Hypertension

Multicenter Cohort Study, With a Nested Randomized Comparison, to Examine the Cardiovascular Impact of Preterm Preeclampsia

Fergus P. McCarthy, Jamie M. O'Driscoll, Paul T. Seed, Anna Placzek, Carolyn Gill, Jenie Sparkes, Lucilla Poston, Mike Marber, Andrew H. Shennan, Basky Thilaganathan, Paul Leeson, Lucy C. Chappell

ABSTRACT: This study evaluated whether planned early delivery would ameliorate cardiovascular dysfunction 6 months postpartum, compared with usual care with expectant management, in women with late preterm preeclampsia. We conducted a mechanistic observational study in women with preterm preeclampsia between 34^{+0} and 36^{+6} weeks' gestation, nested within a randomized controlled trial of planned early delivery versus expectant management (usual care), in 28 maternity hospitals in England and Wales. Women were followed up 6 months postpartum with cardiovascular assessments. The primary outcome was a composite of systolic and diastolic dysfunction (by 2009 and 2016 definitions of diastolic dysfunction). Between April 27, 2016, and November 30, 2018, 623 women were found to be eligible, of whom 420 (67%) were recruited. One hundred thirty-three women were randomized to planned delivery, 137 women were randomized to expectant management within the trial, while 150 women received expectant management outside of the trial. 321 (76.4%) completed their 6 month echocardiography assessment. 10% (31/321) had a left ventricular ejection fraction <55% while 71% (229/321) remained hypertensive. There were no differences in the primary outcome between the 2 randomized groups (planned delivery versus expectant management) using either the 2009 (risk ratio, 1.06 [95% CI, 0.80–1.40]) or 2016 definitions (risk ratio, 0.78 [0.33–1.86]). In conclusion, we demonstrated that late preterm preeclampsia results in persistence of hypertension in the majority and systolic LV dysfunction in 10%, of women 6 months postpartum. Planned early delivery does not affect these outcomes. Preeclampsia is not a self-limiting disease of pregnancy alone. (*Hypertension*. 2021;78:1382–1394. DOI: 10.1161/HYPERTENSIONAHA.121.17171.) • **Data Supplement**

Key Words: cardiovascular diseases ■ dyslipidemia ■ heart disease ■ myocardial ischemia ■ pregnancy

Preeclampsia affects 3% to 5% of pregnancies complicating ≈35 000 pregnancies in the United Kingdom every year. Cardiovascular disease is the leading cause of mortality in women in the United Kingdom.[1] Hypertensive disorders of pregnancy, in particular preterm preeclampsia, have been shown to be associated with an increased risk of developing a wide range of cardiovascular diseases, with increases in incidences observed as soon as one year postpartum.[2] The absolute risk that a woman with preeclampsia would develop a cardiovascular event including hypertension, ischemic heart disease, stroke, or venous thromboembolism aged 50 to 59 is estimated to be 17.8% compared with 8.3% in those without preeclampsia.[3] The American Heart Association now recognizes preeclampsia as an independent risk factor for future cardiovascular disease.[4] The economic burden of cardiovascular disease is substantial; the British Heart Foundation estimated that in 2006 cardiovascular disease cost the National Health Service in the UK £14.3 billion and the UK economy £30.6 billion,[5] and the costs for EU health care systems related to cardiovascular disease is estimated at €110 billion, ≈10% of the total health care expenditure across the EU. With an increasingly ageing population, costs are set to rise further.

Novelty and Significance

What Is New?

- In women with late preterm preeclampsia there is persistent hypertension in 70% and systolic dysfunction in 10% at 6 months postpartum.
- The relatively short delay in those managed expectantly (compared with planned delivery) does not worsen cardiovascular dysfunction at 6 months postpartum.

What Is Relevant?

- Routine delivery does not improve cardiovascular function, and when to deliver should depend on immediate maternal and fetal concerns.

