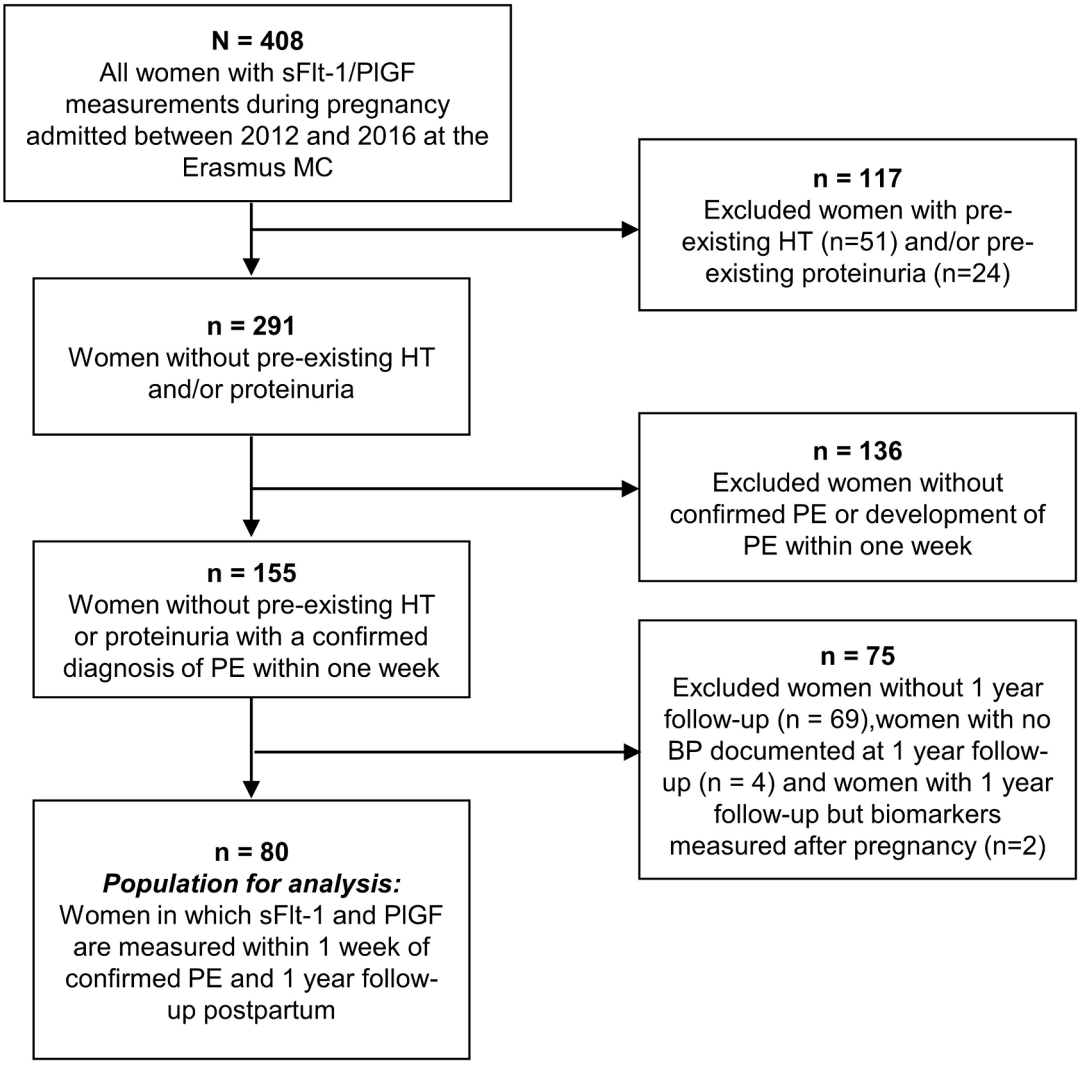

Fig. 1. Flowchart of in- and exclusion criteria in this study. PE indicates preeclampsia. HT indicates hypertension; sFlt-1, soluble Fms-like tyrosine kinase-1; PlGF, placental growth factor.

