

## Angiogenic Markers and Cardiovascular Indices in the Prediction of Hypertensive Disorders of Pregnancy

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**Abstract**—Angiogenic and antiangiogenic factors have proven to be an accurate predictive means of preeclampsia. Echocardiographic studies have shown that women with preeclampsia exhibit significant cardiovascular strain, especially early-onset preeclampsia. The aim of this study is to determine preeclampsia risk with soluble fms-like tyrosin kinase 1/placental growth factor ratio, serum NT-proBNP (N-terminal pro B-type natriuretic peptide), and biophysical markers of cardiovascular function in a prospective case-control study. We examined a cohort of 110 pregnant women with uneventful pregnancy outcome (controls) and 129 with hypertensive pregnancy disorders, including 77 with preeclampsia and 52 with pregnancy-induced hypertension. Cardiac indices were obtained with a USCOM-1A monitor, and soluble fms-like tyrosin kinase 1, placental growth factor, and NT-proBNP were measured in serum samples on automated platforms. Logistic regression, as well as Cox proportional hazard analysis, was performed. There were significant contributions from all variables tested, except for heart rate, stroke volume index, and cardiac index to the prediction model. When testing accuracy of respective markers in combination (full model) versus individual markers (soluble fms-like tyrosin kinase 1/placental growth factor ratio and total peripheral resistance) was compared. The soluble fms-like tyrosin kinase 1/placental growth factor ratio and total peripheral resistance performed as good as the full model, except for hypertensive pregnancy disorders and pregnancy-induced hypertension, where the full model performed better. The additional assessment of biophysical and biochemical markers of cardiovascular strain in pregnancy increases the detection of the composite group of hypertensive pregnancy disorders, while not significantly improving detection of preeclampsia alone. This offers a more precise insight into the pathogenesis of the disease, as well as offering a window for intervention, possibly decreasing cardiovascular mortality in these women. (*Hypertension*. 2017;69:1192-1197. DOI: 10.1161/HYPERTENSIONAHA.117.09256.) • [Online Data Supplement](#)

**Key Words:** angiogenic and antiangiogenic factors ■ cardiovascular indices ■ hypertension ■ NT-proBNP ■ preeclampsia ■ sFlt-1/PlGF ratio

Hypertensive pregnancy disorders (HDPs), namely preeclampsia, are a major contributor to maternal and fetal morbidity and mortality.<sup>1</sup> Definitions of these disease entities rely largely on clinical evaluations, such as blood pressure measurement and proteinuria assessment, which are known to be relatively crude and imprecise, especially in predicting HDP-related adverse outcomes.<sup>2</sup> The understanding of the importance of an imbalance of angiogenic factors, such as soluble fms-like tyrosin kinase 1 (sFlt-1) and placental growth factor (PlGF), in the pathophysiology of preeclampsia has led to the introduction of sFlt-1/PlGF ratio into clinical practice as a predictive test for preeclampsia, as well as other placental-mediated adverse outcomes.<sup>3-6</sup> In nonpregnant patients, circulating sFlt-1 is generated as a result of myocardial injury, and both sFlt-1 and PlGF are associated with the development of heart failure and related

adverse outcomes.<sup>7,8</sup> In accord with this sFlt-1/PlGF data, echocardiographic studies have consistently shown that women with preeclampsia exhibit significant cardiovascular strain, especially early-onset preeclampsia.<sup>9-13</sup> Moreover, women with a history of preeclampsia are known to have an increased risk for premature onset of cardiovascular morbidity and mortality in later life.<sup>14,15</sup> These findings all support the hypothesis that preeclampsia involves a failure of the maternal cardiovascular system to adapt to the demands of pregnancy. While sFlt-1/PlGF ratio and role of echocardiography in preeclampsia have been evaluated, other biomarkers, such as NT-proBNP (N-terminal pro B-type natriuretic peptide), a marker for cardiac volume overload and cardiac insufficiency, and whether combinations of biomarker might add to the predictive accuracy of existing tests have not been studied extensively.<sup>16-20</sup>

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Before biochemical and biophysical cardiovascular markers can be used in combination to predict preeclampsia, their relative importance and independence must first be ascertained. The aim of this study is to determine preeclampsia risk with sFlt-1/PIGF ratio, serum NT-proBNP, and biophysical markers of cardiovascular function in a prospective case-control study of normal and preeclamptic pregnant women.

## Methods

### Patients

This is a nested, prospective case-control study conducted at St George's Hospital London, United Kingdom. Institutional review board approval was granted for this study, and informed written consent was obtained prospectively from all participants in the main ongoing study.