Summary

Preeclampsia should not be considered a self-limiting disease of pregnancy alone and optimal screening and interventional strategies should be explored and evaluated.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
cMyC	cardiac myosin binding protein C
cTnI	cardiac troponin
LV	left ventricle
RR	risk ratio
NT-proBNP	N-terminal pro-B-type natriuretic peptide

To date, only case-control studies and small, single-center cohort studies exist to provide evidence of association between preeclampsia and persistent cardiovascular dysfunction. While some women have preexisting risk factors for preeclampsia that also predispose to cardiovascular disease, for whom preeclampsia may accelerate progression through adding a further stress, in others, preeclampsia occurs with no preexisting factors and may be the first hit in the pathway. There are several possible explanations for the additional cardiovascular insult from preeclampsia. These include subclinical myocardial injury, an increased susceptibility to undiagnosed chronic hypertension and subclinical atherosclerosis and dyslipidemia.[6,7] This proposed research seeks to elucidate the role and extent of the myocardial stress in determining subsequent cardiac dysfunction.

We conducted a multicenter study of women with late preterm preeclampsia to evaluate the development of cardiovascular dysfunction at 6 months postpartum and to examine the cardiovascular effects of planned early delivery (compared with expectant management).

METHODS

Study Design and Participants

A woman was eligible for the study if she was between 34+0 weeks and 36+6 weeks of gestation, had a diagnosis of preeclampsia or superimposed preeclampsia (as defined by the International Society for the Study of Hypertension in Pregnancy),[8] with a singleton or dichorionic diamniotic twin pregnancy and at least one viable fetus, was aged 18 years or older, and was able to give written informed consent. The only exclusion criterion to study participation was if a decision had already been made to deliver within the next 48 hours. There were no substantial changes to the published study design, methods, or outcomes after the start of the trial. The study was approved by the South Central—Hampshire B Research Ethics Committee (no. 13/SC/0645) and was nested within a larger trial of planned delivery versus expectant management in women with late preterm preeclampsia (PHOENIX [Preeclampsia in Hospital: Early Induction or Expectant Management] trial; ISRCTN01879376). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Procedures

Site research teams approached women to confirm eligibility and provided verbal and written information. A trained research midwife or clinician obtained written informed consent. A research team member entered baseline data on a web-based database. All other aspects of pregnancy management were expected to be in accordance with the UK national guidelines at the discretion of the responsible clinician.[9] Usual care in the UK was expectant management until clinical concerns led to delivery or until 37 weeks' gestation was reached. For those women participating in the trial, they were randomly assigned to planned delivery or expectant care in a 1:1 ratio as previously described.[10] The allocation was not masked from women, clinicians, or data collectors due to the nature of the intervention, but the study echocardiographer (J. O'Driscoll) remained masked to randomization group.

Outcomes were recorded on the web-based trial database through case-note review by trained researchers after maternal primary hospital discharge. Women were invited to return to their local hospital at least 6 months following delivery for echocardiography assessment, performed within an 8-week window of the 6-month timepoint. At this assessment, a brief medical history was recorded, blood pressure (BP) assessed, venepuncture, and echocardiography undertaken. Echocardiography was performed locally according to a standard operating procedure circulated by the research team. Echocardiography discs with

anonymized participant information were then sent to the lead echocardiographer (J. O'Driscoll) who analyzed each echocardiogram without knowledge of trial allocation, entering results onto the web-based trial database. Every tenth echo was second read, again masked to trial allocation, by an echocardiographer at the University of Oxford and findings compared by the trial lead cardiologist (P. Leeson) to ensure consistency. When echocardiography assessment demonstrated potentially concerning features that may impact on clinical care, the findings were escalated and reviewed by the lead cardiologist (P. Leeson) and communicated back to the lead clinician at the recruiting site with a recommendation for clinical follow-up.