3.2. Patient characteristics and angiogenic markers according to hypertension at 1 year follow-up

Of the 80 women, 23 (29%) had hypertension 1 year after pregnancy (Table 1). Compared to women without hypertension, participants with hypertension had a lower GA at PE diagnosis (27 vs. 30 weeks, $p < 0.01$) and were more often nulliparous (91% vs 67%, $p = 0.03$). The highest median SBP during pregnancy was higher in women with hypertension 1 year postpartum (168 vs. 155 mmHg, $p = 0.02$), while their GA at delivery (28 vs. 31, $p < 0.01$) and birth weight (955 vs. 1350, $p < 0.01$) were lower in comparison to women without hypertension (Table 1). Women with hypertension at 1 year more often had HELLP syndrome during their pregnancy (57% vs. 28%, $p = 0.02$), but this difference was most likely due to higher SBP in this group. Nine women were still using antihypertensive medication after 1 year, suggesting they had persistent hypertension. Median gestational PlGF levels were lower in women with hypertension 1 year postpartum in comparison to women without hypertension (23 [14–50] vs. 48 [23–80] pg/mL, $p = 0.02$), while no differences in sFlt-1 or sFlt-1/PlGF ratio were observed between the two groups (Table 1, Fig. 2). Median GA at study entry (biomarker measurement) was three weeks earlier in the hypertension group (Table 1). The non-response analysis showed that women without follow-up had milder forms of preeclampsia, as observed by the later GA at study entry (35 vs. 30 weeks, $p < 0.01$), GA at delivery (37 vs. 30 weeks, $p < 0.01$) and lower sFlt-1/PlGF ratio (67 vs. 296, $p < 0.01$). No differences in age, race or parity were observed (Table 2).

3.3. Prediction of hypertension based on office BP at 1 year follow-up

The clinical parameters nulliparity and highest SBP were significantly associated with the occurrence of hypertension at 1 year follow-up, although their discriminative ability was limited (C-index of 0.62, $p = 0.04$ and C-index of 0.65, $p = 0.04$) (Table 3A). The GA at delivery showed good value to predict postpartum hypertension with a C-index of 0.72, while GA at diagnosis performed significantly better as a continuous value in comparison to the cut-off value of 34 weeks (C-index = 0.73, $p < 0.001$ vs. C-index of 0.61, $p = 0.06$). PlGF was not significantly associated with the occurrence of hypertension at 1 year (C-index = 0.67, OR [95% CI] 0.3 [0.1–0.9], $p = 0.06$), neither were sFlt-1 or the sFlt-1/PlGF ratio. When corrected for GA at biomarker measurement in multivariable analysis, the model with angiogenic markers showed no significant association with the occurrence of hypertension at 1 year postpartum (Table 3B).

3.4. Correlations between angiogenic markers and BP during and after pregnancy

Angiogenic markers were evaluated in women during pregnancy

Table 1
Patient demographics of all included women and according to hypertension based on office BP.