Women with singleton pregnancies attending for prenatal care in the Fetal Medicine Unit were recruited. Patients were eligible for recruitment if they presented with either de novo hypertension, de novo proteinuria, or clinical signs and symptoms of preeclampsia. Patients were followed up, and clinical outcome was recorded. Clinical outcome was categorized according to the guidelines of the Royal College of Obstetricians and Gynaecologists. Briefly, hypertension was defined as the repeated measurement of systolic blood pressure of  $\geq 140$  mm Hg (Korotkoff I) and diastolic blood pressure of  $\geq 90$  mm Hg (Korotkoff V). Proteinuria was defined as the excretion of 300 mg protein or greater per day in the 24-hour urine collection or a repeated dipstick of  $\geq 1+$ . Pregnancy-induced hypertension (PIH) was defined as the new onset of hypertension after 20 weeks of gestation, and preeclampsia (PE) was defined when additional proteinuria was diagnosed. Pregnant women who had an uneventful pregnancy outcome were classified as controls. PE and PIH were analyzed together as HDP, and an optimal control group was constructed of non-hypertensive pregnancies filtered to exclude women with birth weight below 25th percentile, uterine artery (UtA) Doppler mean pulsatility index (PI)  $> 1.25$ , and cerebro-placental ratio multiples of the medians (MoM) below 5th percentile.

### Ultrasound and Doppler Assessments

Gestational age was calculated from the crown-rump length measurement at 11 to 13 weeks, and only 1 (the last) examination per pregnancy was included in the analysis. The umbilical artery and middle cerebral artery Doppler waveforms were recorded using color Doppler, and the PI calculated according to a standard protocol. In brief, middle cerebral artery PI values were obtained in the space where the artery passes by the sphenoid wing close to the Willis circle, and umbilical artery PI values were obtained in free loops of umbilical cord. The measurements were obtained in the absence of fetal movement and keeping the insonation angle with the examined vessels  $< 30^\circ$ . The cerebro-placental ratio was calculated as the simple ratio between the middle cerebral artery PI and the umbilical artery PI. To record the UtA Doppler, the transducer was placed over the iliac fossa and the course of the UtA followed from the lateral pelvic wall across the external iliac artery using color Doppler. Pulsed Doppler was then applied 1 cm medial to the crossover point. The angle of insonation used was  $< 30^\circ$ . When 3 similar consecutive waveforms were obtained, the PI was measured, and the mean PI of the left and the right UtA was calculated. The operators were blinded to the clinical information of the patients.

### Biophysical Cardiovascular Marker Assessments

Maternal height, weight, and blood pressure were obtained prior to hemodynamic assessment. Blood pressure was obtained using an upper arm automatic blood pressure monitor (Microlife; Microlife AG Swiss Corporation, Switzerland) in a semi-recumbent position, with the arm well supported and using an appropriate-sized cuff. Cardiac indices (CIs) were obtained with an USCOM-1A monitor, which uses continuous wave Doppler, with a nonimaging probe in the suprasternal

notch to obtain velocity time integrals of transaortic blood flow at the left ventricular outflow tract. Using an anthropometric algorithm, which correlates the outflow tract diameter with the patient's given height, USCOM-1A uses the velocity time integrals to compute stroke volume (SV) and, therefore, cardiac output and produce a complete hemodynamic profile, including heart rate, SV, cardiac output, and total peripheral vascular resistance (TPR). Each Doppler acquisition used for analysis had a minimum of 2 consecutive Doppler profiles (cardiac cycles). Acquisitions with the least amount of interference and the best quality velocity time integrals, deemed by the study investigator to best represent transaortic blood flow, were obtained in the device's flowtracer mode. By calculating the body surface area using examination weight and height, USCOM-1A calculates the indexed hemodynamic variable corrected for body surface area. The parameters examined include CI, SV index, and TPR index (TPRI). The operators were blinded to the clinical information of the patients.

### Biochemical Cardiovascular Marker Assessments

sFLT-1, PIGF, and NT-proBNP were measured using automated electrochemiluminescence immunoassays on the Roche cobas platform (Roche Diagnostics GmbH, Mannheim, Germany). Intra- and interassay coefficients of variation were found to be  $< 5\%$ . The assay operators were blinded to the clinical information of the patients.

### Statistics

Measures have been adjusted to an expected value for the respective pregnancy week. We computed expected values for control subjects by linear modeling and computed MoM. These values were computed by dividing measures by the expected median of control group. Group comparisons were done by analysis of variance, followed by a post hoc Dunnett test, with controls as the reference group. Analysis was based on the adjusted MoM values. NT-proBNP and sFlt-1/PIGF ratio followed a log-normal distribution and were transformed before analysis. For the logistic regression, an odds ratio of 2 indicates an increase of 1 step in the log scale doubles the risk as compared with the MoM norm. For the stepwise forward regression, variables CI MoM, TPRI MoM, NT-proBNP MoM, and sFlt-1/PIGF ratio MoM were included. Because of scattered missing values in these measurements, the overall sample size was reduced ( $n=203$ ). For each step, we calculated sensitivity and specificity. Cox proportional Hazard analysis was performed. Because of missing values, this analysis was calculated in a univariate way for various potential predictors. A significant odds ratio  $> 1$  indicates a proportional increase in risk for shorter pregnancy.