Outcomes

The primary outcome was a composite of diastolic and systolic function at 6 months' postpartum classified according to the joint recommendation by the American Society of Echocardiography and the European Association of Cardiovascular Imaging as assessed by transthoracic echocardiography with tissue Doppler studies classified originally in 2009[11] (at the time of study inception) and reclassified before study completion in 2016.[12] The primary outcome was chosen to reflect the subclinical myocardial injury in preeclampsia. Additional secondary outcomes included the cardiovascular components of a maternal morbidity composite outcome used in the main trial (severe hypertension post randomization; systolic BP ≥160 mm Hg on at least one occasion), positive inotropic support, infusion of a third parenteral antihypertensive drug, myocardial ischemia or infarction, SpO2 <90%, ≥50% FiO2 for >1 hour, intubation (other than for caesarean section), and pulmonary edema. The composite was chosen as an internationally accepted validated method for describing adverse maternal outcome from preeclampsia.[13]

Echocardiographic Assessment

All participants were studied by standard 2-dimensional and Doppler transthoracic echocardiography at rest. Women were studied in the left lateral decubitus position and data acquired at end expiration from standard parasternal/apical views using a GE Vivid or Philips scanner.[11,14] For each acquisition, 3 cardiac cycles of noncompressed data were stored in cine-loop format and analyzed masked to group allocation by one investigator (J. O'Driscoll), with second read as described above. Cardiac indices were normalized for body surface area, height, and end-diastolic left ventricle (LV) long or short axis lengths, as appropriate.[15–17] Tissue Doppler imaging, strain, and strain rate indices are given as absolute values.

Heart Remodeling

Chamber quantification and left ventricular geometric pattern were estimated using M-mode as previously described.[14] Proximal septal bulging was assessed in the parasternal long-axis and apical 4-chamber views.[18]

Systolic and Diastolic Dysfunction

Global LV diastolic function, estimated left heart filling pressures, and geometry was assessed and graded using standard diagnostic algorithms with the recommended adjustments reflecting the concomitant systolic function and age.[19] LV volumes and ejection fraction were derived from Simpson's modified biplane method from apical 4-chamber and 2-chamber views, and LV systolic dysfunction was defined as ejection fraction <55%.[14] Hemodynamic and systolic cardiac indices were calculated as described before.[20] Longitudinal and radial systolic function were assessed both globally and regionally using color and pulsed tissue Doppler velocity indices and strain rate indices using speckle tracking as previously described.[21–25] Regional peak systolic strain rate index was considered abnormal if it was 2 SDs below the expected mean for age.[26] This abnormality was defined as segmental myocardial impaired contractility. Regional diastolic dysfunction was defined as early to late strain rate ratio <1. This abnormality was defined as segmental impaired myocardial relaxation. Maternal BP was measured following the recommendations of the International Society for the Study of Hypertension in Pregnancy and National High Blood Pressure Education Programme Working Group on High Blood Pressure in Pregnancy.[27]

LV global systo-diastolic dysfunction was defined as LV global diastolic dysfunction in the presence of reduced ejection fraction (<55%). Right heart function and remodeling was assessed using integrating conventional echocardiographic indices and tissue Doppler velocity and deformation indices following published guidelines. The severity of left and right ventricle hypertrophy and dysfunction was graded according to the European Association and American Society of Echocardiography guidelines[11,14] with the following adjustments described by Melchiorre et al[27]: age; increased circulating volume in pregnancy and the acute nature of preeclampsia on a previously normal cardiovascular system. For our primary outcome, diastolic dysfunction was classified as; normal; impaired myocardial relaxation with normal LV end diastolic pressure (GRADE I); pseudonormal filling pattern (GRADE II); and restrictive pattern (GRADE III) as previously described.[23] Findings were also reported according to American Society of Echocardiography/European Association of Cardiovascular Imaging 2016 guidelines, published after study conception and start of recruitment.[28]