Parameter	All Women	No Hypertension	Hypertension	P-Value
Characteristics during pregnancy	80	57	23	
Age at study entry, yrs	30 (27–34)	30 (27–35)	29 (27–34)	0.59
GA at study entry*, wks	30 (27–33)	30 (29–33)	27 (26–30)	<0.01
Preconceptional BMI, kg/m^2	23 (22–27)	23 (21–26)	26 (23–30)	0.07
Race, n (%)				
White	56 (70)	37 (65)	19 (83)	0.18
Black	9 (11)	6 (11)	3 (13)	0.71
Other	15 (19)	14 (25)	1 (4)	0.06
Nulliparous, n (%)	59 (74)	38 (67)	21 (91)	0.03
Smoking at inclusion, n (%)	4 (5)	3 (5)	1 (4)	1.00
History of PE, n (%)	8 (10)	8 (14)	0 (0)	0.10
Clinical parameters				
GA at diagnosis PE, wks	30 (27–33)	30 (29–34)	27 (26–30)	<0.01
Highest SBP, mmHg	157 (140–165)	155 (140–162)	168 (146–174)	0.02
Highest DBP, mmHg	97 (90–105)	95 (90–105)	100 (91–110)	0.18
Antihypertensive drug use at study entry, n (%)	56 (70)	40 (70)	16 (70)	0.96
Highest uPCR, g/mol	98 (38–262)	104 (40–240)	59 (24–397)	0.37
Highest Uric acid, mmol/L	0.37 (0.32–0.44)	0.37 (0.32–0.43)	0.38 (0.29–0.47)	0.84
Highest Creatinine, μmol/L	67 (58–73)	65 (58–73)	68 (60–73)	0.74
Highest ALAT, U/L	47 (24–175)	33 (20–169)	81 (38–193)	0.06
Highest LD, U/L	289 (223–443)	269 (219–419)	323 (254–602)	0.09
Lowest Platelet Count,10^9/L	149 (100–203)	158 (104–223)	125 (66–172)	0.04
HELLP syndrome, n (%)	29 (36)	16 (28)	13 (57)	0.02
Highest SBP, mmHg	159 (140–170)	148 (140–160)	168 (149–178)	0.03
Highest DBP, mmHg	96 (88–105)	90 (86–103)	100 (95–107)	0.09
Pregnancy Outcome				
GA at delivery, wks	30 (28–34)	31 (29–34)	28 (27–31)	<0.01
Girls, n (%)	40 (50)	27 (47)	13 (57)	0.35
Birth weight, grams	1210 (863–1798)	1350 (1070–2083)	955 (760–1440)	<0.01
Birth weight percentile < 10, n (%)	20 (25)	15 (26)	5 (22)	1.00
Time to delivery‡, days	2 (1–8)	2 (1–8)	4 (2–12)	0.06
Angiogenic Markers				
sFlt-1, pg/mL	9405 (5066–15839)	10295 (4741–16809)	8801 (5283–12888)	0.29
PlGF, pg/mL	32 (18–69)	48 (23–80)	23 (14–50)	0.02
sFlt-1/PlGF ratio	296 (68–602)	208 (62–580)	498 (92–704)	0.24
sFlt-1/PlGF ratio ≤ 38, n (%)	11 (14)	8 (14)	3 (13)	1.00
sFlt-1/PlGF ratio ≥85, n (%)	56 (70)	38 (67)	18 (78)	0.42
Characteristics at 1-year Follow-up				
Office SBP, mmHg	124 (114–135)	119 (111–128)	141 (131–150)	<0.01
Office DBP, mmHg	76 (70–83)	73 (68–80)	86 (79–95)	<0.01
BMI, kg/m^2	25 (23–30)	24 (22–29)	29 (24–31)	0.17
Antihypertensive drug use, n (%)	9 (11)	0 (0)	9 (39)	<0.01
uPCR ≥ 30 g/mol	3 (4)	3 (5)	0 (0)	0.25

Hypertension defined as office SBP ≥ 140 mmHg and/or office DBP ≥ 90 mmHg and/or antihypertensive drug use. Values are median (interquartile range) or number (percentage). GA, gestational age; BMI, body mass index; PE, preeclampsia; SBP, systolic blood pressure; DBP, diastolic blood pressure; uPCR, urinary protein-to-creatinine ratio; LD, lactate dehydrogenase; ALAT, alanine-aminotransferase; sFlt-1 indicates soluble Fms-like tyrosine kinase-1; PlGF, placental growth factor. P-value depicts difference between hypertension and no hypertension group. *Biomarkers were determined at time of study entry. ‡Time to delivery is defined as the amount of days between study entry and delivery.

(with and without follow-up, n = 155) and at follow-up, as depicted in Table 4. sFlt-1 and sFlt-1/PlGF ratio showed a significant negative correlation with GA at inclusion ($r = -0.193$ and $r = -0.539$, $p < 0.001$), while PlGF showed a positive correlation with GA at inclusion ($r = 0.672$, $p < 0.001$). The angiogenic markers did not significantly correlate with SBP or DBP at inclusion, but both PlGF and sFlt-1/PlGF ratio showed a significant correlation with highest SBP and DBP during pregnancy. No significant correlations between sFlt-1, PlGF or sFlt-1/PlGF ratio and office BP at 1 year follow-up were observed.

