ANGIOGENIC MARKERS AND MATERNAL ECHOCARDIOGRAPHIC INDICES IN WOMEN WITH HYPERTENSIVE DISORDERS OF PREGNANCY

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NOVELTY AND RELEVANCE

1. What are the novel findings of this work?
    - In women with hypertensive disorders of pregnancy (HDP) and normotensive pregnancy, angiogenetic markers correlate with maternal echocardiographic parameters used to evaluate left ventricular morphology and diastolic function. The relationship between sFlt-1, PlGF and their ratio and maternal cardiac indices in HDP patients might explain why an angiogenic imbalance during pregnancy is associated with maternal adverse cardiovascular outcomes in pregnancy and in the postpartum.
2. What are the clinical implications of this work?
    - Angiogenic markers, which are widely used for the diagnosis and management of HDP, might also give crucial information on the maternal cardiovascular system during pregnancy. And, 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) remodelling and diastolic dysfunction compared to normotensive pregnancies. 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: 95 women with a pregnancy complicated by HDP and a group of 25 uncomplicated pregnancies at term underwent TTE and blood tests to measure sFlt-1 and PLGF during the peripartum period (before delivery and within a week of giving birth). Spearman's rank correlation was used to report correlation coefficients between biomarkers and cardiac indices in the HDP population and controls.

Results: HDP group included 61 (64.2%) preeclamptic patients and, among them, 42 (68.9%) delivered before 37 weeks. 12 HDP out of 95 (12.6%) patients underwent blood samples 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 LVMI (r=0.246, p=0.026) and E/e' (r=0.272, p=0.014) in HDP (n=83), while in controls 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 controls. sFlt-1/PlGF ratio correlated with lateral e' (r=-0.568, p=0.004) and E/e' (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 HDP.

Conclusions: Although the current data are not able to infer causality, they confirm the intimate relationship between the maternal cardiovascular system and endothelial markers that are used both to diagnose and indicate the severity of HDP.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) affect up to 10% of 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) remodelling is a common finding among women with HDP compared to normotensive pregnancies.[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 and early diastolic mitral annular velocity (E/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 markedly increased 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 birth 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 aims 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, between February 2019 and August 2021. The Brent Research Ethics Committee in London gave favourable ethical approval for this study (reference: 19/LO/0794).[16] All participants provided

written informed consent for TTE and blood samples 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 and 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 largely determined by the number of women who would donate blood at the same time of TTE.[16]

Clinical Definitions

HDP, including both gestational hypertension and preeclampsia, 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 four hours after 20 weeks gestation, in the absence of proteinuria and without biochemical or haematological abnormalities. Pre-eclampsia comprises new-onset hypertension accompanied by one or more additional features, including proteinuria (defined as 24-hour urinary protein ≥300 mg per day or a protein/creatinine ratio ≥30 mg per mmol), other maternal organ dysfunctions (including liver, kidney, neurological), or haematological involvement, and/or uteroplacental dysfunction. Birthweight below the 10th centile was used to define small-for-gestational-age (SGA) neonates. 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 one 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, Horten, Norway) by clinicians who were blinded to diagnosis, maternal demographics and gestational age. Two-dimensional, 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 cine-loop format and analyzed off-line. Using the parasternal long-axis view, interventricular septum (IVS, mm), left ventricular end-diastolic diameter (LVEDd, mm), and posterior wall thickness (PWT, mm) were measured. Left ventricular mass (LVM, g) was calculated using the formula $0.8*(1.04*(LVEDd+PWT+IVS)^3-LVEDd^3)+0.6$ and indexed for body surface area (BSA) to obtain LVM index (LVMI). Relative wall thickness (RWT) was calculated as follows: RWT=2xPWT/LVEDd. Normal cardiac geometry, concentric remodelling, concentric hypertrophy and eccentric remodelling 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. The ratio between E and average e' was calculated. Lateral e' and E/e' cut-offs were derived from gender- and age-specific normal range in women 20-40 years of age using mean± 2SD reference.[20, 21] Left atrial volume index (LAVI) was also included as a parameter to evaluate diastolic function.

Biological Samples

Maternal plasma samples were drawn at the time of cardiovascular assessment during the peripartum period. Plasma samples were obtained by venepuncture, collected in pre-chilled tubes containing EDTA (BD Vacutainer), centrifuged (1500 x g for 15 minutes) and subsequently, stored at -80 °C. Analysis of plasma samples was conducted in the Immunoassay Biomarker Core Laboratory, School of Medicine, University of Dundee. Plasma sFLT-1 levels were measured using bead-based immunoassays on a Human ProcartaPlex Panels (ThermoFisher) on a Luminex Bio-plex 200 (ThermoFisher), with a lower limit of quantification of 48.8 pg/ml. Plasma PLGF levels were measured using Human V-Plex kit (K151MED-1, MesoScale Discovery) on the Meso Sector S 600nM (MesoScale Discovery), 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 perfumed 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 report correlation coefficients between biomarkers and echocardiographic indices in the HDP population and controls. Bonferroni correction was used to adjust for a type 1 error because of multiple comparisons for 6 primary cardiac indices (0.05/6=0.0083). Kruskal-Wallis H test and Wilcoxon-Mann-Whitney test were used to compare biomarkers in pre-specified subgroups. STATA software 17 (StataCorp. 2021. College Station, TX: StataCorp LLC.) was used to perform statistical analyses.

