Maternal cardiac function at 19–23 weeks' gestation in the prediction of pre-eclampsia

E. GIBBONE,[1] A. WRIGHT,[2] R. VALLENAS CAMPOS,[1] A. SANCHEZ SIERRA,[1] K. H. NICOLAIDES,[1] M. CHARAKIDA.[1,3]

1. Harris Birthright Research Centre for Fetal Medicine, King's College, London, UK.
2. Institute of Health Research, University of Exeter, Exeter, UK.
3. School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK

Correspondence:
Professor KH Nicolaides, Fetal Medicine Research Institute,
King's College Hospital, 16-20 Windsor Walk, Denmark Hill, London SE5 8BB
email: kypros@fetalmedicine.com

Short title: Maternal cardiac function and preeclampsia

Keywords: Screening, pre-eclampsia, echocardiography, ultrasound, maternal cardiac functiom

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.23568

What are the novel findings of this work

Maternal cardiovascular indices at 19-23 weeks' gestation are significantly affected by maternal demographic characteristics and elements of medical history known to be associated with increased risk for subsequent development of preeclampsia (PE). After adjustment for these maternal factors, only peripheral vascular resistance was affected by PE.

What are the clinical implications of this work

Assessment of maternal cardiovascular function provides information on the pathophysiology of PE but is not useful in the prediction of PE.

ABSTRACT

Objectives: First, to examine the factors from maternal characteristics and medical history that affect maternal cardiovascular indices, and second, to examine the potential value of maternal cardiovascular indices at 19-23 weeks' gestation on their own and in combination with the established biomarkers of preeclampsia (PE), including uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFLT), in the prediction of subsequent development of PE.

Methods: This was a prospective observational study in women attending for a routine hospital visit at 19^{+1} - 23^{+3} weeks' gestation. This visit included recording of maternal demographic characteristics and medical history, assessment of maternal E/A, E/e', myocardial performance index, global longitudinal systolic strain, left ventricular ejection fraction, peripheral vascular resistance, left ventricular cardiac output and left ventricular mass indexed for body surface area, and measurement of MAP, UtA-PI, serum PlGF and serum sFLT-1. The measurements of the eight maternal cardiac indices were standardized to remove the effects of maternal characteristics and elements from the medical history. The competing risks model was used to estimate the individual patient-specific risks of delivery with PE and determine the detection rate (DR), at 10% false positive rate (FPR), in screening by a combination of maternal demographic characteristics and medical history with biomarkers.

Results: The study population of 2,853 pregnancies contained 76 (2.7%) that developed PE. The main findings of the study were: first, in pregnancies that subsequently developed PE there was evidence of altered cardiac geometry, impaired myocardial function and increased peripheral vascular resistance; second, all maternal cardiovascular indices were significantly affected by maternal demographic characteristics and elements of medical history known to be associated with increased risk for subsequent development of PE; third, after adjustment for maternal demographic characteristics and medical history the only cardiovascular index that was significantly affected by subsequent development of PE was peripheral vascular resistance; fourth, peripheral vascular resistance MoM was correlated with MAP MoM, which is not surprising because blood pressure is involved in the estimation of both; fifth, there were small correlations between several cardiovascular indices with MAP MoM, but none with MoM values of UtA-PI, PlGF or sFLT-1; sixth, the performance of screening of delivery with PE at <37 weeks' gestation or delivery with PE at any gestational age in screening by maternal demographic characteristics and medical history or combinations of maternal factors with MAP, UtA-PI, PlGF and sFLT-1 were not improved by the addition of peripheral vascular resistance.

Conclusion: Assessment of maternal cardiovascular function provides information on the pathophysiology of PE but is not useful in the prediction of PE.

INTRODUCTION

Maternal echocardiographic studies have demonstrated that in women with preeclampsia (PE), compared to normotensive controls, there is evidence of impaired myocardial function and increased peripheral vascular resistance.[1-13] A few studies in high-risk pregnant women have demonstrated hemodynamic and subclinical cardiac dysfunction may precede the onset of PE.[14-17]

Effective prediction of PE at mid-gestation is provided by a combination of maternal demographic characteristics and medical history with measurements of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PLGF) and serum soluble fms-like tyrosine kinase-1 (sFLT-1).[18-20] The competing risks model is used, whereby the *posterior* distribution of gestational age at delivery with PE is obtained using Bayes theorem by multiplying the *prior* probability density from demographic characteristics and elements from the medical history by the likelihood function from biomarker multiple of the median (MoM) or Delta values, where appropriate.[21] The measured values of biomarkers are converted to MoMs or Deltas to remove the effects of characteristics such as gestational age, and those maternal factors that are included in the calculation of the *prior* probability density.

The objectives of this study in an unselected population undergoing detailed cardiovascular assessment at 19-23 weeks' gestation are to first, examine the factors from maternal characteristics and medical history that affect maternal cardiovascular indices, and second, determine the performance of maternal cardiovascular indices in combination with the established biomarkers of PE, including MAP, UtA-PI, PlGF and sFLT, in the prediction of subsequent development of PE.

METHODS

Study design and participants

This was a prospective observational study in women attending for a routine hospital visit at 19^{+1} - 23^{+3} weeks' gestation at King's College Hospital, London, UK between August 2019 and April 2020. This visit included recording of maternal demographic characteristics and medical history, ultrasound examination for fetal anatomy and growth, maternal cardiovascular assessment, measurement of MAP by validated automated devices and a standardized protocol [22] transvaginal color Doppler ultrasound of the left and right uterine arteries and calculation of the mean UtA-PI,[23] and measurement of serum concentration of PlGF and sFLT by an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS, Thermo Fisher Scientific, Hennigsdorf, Germany). During the study period there was no policy of first-trimester screening for PE by a combination of maternal factors, MAP, UtA-PI and PlGF and treatment of the high-risk group with aspirin and we do not have available data on such therapy. Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks.[24,25] The women gave written informed consent to participate in the Advanced Cardiovascular Imaging Study (REC No 18/NI/0013, IRAS ID:237936) which was approved by the NHS Research Ethics Committee.