4. Discussion

In this study of 80 women with previous preeclampsia, we examined whether the angiogenic factors sFlt-1, PlGF and sFlt-1/PlGF ratio could be associated with postpartum hypertension at 1 year follow-up based on office BP measurements. Twenty-nine percent of women in our cohort showed office hypertension 1 year after pregnancy. This percentage was lower than recently reported in 200 women with severe preeclampsia (42%) [3], however in that study hypertension was diagnosed by 24-h ambulatory BP measurements (ABPM). Hence, the discrepancy between these numbers is most likely explained by women with masked hypertension who are missed by an office BP measurement alone. Indeed, about 18% of women in that study had masked hypertension [3].

When evaluating the angiogenic factors, we found lower levels of the proangiogenic factor PlGF in women with office hypertension at 1 year follow-up. However, this marker did not show significant value to predict hypertension 1 year after delivery, even when corrected for GA at time of biomarker measurement in multivariable analysis. Moreover, both sFlt-1 and sFlt-1/PlGF ratio showed limited predictive performance to determine whether women had hypertension both in uni- and multivariable analysis, suggesting that their levels during preeclampsia are not associated with persistence or the development of hypertension 1 year after delivery. These observations remained similar when evaluating hypertension based on 24-h ABPM at 1 year postpartum in a small subset of women (n = 49) (data not shown).

That women with previous preeclampsia are at increased risk of CVD including chronic hypertension in later life has been well established [10]. Whether this is an effect of pre-pregnancy cardiovascular risk factors or a direct consequence of preeclampsia itself, remains a matter of debate. Despite our understanding that a high antiangiogenic state (reflected by elevated sFlt-1 and low PlGF levels) is a key mechanism underlying endothelial dysfunction in preeclampsia [5], only a few studies evaluated the relationship between these factors and the