**Table 1. Baseline Characteristics and Descriptive Statistics**

| Variable                | Controls (n=110)  | HDP (n=129)      |
|-------------------------|-------------------|------------------|
| Age                     | 31 (27/35)        | 33 (28/36)       |
| Ethnicity               |                   |                  |
| White                   | 77 (70%)          | 79 (61%)         |
| Asian                   | 16 (15%)          | 24 (19%)         |
| Black                   | 12 (11%)          | 24 (19%)         |
| Mixed                   | 5 (5%)            | 2 (2%)           |
| Booking BMI             | 24.1 (22.3/28.2)* | 27 (24/32)       |
| Exam sBP                | 115 (108/124)*    | 144 (135/152)    |
| Exam dBP                | 72 (68/81)*       | 93 (89/100)      |
| Birth weight            | 3495 (3212/3729)* | 2875 (1870/3340) |
| Gestation at assessment | 35 (28/36)        | 35 (31/36)       |
| Gestation at delivery   | 40 (39/41)*       | 37 (35/39)       |

Values are median (25th/75th percentile) or frequency (%). BMI indicates body mass index; dBP, diastolic blood pressure; HDP, hypertensive pregnancy disorders; and sBP, systolic blood pressure.

\*Significance  $P < 0.05$ .

**Table 2. Group Differences, Median (Quartiles) of Raw Data, Mean±SD of MoM Values and *t* Test Results**

| Predictor         | Controls (n=110) | Control MoM Values | HDP (n=129)      | HDP MoM Values | <i>P</i> Value |
|-------------------|------------------|--------------------|------------------|----------------|----------------|
| UAD mean PI       | 0.66 (0.56/0.81) | 0.97±0.241         | 0.91 (0.66/1.33) | 1.46±0.7       | 0.001          |
| UA PI             | 0.94 (0.85/1.02) | 1±0.132            | 1 (0.85/1.17)    | 1.14±0.39      | 0.001          |
| MCA PI            | 1.79 (1.6/2)     | 1.02±0.18          | 1.64 (1.47/1.88) | 0.94±0.212     | 0.003          |
| CPR               | 1.91 (1.67/2.17) | 1.02±0.194         | 1.73 (1.41/2)    | 0.9±0.34       | 0.002          |
| HR                | 85 (76/93)       | 1±0.147            | 80 (70/94)       | 0.98±0.189     | 0.374          |
| SVI               | 40 (35/45)       | 0.99±0.226         | 39 (32/44)       | 0.98±0.233     | 0.730          |
| CI                | 3.3 (2.9/3.7)    | 1±0.244            | 3.1 (2.8/3.8)    | 0.95±0.202     | 0.151          |
| MAP               | 86 (82/92)       | 0.99±0.091         | 110 (104/117)    | 1.24±0.176     | 0.001          |
| TPRI              | 2084 (1853/2455) | 1±0.33             | 2813 (2447/3225) | 1.31±0.4       | 0.001          |
| NT-proBNP         | 31 (19/52)       | 1±0.224            | 56 (28/124)      | 1.22±0.32      | 0.001          |
| sFlt-1/PlGF ratio | 4.3 (2.2/11.6)   | 1±0.66             | 52 (16/157)      | 3.14±4.3       | 0.001          |

CI indicates cardiac index; CPR, cerebro-placental ratio; HDP, hypertensive pregnancy disorders; HR, heart rate; MAP, mean arterial pressure; MCA, middle cerebral artery; MoM, multiples of the medians; NT-proBNP, N-terminal pro B-type natriuretic peptide; PI, pulsatility index; sFlt-1/PlGF, soluble fms-like tyrosin kinase 1/placental growth factor; SVI, stroke volume index; TPRI, total peripheral resistance index; UA, umbilical artery; and UAD mean PI, mean uterine artery pulsatility index.

## Results

### Baseline Characteristics and Descriptive Statistics

A total of 110 pregnant women with uneventful pregnancy outcome (controls) and 129 with HDP (77 with PE and 52 with PIH) were included in the analysis. Patients with HDPs were more likely to have a higher BMI at booking, a higher systolic and diastolic blood pressure at examination, shorter pregnancy duration, and a smaller baby (Table 1). No differences existed in the gestational week at examination (median 35 weeks), maternal age, or ethnicity (Table 1). At examination, patients with HDP had a significant higher mean UtA PI, umbilical artery PI, and lower middle cerebral artery PI, as well as lower cerebro-placental ratio (Table 2). Mean arterial pressure, TPRI, sFlt-1/PlGF ratio, and NT-proBNP levels were significantly higher in HDP compared with controls, but no differences existed in heart rate, SV index, or CI (Table 2).

