Postnatal cardiovascular morbidity following preterm pre-eclampsia: an observational study.

Laura Ormesher[1,2], Suzanne Higson[3], Matthew Luckie[3], Stephen A Roberts[4], Heather Glossop[2], Andrew Trafford[5], Elizabeth Cottrell[1], Edward D Johnstone[1,2], Jenny E Myers[1,2]

1. Maternal and Fetal Health Research Centre, Division of Developmental Biology and Medicine, University of Manchester, UK
2. St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester, UK
3. Manchester Heart Centre, Manchester University NHS Foundation Trust, Manchester, UK
4. Centre for Biostatistics, University of Manchester, UK
5. Division of Cardiovascular Sciences, University of Manchester, UK

Corresponding author: Dr Laura Ormesher
Maternal and Fetal Health Research Centre, St Mary's Hospital, Manchester University NHS Foundation Trust, Oxford Road, Manchester M13 9WL.
0161 701 6960 / laura.ormesher@manchester.ac.uk

Short title: Cardiac morbidity following preterm pre-eclampsia

Abstract

Objective

Explore the nature of postnatal cardiovascular morbidity following pregnancies complicated by preterm pre-eclampsia and identify associations between pregnancy characteristics and postnatal cardiovascular function.

Design

Observational sub-study of a single-centre feasibility randomised double-blind placebo-controlled trial.

Setting

Tertiary maternity hospital, UK.

Population

Women with preterm pre-eclampsia, delivering <37 weeks.

Methods

Eligible women underwent echocardiography, arteriography and blood pressure monitoring <3 days, 6 weeks and 6 months postpartum. Correlations between pregnancy and cardiovascular characteristics were assessed using Spearman's correlation.

Main Outcome Measure

Prevalence of cardiovascular dysfunction and remodelling 6 months following preterm pre-eclampsia.

Results

Forty-four women completed the study. At 6 months, 27 (61%) had diastolic dysfunction, 33 (75%) had raised total vascular resistance (TVR) and 18 (41%) had left ventricular remodelling. Sixteen (46%) women had *de novo* hypertension by 6 months and only 2 (5%) women had a completely normal echocardiogram. Echocardiography did not change significantly from 6 weeks to 6 months. Earlier gestation at delivery and lower birthweight centile were associated with worse 6-month diastolic dysfunction (E/E': rho=-0.39, p=0.001 & rho=-0.42, p=0.005) and TVR (rho=-0.34, p=0.02 & rho=-0.37, p=0.01).

Conclusions

Preterm pre-eclampsia is associated with persistent cardiovascular morbidity 6 months postpartum in the majority of women. These cardiovascular changes have significant implications to long-term cardiovascular health. The graded severity of diastolic dysfunction and TVR with worsening pre-eclampsia phenotype suggests a dose-effect. However, the mechanistic link remains uncertain.

Funding

Medical Research Council (MR/R001693/1).

Registration

https://www.clinicaltrials.gov; NCT03466333.

Key words

Pre-eclampsia: clinical research; radiological imaging: ultrasound; medical disorders in pregnancy.

Tweetable abstract

Preterm pre-eclampsia is associated with persistent cardiovascular morbidity 6 months postpartum.

Introduction

Pre-eclampsia complicates 3-5% of pregnancies[1] and is associated with significant perinatal and maternal morbidity and mortality[2]. A contributory factor in the disease pathophysiology is failure of maternal cardiovascular adaptation to pregnancy[3,4] and subsequent impairment to placental development[5]. Furthermore, there is abundant observational data linking pre-eclampsia with postnatal maternal cardiovascular dysfunction[6–9] and long-term cardiovascular risk[10,11,20,12–19]. This association is independent of mutual risk factors, including age, obesity and pre-existing hypertension[11].

Future maternal cardiovascular risk in women with preeclampsia is graded in terms of severity and recurrence of pre-eclampsia; i.e. presence of severe features[14,21–25], prematurity[10,13,19,26], fetal growth restriction (FGR)[16,23] or pre-eclampsia recurrence[15,21] are associated with particularly increased cardiovascular risk in epidemiological studies. In addition, women with gestational hypertension alone[14], remain at increased risk of cardiovascular disease, compared to the women with previous normotensive pregnancies. Compared with normotensive term pregnancies, preterm pre-eclampsia is associated with 2- to 8-fold and 3- to 8-fold risks of cardiovascular events[10,11,17,19] and deaths[10,13,16], respectively.

This study focuses on women with preterm pre-eclampsia, requiring delivery before 37 weeks' gestation, which affects 0.6-0.8% of pregnancies in the United Kingdom (UK)[27]. The aim of this study was to explore the nature of postnatal cardiovascular dysfunction and remodelling following pregnancies complicated by preterm pre-eclampsia and identify any

associations between pregnancy characteristics and cardiovascular function at 6 months. Identification of the association between preeclampsia characteristics and cardiovascular function at 6 months could aid appropriate counselling for affected women and potentially identify subgroups who could benefit from intervention targeted in the postnatal period.

Methods

Study design

This was a sub-study of PICk-UP (Postnatal enalapril to Improve Cardiovascular fUnction following Preterm pre-eclampsia), which was a single-centre feasibility randomised double-blind placebo-controlled trial (RCT), carried out at St Mary's Hospital, Manchester, UK[28]. Eligible women who declined participation to the interventional trial or were recruited following completion of recruitment to the interventional trial were invited to participate in the observational study. For the purpose of this report, data were combined from the observational study and the placebo arm of the RCT. The RCT and observational study were funded by the Medical Research Council and prospectively registered at clinicaltrials.gov (NCT03466333).

