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Angiogenic markers and maternal echocardiographic indices in women with hypertensive disorders of pregnancy

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KEYWORDS: angiogenic markers; cardiovascular; echocardiography; hypertensive disorder of pregnancy; PlGF; pre-eclampsia; sFlt-1

CONTRIBUTION

What are the novel findings of this work?
In women with hypertensive disorders of pregnancy (HDP) and in those with normotensive pregnancy, angiogenic markers correlate with maternal echocardiographic parameters used to evaluate left ventricular morphology and diastolic function. The relationship between soluble fms-like tyrosine kinase-1, placental growth factor, their ratio and maternal cardiac indices in HDP patients might explain why an angiogenic imbalance during pregnancy is associated with maternal adverse cardiovascular outcome in pregnancy and in the postpartum period.

What are the clinical implications of this work?
Angiogenic markers, which are used widely for the diagnosis and management of HDP, might also give important information on the maternal cardiovascular system during pregnancy. Further studies are needed to evaluate the nature of this correlation and if they could be used as predictors of maternal cardiovascular disease after HDP.

ABSTRACT

Objective *The maternal cardiovascular system of women with hypertensive disorders of pregnancy (HDP) can be impaired, with higher rates of left ventricular (LV) remodeling and diastolic dysfunction compared to those with normotensive pregnancy. The primary objective of this prospective study was to correlate cardiac indices obtained by transthoracic echocardiography (TTE) and circulating angiogenic markers, such as soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF).*

Methods *In this study, 95 women with a pregnancy complicated by HDP and a group of 25 with an uncomplicated pregnancy at term underwent TTE and blood tests to measure sFlt-1 and PlGF during the peripartum period (before delivery or within a week of giving birth). Spearman's rank correlation was used to derive correlation coefficients between biomarkers and cardiac indices in the HDP and control populations.*

Results *The HDP group included 61 (64.2%) pre-eclamptic patients and, among them, 42 (68.9%) delivered before 37 weeks' gestation. Twelve women with HDP (12.6%) underwent blood sampling and TTE after delivery, and, as they showed significantly lower levels of angiogenic markers, they were excluded from the analysis. There was a correlation between sFlt-1 and LV mass index (LVMI) (*$r = 0.246$*; *$P = 0.026$*) and early diastolic mitral inflow velocity (E) and early diastolic mitral annular velocity (e′) ratio (*$r = 0.272$*; *$P = 0.014$*) in the HDP group (*$n = 83$*), while in the controls, sFlt-1 showed a correlation with relative wall thickness (*$r = 0.409$*; *$P = 0.043$*), lateral e′ (*$r = -0.562$*; *$P = 0.004$*) and E/e′ ratio (*$r = 0.417$*; *$P = 0.042$*). PlGF correlated with*

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LVMI (r = −0.238; P = 0.031) in HDP patients and with lateral e′ (r = 0.466; P = 0.022) in controls. sFlt-1/PlGF ratio correlated with lateral e′ (r = −0.568; P = 0.004) and E/e′ ratio (r = 0.428; P = 0.037) in controls and with LVMI (r = 0.252; P = 0.022) and E/e′ ratio (r = 0.269; P = 0.014) in HDP.

Conclusions *Although the current data are not able to infer causality, they confirm the intimate relationship between the maternal cardiovascular system and angiogenic markers that are used both to diagnose and indicate the severity of HDP.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) affect up to 10% of all pregnancies and are associated with significant maternal and perinatal morbidity[1,2]. The maternal cardiovascular system has been shown to be impaired during HDP[3,4]. Transthoracic echocardiography (TTE) studies have demonstrated that left ventricular (LV) remodeling is a common finding among women with HDP when compared to those with a normotensive pregnancy[4,5]. Most data also suggest an association with diastolic dysfunction for all types of HDP, particularly in patients with pre-eclampsia (PE)[4,6]. Indeed, when LV filling pressures were estimated using the early diastolic mitral inflow velocity (E) and early diastolic mitral annular velocity (e′) ratio, a higher ratio was reported in women with PE[4]. In addition, women with HDP have significantly worse myocardial function as demonstrated by global longitudinal strain assessment[7]. The strain imposed by HDP on maternal LV morphology and function is supported by the finding of elevated levels of cardiac biomarkers that, interestingly, are also found to be abnormal in heart failure and other cardiac diseases outside pregnancy[8,9].