Secondary outcomes included systolic BP and diastolic BP at 6 months postpartum, together with the cardiovascular components of a composite maternal morbidity outcome adapted from the fullPIERS prediction of adverse events in preeclampsia study.[13,29]

Myocardial Necrosis Assessment

Participants were also consented to at least 2 blood sampling time points, most commonly performed at initial recruitment and 6 month postpartum assessment. These samples were analyzed for markers of myocardial necrosis/ischemia: high sensitivity cTnI (cardiac troponins), with a sex specific level of >16 ng/L considered elevated.[30] At 6 months postpartum, cMyC (cardiac myosin binding protein C; using Singulex's Single Molecule Counting Technology SMC a quantitative fluorescent sandwich immunoassay technique) and NT-proBNP (N-terminal pro-B-type natriuretic peptide; Alere NT-proBNP for Alinity) were also assessed.

Statistical Analysis

Based on previous studies of postpartum echocardiography, assuming an anticipated incidence of 70% of women with

preterm preeclampsia having evidence of systolic and diastolic dysfunction at 6 months' postpartum,[23,31,32] a sample size of 322 women were needed to detect a 25% relative risk reduction (from 70% to 52.5%; deemed clinically important) in the primary outcome in the planned delivery group compared with those managed expectantly with a 2 sided 5% significance level and 90% power. With 20% loss of women in follow-up the overall target for recruitment was 404 women. The primary analysis for all maternal outcomes was by intention to treat with participants analyzed in the groups to which they were assigned regardless of protocol noncompliances.

Risk ratios (RRs) were estimated for binary outcomes with associated 95% CIs. Simple and multiple regression analysis were used to assess the influence of early pregnancy factors including BP, demographic variables (maternal age, body mass index), pregnancy characteristics (parity, gestation at delivery, gestation at onset, and severity of preeclampsia), on indices of cardiac function and remodeling as detailed above under proposed outcome measures. All of the conventional echocardiographic indices were adjusted for body surface area[14] and all of the tissue Doppler velocity and deformation indices to the end-diastolic left or right ventricle long axis length.[15] Prespecified subgroup analyses were performed for co-primary outcomes in view of changes to definitions of systolic and diastolic dysfunction over the study period. Data analyses and power calculations were performed using STATA/SE version 15.1.

RESULTS

Participants

Between April 27, 2016, and November 30, 2018, 623 women were found to be eligible, of whom 420 (67%) were recruited, across 28 maternity units in England and Wales. Of these 420, 133 women were randomly allocated to planned delivery, 137 women were randomly allocated to expectant management, and 150 received usual care and were managed expectantly as indicated by national guidelines (Figure). In total, 99 (23.6%) of women did not attend their 6-month echocardiography appointment; 321 women (76.4%) completed their 6-month follow-up and had cardiac echocardiography. For the intention-to-treat analysis, data from 100 women in the planned delivery group and 107 women in the expectant management group were included. Follow-up to 6 months postpartum assessments continued until 20 June 2019. Baseline characteristics appeared similar between the 2 groups, with groups well balanced on minimization factors (Table 1). Women who did not attend their 6-month follow-up (n=99) were similar in baseline characteristics compared with women who completed their 6-month follow-up (Tables S1 and S2 in the Data Supplement).

Outcome Data

Of the 321 women within the cohort, 51% (n=164) and 10% (n=31) had the primary outcome using 2009 and 2016 definitions, respectively. Overall, 10% (31/321) of women had an LVEF <55% 6 months postpartum. Using 2009 diastolic dysfunction sub-classification, 9% (n=27) of women had grade I, 40% (n=123) grade II and 1% (n=3) grade III dysfunction. Using the newer 2016 diastolic sub-classification, 18% (n=58), 2% (n=5), and 0% (n=1) had 1, 2, and 3 diastolic dysfunction criteria present, respectively (Table 3). Hypertension prevalence, defined as on antihypertensive treatment or systolic BP >140 mm Hg ±diastolic BP >90 mm Hg 6 months postpartum was present in 71% (n=229) of the cohort. Seventeen percent (n=50) of women had evidence of concentric remodeling and 1% (n=3) had evidence of eccentric remodeling. At 6 months postpartum, 1% (n=4) of women had a high sensitivity cTnI >16 ng/L, 13.2% (n=38) NT-proBNP >100 ng/L, and 0.7 (n=2) had a MyC >87 ng/L.