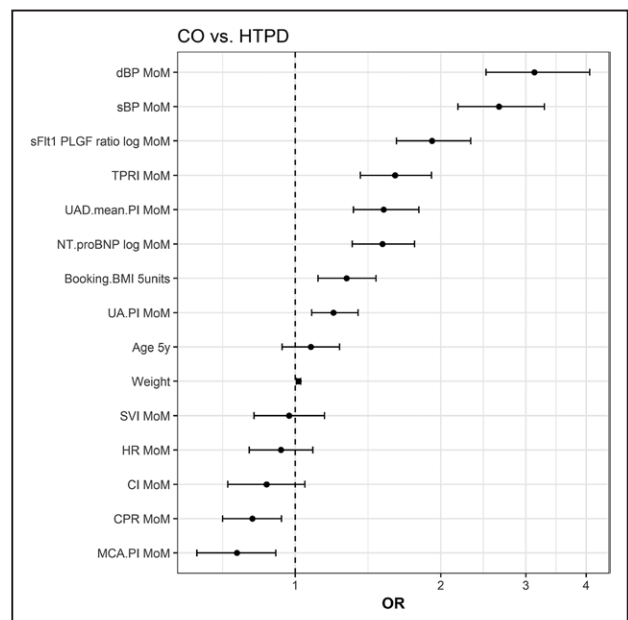
### Univariate Logistic Regression and Correlation of Markers

There were significant contributions from all variables tested except for heart rate, SV index, and CI (Figure 1; Table S1 in the [online-only Data Supplement](#)). Excluding blood pressure, the highest significant odds ratio was for sFlt-1/PlGF ratio (odds ratio, 1.92; 95% confidence interval, 1.62–2.31), NT-proBNP (odds ratio, 1.51; 95% confidence interval, 1.31–1.76), and TPRI (odds ratio, 1.61; 95% confidence interval, 1.36–1.91). The corresponding receiver operating characteristic analysis gave area under the curve values of 84% for sFlt-1/PlGF ratio, 79% for TPRI, and 69% for NT-proBNP (Table 3). When comparing markers in various quartiles, there is a significant positive correlation between sFlt-1/PlGF ratio and NT-proBNP in HDP but not control pregnancies (Figure 2). There is a moderate but significant correlation of TPRI with sFlt-1/PlGF ratio in HDP, but not control pregnancies (Figure S1).

### Multivariable Logistic Regression

For distinction between HDP and control pregnancies, CI, TPRI, sFlt-1/PlGF ratio, but not NT-proBNP, were statistically

significant on multivariable logistic regression analysis (Figure 3; Table S2). When testing accuracy of respective markers in combination (full model) versus individual markers (sFlt-1/PlGF



**Figure 1.** Univariate analyses (logistic regression) for preselection of variables and receiver operating characteristic (ROC) analysis for sensitivity and specificity. For the comparison of the control group (CO) with hypertensive pregnancy disease group (HTPD), odds ratios (OR) and confidence intervals (CI) are displayed for multiples of the medians (MoM) of the following parameters: diastolic blood pressure at examination (Exam.dBP), systolic blood pressure at examination (Exam.sBP), soluble fms-like tyrosin kinase 1/placental growth factor (sFlt-1/PlGF) ratio in logarithmic scale (sFlt1\_PlGF\_ratio\_log), total peripheral resistance index (TPRI), mean uterine artery pulsatility index (UAD.mean.PI), NT-proBNP (N-terminal pro B-type natriuretic peptide) in logarithmic scale (NT.proBNP\_log), body mass index at booking for an increase of 5 U (Bookin.BMI\_5units), umbilical artery pulsatility index (UA.PI), age for an increase of 5 years (Age\_5y), weight at examination (Exam.Weight), stroke volume index (SVI), heart rate (HR), cardiac index (CI), cerebro-placental ratio (CPR), and middle cerebral artery (MCA).