An imbalance in circulating vascular factors soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) are implicated in the pathophysiology of multiorgan endothelial dysfunction seen in PE. In particular, circulating levels of sFlt-1 are increased markedly in women with PE, while free levels of its ligand PlGF are significantly diminished[10,11]. Both biomarkers can be measured in maternal plasma and serum and have demonstrated clinical utility in predicting the risk of PE in asymptomatic women, ruling out PE in women with possible clinical features, diagnosing PE and helping with timing of delivery in women with confirmed PE[12]. There is a paucity of studies assessing the relationship between cardiac indices and sFlt-1 or PlGF in HDP[13–15]. This pilot study aimed to investigate these correlations in a cohort of HDP women and normotensive controls who underwent maternal TTE in the peripartum period.

METHODS

Patient recruitment and ethics

This study was part of a prospective longitudinal cohort recruited at St George's University Hospital NHS Foundation Trust, London, UK between February 2019 and August 2021. The Brent Research Ethics Committee in London, UK gave favorable ethical approval for this study (reference: 19/LO/0794)[16]. All participants provided written informed consent for TTE and blood sampling that were performed at the same time during the peripartum period.

Recruitment criteria

Pregnancies complicated by genetic syndromes or major fetal abnormalities and patients affected by known cardiac conditions or pre-existing chronic hypertension were not included. Women with a pregnancy complicated by HDP and a group of normotensive uncomplicated pregnancies at term were recruited consecutively in the maternity department. A sample size was not calculated because it was not the primary outcome of the main study, and it was determined largely by the number of women who would donate blood at the same time as TTE[16].

Clinical definitions

HDP, including both gestational hypertension and PE, were defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy[17]. Gestational hypertension is defined as *de-novo* systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, measured on two occasions separated by at least 4 h and after 20 weeks' gestation, in the absence of proteinuria and without biochemical or hematological abnormalities. PE comprises new-onset hypertension accompanied by one or more additional features, including proteinuria (defined as 24-h urinary protein ≥ 300 mg/day or a protein/creatinine ratio ≥ 30 mg/mmol), other maternal organ dysfunctions (including liver, kidney, neurological) or hematological involvement and/or uteroplacental dysfunction. A preterm HDP was defined when delivery occurred before 37 weeks or before 34 weeks' gestation. Controls included normotensive and uncomplicated pregnancies at term. The peripartum period was defined as before delivery or within 1 week of delivery.

Echocardiography

TTE was performed using a commercially available ultrasound Doppler system (GE Vivid E95 with a M5Sc-D probe; GE Healthcare, Horten, Norway) and the offline analysis was performed using EchoPAC version 203 (GE Healthcare) by clinicians who were blinded to diagnosis, maternal demographics and gestational age. Two-dimensional grayscale, color Doppler and tissue

Doppler imaging (TDI) TTE was performed following international guidelines[18]. For each image acquisition, three cardiac cycles of non-compressed data were stored in cineloop format and analyzed offline. Using the parasternal long-axis view, interventricular septum (IVS; mm), LV end-diastolic diameter (LVEDd; mm) and posterior wall thickness (PWT; mm) were measured. LV mass (LVM; g) was calculated using the formula $0.8 \times (1.04 \times (\text{LVEDd} + \text{PWT} + \text{IVS})^3 - \text{LVEDd}^3) + 0.6$ and indexed for body surface area to obtain LVM index (LVMI). Relative wall thickness (RWT) was calculated as follows: $\text{RWT} = 2 \times \text{PWT/LVEDd}$. Normal cardiac geometry, concentric remodeling, concentric hypertrophy and eccentric hypertrophy were defined according to guidelines[19]. Diastolic function is a multiparametric evaluation and the following TTE indices were used: peak early diastolic E-wave velocity (m/s) was measured by pulsed-wave Doppler with the sample volume positioned at the tip of the mitral valve leaflets; lateral and septal e′ velocity (m/s) were obtained by pulsed-wave TDI at the lateral and septal mitral annulus; and the ratio between E and average e′ was calculated. Lateral e′ and E/e′ cut-offs were derived from gender- and age-specific normal ranges in women 20–40 years of age using mean ± 2SD reference[20,21]. Left atrial volume index was also included as a parameter to evaluate diastolic function.