Inclusion and exclusion criteria

Postnatal women with preterm pre-eclampsia (requiring delivery before 37 weeks) were consented to take part in the studies within 3 days of delivery. Pre-eclampsia was defined as new or worsening hypertension with proteinuria and/or evidence of organ dysfunction and/or placental dysfunction, as per the International Society of the Study of Hypertension in Pregnancy (ISSHP) guidelines[29]. Abnormal angiogenic markers (sFlt:PLGF > 85) in combination with new/worsening hypertension were also included in the definition[30]. Women had to be able to give informed consent and be 18 years or older. Women with

known cardiac disease were excluded. In the interventional trial, additional exclusion criteria included current use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers or contraindication to ACE inhibitors (including renal artery stenosis).

Study procedures

Women underwent three research visits, at baseline (within 3 days of delivery), 6 weeks and 6 months postpartum, as illustrated in Figure S1. Cardiovascular investigations included peripheral blood pressure (Alere Microlife BP monitors, Cheshire, UK); echocardiography (VIVID S70, GE Healthcare, UK) to assess haemodynamics, left ventricular remodelling and systolic and diastolic dysfunction; arteriography to assess arterial stiffness and blood pressure, and venepuncture for cardiovascular and placental biomarkers (including high sensitivity troponin [HScTnT], N-terminal pro-brain natriuretic peptide [NTproBNP], placental growth factor [PlGF] and soluble fms-like tyrosine kinase-1 [sFlt]). All study procedures have been described in detail previously[28].

Aims

The primary aim was to describe the natural history of postnatal cardiovascular dysfunction following preterm pre-eclampsia, using longitudinal data from three postnatal timepoints. Secondary aims included correlation of i) pregnancy and pre-eclampsia phenotypes, ii) maternal characteristics and iii) biomarkers with maternal cardiovascular phenotype at 6 months postpartum. Additionally, we aimed to assess the correlation between the above factors and change in cardiovascular parameters over time.

Echocardiography-defined classifications

Abnormal echocardiography values were pre-defined, as per the main RCT[28]. Systolic dysfunction was determined using a combination of Simpson's BiPlane measurement of the

left ventricle (left ventricular ejection fraction [LVEF] <55%)[31], 2-dimensional speckle-tracking (global longitudinal strain [GLS] >-18%)[32] and tissue Doppler at the mitral annulus (S' <0.064 m/s)[31]. Diastolic dysfunction was defined using the British Society of Echocardiography (BSE) clinical flow chart[33], using discrete cut-offs for pulse wave Doppler measures (E/A and deceleration time) and age-adjusted reference ranges for tissue Doppler (E') and left atrial volume. Given the relatively young age of this cohort, inclusion of criteria using age-adjusted reference ranges was considered most suitable. Concentric left ventricular remodelling was defined as relative wall thickness (RWT) > 0.42 and hypertrophy was defined as left ventricular mass index (LVMi) >95g/m^2[34]. Raised total vascular resistance (TVR) was defined as >1200 dyne.s^{-1}cm^{-5}[35].

Statistical analysis

All statistical analyses were performed using Stata v14.2. Skewness of continuous variables was assessed using the Jarque-Bera skewness-kurtosis test and histograms. Continuous variables were presented as mean (standard deviation) and median (interquartile range), as appropriate. Categorical variables were presented as counts (percentage). Continuous variables were compared between timepoints and groups using paired t-test, following log-transformation if required. Correlations between continuous variables were assessed using Spearman's correlation coefficient. The relationship between baseline variables and change in cardiovascular parameters (from baseline to 6 months) was assessed using Spearman's correlation coefficient. Correlations between baseline placental biomarkers and cardiovascular parameters were assessed using a linear regression model with number of days postpartum as a covariate. Intermodality agreement was assessed using intraclass correlation coefficients (ICC) and linear regression analyses. This was an exploratory study exploring natural history with no prior data to inform the correlation between baseline and

6-month cardiovascular parameters and therefore no a priori sample size calculation was possible.

Results

Forty women were recruited to the observational study and 30 were recruited to the placebo arm of the PICk-UP trial from September 2018 to February 2020. Follow-up for the observational study was affected by the Covid-19 global pandemic which prevented 4 of the 6-week and 8 of the 6-month follow-up visits. One woman was excluded due to inaccurate diagnosis of pre-eclampsia, which meant that 44/69 women completed the study to 6 months (Figure 1).

Baseline characteristics

Cohort baseline characteristics are summarised in Table 1. Twelve (17%) women had underlying hypertension and 20 (29%) women had an underlying medical condition, including hypertension, renal disease, diabetes, previous thromboembolism and antiphospholipid syndrome. The majority of women were delivered due to maternal indications (n=37, 54%) and 23 (33%) women required delivery before 34 weeks' gestation. Forty-four (73%) women had pre-eclampsia with severe features. Twenty-six (33%) babies had adverse perinatal outcomes (Table 2).