**Table 3. Comparative ROC Analysis of Prediction Models**

| Groups              | AUC Full Model | AUC sFlt-1/PlGF | AUC TPRI | P Value           |              |                   |
|---------------------|----------------|-----------------|----------|-------------------|--------------|-------------------|
|                     |                |                 |          | Full vs sFlt/PlGF | Full vs TPRI | TPRI vs sFlt/PlGF |
| Control vs HDP      | 0.903          | 0.837           | 0.786    | 0.026             | 0.001        | 0.213             |
| Control vs PIH      | 0.844          | 0.689           | 0.752    | 0.003             | 0.113        | 0.322             |
| Control vs PE       | 0.966          | 0.942           | 0.807    | 0.104             | 0.001        | 0.001             |
| PIH vs PE           | 0.916          | 0.878           | 0.564    | 0.167             | 0.001        | 0.001             |
| Late PE vs early PE | 0.978          | 0.982           | 0.644    | 0.421             | 0.001        | 0.001             |

AUC indicates area under the curve; HDP, hypertensive pregnancy disorders; PE, preeclampsia; PIH, pregnancy-induced hypertension; ROC, receiver operating characteristic; sFlt-1/PlGF, soluble fms-like tyrosin kinase 1/placental growth factor; and TPRI, total peripheral resistance index.

ratio and TPRI) was compared, the sFlt-1/PlGF ratio performed as good as the full model, except for controls versus HDP and controls versus PIH, where the full model performed better. TPRI performed as well as the full model in controls versus HDP; in all other comparisons, the full model performed better. TPRI performed as well as the sFlt-1/PlGF ratio for controls versus HDP and controls versus PIH. In controls versus PE, the sFlt-1/PlGF ratio performed significantly better than TPRI (Table 3).

**Cox Proportional Hazard**

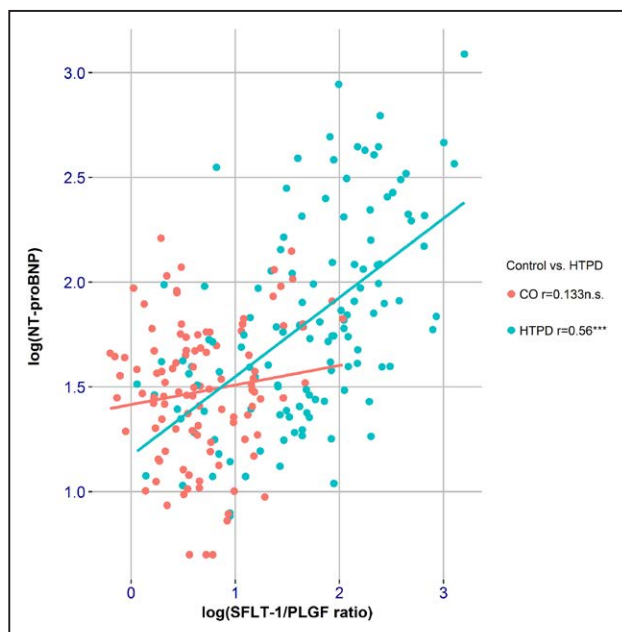
An analysis of the prediction of using Cox proportional hazard showed that lower CI and higher TPRI, NT-proBNP, and sFlt-1/PlGF ratio corresponded with shorter remaining pregnancy duration (Table S3).

**Discussion**

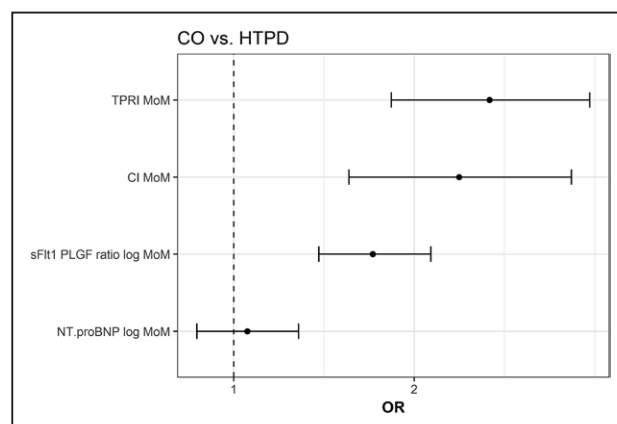
This is the first study to prospectively assess both biochemical and biophysical markers of cardiovascular strain or placenta

dysfunction in a cohort of patients with HDP and in healthy pregnant women. Many studies have shown the potential usefulness of biochemical markers, namely sFlt-1/PlGF ratio, in predicting preeclampsia.<sup>6</sup> More recently, studies have demonstrated that preeclampsia involves maternal cardiovascular impairment—principally involving adverse cardiac remodeling and diastolic dysfunction.<sup>11</sup> While the sFlt-1/PlGF ratio is increasingly becoming a part of routine clinical care and was recently recommended as a rule out test by the National Institute for Health and Care Excellence in the United Kingdom, biophysical assessment of maternal cardiovascular function does not yet have a defined role in clinical practice.<sup>21</sup>