Biological samples

Maternal blood samples were drawn at the time of cardiovascular assessment during the peripartum period. Plasma samples were obtained by venipuncture, collected in prechilled tubes containing ethylenediamine tetra-acetic acid (BD Vacutainer Systems, Plymouth, UK), centrifuged (1500 *g* for 15 min) and subsequently stored at −80°C. Analysis of plasma samples was conducted in the Immunoassay Biomarker Core Laboratory, School of Medicine, University of Dundee, Dundee, UK. Plasma sFlt-1 levels were measured using bead-based immunoassays on a human ProcartaPlex panel (ThermoFisher Scientific, Waltham, MA, USA) on a Luminex Bio-plex 200 platform (ThermoFisher Scientific), with a lower limit of quantification of 48.8 pg/ml. Plasma PlGF levels were measured using human V-Plex kit (K151MED-1; MesoScale Diagnostics LLC, Rockville, MD, USA) on the MesoSector S 600nM (MesoScale Diagnostics), with a lower limit of 0.32 pg/ml. A ratio between sFlt-1 and PlGF was computed.

Statistical analysis

Preliminary analyses were performed to examine variable distributions and identify outliers, which were removed. Median and missing percentages were reported for all biomarkers. Analyses were performed as complete-case and using rank-based methods. The ranked biomarkers were compared between main groups (HDP and controls) using a two-sample rank-sum (Wilcoxon–Mann–Whitney) test with two-sided *P*-value of 0.05. Spearman's rank correlation with two-sided *P*-value of 0.05 was used to derive correlation coefficients between biomarkers and echocardiographic indices in the HDP population and in controls. Bonferroni correction was used to adjust for a Type-1 error because of multiple comparisons for six primary cardiac indices ($0.05/6 = 0.0083$). Kruskal–Wallis *H*-test and Wilcoxon–Mann–Whitney test were used to compare biomarkers in prespecified subgroups. STATA software version 17 (StataCorp., College Station, TX, USA) was used to perform statistical analyses.

RESULTS

Population characteristics

A total of 95 pregnancies with HDP and 25 normotensive pregnancies at term were recruited. Maternal characteristics, biomarker levels and summary echocardiographic indices in these two groups are illustrated in Table 1. Among those with HDP, there were 61 (64.2%) PE patients and 34 (35.8%) with gestational hypertension; preterm delivery < 37 weeks and < 34 weeks of gestation occurred in 42 (68.9%) and 21 (34.4%) PE patients, respectively. Of the 95 HDP patients, 12 (12.6%) underwent blood sampling and TTE within 1 week after delivery and they showed significant differences in biomarkers, but not in echocardiographic indices, compared to HDP patients assessed before delivery (Table S1). In view of this difference in biomarker levels, only the 83 cases in which samples were taken just prior to the time of delivery were included in the analysis.

Biomarker and cardiac index correlation

There was a correlation between sFlt-1 and LVMI ($r = 0.246$; $P = 0.026$) and E/e′ ($r = 0.272$; $P = 0.014$) in the HDP group ($n = 83$), while in the control group ($n = 25$), sFlt-1 showed a correlation with RWT ($r = 0.409$; $P = 0.043$), lateral e′ ($r = -0.562$; $P = 0.004$) and E/e′ ($r = 0.417$; $P = 0.042$). PlGF correlated with LVMI ($r = -0.238$; $P = 0.031$) in HDP patients and with lateral e′ ($r = 0.466$; $P = 0.022$) in non-hypertensive controls. sFlt-1/PlGF ratio correlated with lateral e′ ($r = -0.568$; $P = 0.004$) and E/e′ ratio ($r = 0.428$; $P = 0.037$) in controls and with LVMI ($r = 0.252$; $P = 0.022$) and E/e′ ($r = 0.269$; $P = 0.014$) in the HDP group. The correlations between angiogenic markers and echocardiographic parameters in HDP patients and controls are shown in Table 2 and Figure 1.