Change in cardiovascular parameters over time

At 6 months, diastolic and systolic dysfunction affected 61% and 7% of women, respectively (Table 3). When using age-adjusted reference ranges for all diastolic functional measures[33] including E/A and deceleration time, diastolic dysfunction affected 32 (73%) women. Prevalence of diastolic dysfunction is significantly impacted by the classification used. For example, the 2016 American Society of Echocardiography and European Association of

Cardiovascular Imaging guideline does not use age-adjusted reference ranges, in contrast with BSE[33,36]. For this reason, prevalence of diastolic dysfunction using the different definitions is summarised in Table S1. TVR was raised in 75% and 41% of women had persistent left ventricular remodelling at 6 months (Table 3). Of those with no pre-existing hypertension (diagnosed before or during the first half of pregnancy), 6/35 (17%) required antihypertensives and 16/35 (46%) had a diagnosis of hypertension, defined by clinic BP≥140/90[37] and/or need for antihypertensives, at 6 months. There was considerable overlap in echocardiography abnormalities and only 2 (5%) women had a completely normal echocardiogram at 6 months (Figure 2). Details of echocardiography measures at each timepoint are summarised in Table 4. The majority of echocardiography parameters (including E/E' and left ventricular remodelling) significantly improved from baseline to 6 weeks; however there was no significant change in any echocardiography parameter from 6 weeks to 6 months. TVR increased from baseline to 6 weeks and systolic function (LVEF, GLS and S') did not significantly change over time (Table 4).

Six (8%) women had raised HScTnT (16-18ng/L) or NTproBNP (468-1259pg/mL) at baseline. All cardiac biomarkers had normalised by 6 weeks postpartum. The change in placental and cardiovascular biomarker levels over time is summarised in Table S2. Baseline placental biomarkers were significantly influenced by the number of days postpartum (PlGF: linear regression coefficient -21.5pg/mL/day (95% CI -38.6 - -4.5), p=0.01 and sFlt: linear regression coefficient -1145.6pg/mL/day (95% CI –1717.8 - -573.4), p<0.001). All biomarkers declined from baseline to 6 weeks; only sFlt continued to decline from 6 weeks to 6 months (88 (17) versus 80.0 (14), p=0.01; Table S2)

Table S3 summarises the change in blood pressure (BP) and arterial stiffness over time. There was no significant change in pulse wave velocity, aortic or brachial augmentation index from baseline to 6 months. Central and peripheral systolic BP (sBP) declined significantly from baseline to 6 months postpartum; however, there was no significant change in diastolic BP (dBP). With the exception of arteriography-measured sBP (which increased), there was no significant difference in arteriography measures or peripheral BP between 6 weeks and 6 months.

Relationship between pre-eclampsia and cardiovascular phenotypes

The presence of pre-existing hypertension did not influence systolic or diastolic function at 6 months (GLS: -19.96 (2.34) versus -20.88 (1.55), p=0.16; E/E': 7.93 (1.13) versus 7.43 (1.59), p=0.38). However, women with pre-existing hypertension had worse left ventricular remodelling (LVMi: 81.91 (21.24) versus 63.06 (10.70), p=0.001) and higher TVR (2034 (795) versus 1567 (323), p=0.009) at 6 months, compared to those without (Figure 3). Pre-eclampsia with severe features, as defined by the National Institute for Health and Care Excellence (NICE)[38] was not significantly associated with any 6-month echocardiography parameter (Figure 3).

Earlier gestations at pre-eclampsia diagnosis and delivery were associated with worse diastolic dysfunction (E/E': rho=-0.34, p=0.03 and rho=-0.39, p=0.001, respectively) and TVR (rho=-0.42, p=0.004 and rho=-0.34, p=0.02, respectively) at 6 months (Figure 4). Prolonged pre-eclampsia duration (up to 48 days) was associated with increased TVR, but not E/E' at 6 months (rho=0.36, p=0.02 and rho=0.20, p=0.20, respectively; Figure S2). On the other hand, prolonged pre-eclampsia duration was associated with reduced improvement in remodelling and a trend toward reduced improvement in diastolic dysfunction from

baseline to 6 months (LVMi: rho=-0.33, p=0.03; E/E': rho=-0.27, p= 0.08). Lower birthweight centile was also associated with worse diastolic dysfunction and TVR at 6 months (E/E': rho=-0.42, p=0.005 and TVR: rho=-0.37, p=0.01; Figure 4). There was no correlation between birthweight centile, gestation at diagnosis or delivery, and LV remodelling (LVMi and RWT) or systolic function (LVEF, GLS and S').

Relationship between biomarkers and cardiovascular phenotype

There were no correlations between baseline PlGF , sFlt or sFlt:PlGF and 6-week or 6-month echocardiography measures. Baseline sFlt:PlGF (log-transformed) only correlated with baseline TVR (adjusted coefficient: 128.00 dyne.$s^{-1}cm^{-5}$ (95% CI 10.17 - 247.83), p=0.03). This correlation was not replicated with baseline sFlt (adjusted coefficient: 54.61 (95% CI -75.46 - 184.69), p=0.41) or PlGF (adjusted coefficient: -116.12 (95% CI --261.11 - 28.87), p=0.12) and it did not persist at 6 weeks or 6 months (6-week adjusted coefficient: 84.97 dyne.$s^{-1}cm^{-5}$ (95% CI -66.67 - 236.61), p=0.27; 6-month adjusted coefficient: -78.00 (95% CI -277.57 - 121.57), p=0.43). Baseline NTproBNP (log-transformed) correlated with baseline E/E' (coefficient: 0.42 (95% CI 0.04 - 0.81), p=0.03) and 6-week TVR (coefficient: 106.59 dyne.$s^{-1}cm^{-5}$ (95% CI 6.05 - 207.13), p=0.04). Again, these associations did not retain statistical significance at 6 months (E/E' coefficient: 0.12 (95% CI -0.28 - 0.53), p=0.55; TVR coefficient: 51.04 dyne.$s^{-1}cm^{-5}$ (95% CI -79.25 - 181.33), p=0.43). Baseline HScTnT (log-transformed) correlated with baseline RWT (coefficient: 0.05 (95% CI 0.01 - 0.08), p=0.009) but this did not remain statistically significant at 6 weeks or 6 months (6-week coefficient: 0.04 (95% CI 0.00 - 0.08), p=0.06; 6-month coefficient: 0.02 (95% CI -0.02 - 0.06), p=0.31). Lastly, there was a modest association between baseline HScTnT (log-transformed) and 6-week GLS (coefficient: 0.96% (95% CI 0.07 - 1.85), p=0.04), which did not persist at 6 months