The inclusion criteria for this study were singleton pregnancies delivering a non-malformed live birth or stillbirth. We excluded pregnancies with aneuploidies and major fetal abnormalities.

Maternal cardiovascular assessment

All participants were studied by 2-dimensional and Doppler transthoracic echocardiography at rest in the left lateral decubitus position and data were acquired during unforced expiration. The protocol included standard parasternal and apical views acquired with a Canon Aplio i900 scanner (Canon Medical Systems Europe BV, Zoetermeer, The Netherlands) as per American Society of Echocardiography (EAE/ASE) guidelines.[26,27] Echocardiography was performed by 7 Fetal Medicine Fellows who were trained in acquisition and analysis of echocardiograms. In a previous study we reported excellent Interobserver reproducibility of various cardiac indices.[28]

Cardiac output was calculated from stroke volume (derived from the left ventricular outflow tract velocity-time integral) multiplied by heart rate. Left atrial area was calculated in end-systole from the four-chamber view. Left ventricular mass was calculated with the Devereux formula using measurements of the anatomical M-mode applied in the parasternal long axis. The mitral peak early (E) and late (A) diastolic flow velocities were measured, and the E/A ratio was calculated. Pulsed tissue Doppler recordings were obtained at the septal and lateral aspects of basal left ventricle at the junction with the mitral valve annulus in the apical four-chamber view. The E/e' ratio was calculated using the mean value between septal and lateral peak e' waves. Speckle tracking was employed to assess global longitudinal systolic strain of the left ventricle.

Outcome measure

Outcome measure was delivery with PE. Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with chronic hypertension or pregnancy associated hypertension were examined to determine the diagnosis of PE. This was based on the finding of new onset hypertension (systolic blood pressure of $\geq$140 mm Hg or diastolic blood pressure of $\geq$90 mmHg on at least two occasions four hours apart developing after 20 weeks' gestation in previously normotensive women) or chronic hypertension and at least one of the following: proteinuria (≥300 mg/24h or protein to creatinine ratio $\geq$30 mg/mmoL or $\geq$2 + on dipstick testing), renal insufficiency with serum creatinine >97 μmol/L in the absence of underlying renal disease, hepatic dysfunction with blood concentration of transaminases more than twice the upper limit of normal (≥65 IU/L for our laboratory), thrombocytopenia (platelet count <100,000/μL), neurological complications (e.g. cerebral or visual symptoms), or pulmonary edema.[29]

Statistical analysis

Data were expressed as median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. Students t-test and χ2-square test or Fisher's exact test, were used for comparing outcome groups for continuous and categorical data, respectively.

The following eight cardiovascular indices were examined: E/A, E/e', myocardial performance index, global longitudinal systolic strain, left ventricular ejection fraction, peripheral vascular resistance, left ventricular cardiac output and left ventricular mass indexed for body surface area. Distributional properties of each index were investigated using histograms and by plotting marker measurements against gestational age and maternal weight in PE and unaffected pregnancies. On the basis of these exploratory analyses, we determined the relevancy or need for transformation, for example $\log_{10}$, of any of the eight indices, to achieve homogeniety of variance and approximate Gaussian distributional form. Multivariable linear regression models were then fitted between each of the eight indices and the following maternal characteristics and elements from their medical history: maternal age, racial origin (White, Black, South Asian, East Asian and mixed), method of conception (natural, *in vitro* fertilization, use of ovulation drugs), cigarette smoking during pregnancy (yes or no), history of chronic hypertension (yes or no), history of pre-existing diabetes mellitus (yes or no), history of systemic lupus erythematosus or anti-phospholipid syndrome (yes or no), family history of PE in the mother of the patient (yes or no) and obstetric history including parity (parous or nulliparous if no previous pregnancies at ≥ 24 weeks' gestation), previous pregnancy with PE (yes or no), gestational age at delivery and birth weight of the neonate in the last pregnancy and interval in years between birth of the last child and estimated date of conception of the current pregnancy. These are the factors which are known to affect the risk for development of PE and are used in the competing risk model for calculating the *prior* risk for PE.[30]

To determine whether the cardiovascular indices would be useful in predicting PE, terms for PE and the gestational age at delivery with PE were included in the models. Backwards elimination was used for variable selection. The partial residuals, after excluding the contribution of PE, comprised either the $\log_{10}$ multiples of the median (MoM) values, or the deviations from the median (Deltas) depending on the transformation of the outcome variable in the original model fitting. Regression analysis was used to examine the significance of association between MoM or Delta values of each cardiovascular index with MoM values of MAP, UtA-PI, PlGF and sFLT-1.

The competing risks model was used to estimate the individual patient-specific risks of delivery with PE by a combination of maternal demographic characteristics and medical history with potential cardiovascular biomarkers.[30] The *posterior* distribution of gestational age at delivery with PE was obtained using Bayes theorem by multiplying the *prior* probability density from maternal factors by the likelihood function from biomarker MoM or Delta values, where appropriate. The detection rates of delivery with PE, at 10% false positive rate (FPR), were assessed for combinations of maternal factors and potential cardiovascular biomarkers.