Biomarkers in HDP with LV diastolic dysfunction and abnormal morphology

When considering only women with HDP, sFlt-1 was significantly higher when LVMI was ≥ 95 g/m^2 and RWT was ≥ 0.42 during pregnancy (Table 3). In the entire cohort, sFlt-1 and sFlt-1/PlGF values increased, and PlGF decreased, with LV remodeling severity, as shown in Table S2 and Figure 2.

DISCUSSION

The current findings demonstrate significant correlation between sFlt-1, PlGF and the sFlt-1/PlGF ratio with cardiac remodeling and indices of diastolic function in a cohort of hypertensive and normotensive pregnant women during pregnancy. Although the current data are not able to infer causality, they confirm the intimate relationship between the maternal cardiovascular system and angiogenic markers that are used to diagnose and indicate severity of HDP[22].

Interpretation of study findings and comparison with published literature

While other cardiac biomarkers, such us serum N-terminal pro-B type natriuretic peptide, have been correlated extensively with cardiac dysfunction that can develop in hypertensive pregnancies, there are very few data on the relationship between angiogenic markers and echocardiographic findings in pregnancy with HDP[8,9,23,24]. The use of angiogenic markers in women with suspected PE is of established clinical value in predicting the interval between diagnosis and delivery and maternal adverse outcome in HDP[25–30]. In a study on 1043 patients with suspected and/or confirmed PE, sFlt-1/PlGF ratio > 85 was good at ruling-in PE with severe features within 2 weeks among women with suspected PE, either before or after 35 weeks' gestation, and fair at ruling-in PE with severe features within 2 weeks in women with PE at < 35 weeks[28]. These findings were confirmed by a multicenter study in which measurement of sFlt-1/PlGF provided stratification of the risk of progressing to severe PE within the coming 2 weeks in women with HDP presenting between 23 and 35 weeks of gestation[29]. The correlation between angiogenic markers and cardiac indices revealed by our data may explain why women with a higher sFlt-1/PlGF ratio are at increased risk of developing severe features of PE and adverse pregnancy outcome. For instance, diastolic dysfunction and increased LV filling pressure might predispose women to pulmonary edema and other cardiovascular complications[6].

The correlations between sFlt-1/PlGF ratio and maternal cardiac maladaptation in pregnancy may also explain why abnormal levels of angiogenic markers are associated with postpartum cardiovascular disease (CVD) in women

Table 1 Maternal characteristics at presentation, birth characteristics, peripartum angiogenic marker levels and echocardiographic indices in 25 normotensive control pregnancies and in 95 women with hypertensive disorders of pregnancy (HDP)