(coefficient: 0.41% (95% CI -0.40 - 1.21), p=0.31). These associations are illustrated in Figure S3.

Intermodality correlations

There was good to excellent agreement between Alere Microlife and TensioClinic arteriography in the measurement of sBP (ICC 0.87 (95% CI 0.83 – 0.91)) and dBP (ICC 0.92 (95% CI 0.89 – 0.95). Although there was a significant linear relationship between E/A (measured by pulse wave Doppler at the mitral inlet) and E/A strain rate (measured using speckle-tracking software; coefficient: 1.48 (95% CI 1.15 - 1.81, p < 0.001, Figure S4), absolute values showed poor agreement (ICC 0.56 (95% CI 0.40 – 0.68). In terms of different echocardiographic measures of systolic dysfunction, LVEF had a significant linear correlation with GLS (coefficient: -0.82 (95% CI -1.07 - -0.56), p<0.001, Figure S4).

Discussion

Main findings

In this prospective longitudinal study, we demonstrated a high prevalence of persistent cardiovascular abnormalities at 6 months postpartum, following preterm pre-eclampsia. Only two women (5%) had a completely normal echocardiogram at 6 months, with the majority of abnormalities attributable to raised TVR, diastolic dysfunction and left ventricular remodelling. In those who were not known to be hypertensive before 20 weeks' gestation, 17% women required antihypertensives at 6 months and nearly half (46%) had *de novo* hypertension at 6 months postpartum.

Correlations between pre-eclampsia and cardiovascular phenotypes were investigated in order to explore a potential causal relationship between the two. None of the standard

metrics defining maternal disease severity[39] correlated with 6-month postpartum cardiovascular phenotype. On the other hand, other markers of severity (including lower birthweight centile and earlier gestation at diagnosis / delivery) were associated with worse diastolic dysfunction (E/E') and TVR at 6 months. Longer duration of pre-eclampsia prior to delivery was also associated with higher 6-month TVR, indicating a potential dose-effect.

Strengths and limitations

To our knowledge, this is the largest longitudinal dataset describing postnatal cardiovascular structure and function following preterm pre-eclampsia. This study describes a multi-ethnic cohort with a severe pre-eclampsia phenotype (77% had severe maternal features and 44% had FGR < 3rd centile). A significant limitation of the study is the modest sample size, which was exacerbated by non-completion due to the concurrent pandemic. Due to the lack of pre-pregnancy echocardiography data, it is not possible to confirm direction of causality between pre-eclampsia and cardiovascular dysfunction. Additionally, the 3 day window for the baseline visit potentially limited our ability to relate baseline placental biomarkers with 6-month cardiovascular outcomes, given the rapid decline in sFlt and PlGF in the first 48 hours postpartum[40].

Interpretation

In the absence of any cardioprotective intervention, women with preterm pre-eclampsia have a high prevalence of cardiovascular abnormalities 6 months postpartum. This is consistent with previous studies[7,8]. Diastolic dysfunction, as defined by the BSE[33], affected 61% women, compared with 8% two years following a normotensive pregnancy[7]. These findings have significant implications to long-term cardiovascular risk[41–43]. Ladeiras-Lopes et al.'s meta-analysis[41] demonstrated a 3.53-fold increase in cardiovascular events or death associated with a diagnosis of diastolic dysfunction within 11 years. Diastolic dysfunction

precedes and independently predicts left ventricular remodelling following myocardial infarction[44,45]. It is therefore likely that the prevalence of adverse remodelling will increase over time, despite already affecting 41% of the cohort. Remodelling is an independent predictor of cardiovascular events (hazard ratio 1.70 (95% CI 1.34-2.16) within 10 years)[46] and overt hypertension[7,47], which is the leading modifiable risk factor for all-cause mortality[48]. Hypertension frequently requires lifelong therapy[49], thereby constituting an important outcome to clinicians and patients alike. Hypertension affected 57% of the total cohort at 6 months. This is higher than Melchiorre et al.'s finding of 40% hypertension prevalence at 2 years postpartum[7], potentially reflecting a different population or attenuation of hypertension over time.

The association between pre-eclampsia phenotype (birthweight centile and gestation at diagnosis / delivery) and diastolic function, suggests a potential dose-effect. Although the lack of pre-pregnancy echocardiography data limits our ability to confirm direction of causation, the lack of relationship between pre-pregnancy cardiovascular risk factors (including hypertension) and postnatal diastolic dysfunction function points away from pre-eclampsia being solely a consequence of cardiovascular dysfunction. On the other hand, there was an association between remodelling and pre-existing hypertension, highlighting the possibility that women with pre-existing hypertension had some degree of pre-pregnancy cardiovascular changes. One could speculate that if pre-eclampsia is a cause of cardiovascular dysfunction, duration of exposure should correlate with severity of cardiovascular dysfunction; this was only observed for TVR in this cohort. This could be attributable to insufficient power or inaccurate timing of pre-eclampsia diagnosis.