The statistical software package R was used for data analyses.[31]

RESULTS

Study participants

The study population of 2853 pregnancies contained 76 (2.7%) that developed PE, including 18 (0.6%) that delivered with PE at <37 weeks' gestation; there were 64 cases that developed gestational hypertension (GH) and 2713 unaffected by PE or GH. The cases of GH were excluded from further analysis. The same population was used for our previous study investigating the value of ophthalmic artery Doppler in the prediction of PE.[32]

Maternal and pregnancy characteristics of the study population are summarized in Table 1. In the PE group, compared to the unaffected pregnancies, there was a higher median maternal weight and body mass index, and higher incidence of chronic hypertension, diabetes mellitus, family history of PE, conception by assisted reproduction, nulliparity and previous history of PE.

Factors affecting cardiovascular indices

Preliminary analysis of cardiovascular indices unadjusted for maternal characteristics and medical history demonstrated that in the pregnancies that subsequently developed PE, compared to those that remained normotensive, there was a higher median E/e', myocardial performance index, global longitudinal systolic strain and peripheral vascular resistance and lower left ventricular ejection fraction; there were no significant differences in E/A, left ventricular cardiac output or left ventricular mass indexed for body surface area (Figure 1).

Multivariable linear regression models were fitted to $\log_{10}$ values of E/A, E/e', myocardial performance index, peripheral vascular resistance and left ventricular cardiac output and untransformed values of global longitudinal systolic strain, left ventricular ejection fraction and left ventricular mass indexed for body surface area. The effects of variables significantly contributing to measurement levels of each cardiovascular index are shown in Table 2. Those variables relating to maternal characteristics and medical history were used for standardisation into MoM or Delta values. Peripheral vascular resistance was significantly affected by PE and the effect was not dependent on gestational age at delivery with PE; when maternal characteristics and medical history were accounted for, E/A, E/e', myocardial performance index, left ventricular cardiac output, global longitudinal systolic strain, left ventricular cardiac output and left ventricular mass indexed for body surface area were not significantly affected by PE (Table 2).

Distribution of biomarkers

The distribution of MoM or Delta values of the cardiovascular indices in pregnancies that developed PE are shown in Figure 2; the only index with significantly different median value between PE and unaffected pregnancies was peripheral vascular resistance. The correlations of MoM or Delta values of the cardiovascular indices with MoM value of MAP, UtA-PI, serum PlGF and sFLT-1 are shown in Table 3. Adjusted peripheral vascular resistance was found to be correlated with MAP MoM and to a lesser extent with PlGF MoM, in general however, correlations between the previously established markers and the cardiovascular markers were small.

Performance of screening

The detection rates, at 10% FPR, of delivery with PE at <37 weeks' gestation or delivery with PE at any gestational age in screening by maternal demographic characteristics and medical history or combinations of maternal factors with MAP, UtA-PI, PlGF and sFLT-1 were not improved by the addition of peripheral vascular resistance (Table 4).

DISCUSSION

Principal findings of this study

In this prospective screening study of an unselected population at 19-23 weeks' gestation we used standard echocardiographic techniques but also employed more advanced imaging modalities, such as speckle tracking, which allowed us to detect subtle cardiac functional changes. The data demonstrated that first, in pregnancies that subsequently developed PE there was evidence of impaired myocardial function and increased peripheral vascular resistance; second, all maternal cardiovascular indices were significantly affected by maternal demographic characteristics and elements of medical history known to be associated with increased risk for subsequent development of PE; third, after adjustment for maternal demographic characteristics and medical history the only cardiovascular index that was significantly affected by PE was peripheral vascular resistance; fourth, peripheral vascular resistance MoM was correlated with MAP MoM, which is not surprising because blood pressure is involved in the estimation of both; fifth, there were small correlations between several cardiovascular indices with MAP MoM, but none with MoM values of UtA-PI, PlGF or sFLT-1; sixth, the performance of screening of delivery with PE at <37 weeks' gestation or delivery with PE at any gestational age in screening by maternal demographic characteristics and medical history or combinations of maternal factors with MAP, UtA-PI, PlGF and sFLT-1 were not improved by the addition of peripheral vascular resistance.

Comparison with findings of previous studies

Several cross sectional and cohort studies have consistently demonstrated that women with established PE compared to those with normotensive pregnancy have impaired cardiac function[1-13] and are twice as likely to develop future ischaemic heart disease.[33] Few studies in high-risk pregnancies have shown that cardiac dysfunction precedes the development of PE,[14-17] suggesting that PE is acting as a marker of a woman's chronic underlying susceptibility to future disease rather than PE causing harm on maternal cardiovascular system. Vasapollo *et al* examined 526 normotensive high-risk women at 24 weeks' gestation and demonstrated that measurement of peripheral vascular resistance offers incremental value to abnormal uterine artery Dopplers in the prediction of adverse pregnancy outcomes, including PE.[14] In a subsequent study, by the same group, in 1345 pregnancies at 24 weeks' gestation those who subsequently developed early or late PE had increased left ventricular mass and higher diastolic functional indices than those with uncomplicated pregnancy.[15] Melchiorre *et al.*, examined 269 women at 20-23 weeks' gestation and reported cardiac diastolic dysfunction only in 18 women who developed preterm PE but not in 28 women who developed term PE.[16] Shahul *et al.*, examined 60 women with chronic hypertension at 20 weeks' gestation and reported that in the group of 34 women with abnormal global longitudinal strain there was a significantly higher incidence of subsequent development of superimposed PE.[17] There is one previous screening study in an unselected population; in this study we examined 1602 women with singleton pregnancies at 35-37 weeks' gestation and showed that women that subsequently developed PE, compared to those that remained normotensive, had distinct cardiac functional and structural changes and that cardiac assessment could offer incremental prognostic value to available scoring systems for the development of term PE.[34]

Strengths and limitations

The main strengths of the study are first, prospective examination of a large unselected population of pregnant women attending for a routine ultrasound examination at mid-gestation and measurement of all potentially useful biomarkers of PE, second, use of a standardized technique for maternal cardiovascular assessment by appropriately trained research fellows, third, adjustment of the cardiovascular indices for maternal characteristics and elements from the medical history known to be associated with increased risk for PE, and fourth, application of the competing risks approach to estimate patient-specific risks and determine the potential additive value of cardiovascular indices in the prediction of PE achieved by maternal demographic characteristics and medical history or combinations of maternal factors with each of the established mid-gestation biomarkers of PE.