Characteristic	*Control* (n = *25*)	*HDP* (n = *95*)	P	*GH* (n = *34*)	*Term PE* (n = *19*)	*Preterm PE* (n = *42*)
Maternal age (years)	34.91 ± 5.57	33.50 ± 5.66	0.267	34.00 ± 3.20	31.77 ± 4.63	34.00 ± 7.41
BMI (kg/m^2)*	24.45 ± 4.68	29.52 ± 6.01	< 0.001	27.53 ± 5.0	27.75 ± 5.00	30.93 ± 6.81
MAP (mmHg)*	83.28 ± 6.63	96.52 ± 9.34	< 0.001	96.52 ± 7.01	95.85 ± 5.24	96.89 ± 12.65
Assisted conception	4 (16)	4 (4.2)	0.058	1 (2.9)	0 (0)	3 (7.1)
Nulliparous	11 (44.0)	59 (62.1)	0.115	25 (73.5)	15 (78.9)	19 (45.2)
Ethnicity						
White	22 (88.0)	54 (56.8)	0.005	29 (85.3)	9 (47.4)	16 (38.1)
Non-white	3 (12.0)	41 (43.2)		5 (14.7)	10 (52.6)	26 (61.9)
GA at cardiovascular assessment (weeks)	38.87 ± 0.67	34.66 ± 4.45	< 0.001	38.03 ± 1.58	37.05 ± 1.37	30.79 ± 3.87
GA at birth (weeks)	39.18 ± 0.56	35.93 ± 4.19	< 0.001	39.12 ± 1.06	37.95 ± 0.85	32.29 ± 3.96
Birth-weight centile	63.39 ± 25.58	28.68 ± 30.18	< 0.001	42.43 ± 28.17	33.91 ± 30.08	14.72 ± 26.11
sFlt-1 (pg/mL)	1634.06 (945.46–3397.66)	6489.77 (1663.01–12 684.26)	< 0.001	2079.44 (1253.10–7063.35)	8301.12 (2813.30–14 401.97)	8843.56 (1663.02–16 387.46)
PlGF (pg/mL)	1048.24 (708.68–1786.89)	185.52 (81.69–385.29)	< 0.001	306.72 (211.45–449.12)	183.72 (136.18–317.75)	83.15 (42.95–225.22)
sFlt-1/PlGF ratio	1.26 (0.53–2.51)	18.90 (6.57–91.73)	< 0.001	8.75 (3.51–18.90)	35.87 (13.73–76.69)	81.55 (7.66–376.79)
LVMI (g/m^2)	66.54 (55.70–73.82)	77.57 (67.34–88.51)	< 0.001	75.05 (64.25–80.62)	80.25 (73.49–94.57)	78.57 (71.56–91.51)
RWT	0.30 (0.26–0.38)	0.43 (0.36–0.47)	< 0.001	0.43 (0.33–0.47)	0.45 (0.38–0.47)	0.43 (0.37–0.47)
LAVI (mL/m^2)	23.79 (22.10–27.78)	27.15 (23.63–31.69)	0.014	26.66 (23.67–29.16)	26.81 (22.29–30.45)	28.52 (24.25–32.05)
Lateral e′ (m/s)	0.16 (0.14–0.18)	0.12 (0.10–0.14)	< 0.001	0.12 (0.11–0.15)	0.12 (0.11–0.15)	0.11 (0.07–0.11)
Septal e′ (m/s)	0.12 (0.10–0.13)	0.09 (0.08–0.11)	< 0.001	0.08 (0.08–0.10)	0.10 (0.09–0.11)	0.10 (0.07–0.11)
E/e′ ratio	5.65 (4.78–6.59)	7.33 (6.27–9.00)	< 0.001	6.93 (6.11–7.60)	7.09 (6.17–8.60)	8.23 (6.73–9.65)

Data are given as mean ± SD, *n* (%) or median (interquartile range). *First trimester. BMI, body mass index; E, early diastolic mitral inflow velocity; e′, early diastolic mitral annular velocity; GA, gestational age; GH, gestational hypertension; LAVI, left atrial volume index; LVMI, left ventricular mass index; MAP, mean arterial pressure; PE, pre-eclampsia; PlGF, placental growth factor; RWT, relative wall thickness; sFlt-1, soluble fms-like tyrosine kinase-1.

Table 2 Correlation between angiogenic markers and echocardiographic indices in normotensive controls and women with hypertensive disorders of pregnancy (HDP)

	Controls (n = *25*)		*HDP* (n = *83*)*	
Parameter	r	P	r	P
sFlt-1 (in pg/mL)				
LVMI (in g/m^2)	0.206	0.323	0.246	0.026
RWT	0.409	0.043	0.212	0.056
LAVI (in mL/m^2)	−0.023	0.916	0.042	0.710
Lateral e′ (in m/s)	−0.562	0.004†	−0.058	0.607
Septal e′ (in m/s)	−0.338	0.107	−0.031	0.781
E/e′ ratio	0.417	0.042	0.272	0.014
PlGF (in pg/mL)				
LVMI (in g/m^2)	0.213	0.306	−0.238	0.031
RWT	0.156	0.455	−0.056	0.618
LAVI (in mL/m^2)	−0.261	0.218	−0.131	0.242
Lateral e′ (in m/s)	0.466	0.022	0.132	0.237
Septal e′ (in m/s)	0.265	0.211	0.070	0.529
E/e′ ratio	−0.351	0.092	−0.152	0.173
sFlt-1/PlGF ratio				
LVMI (in g/m^2)	0.138	0.948	0.252	0.022
RWT	0.108	0.604	0.147	0.189
LAVI (in mL/m^2)	0.170	0.426	0.097	0.385
Lateral e′ (in m/s)	−0.568	0.004†	−0.104	0.351
Septal e′ (in m/s)	−0.371	0.074	−0.057	0.610
E/e′ ratio	0.428	0.037	0.269	0.014

*HDP patients for whom cardiovascular assessments (echocardiography and biomarkers) performed after delivery were excluded.
†Statistical significance shown after Bonferroni correction. E, early diastolic mitral inflow velocity; e′, early diastolic mitral annular velocity; LAVI, left atrial volume index; LVMI, left ventricular mass index; PlGF, placental growth factor; RWT, relative wall thickness; sFlt-1, soluble fms-like tyrosine kinase-1.