Preterm pre-eclampsia is a heterogenous condition defined by clinical manifestations of endothelial dysfunction (proteinuria and hypertension)[29] rather than the underlying pathology. It therefore likely comprises more than one pathological process, as supported by Leavey et al.'s placental microarray studies[50,51] in which three subclasses of pre-eclampsia were identified. These subclasses were defined as reflecting maternal maladaptation, placental insufficiency or immunological overactivation[50,51]. It is plausible that the direction of causality differs between subclasses, with a more consequential role of pre-eclampsia on cardiovascular dysfunction in the maternal maladaptation subclass and a more causal role in the latter two subclasses. This potential multifactorial and multidirectional relationship is supported by the inconsistencies observed in the correlations between maternal / pregnancy characteristics and 6-month echocardiography in this cohort.

The mechanism by which pre-eclampsia might be a cause of cardiovascular dysfunction is not known. Shahul et al.[52] proposed a mechanistic link through sFlt. In non-pregnant animals, sFlt administration causes deficient cardiac microvasculature and subsequent hypoxia-induced cardiac remodelling[53]. sFlt levels are predictive of heart failure[54–56] and have been positively linked with arterial aging[57]. In Shahul et al.'s[52] prospective study of hypertensive disorders of pregnancy, third trimester sFlt levels independently correlated with GLS. This correlation persisted after adjusting for age and other medical confounders[52], demonstrating a plausible aetiological role of sFlt in pre-eclampsia-related cardiovascular dysfunction. Previous studies have reported an inverse relationship between sFlt levels and both gestation at delivery and birthweight centile[58,59]. Both of these outcomes were associated with worse diastolic dysfunction in our cohort, supporting a potential role of sFlt in the development of cardiovascular dysfunction. However, in our cohort an association

between baseline postnatal sFlt and 6-month cardiovascular parameters was not demonstrated. This could represent divergent mechanistic pathways in different subclasses of pre-eclampsia, absence of causality or data limitations (due to variable postnatal timing and insufficient sample size).

The absence of relationship between baseline HScTnT and NTproBNP and 6-month cardiovascular parameters suggests that early postnatal cardiovascular biomarkers are unlikely to be effective in identifying women at particular risk of persistent cardiovascular morbidity. In order to relate our findings to long-term cardiovascular function, all participants have been consented to follow-up in the future. However, given the moderate overall sample size (n=99, including the enalapril, placebo and observational arms), correlation of early postnatal cardiovascular dysfunction with long-term cardiovascular events will not be possible with this cohort alone. Our findings justify larger prospective cohort and/or intervention studies to investigate the significance of postnatal cardiovascular dysfunction.

This study clearly demonstrates, in line with previous work, that women with preterm pre-eclampsia will benefit from appropriate counselling, lifestyle changes and therapeutic interventions to improve cardiovascular function, remodelling and long-term risk. The intention for future pregnancy needs to be considered in the design of future interventions. Cardioprotective therapies need to either be safe in pregnancy or have short-term efficacy, to allow conception following treatment cessation. The interventional arm of PICk-UP[28] demonstrated an improvement in diastolic function and remodelling with 6 months' treatment with enalapril compared with placebo. Enalapril is safe in breastfeeding

mothers[38,60], but contraindicated in pregnancy[61]. Further work is needed to determine whether 6 months' treatment is sufficient to confer long-term reduction in cardiovascular risk.

Conclusion

Preterm pre-eclampsia is associated with persistent diastolic dysfunction, left ventricular remodelling and hypertension at 6 months postpartum. These have significant implications to long-term cardiovascular health. The graded severity of diastolic dysfunction with worsening prematurity and FGR suggests a dose-effect. However, the mechanism linking pre-eclampsia and cardiovascular dysfunction remains uncertain and requires further investigation.

Acknowledgements

The authors would like to acknowledge the following contributions: the research midwives and assistants (Clare Waters, Christine Hughes and Jess Morecroft), Clinical Research Fellows (Lynne Warrander and Alice Dempsey), Pankaj Gupta and Prashanth Patel from the University Hospitals of Leicester Pathology Services, who carried out the urinary HP LC-MS/MS; Gillian Tranter from Trafford General Hospital who measured sFlt:PlGF levels; protocol reviewers (Lucy Chappell, Basky Thilaganathan and Paul Leeson); the Manchester University NHS Foundation Trust Sponsor, and the independent Trial Steering Committee: Bernadette Brennan, Lynne Webster, Fergus McCarthy, Jamie Kitt, Rose McGarty and Stephen Roberts.

Disclosure of interests

None.

Contribution to authorship

LO carried out the study, with assistance from HG and SH, supervised by JM. LO, SH, ML, SR, HG, AT, EC, EJ and JM were responsible for writing / reviewing the paper. LO was responsible for data analysis, supervised by SR.

Details of ethics approval

Study approvals were received from Haydock Research Ethics Committee (18/NW/0253; 15/6/2018), Health Research Authority and Medicines and Healthcare products Regulatory Agency.

Funding

This study was funded by the Medical Research Council (MR/R001693/1). Roche provided the Diagnostics Cobas e601 system kits for measurement of sFlt:PlGF levels.