Despite the relatively large study population the number of cases of PE, especially preterm PE, was small; consequently, there is a degree of uncertainty surrounding the potential contribution of cardiovascular indices in the prediction of PE.

Conclusions

The current study showed that women at risk for PE have distinct cardiac functional changes prior to the clinical development of PE, but these are largely explained by differences in maternal characteristics. Our data would, therefore, suggest that routine maternal cardiovascular assessment in mid-gestation would not offer incremental information for the prediction of PE.

Conflict of interest: None

Sources of Funding: The study was supported by a grant from the Fetal Medicine Foundation (Charity No: 1037116). The ultrasound machines for fetal echocardiography and the software for speckle tracking analysis were provided free-of-charge by Canon Medical Systems Europe BV, Zoetermeer, The Netherlands. The reagents and equipment for the measurement of serum placental growth factor and soluble fms-like tyrosine kinase-1 were provided by Thermo Fisher Scientific. These bodies had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

REFERENCES

1. Simmons LA, Gillin AG, Jeremy RW. Structural and functional changes in left ventricle during normotensive and preeclamptic pregnancy. *Am J Physiol Heart Circ Physiol* 2002; **283:** H1627-H1633.

2. Bamfo JE, Kametas NA, Chambers JB, Nicolaides KH. Maternal cardiac function in normotensive and preeclamptic intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2008; **32:** 682-686.

3. Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. *Hypertension* 2011; **57:** 85–93.

4. Solanki R, Maitra N. Echocardiographic assessment of cardiovascular hemodynamics in preeclampsia. J Obstet Gynaecol India 2011; 61: 519-522.

5. Melchiorre K, Sutherland GR, Watt-Coote I, Liberati M, Thilaganathan B, Severe myocardial impairment and chamber dysfunction in preterm preeclampsia. *Hypertens Pregnancy* 2012; **31:** 454-471.

6. Shahul S, Rhee J, Hacker MR, Gulati G, Mitchell JD, Hess P, Mahmood F, Arany Z, Rana S, Talmor D. Subclinical left ventricular dysfunction in preeclamptic women with preserved left ventricular ejection fraction: a 2D speckle-tracking imaging study. *Circ Cardiovasc Imaging* 2012; **5:** 734–739.

7. Tyldum EV, Backe B, Støylen A, Slørdahl SA. Maternal left ventricular and endothelial functions in preeclampsia. *Acta Obstet Gynecol Scand* 2012; **91:** 566-573.

8. Cong J, Fan T, Yang X, Shen J, Cheng G, Zhang Z. Maternal cardiac remodeling and dysfunction in preeclampsia: a three-dimensional speckle-tracking echocardiography study. *Int J Cardiovasc Imaging* 2015; **31:** 1361-1368.

9. Guirguis GF, Aziz MM, Boccia Liang C, Williams SF, Apuzzio JJ, Bilinski R, Mornan AJ, Shah LP. Is preeclampsia an independent predictor of diastolic dysfunction? A retrospective cohort study. *Pregnancy Hypertens* 2015; **5:** 359-361.

10. Çağlar FN, Ozde C, Bostancı E, Çağlar İM, Çiftçi S, Unğan İ, Demir B, Karakaya O. Assessment of right heart function in preeclampsia by echocardiography. *Pregnancy Hypertens* 2016; **6:** 89-94.

11. Muthyala T, Mehrotra S, Sikka P, Suri V. Maternal Cardiac Diastolic Dysfunction by Doppler Echocardiography in Women with Preeclampsia. *J Clin Diagn Res* 2016; **10:** QC01-3.

12. Vaddamani S, Keepanasseril A, Pillai AA, Kumar B. Maternal cardiovascular dysfunction in women with early onset preeclampsia and late onset preeclampsia: A cross-sectional study. *Pregnancy Hypertens* 2017; **10:** 247-250.

13. Buddeberg BS, Sharma R, O'Driscoll JM, Kaelin Agten A, Khalil A, Thilaganathan B. Cardiac maladaptation in term pregnancies with preeclampsia. *Pregnancy Hypertens* 2018; **13:** 198-203.

14. Vasapollo B, Novelli GP, Valensise H. Total vascular resistance and left ventricular morphology as screening tools for complications in pregnancy. *Hypertension* 2008; **51:** 1020-1026.

15. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension* 2008; **52:** 873-880.

16. Melchiorre K, Sutherland GR, Sharma R, Nanni M, Thilaganathan B. Mid-gestational maternal cardiovascular profile in preterm and term pre-eclampsia; a prospective study. *BJOG* 2013; **120:** 496-504.

17. Shahul S, Ramadan H, Mueller A, Shahul S, Ramadan H, Mueller A, Nizamuddin J, Nasim R, Lopes Perdigao J, Chinthala S, Tung A, Rana S. Abnormal mid-trimester cardiac strain in women with chronic hypertension predates superimposed preeclampsia. *Pregnancy Hypertens* 2017; **10:** 251-255.