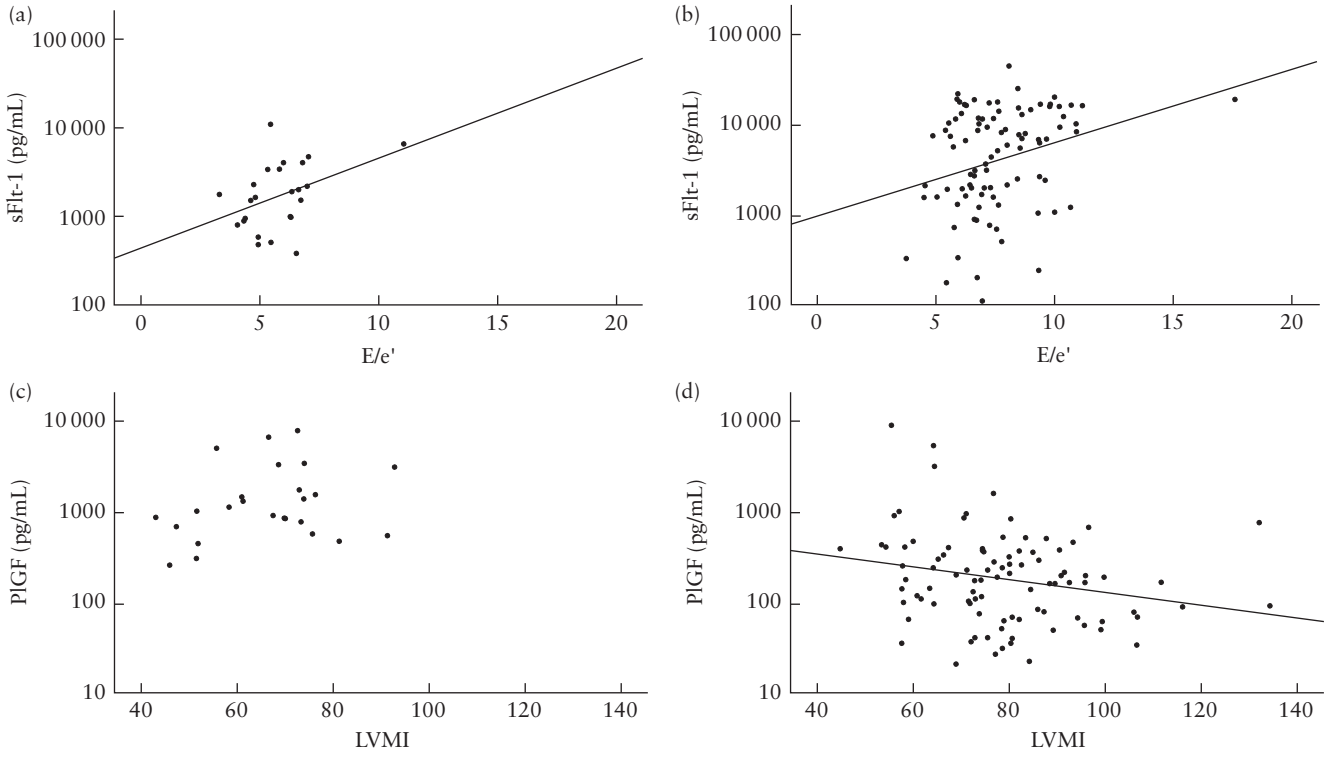

Figure 1 Correlation between soluble fms-like tyrosine kinase-1 (sFlt-1) and echocardiographic early diastolic mitral inflow velocity/early diastolic mitral annular velocity (E/e′) ratio (a,b) and placental growth factor (PlGF) and left ventricular mass index (LVMI) (c,d) before delivery in 25 normotensive pregnancies (a,c) and 83 pregnancies with hypertensive disorders of pregnancy (b,d). *y*-axis is on logarithmic scale.