In our cohort, we aimed to clarify to what extent the assessment of biochemical and biophysical cardiovascular marker in isolation or combination could improve prediction of preeclampsia. In addition to routinely collected clinical data and standard Doppler evaluations, we evaluated biophysical (heart rate, SV, CI, and TPRI) as well as biochemical (sFlt-1/PlGF ratio and NT-proBNP) markers of cardiovascular function in women with a healthy pregnancy and those with HDP—a group that included preeclampsia and PIH. The rationale for combining these different HDP groups was that both categories have been shown to exhibit cardiovascular strain.<sup>12</sup> To eliminate the bias of latent placental dysfunction in the



**Figure 2.** Relation of NT-proBNP (N-terminal pro B-type natriuretic peptide) to soluble fms-like tyrosin kinase 1/placental growth factor (sFlt-1/PlGF) ratio. For the comparison of the control group (CO) with hypertensive pregnancy disease group (HTPD), the correlation between NT-proBNP (logarithmic scale, y axis) and sFlt-1/PlGF ratio (logarithmic scale, x axis) is displayed. In controls, this correlation is not significant ( $r=0.133$ ), while it is in HTPD ( $r=0.56$ ).



**Figure 3.** Multivariate logistic regressions for controls (CO) versus hypertensive pregnancy disease group (HTPD). The variables contributing to the model were total peripheral resistance index (TPRI), cardiac index (CI), soluble fms-like tyrosin kinase 1/placental growth factor (sFlt-1/PlGF) ratio in logarithmic scale (sFlt1\_PlGF\_ratio\_log), and NT-proBNP (N-terminal pro B-type natriuretic peptide) in logarithmic scale (NT.proBNP\_log). MoM indicates multiples of the medians.



control group, we constructed an optimal control cohort containing well-grown fetuses with normal uterine and umbilical Doppler indices.<sup>22</sup> We demonstrated that sFlt-1/PIGF ratio and TPRI showed usefulness in the prediction for HDP, with some additional, moderate contribution from NT-proBNP and CI.

### Clinical and Research Implications

There are several implications for clinical practice arising from these findings apart from confirming the high predictive accuracy of the sFlt-1/PIGF ratio in line with recent findings from large prospective studies.<sup>6</sup> Our analysis demonstrated that several additional biochemical and biophysical cardiovascular markers are also related to HDP, namely NT-proBNP, TPRI, and UtA Doppler assessment, suggesting that these variables may potentially contribute toward HDP prediction. However, an analysis of correlations demonstrated a strong interdependence of the putative placental biomarkers sFlt-1/PIGF to NT-proBNP, an established cardiovascular biomarker produced by cardiac myocytes exposed to volume overload. This is an interesting finding, which suggests that either NT-proBNP is also related to placental dysfunction or that sFlt-1/PIGF may also be acting as a cardiovascular biomarker in HDP. Multivariable logistic regression analysis demonstrated that only TPRI, CI, and sFlt-1/PIGF, but not NT-proBNP, were independent predictors of HDP, suggesting that prediction models using combinations of these cardiovascular markers may have increased performance and predictive accuracy for HDP. Similarly, the Cox proportional hazard analysis showed that an increase in the sFlt-1/PIGF ratio, TPRI, and NT-proBNP or decrease in CI were all associated with a higher likelihood for imminent delivery.

Assessment of biomarker performance by comparative receiver operating characteristic curve analysis demonstrated similar performance for prediction models of HDP containing all biomarkers, TPRI alone, or sFlt-1/PIGF alone. It is important to acknowledge that as a case-cohort rather than a screening study, measures of test performance are biased with attenuation of the receiver operating characteristic curve because of pooled covariate data.<sup>23</sup> Regardless of this limitation, the data provide cause for optimism that assessing biophysical and biochemical markers of cardiovascular strain in pregnancy offers a more precise insight into the pathogenesis of HDP, as well as offering a window for prediction, intervention, and possibly decreasing subsequent cardiovascular mortality in these women.

### Study Strengths and Limitations

The strength of the study is that biochemical and biophysical marker of cardiovascular function have been concurrently in the same patients nested within a large prospective study cohort. The study has only a single assessment point, when >1 measurement and analysis of marker slopes may have yielded higher predictive accuracy. Our mean time of assessment was 35 weeks of gestation corresponding to a mainly late-onset HDP cohort. Furthermore, the majority of patients with preeclampsia had mild rather than severe disease. Future studies should distinguish between early and late HDP cohorts because this disease classification may affect precision in detection. Finally, as previously mentioned, the case-control

study design does not lend itself to accurate assessment of screening performance by receiver operating characteristic analysis.