References

1. Hernández-Díaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: Prospective cohort study. *BMJ*. 2009;339(7711):34. doi:10.1136/bmj.b2255
2. Knight M, Nair M, Tuffnell D, ShakespeareJ, Kenyon S KJ (Eds.)onbehalfo. M-U. Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2013–15. *Oxford Natl Perinat Epidemiol Unit, Univ Oxford 2017*.
3. Melchiorre K, Sutherland G, Sharma R, Nanni M, Thilaganathan B. Mid-gestational maternal cardiovascular profile in preterm and term pre-eclampsia: A prospective study. *BJOG An Int J Obstet Gynaecol*. 2013;120(4):496-504. doi:10.1111/1471-0528.12068
4. Plasencia W, Maiz N, Poon L, Yu C, Nicolaides KH. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks and 21 + 0 to 24 + 6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol*. 2008;32(2):138-146. doi:10.1002/uog.5402
5. Thilaganathan B. Cardiovascular origins of Preeclampsia. *Pregnancy Hypertens An Int J Women's Cardiovasc Heal*. 2017;7:62-63. doi:10.1016/j.preghy.2016.10.022
6. Evans CS, Gooch L, Flotta D, et al. Cardiovascular system during the postpartum state in women with a history of preeclampsia. *Hypertension*. 2011;58(1):57-62. doi:10.1161/HYPERTENSIONAHA.111.173278
7. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension*. 2011;58(4):709-715. doi:10.1161/HYPERTENSIONAHA.111.176537

8. Fcog PSP, Priya SA, Adeyemo AO, et al. Cardiac diastolic function after recovery from pre-eclampsia. *Cardiovasc J Afr*. 2018;29(1):26-31. doi:10.5830/CVJA-2017-031

9. 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. doi:10.1016/j.preghy.2017.10.010

10. Leon LJ, McCarthy FP, Direk K, et al. Preeclampsia and Cardiovascular Disease in a Large UK Pregnancy Cohort of Linked Electronic Health Records: A CALIBER Study. *Circulation*. 2019;140(13):1050-1060. doi:10.1161/CIRCULATIONAHA.118.038080

11. Bellamy L, Casas J-P, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *Bmj*. 2007;335(7627):974-974. doi:10.1136/bmj.39335.385301.BE

12. McDonald 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(5):918-930. doi:10.1016/j.ahj.2008.06.042

13. Irgens HU, Reisæter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: Population based cohort study. *Br Med J*. 2001;323(7323):1213-1217. doi:10.1136/bmj.323.7323.1213

14. Grandi SM, Filion KB, Yoon S, et al. Cardiovascular Disease-Related Morbidity and Mortality in Women with a History of Pregnancy Complications: Systematic Review and Meta-Analysis. *Circulation*. 2019;139(8):1069-1079. doi:10.1161/CIRCULATIONAHA.118.036748

15. Auger N, Fraser WD, Schnitzer M, Leduc L, Healy-Profitós J, Paradis G. Recurrent pre-eclampsia and subsequent cardiovascular risk. *Heart*. 2017;103(3):235-243.

doi:10.1136/heartjnl-2016-309671

16. Riise HKR, Sulo G, Tell GS, et al. Incident coronary heart disease after Preeclampsia: Role of reduced fetal growth, preterm delivery, and parity. *J Am Heart Assoc*. 2017;6(3). doi:10.1161/JAHA.116.004158

17. Arnott C, Nelson M, AlfaroRamirez M, et al. Maternal cardiovascular risk after hypertensive disorder of pregnancy. *Heart*. 2020;0:1-7. doi:doi:10.1136/heartjnl-2020-316541

18. Wikström AK, Haglund B, Olovsson M, Lindeberg SN. The risk of maternal ischaemic heart disease after gestational hypertensive disease. *BJOG An Int J Obstet Gynaecol*. 2005;112(11):1486-1491. doi:10.1111/j.1471-0528.2005.00733.x

19. Smith GCS, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: A retrospective cohort study of 129 290 births. *Lancet*. 2001;357(9273):2002-2006. doi:10.1016/S0140-6736(00)05112-6

20. Wu R, Wang T, Gu R, et al. Hypertensive Disorders of Pregnancy and Risk of Cardiovascular Disease-Related Morbidity and Mortality: A Systematic Review and Meta-Analysis. *Cardiology*. 2020;145(10):633-647. doi:10.1159/000508036

21. Wikström AK, Haglund B, Olovsson M, Lindeberg SN. The risk of maternal ischaemic heart disease after gestational hypertensive disease. *BJOG*. 2005;112(11):1486-1491. doi:10.1111/j.1471-0528.2005.00733.x

22. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension*. 2009;53(6):944-951. doi:10.1161/HYPERTENSIONAHA.109.130765

23. Lykke JA, Langhoff-Roos J, Lockwood CJ, Triche EW, Paidas MJ. Mortality of mothers

from cardiovascular and non-cardiovascular causes following pregnancy complications in first delivery. *Paediatr Perinat Epidemiol*. 2010;24(4):323-330. doi:10.1111/j.1365-3016.2010.01120.x

24. McDonald 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(5):918-930. doi:10.1016/j.ahj.2008.06.042

25. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: Systematic review and meta-analysis. *Br Med J*. 2007;335(7627):974-977. doi:10.1136/bmj.39335.385301.BE

26. arnott clare, nelson M, alfaro ramirez M, et al. Maternal cardiovascular risk after hypertensive disorder of pregnancy Cardiac risk factors and prevention. *Heart*. 2020;0:1-7. doi:10.1136/heartjnl-2020-316541