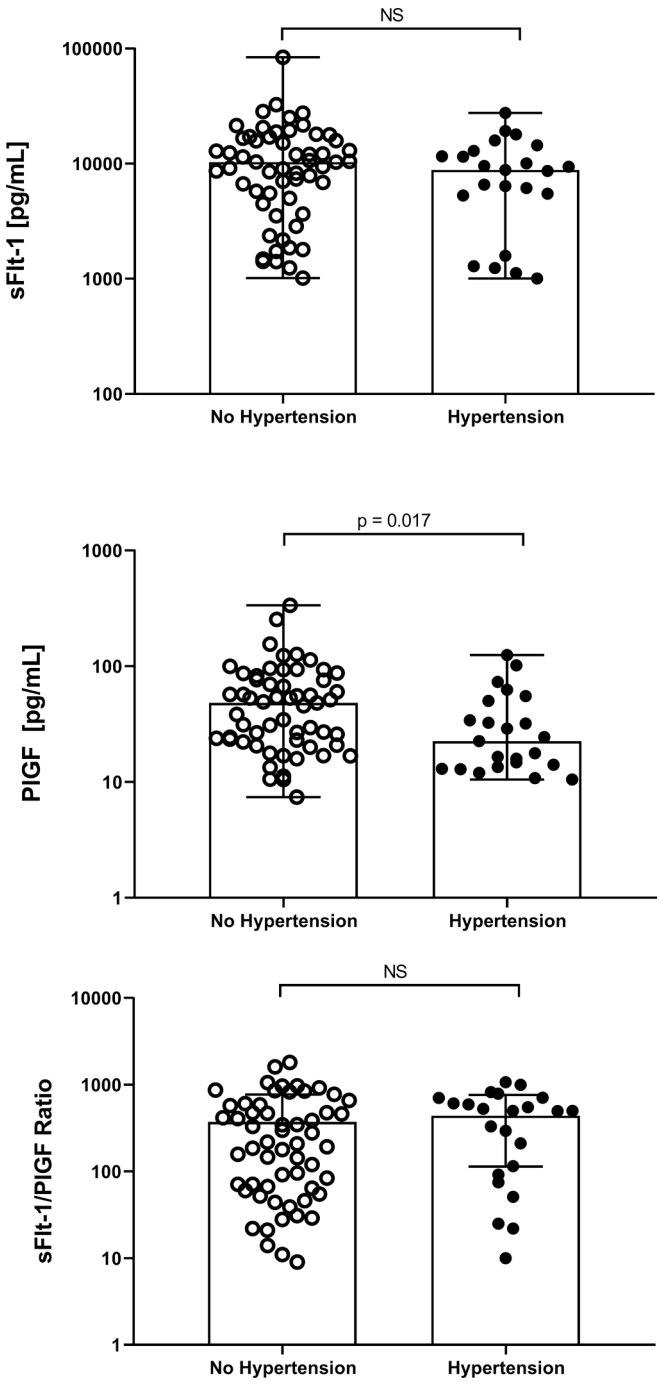

Fig. 2. sFlt-1, PlGF and sFlt-1/PlGF ratio levels in the 80 women according to the occurrence of hypertension at 1 year follow-up. sFlt-1 indicates soluble Fms-like tyrosine kinase-1, PlGF, placental growth factor.

occurrence of hypertension postpartum. In a cohort of 988 women, Goel et al. [11] demonstrated that antepartum levels of the angiogenic markers were independently associated with persistent or de novo hypertension postpartum. While these findings are in contrast with our observations, they only evaluated the development of hypertension up to six weeks postpartum. Interestingly, a recent large study (n = 5475) showed that lower mid-pregnancy (mean 20.6 weeks of gestation) serum PlGF levels were associated with higher systolic blood pressure six and nine years after pregnancy [12]. Of note, the latter study mostly evaluated PlGF levels in uncomplicated pregnancies, which differs from our population consisting only of women with preeclampsia. In addition, the effect of lower mid-pregnancy PlGF levels on systolic blood pressure was very limited (i.e. regression coefficient β [95% CI] of 1.8 [0.35–3.2] mmHg in comparison to women with high PlGF) [12]. It is also important to note that the GA at time of biomarker measurement in our cohort was much later (median 27 weeks). Possibly, the contribution of PlGF to blood pressure is evident only when considering all pregnancies (including cases of mild preeclampsia or gestational hypertension) and can no longer be detected when focusing on women with only severe features of preeclampsia. Indeed, when we compared pregnancy characteristics between the women included in this study and the women that were lost to follow-up, it seems that our cohort consisted mostly of women with severe forms of preeclampsia, as reflected by the higher sFlt-1 and lower PlGF levels, and earlier GA at study entry and delivery (Table 2). We also evaluated other factors during pregnancy that could be associated with postpartum hypertension and found that the GA when preeclampsia occurred showed the highest value to predict the occurrence of hypertension 1 year postpartum. Interestingly, the continuous value of GA showed significantly better prediction than a cut-off value of 34 weeks (early-onset vs. late-onset). Indeed, some studies have shown that both women with early and late-onset preeclampsia are at risk of developing hypertension postpartum [13,14]

Table 2
Difference in Pregnancy Characteristics between Included Women (n = 80) and Women that were Lost to Follow-Up (n = 75).