Nested Randomized Comparison

There were no differences between women in the planned delivery group compared with the expectant management group in the primary outcome using either the 2009 (RR, 1.06 [0.80–1.40]) or 2016 definitions (RR, 0.78 [0.33–1.86]) shown in Table 3. No between group differences were observed in 2009 diastolic dysfunction grade 1 (RR, 1.40 [0.59–3.31]), grade 2 (1.11 [0.78–1.57]), or grade 3 (1.18 [0.08–18.43]) diastolic dysfunction sub-classification nor in 2016 diastolic dysfunction classification. Using the more recent 2016 classification for systolic and diastolic dysfunction, similarly no differences were observed in systolic (RR, 0.76 [0.32–1.80]) or any of the diastolic dysfunction parameters. Hypertension prevalence 6 months postpartum was similar between those managed with planned delivery compared with those expectantly managed (RR, 1.01 [0.85–1.20]). No significant differences were observed in any of the cardiac parameters including geometric and hemodynamic parameters, LV global cardiac parameters, myocardial mechanics, and LV basal or apical parameters between those women with planned delivery compared with those expectantly managed (Table 3 and Table S3). The high prevalence of systolic and diastolic dysfunction or persistent hypertension was not explained by preexisting chronic hypertension as when these women were excluded (n=37, 11%), systolic and diastolic dysfunction was evident in 49.5% and hypertension in 68.7% of women.

Mean time from enrolment to delivery was 2.5 (SD 1.9) days in the planned delivery group compared with 6.8 (5.3) days in the expectant management group. No differences were observed between groups in cardiorespiratory outcomes before discharge from hospital nor in any systolic or diastolic BP measurements (Table 4).

Within the entire cohort (n=321), the only variables affecting development of systolic and diastolic dysfunction 6 months postpartum (2009 definition) was maternal
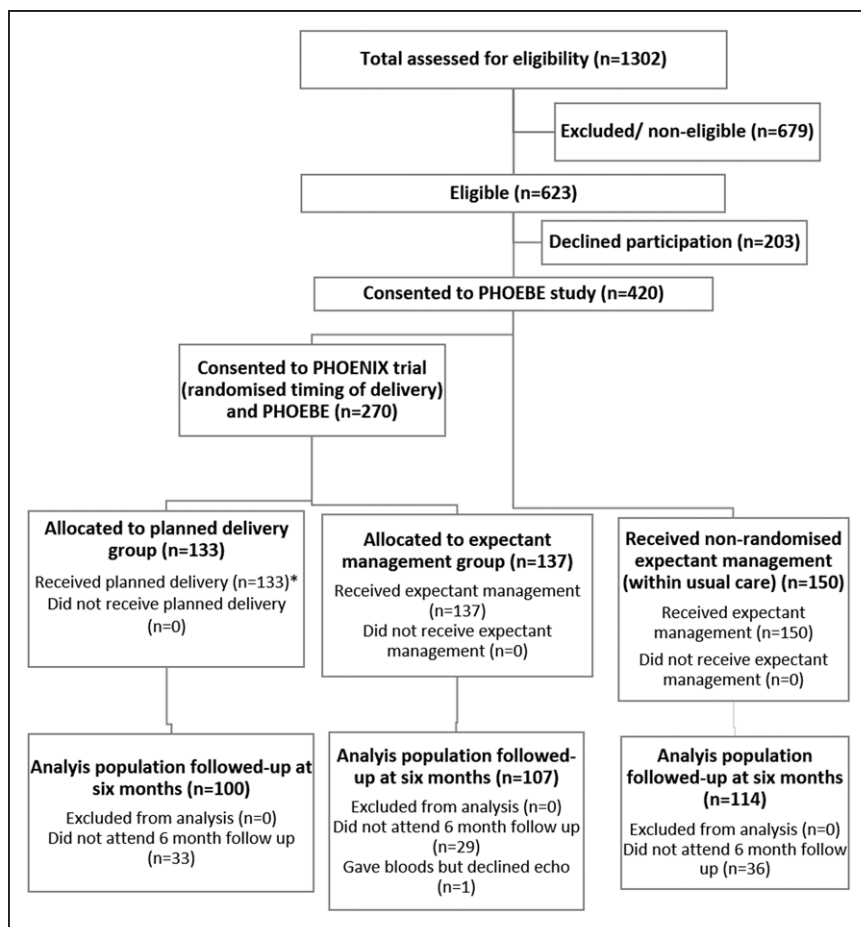
PREECLAMPSIA