RESULTS

Population description

Ninety-five pregnancies with HDP and 25 normotensive term pregnancies were recruited. Maternal characteristics, biomarker levels and summary echocardiographic indices in these two groups are illustrated in Table 1. Among HDP patients, there were 61 (64.2%) preeclamptic patients and 34 (35.8%) with gestational hypertension; preterm delivery <37 weeks and <34 weeks occurred in 42 (68.9%) patients and 21 (34.4%) patients, respectively. 12 HDP out of 95 (12.6%) patients underwent blood samples 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 where samples were taken just prior to the time of birth were included in the analysis.

Correlation between biomarkers and cardiac indices

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 HDP group (n=83), while in the control group 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) (Figure 1). 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' (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 HDP. The correlations between angiogenic factors and echo parameters in HDP patients and controls are shown in Table 2 and Figure 3.

Biomarkers in women with LV diastolic dysfunction and abnormal morphology

Considering only women with HDP, sFlt-1 was 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 with LV remodelling severity, and PlGF decreased with LV remodelling severity, as shown in Table S2 and Figure 4.

Discussion

The current findings demonstrated significant correlations between sFlt-1, PlGF and the sFlt-1/PlGF ratio with cardiac remodelling 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 endothelial 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 extensively correlated with cardiac dysfunction that can develop in hypertensive pregnancies, there are very little data on the relationship between angiogenetic biomarkers and echocardiographic findings in pregnancies 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 outcomes 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 preeclampsia with severe features within 2 weeks among women with suspected preeclampsia, either before or after 35 weeks, 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 multicentre study where measurement of sFlt-1/PlGF provided stratification of the risk of progressing to severe PE within the coming fortnight in women with HDP presenting between 23 and 35 weeks of gestation.[29] The correlation between endothelial markers and cardiac indices revealed by our data may explain why women with a higher sFlt-1/PlGF ratios are at increased risk of developing severe features of PE and adverse outcomes of pregnancy. For instance, diastolic dysfunction and increased LV filling pressure might predispose women to pulmonary oedema 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 with HDP. Hypertension in pregnancy is recognised as an important risk factor for CVD later in a women's life.[31, 32] PlGF, sFlt 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 centre for caesarean sections, where 184 (18.6%) developed postpartum hypertension. In addition to a higher BMI and history of diabetes mellitus, the antepartum sFlt-1/PlGF ratio positively correlated with BP 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 mid-pregnancy PlGF concentrations with worse cardiac structure and higher SBP at 6–9 years postpartum in a cohort of 5,475 women with normal and pathological pregnancies. These associations persevered after the exclusion of women with complicated pregnancies, highlighting a possible role for even normal pregnancy in screening for postpartum cardiovascular disease. Another study associated increased sFlt-1 and decreased PlGF values in the third trimester of PE pregnancies with cardiometabolic risk factors at 12 years postpartum.[37]

It is also important to consider that the vascular remodelling 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 ischaemia and some studies have shown that PlGF, sFlt-1 or sFlt-1/PlGF ratio, when used in combination with standard biomarkers, strengthens predictions of outcomes. sFlt-1 and PlGF are elevated in heart failure and sFlt-1 is a good predictor of outcomes.[38, 39]. Consistent with these findings, in the current study, endothelial biomarkers were associated with LV remodelling and diastolic dysfunction in the entire cohort.

Clinical and Research Implications

The planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX) RCT showed that planned early delivery in women with late preterm PE significantly reduced maternal adverse outcomes, 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 women at increased risk of adverse outcomes helping the decision-making process regarding the timing of birth.[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 CVD risk after pregnancies 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 the majority of women who went onto to develop postpartum hypertension within six months with excellent discrimination.[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 certificate 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 normotensive pregnancies.[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 GH cases at any gestational age. Our biomarker data are not comparable to the most used immunoassays to measure angiogenetic factors. Moreover, data were not adjusted for gestational age at sampling and other maternal factors.

Perspectives

Maternal angiogenic factors, cardiac morphology and diastolic function are significantly correlated in both women 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 outcomes in pregnancy and in the postpartum period.

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TABLES

Table 1. Maternal characteristics at booking, peripartum serum angiogenic biomarker levels and echo indices in controls and women with hypertensive disorders of pregnancy. Data shown as number (%), mean (±standard deviation) or median (interquartile range).