Parameter	Follow-Up	No Follow-Up	*P-Value*
Characteristics during pregnancy	80	75	
Age at study entry, yrs	30 (27–34)	32 (27–35)	0.39
GA at study entry, wks	30 (27–33)	35 (31–37)	<0.01
Preconceptional BMI, kg/m^2	23 (22–27)	25 (22–30)	0.11
Race, n (%)			
White	56 (70)	46 (61)	0.30
Black	9 (11)	16 (21)	0.08
Other	15 (19)	13 (17)	0.68
Nulliparous, n (%)	59 (74)	46 (61)	0.10
Smoking at inclusion, n (%)	4 (5)	4 (5)	1.00
History of PE, n (%)	8 (10)	9 (12)	0.69
Clinical parameters			
GA at diagnosis PE, wks	30 (27–33)	36 (31–40)	<0.01
Highest SBP, mmHg	157 (140–165)	150 (140–160)	0.41
Highest DBP, mmHg	97 (90–105)	99 (90–100)	0.94
Antihypertensive drug use, n (%)	56 (70)	44 (59)	0.18
Highest uPCR, g/mol	98 (38–262)	57 (32–153)	0.18
Highest Uric acid, mmol/L	0.37 (0.32–0.44)	0.36 (0.31–0.41)	0.44
Highest Creatinine, μmol/L	67 (58–73)	69 (56–78)	0.56
Highest ALAT, U/L	47 (24–175)	18 (13–35)	<0.01
Highest LD, U/L	289 (223–443)	235 (198–292)	<0.01
Lowest Platelet Count, 10^9/L	149 (100–203)	163 (137–216)	0.04
Pregnancy Outcome			
GA at delivery, wks	30 (28–34)	37 (32–38)	<0.01
Girls, n (%)	40 (50)	30 (40)	0.43
Birth weight, grams	1210 (863–1798)	2505 (1435–3190)	<0.01
Birth weight percentile <10, n (%)	20 (25)	14 (19)	0.44
Time to delivery‡, days	2 (1–8)	5 (2–12)	0.08
Angiogenic Markers			
sFlt-1, pg/mL	9405 (5066–15839)	6435 (1977–10495)	0.01
PlGF, pg/mL	32 (18–69)	74 (44–127)	<0.01
sFlt-1/PlGF ratio	296 (68–602)	67 (25–197)	<0.01

Values are median (interquartile range) or number (percentage). PE indicates preeclampsia; GA, gestational age: SBP, systolic blood pressure; DBP, diastolic blood pressure; uPCR, urinary protein-to-creatinine ratio; LD, lactate dehydrogenase; ALAT, alanine-aminotransferase; sFlt-1, soluble Fms-like tyrosine kinase-1; PlGF, placental growth factor. *Biomarkers were determined at time of study entry. ‡Time to delivery is defined as the amount of days between study entry and delivery.

Table 3A
Univariable Analysis for the Prediction of Hypertension at 1 year Follow-up.

All Women (n = 80)	Univariable Analysis		
	Odds Ratio	C-index	P-Value
Nulliparity	5.3 (1.1–25)	0.62	0.04
Highest SBP	2.1 (0.8–6.0)	0.65	0.04
Preconceptional BMI	2.9 (0.9–10)	0.66	0.15
GA at study entry*	0.3 (0.1–0.7)	0.74	<0.001
GA at PE diagnosis	0.3 (0.1–0.7)	0.73	<0.001
GA at PE diagnosis <34 wks	4.7 (0.9–21)	0.61	0.06
Time to delivery‡	1.4 (0.9–2.3)	0.64	0.09
GA at delivery	0.3 (0.1–0.7)	0.72	<0.001
sFlt-1	0.8 (0.3–1.7)	0.55	0.54
PlGF	0.3 (0.1–0.9)	0.67	0.06
sFlt-1/PlGF ratio	2.4 (0.8–7.7)	0.63	0.32

Hypertension defined as office SBP ≥ 140 mmHg and/or office DBP ≥ 90 mmHg and/or antihypertensive drug use. Interquartile odds ratio and associated 95% confidence interval was calculated to aid interpretation of continuous predictors. It is defined as comparing the risk of hypertension after 1 year at the 75th percentile of the marker value versus the 25th percentile. SBP indicates systolic blood pressure; BMI, body mass index; GA, gestational age; PE, pre-eclampsia; sFlt-1, soluble Fms-like tyrosine kinase-1; PlGF, placental growth factor. *Biomarkers were determined at time of study entry. ‡Time to delivery is defined as the amount of days between study entry and delivery.

Table 3B
Multivariable analysis for the Prediction of Hypertension at 1 year Follow-Up.