18. Gallo DM, Wright D, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19-24 weeks' gestation. *Am J Obstet Gynecol* 2016; **214**: 619.e1-619.e17.

19. Litwinska M, Wright D, Efeturk T, Ceccacci I, Nicolaides KH. Proposed clinical management of pregnancies after combined screening for pre-eclampsia at 19-24 weeks' gestation. *Ultrasound Obstet Gynecol* 2017; **50**: 367-372.

20. Litwinska M, Syngelaki A, Wright A, Wright D, Nicolaides KH. Management of pregnancies after combined screening for pre-eclampsia at 19-24 weeks' gestation. *Ultrasound Obstet Gynecol* 2018; **52**: 365-372.

21. Wright D, Wright A, Nicolaides KH. The competing risk approach for prediction of preeclampsia. *Am J Obstet Gynecol* 2020; **223:** 12-23.e7.

22. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. *Fetal Diagn Ther* 2012; **31**: 42-48.

23. Papageorghiou AT, Yu CKH, Bindra R, Pandis G and Nicolaides KN. Multicentre screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; **18**: 441-449.

24. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *Br J Obstet Gynaecol* 1975; **82**: 702-710.

25. Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34-38.

26. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016; **17:** 1321-1360.

27. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16:** 233-271.

28. Garcia-Gonzalez C, Abdel-Azim S, Galeva S, Georgiopoulos G, Nicolaides KH, Charakida M. Placental function and fetal weight are associated with maternal hemodynamic indices in uncomplicated pregnancies at 35-37 weeks gestation. *Am J Obstet Gynecol* 2020; **222:** 604.e1-604.e10.

29. American College of Obstetricians and Gynecologists, and the Task Force on Hypertension in Pregnancy. Hypertension in Pregnancy. *Obstet Gynecol* 2013; **122:** 1122-1131.

30. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol* 2015; **213:** 62 e1-10.

31. R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

32. Sapantzoglou I, Wright A, Gallardo Arozena M, Vallenas Campos R, Charakida M, Nicolaides KH. Ophthalmic artery Doppler in combination with other biomarkers in the prediction of preeclampsia at 19-23 weeks' gestation. *Ultrasound Obstet Gynecol* 2020;

33. Mc Donald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J* 2008; **156:** 918-930.

34. Garcia-Gonzalez C, Georgiopoulos G, Azim SA, Macaya F, Kametas N, Nihoyannopoulos P, Nicolaides KH, Charakida M. Maternal cardiac assessment at 35 to 37 weeks improves prediction of development of preeclampsia. *Hypertension* 2020; **76:** 514-522.

FIGURE LEGENDS

Figure 1. Box and whisker plots of cardiovascular indices unadjusted for maternal characteristics and medical history in pregnancies that subsequently developed PE (grey boxes), compared to those that remained normotensive (white boxes). There was a significantly higher median E/e', myocardial performance index, global longitudinal systolic strain and peripheral vascular resistance and lower left ventricular ejection fraction.

Figure 2. Relationship between MoM or delta values of cardiovascular indices in pregnancies that developed preeclampsia with gestational age at delivery.

Table 1. Maternal and pregnancy characteristics of the study population.

Characteristic	Unaffected (n=2,713)	Preeclampsia (n=76)	p-value
Maternal age (years)	33.3 (30.3, 36.5)	34.95 (30.0, 38.1)	0.414
Maternal weight (kg)	70.6 (63.4, 79.5)	74.5 (65.8, 86.7)	0.005
Maternal height (cm)	166 (162, 171)	165 (158, 171)	0.310
Body mass index (kg/m^2)	25.4 (23.0, 28.6)	27.3 (24.0, 32.0)	0.0009
Gestational age (weeks)	21.4 (21.0, 21.6)	21.3 (20.7, 21.6)	0.039
Racial origin			0.069
White	2,013 (74.2)	47 (61.8)	
Black	367 (13.5)	19 (25.0)	
South Asian	153 (5.6)	5 (6.6)	
East Asian	80 (3.0)	2 (2.6)	
Mixed	100 (3.7)	3 (4.0)	
Medical history			
Chronic hypertension	39 (1.4)	7 (9.2)	<0.0001
Diabetes mellitus	27 (1.0)	3 (3.9)	0.003
SLE/APS	5 (0.2)	0 (0.0)	
Smoker	37 (1.4)	0 (0.0)	0.605
Family history of PE	79 (2.9)	9 (11.8)	<0.0001
Method of conception			<0.0001
Natural	2,534 (93.4)	60 (79.0)	
In vitro fertilization	163 (6.0)	15 (19.7)	
Ovulation drugs	16 (0.6)	1 (1.3)	
Parity			<0.0001
Nulliparous	1,452 (53.5)	54 (71.1)	
Parous no previous PE	1,219 (44.9)	12 (15.8)	
Parous previous PE	42 (1.6)	10 (13.2)	
Birth weight of last neonate (g)	3377 (3028, 3700)	3300 (2400, 3900)	0.999
Interpregnancy interval (years)	2.4 (1.5, 4.3)	4.5 (1.8, 7.4)	0.058

Values given as median (interquartile range) or n (%)
PE = preeclampsia; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome.

Comparisons between outcome groups were by chi-square or Fisher exact test for categorical variables and Mann Whitney-U test for continuous variables.

Table 2. Effects of variables from maternal characteristics and medical history with significant contribution to the measurement of cardiovascular index.