### Perspectives

Including markers of cardiovascular function into assessment of HDPs takes into account the contribution of cardiovascular alterations to the pathophysiology of HDPs. The failure of the maternal heart to adapt to the demands of pregnancy is seen to contribute substantially to hypertensive disorder-related adverse outcomes.<sup>24</sup> Moreover, echocardiographic alterations are observed to persist postpartum, contributing potentially to premature onset of cardiovascular morbidity in later life.<sup>13,15</sup> The additional assessment of biophysical and biochemical markers of cardiovascular strain in pregnancy does not seem to significantly improve the detection of preeclampsia as yielded by the sFlt-1/PIGF ratio. However, it does increase the detection of the composite group of HDPs. This offers a more precise insight into the pathogenesis of the disease, as well as offering a window for intervention, possibly decreasing cardiovascular mortality in these women.

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### Disclosures

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## Novelty and Significance

### What Is New?

- Assessing biophysical and biochemical markers of cardiovascular function can help to predict hypertensive pregnancy disorders. This is the first study evaluating this combination of diagnostic tools.

### What Is Relevant?

- Hypertensive pregnancy disorders, especially preeclampsia, go along with cardiovascular impairment. Noninvasively measuring cardiac index and total peripheral resistance, as well as maternal serum NT-proBNP (N-terminal pro B-type natriuretic peptide), can help to improve predic-

tive accuracy of the soluble fms-like tyrosin kinase 1/placental growth factor ratio in certain patients.

### Summary

The prediction of hypertensive pregnancy disorders but not preeclampsia is improved by adding cardiovascular markers to placental markers. In preeclampsia, the soluble fms-like tyrosin kinase 1/placental growth factor ratio remains the most accurate means of prediction.

## Angiogenic Markers and Cardiovascular Indices in the Prediction of Hypertensive Disorders of Pregnancy

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## Online Supplement

### Angiogenic markers and cardiovascular indices in the prediction of hypertensive disorders of pregnancy

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**Table S1**

| <b>Predictor</b>         | <b>OR (CI)</b>   | <b>p-value</b> | <b>Specificity</b> | <b>Sensitivity</b> | <b>ROC AUC</b> |
|--------------------------|------------------|----------------|--------------------|--------------------|----------------|
| Age (5years)             | 1.08 (0.94/1.23) | 0.28910        | n/a                | n/a                | n/a            |
| Booking BMI (5units)     | 1.28 (1.11/1.47) | 0.00051        | n/a                | n/a                | n/a            |
| Exam Weight              | 1.02 (1.01/1.03) | 0.00420        | n/a                | n/a                | n/a            |
| Exam sBP MoM             | 2.64 (2.2/3.3)   | 0.00001        | 86                 | 83                 | 91 (88-95)     |
| Exam dBP MoM             | 3.12 (2.5/4.1)   | 0.00001        | 93                 | 85                 | 94 (91-97)     |
| UtA mean PI MoM          | 1.52 (1.32/1.8)  | 0.00001        | 92                 | 50                 | 73 (66-80)     |
| UA PI MoM                | 1.2 (1.08/1.35)  | 0.00104        | 95                 | 27                 | 61 (54-68)     |
| MCA PI MoM               | 0.76 (0.63/0.91) | 0.00346        | 72                 | 53                 | 62 (54-70)     |
| CPR MoM                  | 0.81 (0.71/0.94) | 0.00523        | 87                 | 42                 | 64 (57-72)     |
| HR MoM                   | 0.93 (0.8/1.09)  | 0.37800        | 63                 | 55                 | 55 (47-63)     |
| SVI MoM                  | 0.97 (0.82/1.15) | 0.72925        | 84                 | 25                 | 53 (45-61)     |
| CI MoM                   | 0.87 (0.72/1.05) | 0.14402        | 16                 | 96                 | 54 (46-62)     |
| TPRI MoM                 | 1.61 (1.36/1.91) | 0.00001        | 87                 | 61                 | 79 (72-85)     |
| NTproBNP logMoM          | 1.51 (1.31/1.76) | 0.00001        | 76                 | 56                 | 69 (63-76)     |
| sFlt-1/PIGF-ratio logMoM | 1.92 (1.62/2.31) | 0.00001        | 76                 | 81                 | 84 (79-89)     |

**Supplementary Table S1** Univariate logistic regression and ROC analysis (AUC: 95% confidence interval) for control versus HDP