Figure. Participant flow chart.

body mass index (adjusted odds ratio, 1.33 [1.12–1.59] per 5 kg/m^2) and maternal age (2.16 [1.44–3.22] per 10 years; Table 5). Interval from study enrolment to delivery was not associated with development of the primary outcome. There were no significant predictor variables for systolic and diastolic dysfunction 6 months postpartum by the updated 2016 definition (Table 5). Inclusion of antenatal high sensitivity cTnI did not alter the results.

Overall, 8% (n=25) women had their clinical echocardiograms escalated by the trial cardiologist with clinical follow-up recommended. These were for a combination of structural (n=8), valvular (n=8), functional (n=9), or combined (n=2) findings. These clinical escalations accounted for 12% of those with the primary outcome (2009 definition), with 88% of those with systolic and diastolic dysfunction not requiring clinically escalation.

DISCUSSION

This large multicenter study highlights the substantial adverse cardiovascular sequelae of preterm preeclampsia; 10% of women with preterm preeclampsia had a LVEF <55%, 71% remained hypertensive, and 49% of women had evidence of impaired diastolic dysfunction of undetermined long-term clinical importance 6 months postpartum. In the nested randomized controlled trial of

women with late preterm preeclampsia, planned delivery did not reduce cardiovascular dysfunction 6 months postpartum. Women in the planned delivery group had a mean shortening of pregnancy from enrolment to delivery of 4 days, but this did not result in decreased hypertension or cardiovascular dysfunction compared with those managed with usual care by expectant management. Only elevated body mass index and higher age at enrolment predicted the occurrence of postpartum systolic and diastolic dysfunction. The short time to delivery in the expectant arm may not have resulted in sufficient time for any longer term cardiovascular insult to be exacerbated, explaining why earlier delivery does not benefit the mother in this outcome.

This large, multicenter trial represents UK contemporaneous management of women with late preterm preeclampsia, subsequently followed up by detailed standardized BP and echocardiography assessment 6 months postpartum. Our cohort sample size (321 women) is considerably larger than any other postpartum cardiovascular study previously performed. We are unaware of any published randomized controlled trials evaluating the impact of timing of delivery on subsequent maternal cardiovascular function. The randomized design allowed us a unique opportunity to explore the impact of earlier delivery on postpartum cardiovascular function.