	Estimate (95% CI)	p-value
LEFT VENTRICULAR DIASTOLIC FUNCTION		
E/A		
Intercept	2.790675 (1.654357, 3.926993)	<0.0001
Heart rate	-0.010327 (-0.014345, -0.006308)	<0.0001
(Heart rate)^2	0.000032 (0.000005, 0.000058)	0.021
Gestational age in days - 77	-0.051885 (-0.083210, -0.020559)	0.001
(Gestational age in days - 77)^2	0.000364 (0.000145, 0.000582)	0.001
Maternal weight in Kg	-0.001448 (-0.001829, -0.001067)	<0.0001
Maternal age in years - 35	-0.004226 (-0.005300, -0.003151)	<0.0001
Black racial origin	-0.018369 (-0.034075, -0.002662)	0.022
Systemic lupus erythematosus / APS	-0.118407 (-0.223383, -0.013430)	0.027
E/e'		
Intercept	0.789408 (0.784960, 0.793855)	<0.0001
Maternal weight in Kg - 69	0.001124 (0.000847, 0.001400)	<0.0001
Maternal age in years - 35	0.001808 (0.001054, 0.002562)	<0.0001
Maternal height in cm - 164	-0.001715 (-0.002247, -0.001182)	<0.0001
Black racial origin	0.019391 (0.008511, 0.030271)	0.0005
Conception by *in vitro* fertilization	-0.017777 (-0.032650, -0.002905)	0.019
Chronic hypertension	0.067537 (0.038327, 0.096748)	<0.0001
Diabetes mellitus type 2	0.043540 (0.000355, 0.086725)	0.048
LEFT VENTRICULAR SYSTOLIC FUNCTION		
Myocardial performance index		
Intercept	-0.533018 (-0.555381, -0.510654)	<0.0001
Heart rate	0.001263 (0.000951, 0.001575)	<0.0001
Maternal weight in Kg - 69	0.000937 (0.000698, 0.001175)	<0.0001
Black racial origin	0.011121 (0.001309, 0.020933)	0.026
Chronic hypertension	0.035814 (0.009837, 0.061791)	0.007
Global longitudinal systolic strain		
Intercept	-33.059916 (-35.916979, -30.202853)	<0.0001
Gestational age in days - 77	0.024115 (0.002859, 0.045372)	0.026
Heart rate	0.142205 (0.078245, 0.206165)	<0.0001
(Heart rate)^2	-0.000617 (-0.001044, -0.000190)	0.005
Maternal weight in Kg - 69	0.036008 (0.029516, 0.042500)	<0.0001
Maternal age in years - 35	-0.024189 (-0.041406, -0.006973)	0.006
Maternal height in cm - 164	-0.015941 (-0.028539, -0.003344)	0.013

Black origin	0.871139 (0.616676, 1.125602)	<0.0001
Chronic hypertension	1.408360 (0.737571, 2.079148)	<0.0001
Left ventricular ejection fraction		
Intercept	81.268375 (74.129102, 88.407647)	<0.0001
Heart rate	-0.279365 (-0.439304, -0.119427)	0.0006
(Heart rate)^2	0.001392 (0.000324, 0.002460)	0.011
Gestational age in days - 77	-0.064615 (-0.117715, -0.011515)	0.017
Maternal weight in Kg - 69	0.061881 (0.040257, 0.083504)	<0.0001
(Maternal weight in Kg - 69)^2	-0.001330 (-0.001939, -0.000720)	<0.0001
Maternal age in years - 35	0.133324 (0.090438, 0.176210)	<0.0001
Black origin	-0.764053 (-1.396437, -0.131669)	0.018
Ovulation drugs	-2.980351 (-5.656762, -0.303941)	0.029
HEMODYNAMIC PARAMETERS		
Peripheral vascular resistance		
Intercept	3.312758 (3.290392, 3.335124)	<0.0001
Preeclampsia	0.035997 (0.016409, 0.055584)	0.0003
Gestational hypertension	0.039381 (0.018380, 0.060382)	0.0002
Heart rate	-0.003077 (-0.003383, -0.002772)	<0.0001
Maternal weight in Kg - 69	-0.000512 (-0.000752, -0.000271)	<0.0001
Maternal height in cm - 164	-0.001380 (-0.001856, -0.000904)	<0.0001
South Asian racial origin	0.025632 (0.011952, 0.039312)	0.0002
Chronic hypertension	0.049100 (0.023985, 0.074215)	0.0001
Parous with no previous preeclampsia	-0.013433 (-0.019770, -0.007095)	<0.0001
Left ventricular cardiac output		
Intercept	0.456573 (0.435771, 0.477374)	<0.0001
Heart rate	0.003951 (0.003666, 0.004237)	<0.0001
Maternal weight in Kg - 69	0.001702 (0.001381, 0.002024)	<0.0001
(Maternal weight in Kg - 69)^2	-0.000017 (-0.000025, -0.000008)	0.0001
Maternal height in cm - 164	0.001136 (0.000688, 0.001585)	<0.0001
Black racial origin	-0.012557 (-0.021426, -0.003687)	0.006
East Asian racial origin	-0.026037 (-0.043510, -0.008564)	0.004
South Asian racial origin	-0.037652 (-0.050434, -0.024869)	<0.0001
Mixed racial origin	-0.016718 (-0.032003, -0.001434)	0.032
Parous with no previous preeclampsia	0.006418 (0.000581, 0.012255)	0.031
STRUCTURAL MARKER		
Left ventricular mass indexed for body surface area		
Intercept	-8.205128 (-81.742582, 65.332326)	0.827
Heart rate	-0.128910 (-0.161989, -0.095832)	<0.0001
Gestational age in days - 77	2.125523 (0.075700, 4.175346)	0.042

(Gestational age in days - 77)^2	-0.014441 (-0.028720, -0.000161)	0.048
Maternal age in years - 35	0.136145 (0.065950, 0.206340)	0.0002
Maternal height in cm - 164	-0.117786 (-0.167195, -0.068377)	<0.0001
South Asian racial origin	-4.189198 (-5.679308, -2.699088)	<0.0001
SLE/APS	-7.940230 (-14.774432, -1.106027)	0.023
Chronic hypertension	7.279874 (4.574364, 9.985384)	<0.0001

Table 3. Correlations, with 95% confidence intervals, between cardiovascular indices and mean arterial pressure, uterine artery pulsatility index, placental growth factor and soluble fms-like tyrosine kinase-1.