**Table S2**

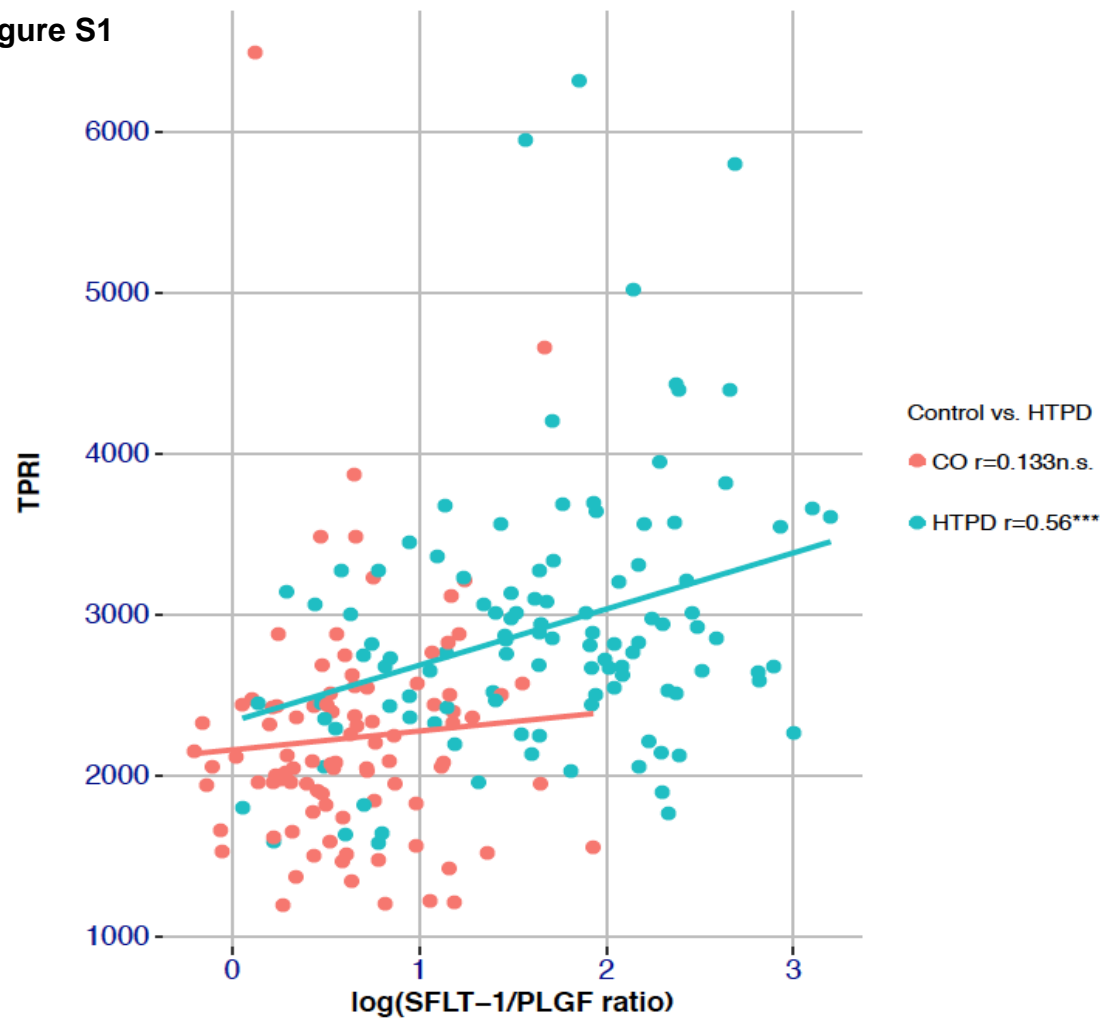
| <b>Predictor</b>         | <b>OR (95% CI)</b> | <b>p</b> |
|--------------------------|--------------------|----------|
| CI MoM                   | 2.38 (1.56-3.66)   | 0.001    |
| TPRI MoM                 | 2.67 (1.83-3.93)   | 0.001    |
| NTproBNP logMoM          | 1.05 (0.87-1.28)   | 0.389    |
| sFlt-1/PIGF-ratio logMoM | 1.71 (1.39-2.13)   | 0.001    |

**Supplementary Table S2:** Multivariate logistic regression for controls versus HDP**Table S3**

| <b>Variable</b>          | <b>OR (95% CI)</b> | <b>p</b> |
|--------------------------|--------------------|----------|
| CI MoM                   | 0.76 (0.60-0.97)   | 0.028    |
| TPRI MoM                 | 1.39 (1.19-1.63)   | 0.001    |
| NTproBNP logMoM          | 1.56 (1.37-1.79)   | 0.001    |
| sFlt-1/PIGF-ratio logMoM | 1.90 (1.69-2.14)   | 0.001    |

**Supplementary Table S3:** Cox proportional hazards for HDP

Figure S1



**Supplementary figure S1:** Relation of TPRI to sFlt-1/PlGF-ratio. For the comparison of the control group (CO) with hypertensive pregnancy disease group (HTPD), the correlation between total peripheral resistance (TPRI, y-axis) and sFlt-1/PlGF ratio (logarithmic scale x-axis) is displayed. In controls, this correlation is not significant ( $r=0.133$ ), while it is in HTPD ( $r=0.56$ ).