Table 1. Baseline Maternal Demographic and Pregnancy Characteristics at Trial Entry on All Women Who Had 6 Month Echocardiography (n=321)

Maternal demographic and pregnancy characteristics	Total cohort at 6 months follow-up (n=321)	Planned delivery (n=100)	Expectant management (randomized; (n=107)	Expectant management (usual care non-randomized; n=114)
	N (%)	N (%)	N (%)	N (%)
Age at randomization, y mean (SD)	31.59 (5.87)	30.56 (6.11)	31.26 (6.14)	32.81 (5.18)
Ethnicity				
White	229 (71.3)	76 (76.0)	83 (77.6)	70 (61.4)
Asian	34 (10.6)	13 (13.0)	10 (9.3)	19 (16.7)
Black	42 (13.1)	8 (8.0)	6 (5.6)	20 (17.5)
Mixed	10 (3.1)	2 (2.0)	6 (5.6)	2 (1.8)
Other	6 (1.9)	1 (1.0)	2 (1.9)	3 (2.6)
Deprivation index quintile				
1 (Least deprived)	24 (7.5)	12 (12.0)	7 (6.5)	5 (4.4)
2	51 (15.9)	13 (13.0)	20 (18.7)	18 (15.8)
3	46 (14.3)	14 (14.0)	13 (12.1)	19 (16.7)
4	77 (24.0)	23 (23.0)	28 (26.2)	26 (22.8)
5 (Most deprived)	123 (38.3)	38 (38.0)	39 (36.4)	46 (40.4)
Parity (previous pregnancies ≥24 wk gestation)*				
0	207 (64.5)	64 (64.0)	68 (64)	75 (66)
1	69 (21.5)	24 (24.0)	19 (18)	26 (23)
2	22 (6.9)	4 (4.0)	11 (10)	7 (6)
>2	23 (7.2)	8 (8.0)	9 (8)	6 (5)
Previous caesarean section*	52 (16)	13 (13)	19 (18)	20 (34)
History of preeclampsia	51 (16)	15 (15)	17 16)	19 (17)
BMI at booking, kg/m²				
Mean (SD)	30.2 (7.5)	30.2 (9.0)	30.0 (7.4)	30.3 (6.2)
Smoking status at booking				
Never smoked	257 (80)	81 (81)	79 (73.8)	97 (85.1)
Quit before booking	47 (14.6)	14 (14)	22 (20.6)	11 (9.6)
Smoking at booking	17 (5.3)	5 (5.0)	6 (5.6)	6 (5.3)
Blood pressure 48 h before enrolment, mm Hg				
Systolic (mean, SD)	153 (15)	153 (15)	155 (15)	154 (15)
Diastolic (mean, SD)	95 (10)	96 (10)	96 (11)	94 (9)

BMI indicates body mass index.
*Minimization factors used in the PHOENIX trial to ensure balance at randomization.

Strengths of this study include a sufficiently large sample of women with late preterm preeclampsia from 28 centers throughout the UK completing a detailed 6-month postpartum cardiovascular assessment to describe the burden of cardiovascular disease in this population, linking preeclampsia with longer term cardiovascular disease. The trial was conducted to rigorous standards, with a prespecified protocol without changes. Findings are likely to be generalizable to similar health care settings, because it was undertaken in a large number of maternity units across England and Wales, with diverse representation of women in terms of both demography and disease spectrum. More than half of eligible women approached agreed to participate in the trial, indicating agreement of equipoise in this scenario.

Echocardiograms were performed by multiple echocardiographers throughout the UK and Wales, representative of cardiology units throughout the National Health Service. We have reported all prespecified secondary outcomes, interpreting them cautiously.

Limitations of the trial include a change in the international definition regarding systolic and diastolic dysfunction, such that interpretation of the findings need to be undertaken in the light of the prespecified 2009 definition[11] and the later 2016 definition.[12] Our results reflect systolic and diastolic definitions used first in 2009 and then updated in 2016. We acknowledge that there is an interim group with a LVEF between 50% and 55% and further prospective follow-up would help our understanding of the implications of this impairment in