Cardiovascular index	MAP MoM	UtA-PI MoM	PlGF MoM	sFLT-1 MoM
E/A MoM	-0.0547 (-0.0913, -0.0179)	0.0322 (-0.0047, 0.0689)	0.0110 (-0.0259, 0.0478)	-0.0020 (-0.0389, 0.0348)
E/e' MoM	0.0363 (-0.0006, 0.0730)	0.0116 (-0.0253, 0.0484)	-0.0070 (-0.0439, 0.0298)	-0.0204 (-0.0572, 0.0165)
Myocardial performance index MoM	0.0639 (0.0271, 0.1005)	-0.0032 (-0.0400, 0.0337)	-0.0163 (-0.0531, 0.0206)	-0.0192 (-0.0560, 0.0177)
Global longitudinal systolic strain Delta	0.0601 (0.0233, 0.0967)	0.0103 (-0.0266, 0.0471)	-0.0244 (-0.0612, 0.0125)	0.0011 (-0.0358, 0.0379)
Left ventricular ejection fraction Delta	-0.0403 (-0.0770, -0.0034)	0.0097 (-0.0272, 0.0465)	0.0183 (-0.0186, 0.0551)	-0.0362 (-0.0730, 0.0006)
Peripheral vascular resistance MoM	0.3717 (0.3395, 0.4030)	0.0073 (-0.0295, 0.0442)	-0.0453 (-0.0821, -0.0085)	-0.0139 (-0.0507, 0.0230)
Left ventricular cardiac output* MoM	-0.0046 (-0.0414, 0.0323)	-0.0200 (-0.0569, 0.0168)	0.0214 (-0.0155, 0.0582)	0.0093 (-0.0276, 0.0461)
Left ventricular mass Delta	0.0687 (0.0319, 0.1053)	-0.0363 (-0.0730, 0.0006)	0.0073 (-0.0295, 0.0442)	0.0267 (-0.0102, 0.0635)

* indexed for body surface area

MAP = mean arterial pressure, UtA-PI = uterine artery pulsatility index, PlGF = placental growth factor, sFLT-1 = soluble fms-like tyrosine kinase-1

Table 4. Detection rate of delivery with pre-eclampsia at <37 weeks' gestation and all pre-eclampsia, at 10% false positive rate, after screening at 19-23 weeks' gestation by maternal factors and mean arterial pressure, uterine artery pulsatility index, serum placental growth factor and soluble fms-like tyrosine kinase-1, with and without the addition of peripheral vascular resistance.

Method of screening	Pre-eclampsia <37 weeks		All pre-eclampsia	
	n/N	DR (95% CI) %	n/N	DR (95% CI) %
Maternal factors	10/18	55.6 (30.8 - 78.5)	29/76	38.2 (27.2 - 50.0)
+ PVR	10/18	55.6 (30.8 - 78.5)	29/76	38.2 (27.2 - 50.0)
+ MAP	11/18	61.1 (35.7 - 82.7)	40/76	52.6 (40.8 - 64.2)
+ MAP + PVR	10/18	55.6 (30.8 - 78.5)	35/76	46.1 (34.5 - 57.9)
+ UtA-PI	11/18	61.1 (35.7 - 82.7)	31/76	40.8 (29.6 - 52.7)
+ UtA-PI + PVR	11/18	61.1 (35.7 - 82.7)	31/76	40.8 (29.6 - 52.7)
+ PlGF	15/18	83.3 (58.6 - 96.4)	39/76	51.3 (39.6 - 63.0)
+ PlGF + PVR	15/18	83.3 (58.6 - 96.4)	39/76	51.3 (39.6 - 63.0)
+ sFLT-1	11/18	61.1 (35.7 - 82.7)	29/76	38.2 (27.2 - 50.0)
+ sFLT-1 + PVR	11/18	61.1 (35.7 - 82.7)	29/76	38.2 (27.2 - 50.0)

PVR = peripheral vascular resistance, MAP = mean arterial pressure, UtA-PI = uterine artery pulsatility index, PlGF = placental growth factor, sFLT-1 = soluble fms-like tyrosine kinase-1