All Women (n = 80)	Multivariable Analysis		
	Odds Ratio	C-index	P-Value
sFlt-1	0.7 (0.3–1.6)		0.68
GA at biomarker measurement	0.3 (0.1–0.7)	0.74	<0.01
PlGF	0.9 (0.2–4.4)		0.97
GA at biomarker measurement	0.3 (0.1–0.7)	0.74	0.03
sFlt-1/PlGF ratio	0.9 (0.2–3.6)		0.98
GA at biomarker measurement	0.3 (0.1–0.7)	0.74	<0.01

Hypertension defined as office SBP ≥ 140 mmHg and/or office DBP ≥ 90 mmHg and/or antihypertensive drug use. Multivariable analysis includes GA at biomarker measurement with one of the angiogenic markers. Interquartile odds ratio and associated 95% confidence interval was calculated to aid interpretation of continuous predictors. It is defined as comparing the risk of hypertension after 1 year at the 75th percentile of the marker value versus the 25th percentile. GA indicates gestational age; sFlt-1, soluble Fms-like tyrosine kinase-1; PlGF, placental growth factor.

Table 4
Correlations between Angiogenic Markers and Blood Pressure Profiles.

Parameter	sFlt-1	PlGF	sFlt-1/PlGF ratio
During Pregnancy (n = 155)			
GA at study entry	−0.193*	0.672**	−0.539**
SBP at study entry	0.023	−0.144	0.118
DBP at study entry	−0.077	−0.077	0.020
Highest SBP	0.105	−0.216*	0.210*
Highest DBP	0.088	0.210*	0.213*
At 1 year Follow-Up (n = 80)			
Office SBP	−0.091	−0.103	0.014
Office DBP	0.029	−0.118	0.154

GA indicates gestational age; SBP, systolic blood pressure; DBP, diastolic blood pressure; sFlt-1, soluble Fms-like tyrosine kinase-1; PlGF, placental growth factor. *p < 0.05, **p < 0.01.

while others have reported increased risk of chronic hypertension when preeclampsia occurred <37 weeks in comparison to >37 weeks [10]. However, none of these studies reported the continuous value of GA, which should be considered in future studies. Our observation that GA at delivery, highest SBP during pregnancy and nulliparity were significantly associated with postpartum hypertension, supports the concept that the severity of the features of preeclampsia is an important determining factor [3,6,15]. Factors at 1 year postpartum that could influence blood pressure such as oral contraceptive use or breastfeeding were not taken into account due to the retrospective nature of this study. However, an effect of breastfeeding is not expected since ~85% of women already stop breastfeeding after 6 months [16].

Our study has some limitations. First of all, the number of women evaluated in this study is limited. A significant proportion of the initial study population (~50%) were lost to follow-up, which were mostly women with milder forms of preeclampsia. Nevertheless, our findings indicate that in women with (mostly severe forms of) preeclampsia, angiogenic factors are not a determining factor for the occurrence of hypertension at 1 year postpartum. Future studies should be conducted in a larger and a more heterogeneous group of women to establish whether this finding is specific to severe pre-eclampsia or that mild pre-eclamptic pregnancies show similar findings. Secondly, since the angiogenic markers vary with GA, it is important to evaluate them at a fixed time-point, preferably at the end of gestation when the largest alteration in biomarker levels occurs. Lastly, future studies should focus on defining hypertension based on 24-h ABPM, since this is the most reliable method to diagnose hypertension and to identify participants with masked and white-coat hypertension.

In conclusion, this study is the first to assess the relationship between angiogenic markers and the occurrence of hypertension 1 year after delivery in a cohort of preeclamptic women. Our data illustrates that sFlt-1, PlGF and sFlt-1/PlGF ratio are not associated with hypertension 1 year postpartum, indicating they are not suitable for the prediction of hypertension and guiding of follow-up of women with previous (mostly severe) preeclampsia. We encourage future prospective studies to 1) validate our findings in a larger cohort of preeclamptic women 2) evaluate other cardiovascular biomarkers during pregnancy that could be associated with postpartum hypertension and other cardiovascular disease and lastly 3) to develop prognostic models to adequately stratify women who are at increased risk for developing chronic hypertension after preeclampsia.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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