Table 3 Categorical analysis of maternal biomarkers in left ventricular (LV) remodeling and LV diastolic dysfunction before delivery in 83 women with hypertensive disorders of pregnancy

Parameter	*sFlt-1(pg/mL)*	P	*PlGF (pg/mL)*	P	*sFlt-1/PlGF ratio*	P
LVMI (g/m^2)		0.045		0.118		0.051
< 95 (n = 70)	6123.00 (1987.45–11 707.28)		238.00 (101.06–407.00)		20.32 (6.85–73.83)	
≥ 95 (n = 13)	13 190.20 (7010.69–17 418.87)		127.92 (61.74–202.29)		90.88 (31.95–271.21)	
RWT		0.038		0.360		0.110
< 0.42 (n = 36)	5609.68 (1809.98–8658.95)		238.14 (102.20–421.22)		18.90 (6.74–43.74)	
≥ 0.42 (n = 47)	10 203.63 (2120.84–16 356.86)		205.84 (67.98–376.82)		55.50 (8.52–191.60)	
Lateral e′ (m/s)		0.454		0.062		0.181
> 0.10 (n = 59)	6962.77 (1987.45–13 035.45)		251.29 (103.34–425.61)		22.71 (6.75–86.82)	
≤ 0.10 (n = 24)	7058.60 (2415.35–16 418.05)		183.39 (59.00–239.34)		43.92 (9.71–323.13)	
E/e′ ratio		0.058		0.570		0.078
< 9 (n = 56)	6776.80 (1996.62–12 333.12)		221.66 (122.24–407.00)		22.93 (7.13–68.29)	
≥ 9 (n = 27)	11 800.96 (1075.46–19 064.55)		66.02 (42.95–792.29)		209.88 (1.11–387.30)	

Data are given as median (interquartile range). E, early diastolic mitral inflow velocity; e′, early diastolic mitral annular velocity; LVMI, left ventricular mass index; PlGF, placental growth factor; RWT, relative wall thickness; sFlt-1, soluble fms-like tyrosine kinase-1.

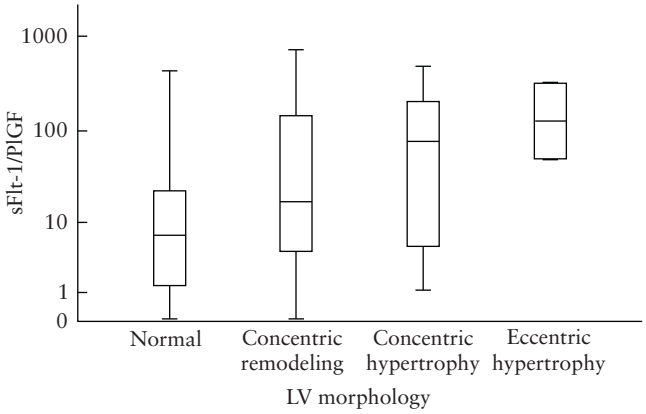

Figure 2 Box-and-whiskers plot showing soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PlGF) ratio, according to left ventricular (LV) morphology in entire cohort (n = 120). Boxes are median and interquartile range and whiskers are range. y-axis is on logarithmic scale.

with HDP. Hypertension in pregnancy is recognized as an important risk factor for CVD later in a woman's life[31,32]. PlGF, sFlt-1 and the sFlt-1/PlGF ratio could provide a better understanding of the pathophysiological mechanism of short- and long-term CVD after HDP. Among 375 patients with HDP, 50% presented with severe and 40% with mild postpartum hypertension, where the sFlt-1/PlGF ratio was significantly higher for postpartum hypertension compared with women who were normotensive postpartum[33]. Similar results were obtained by a prospective study on 988 consecutive women admitted to a tertiary medical center for Cesarean section, in which 184 (18.6%) developed postpartum hypertension. In addition to a higher body mass index and history of diabetes mellitus, the antepartum sFlt-1/PlGF ratio correlated positively with blood pressure in the postpartum period[34]. Another study found significantly lower PlGF levels in women with PE who subsequently developed hypertension at 1 year postpartum (n = 23) compared to women who became normotensive (n = 57)[35]. Benschop *et al.*[36] associated lower midpregnancy PlGF concentrations with worse cardiac structure and higher systolic blood pressure at 6–9 years postpartum in a cohort of 5475 women with normal and pathological pregnancies. These associations persevered after the exclusion of women with complicated pregnancy, highlighting a possible role for normal pregnancy in screening for postpartum CVD. Another study associated increased sFlt-1 and decreased PlGF values in the third trimester of PE pregnancy with cardiometabolic risk factors at 12 years postpartum[37].