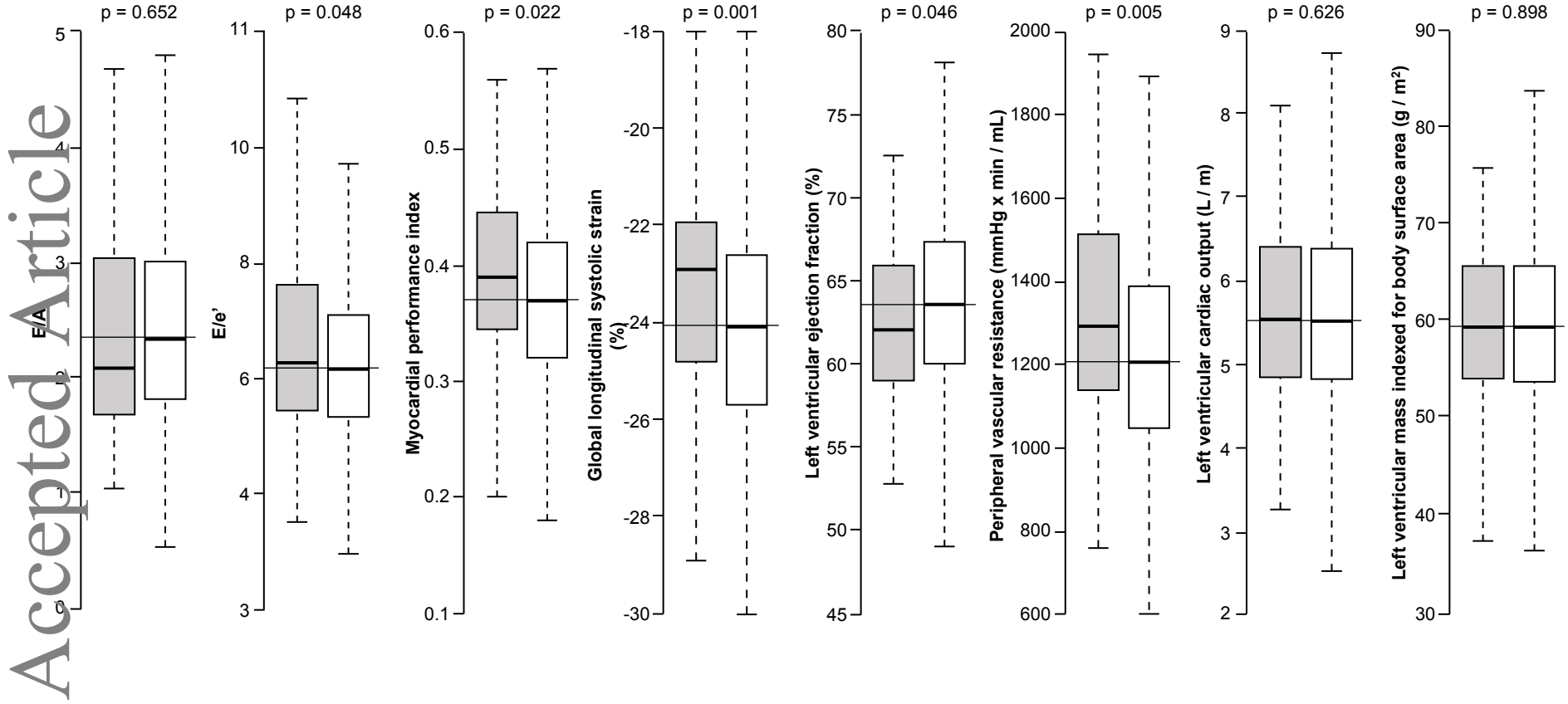

Figure 1

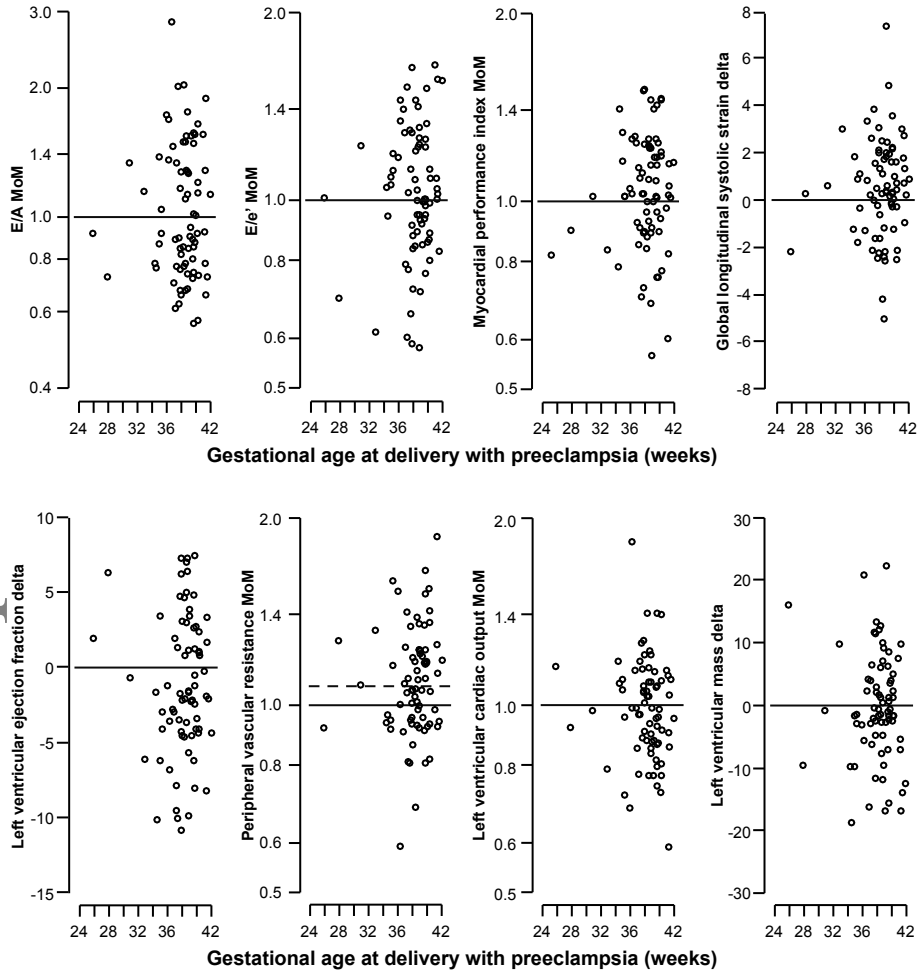

Figure 2