		Control (N=25)	HDP (N=95)	p value	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) 1st trimester		24.45±4.68	29.52±6.01	<0.001	27.53±5.0	27.75±5.00	30.93±6.81
Mean arterial pressure (mmHg) 1st trimester		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 (7.3)
Nulliparous		11 (44.0)	59 (62.1)	0.115	25 (73.5)	15 (75.0)	19 (46.3)
Ethnicity	White	22 (88.0)	54 (56.8)	0.005	29 (85.3)	9 (45.0)	16 (39.0)
	Non-white	3 (22.0)	41 (43.2)		5 (14.7)	10 (55.0)	26 (61)
Details of birth							
Gestation at CV assessment (weeks)		38.87±0.67	34.66±4.45	<0.001	38.03±1.58	37.05±1.37	30.79±3.87
Gestation 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
Birthweight centile		63.39±25.58	28.68±30.18	<0.001	42.43±28.17	33.91±30.08	14.72±26.11
Serum biomarkers							
sFlt-1 (pg/ml)		1,634.06 (945.46-3,397.66)	6,489.77 (1,663.01-12,684.26)	<0.001	2,079.44 (1,253.10-7,063.35)	8,301.12 (2,813.30-14,401.97)	8,843.56 (1,663.02-16,387.46)
PlGF (pg/ml)		1,048.24 (708.68-1,786.89)	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)
Echocardiographic indices							
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	0.40 (3.51-19.90)	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'	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)

HDP hypertensive disorders of pregnancy, GH gestational hypertension, PE preeclampsia, BMI body mass index, CV cardiovascular, LVMI left ventricular mass index, RWT relative wall thickness, LAVI left atrial volume index

Table 2. Correlations between maternal serum biomarker levels and echocardiographic indices in controls and women with hypertensive disorders of pregnancy (HDP). HDP patients with cardiovascular assessments (echocardiography and biomarkers) performed after delivery were excluded. *Statistical significance shown after Bonferroni correction.

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

LVMI left ventricular mass index, RWT relative wall thickness, LAVI left atrial volume index

Table 3. Categorical analysis of maternal serum biomarkers in left ventricular (LV) remodelling and LV diastolic dysfunction in women with hypertensive disorders of pregnancy (HDP) (n=83).

LVMI (g/m^2)	**<95 (n=70)**	**≥95 (n=13)**	**p-value**
sFlt-1(pg/ml)	6123.00 (1987.45-11707.28)	13190.20 (7010.69-17418.87)	**0.045**
PlGF (pg/ml)	238.00 (101.06-407.00)	127.92 (61.74-202.29)	0.118
sFlt-1/PlGF	20.32 (6.85-73.83)	90.88 (31.95-271.21)	0.051
RWT	**<0.42 (n=36)**	**≥0.42 (n=47)**	
sFlt-1 (pg/ml)	5609.68 (1809.98-8658.95)	10203.63 (2120.84-16356.86)	**0.038**
PlGF (pg/ml)	238.14 (102.20-421.22)	205.84 (67.98-376.82)	0.360
sFlt-1/PlGF	18.90 (6.74-43.74)	55.50 (8.52-191.60)	0.110
Lateral e' (m/s)	**>0.10 (n=59)**	**≤0.10 (n=24)**	
sFlt-1 (pg/ml)	6962.77 (1987.45-13035.45)	7058.60 (2415.35-16418.05)	0.454
PlGF (pg/ml)	251.29 (103.34-425.61)	183.39 (59.00-239.34)	0.062
sFlt-1/PlGF	22.71 (6.75-86.82)	43.92 (9.71-323.13)	0.181
E/e'	**<9 (n=56)**	**≥9 (n=27)**	
sFlt-1 (pg/ml)	6776.80 (1996.62-12333.12)	11800.96 (1075.46-19064.55)	0.058
PlGF(pg/ml)	221.66 (122.24-407.00)	66.02 (42.95-792.29)	0.570
sFlt-1/PlGF	22.93 (7.13-68.29)	209.88 (1.11-387.30)	0.078

LVMI left ventricular mass index, RWT relative wall thickness

FIGURE LEGENDS

Figure 1. Correlation between plasma sFlt-1 (pg/ml) and echocardiographic E/e' ratio in normotensive (empty circles, n=25) and hypertensive disorder pregnancy (HDP) patients (filled circles, n=83) before delivery.

Figure 2. Correlation between PlGF and left ventricular mass index (LVMI) in normotensive (empty circles, n=25) and HDP patients (filled circles, n=83) before delivery.

Figure 3. Box plots of sFlt-1/PlGF ratio according to left ventricular morphology (Normal, Concentric remodeling, Concentric hypertrophy, Eccentric hypertrophy) in all women.

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