27. Rolnik DL, Wright D, Poon LCY, et al. ASPRE trial: performance of screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol*. 2017;50(4):492-495. doi:10.1002/uog.18816

28. Ormesher L, Higson S, Luckie M, et al. Postnatal Enalapril to Improve Cardiovascular Function Following Preterm Preeclampsia (PICk-UP):: A Randomized Double-Blind Placebo-Controlled Feasibility Trial. *Hypertens (Dallas, Tex 1979)*. October 2020:HYPERTENSIONAHA12015875. doi:10.1161/HYPERTENSIONAHA.120.15875

29. Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. 2018;13:291-310. doi:10.1016/j.preghy.2018.05.004

30. 1 Recommendations | PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3

test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio) | Guidance | NICE.

31. Harkness A, Ring L, Augustine DX, Oxborough D, Robinson S, Sharma V. Normal reference intervals for cardiac dimensions and function for use in echocardiographic practice: a guideline from the British Society of Echocardiography. *Echo Res Pract*. 2020;7(1):G1-G18. doi:10.1530/ERP-19-0050

32. Yang H, Wright L, Negishi T, Negishi K, Liu J, Marwick TH. Research to Practice: Assessment of Left Ventricular Global Longitudinal Strain for Surveillance of Cancer Chemotherapeutic-Related Cardiac Dysfunction. *JACC Cardiovasc Imaging*. 2018;11(8):1196-1201. doi:10.1016/j.jcmg.2018.07.005

33. Matthew T, Steeds R, Jones R, et al. A Guideline Protocol for the Echocardiographic assessment of Diastolic Function – A Protocol of the British Society of Echocardiography,. https://www.bsecho.org/common/Uploaded files/Education/Protocols and guidelines/Diastolic dysfunction.pdf. Published 2013. Accessed June 1, 2020.

34. Lang RM, Badano LP, Victor MA, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1-39.e14. doi:10.1016/j.echo.2014.10.003

35. Timokhina E, Kuzmina T, Strizhakov A, Pitskhelauri E, Ignatko I, Belousova V. Maternal Cardiac Function after Normal Delivery, Preeclampsia, and Eclampsia: A Prospective Study. *J Pregnancy*. 2019;2019:9795765. doi:10.1155/2019/9795765

36. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of LeftVentricular Diastolic Function by Echocardiography:An Update from the American

Society ofEchocardiography and the European Associationof Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277-314.

37. Overview | Hypertension in adults: diagnosis and management | Guidance | NICE.

38. The National Institute for Health and Care Excellence (NICE). Recommendations - Hypertension in pregnancy: diagnosis and management. NICE guideline [NG133].

39. National Institute for Health and Clinical Excellenc. Hypertension in pregnancy: diagnosis and management. 2011;(August 2010). https://www.nice.org.uk/guidance/cg107/resources/hypertension-in-pregnancy-diagnosis-and-management-pdf-35109334009285.

40. Saleh L, van den Meiracker AH, Geensen R, et al. Soluble fms-like tyrosine kinase-1 and placental growth factor kinetics during and after pregnancy in women with suspected or confirmed pre-eclampsia. *Ultrasound Obstet Gynecol*. 2018;51(6):751-757. doi:10.1002/uog.17547

41. Ladeiras-Lopes R, Araújo M, Sampaio F, Leite-Moreira A, Fontes-Carvalho R. The impact of diastolic dysfunction as a predictor of cardiovascular events: A systematic review and meta-analysis. *Rev Port Cardiol (English Ed*. 2019;38(11):789-804. doi:10.1016/j.repce.2019.03.012

42. Modin D, Biering-Sørensen SR, Mogelvang R, Landler N, Jensen JS, Biering-Sørensen T. Prognostic value of echocardiography in hypertensive versus nonhypertensive participants from the general population. *Hypertension*. 2018;71(4):742-751. doi:10.1161/HYPERTENSIONAHA.117.10674

43. Medina−Lezama J, Narvaez−Guerra O, Herrera−Enriquez K, et al. Hemodynamic Patterns Identified by Impedance Cardiography Predict Mortality in the General Population: The PREVENCION Study. *J Am Heart Assoc*. 2018;7(18):e009259-e009259.

doi:10.1161/JAHA.118.009259

44. Flachskampf FA. Raised Diastolic Pressure as an Early Predictor of Left Ventricular Remodeling After Infarction: Should Echocardiography or Natriuretic Peptides Be Used for Assessment? *Rev Española Cardiol (English Ed*. 2010;63(9):1009-1012. doi:10.1016/s1885-5857(10)70202-4

45. López Haldón J, Quero MF, Mancha F, et al. Value of NT-ProBNP level and echocardiographic parameters in st-segment elevation myocardial infarction treated by primary angioplasty: Relationships between these variables and their usefulness as predictors of ventricular remodeling. *Rev Esp Cardiol*. 2010;63(9):1019-1027. doi:10.1016/S0300-8932(10)70223-2

46. Pierdomenico SD, Di Nicola M, Pierdomenico AM, Lapenna D, Cuccurullo F. Cardiovascular risk in subjects with left ventricular concentric remodeling at baseline examination: A meta-analysis. *J Hum Hypertens*. 2011;25(10):585-591. doi:10.1038/jhh.2011.24

47. Kenchaiah S, Pfeffer MA. Cardiac remodeling in systemic hypertension. *Med Clin North Am*. 2004;88(1):115-130. doi:10.1016/S0025-7125(03)00168-8

48. Stanaway JD, Afshin A, Gakidou E, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1923-1994. doi:10.1016/S0140-6736(18)32225-6

49. Nelson MR, Reid CM, Krum H, Ryan P, Wing LMH, McNeil JJ. Short-term predictors of maintenance of normotension after withdrawal of antihypertensive drugs in the Second Australian National Blood Pressure Study (ANBP2). *Am J Hypertens*.