It is also important to consider that the vascular remodeling modulated by angiogenic ligand PlGF and its target receptor Flt-1 is a crucial compensatory mechanism in many cardiac disorders outside pregnancy[38]. PlGF is elevated during myocardial ischemia and some studies have shown that PlGF, sFlt-1 or sFlt-1/PlGF ratio, when used in combination with standard biomarkers, strengthens prediction of outcome. sFlt-1 and PlGF are elevated in heart failure and sFlt-1 is a good predictor of outcome[38,39]. Consistent with these findings, in the current study, angiogenic markers were associated with LV remodeling and diastolic dysfunction in the entire cohort.

Clinical and research implications

The planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX) randomized controlled trial showed that planned early delivery in women with late preterm PE significantly reduced maternal adverse outcome, but with more neonatal unit admissions related to minor prematurity sequelae, such as short-term neonatal respiratory morbidity[40,41]. An abnormal angiogenic profile in women with an established diagnosis of preterm PE identifies those at increased risk of adverse outcome, helping the decision-making process regarding the timing of delivery[29]. Regarding the risk of postpartum CVD in women with HDP, there is no consensus regarding clinical guidelines on how to optimally screen, prevent and manage cardiovascular risk after pregnancy

complicated by HDP[42]. In addition, not all women who experienced HDP develop CVD later in life, indicating the existence of different levels of future risk[43]. The identification of circulating cardiovascular biomarkers of relevance for myocardial and coronary artery function in pregnancy may be of additional value to determine which women are at greatest risk. Peripartum screening based on maternal factors and echocardiographic data was able to detect, with excellent discrimination, the majority of women who went onto to develop postpartum hypertension within 6 months[16]. Integrating angiogenic markers in peripartum screening might enhance the prediction model or could allow the replacement of TTE, which needs to be performed by certificated and skilled operators, with a blood sample. In addition, PlGF might also be used as a proxy for maternal cardiovascular system adaptation to pregnancy, even in women without HDP. Lower PlGF levels indicate maternal cardiovascular maladaptation and could potentially identify women at risk of postpartum CVD. Although it is well known that women with history of HDP have an increased risk of CVD[22], the vast majority of postpartum CVD still occur in women without HDP. For instance, more than 1 in 10 patients were found to be hypertensive in the first year postpartum after a normotensive pregnancy[44]. As pregnancy offers a window of opportunity for CVD screening in young adult women, vascular markers in isolation or combined with TTE assessment, could help identify women at risk of future CVD[36].

Strengths and limitations

This is the first study demonstrating a correlation between PlGF, sFlt-1 or sFlt-1/PlGF ratio and cardiac parameters obtained using TTE in a cohort of women with and without hypertension during pregnancy. TTE and blood tests were performed at the same gestational age. The main limitations of the study are the relatively small sample size, in particular of the control group, which might make the study underpowered, and the heterogeneity in the HDP group, which included PE and gestational hypertension cases at any gestational age. Our biomarker data were obtained using immunoassays that are not usually used in clinical practice to measure angiogenic factors, and are therefore not comparable. Moreover, data were not adjusted for gestational age at sampling or other maternal factors.

Conclusions

Maternal angiogenic factors, cardiac morphology and diastolic function are correlated significantly in women both with and without HDP. These findings have highlighted a close relationship between the uteroplacental unit and the maternal heart in pregnancy. Further research is needed to understand the nature of this relationship and to elucidate possible clinical implications of these biomarkers in predicting adverse maternal cardiovascular outcome in pregnancy and in the postpartum period.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Angiogenic biomarkers and echocardiographic indices in 95 women with hypertensive disorders of pregnancy, according to whether they had cardiovascular assessment before or after delivery

Table S2 Angiogenic biomarkers in normal left ventricular (LV) morphology, LV remodeling and LV hypertrophy in entire cohort ($n = 120$)