2003;16(1):39-45. doi:10.1016/S0895-7061(02)03143-6

50. Leavey K, Bainbridge SA, Cox BJ. Large Scale Aggregate Microarray Analysis Reveals Three Distinct Molecular Subclasses of Human Preeclampsia. Gleicher N, ed. *PLoS One*. 2015;10(2):e0116508. doi:10.1371/journal.pone.0116508

51. Leavey K, Benton SJ, Grynspan D, Kingdom JC, Bainbridge SA, Cox BJ. Unsupervised Placental Gene Expression Profiling Identifies Clinically Relevant Subclasses of Human Preeclampsia. *Hypertension*. 2016;68(1):137-147. doi:10.1161/HYPERTENSIONAHA.116.07293

52. Shahul S, Medvedofsky D, Wenger JB, et al. Circulating antiangiogenic factors and myocardial dysfunction in hypertensive disorders of pregnancy. *Hypertension*. 2016;67(6):1273-1280. doi:10.1161/HYPERTENSIONAHA.116.07252

53. Di Marco GS, Kentrup D, Reuter S, et al. Soluble Flt-1 links microvascular disease with heart failure in CKD. *Basic Res Cardiol*. 2015;110(3). doi:10.1007/s00395-015-0487-4

54. Gruson D, Hermans MP, Ferracin B, Ahn SA, Rousseau MF. Sflt-1 in heart failure: relation with disease severity and biomarkers. *Scand J Clin Lab Invest*. 2016. doi:10.1080/00365513.2016.1190863

55. Kameda R, Yamaoka-Tojo M, Makino A, et al. Soluble Fms-like Tyrosine Kinase 1 Is a Novel Predictor of Brain Natriuretic Peptide Elevation. *Int Heart J*. 2013. doi:10.1536/ihj.54.133

56. Onoue K, Uemura S, Takeda Y, et al. Usefulness of Soluble Fms-like Tyrosine Kinase-1 as a Biomarker of Acute Severe Heart Failure in Patients With Acute Myocardial Infarction. *Am J Cardiol*. 2009. doi:10.1016/j.amjcard.2009.07.016

57. Akhter T, Wikström AK, Larsson M, Larsson A, Wikström G, Naessen T. Association between angiogenic factors and signs of arterial aging in women with pre-eclampsia.

Ultrasound Obstet Gynecol. 2017;50(1):93-99. doi:10.1002/uog.15981

58. Rana S, Schnettler WT, Powe C, et al. Clinical characterization and outcomes of preeclampsia with normal angiogenic profile. *Hypertens Pregnancy*. 2013;32(2):189-201. doi:10.3109/10641955.2013.784788

59. Bian X, Biswas A, Huang X, et al. Short-Term Prediction of Adverse Outcomes Using the sFlt-1 (Soluble fms-Like Tyrosine Kinase 1)/PlGF (Placental Growth Factor) Ratio in Asian Women with Suspected Preeclampsia. *Hypertension*. 2019;74(1):164-172. doi:10.1161/HYPERTENSIONAHA.119.12760

60. Redman CWG, Kelly JG, Cooper WD. The excretion of enalapril and enalaprilat in human breast milk. *Eur J Clin Pharmacol*. 1990;38(1):99. doi:10.1007/BF00314815

61. Steffensen FH, Nielsen GL, Sorensen HT, Olesen C, Olsen J. Pregnancy outcome with ACE-inhibitor use in early pregnancy [10]. *Lancet*. 1998;351(9102):596. doi:10.1016/S0140-6736(05)78584-6

Figure Legends

Figure 1: Consort diagram.

Figure 2: Venn diagram of 6-month echocardiographic abnormalities.
TVR, total vascular resistance; LV, left ventricular.

Figure 3: Influence of pre-existing hypertension and pre-eclampsia severity on change in echocardiography over time.
Box plots demonstrating the influence of pre-existing hypertension on A. E/E'; B. global longitudinal strain; C. left ventricular mass index; D. total vascular resistance; and the influence of severe features of pre-eclampsia on E. E/E'; F. global longitudinal strain; G. left ventricular mass index; H. total vascular resistance.
The line represents median; the box includes 25th to 75th percentile; the whiskers extend to the upper and lower adjacent values and the dots represent outliers.
P values are derived using paired t-test, comparing the two groups at different time-points.
HTN, pre-existing hypertension diagnosed < 20 weeks gestation.

Figure 4: Relationship between gestation at delivery / birthweight centile and cardiovascular function and remodelling 6 months postpartum.
Scatter plots illustrating the relationship between gestation at delivery and A. E/E'; B. global longitudinal strain; C. left ventricular mass index; D. total vascular resistance; and birthweight centile and E. E/E'; F. global longitudinal strain; G. left ventricular mass index; H. total vascular resistance.
Dots represent individual women; linear regression lines were added to aid interpretation.
GLS, global longitudinal strain, LVMi, left ventricular mass index; TVR, total vascular resistance.