Table 2. Maternal Clinical Characteristics for Women With Primary Outcome

Maternal clinical characteristics	Total cohort at 6 months follow-up (n=321)	Planned delivery (n=100)	Expectant management (randomized; n=107)	Expectant management (usual care nonrandomized; n=114)
Gestational age at enrolment*, wk				
Median (IQR)	35.6 (34.9–36.1)	35.6 (34.9–36.2)	35.6 (34.7–36.1)	34.4 (34.4–34.4)
34^{+0} to 34^{+6}	106 (33.0)	28 (28.0)	32 (29.9)	46 (40.4)
35^{+0} to 35^{+6}	107 (33.3)	34 (34.0)	38 (35.5)	35 (30.7)
36^{+0} to 36^{+6}	108 (33.6)	38 (38.0)	37 (34.6)	33 (28.9)
Pregnancy type				
Singleton	296 (92.2)	90 (90.0)	96 (89.7)	110 (96)
Twin	25 (7.8)	10 (10.0)	11 (10.3)	4 (4)
Comorbidity at study entry (nonexclusive)				
Preexisting chronic hypertension	37 (11.5)	11 (11.0)	13 (12.1)	13 (11.4)
Preexisting chronic renal disease	3 (0.9)	2 (2.0)	1 (0.9)	0 (0.0)
Prepregnancy diabetes	18 (5.6)	6 (6.0)	3 (2.8)	9 (7.9)
Gestational diabetes	40 (12.5)	14 (14.0)	12 (11.2)	14 (12.3)
Severity of hypertension in 48 h before enrolment, mm Hg†				
Systolic BP mean (SD)	153 (14)	153 (14)	155 (15)	154 (15)
Diastolic BP mean (SD)	95 (10)	96 (10)	96 (10)	94 (9)
≤149 mm Hg (n, %)	124 (38.6)	41 (41.0)	38 (35.5)	45 (39.5)
150–159 mm Hg (n, %)	91 (28.3)	28 (28.0)	34 (31.8)	29 (25.4)
≥160 mm Hg (n, %)	106 (33.0)	31 (31.0)	35 (32.7)	40 (35.1)
Oral antihypertensive medications at study entry				
0 agents	53 (16.5)	21 (21.0)	15 (14.0)	17 (14.9)
1 agent	171 (53.3)	53 (53.0)	59 (55.1)	59 (51.8)
≥2 agents	97 (30.2)	26 26.0)	33 (30.8)	38 (33.3)
Aspirin prescribed during pregnancy	138 (43)	47 (47.0)	42 (39.3)	49 (43.0)
LMWH prescribed at enrolment‡	114 (35.5)	32 (32.0)	38 (35.5)	44 (38.6)
Most recent lab parameters before study entry (mean; SD)				
Protein-creatinine ratio, mg/mol	158 (260)	137 (160)	210 (389)	128 (151)
Hemoglobin, g/L	116 (12)	117 (11)	117 (12)	115 (12)
Platelets, ×10^9/L	217 (75)	228 (101)	207 (52)	217 (65)
Creatinine, µmol/L	61 (14)	58 (14)	61 (12)	63 (15)
Alanine aminotransferase, U/L	26 (36)	25 (28)	22 (34)	30 (43)
Aspartate aminotransferase, U/L	54 (151)	125 (295)	20 (9)	22 (18,31)
Suspected fetal growth restriction	63 (22.6)	22 (27.8)	20 (20.4)	21 (20.6)
Antenatal ultrasound findings				
AC <10th	14 (5.0)	5 (6.3)	4 (4.1)	5 (6.3)
EFW <10th	54 (19.4)	18 (22.8)	19 (19.4)	17 (16.7)
Umbilical artery PI >95th	9 (3.2)	5 (6.3)	1 (1.0)	3 (2.9)
AREDF	2 (0.7)	0 (0.0)	0 (0.0)	2 (2.0)
AFI <5th	5 (1.8)	2 (2.5)	1 (1.0)	2 (2.0)
In-patient at time of trial entry				
Yes	262 (81.6)	75 (75.0)	90 (84.1)	97 (85.1)
Biomarkers at enrolment				
High sensitivity cardiac troponin I median (IQR), ng/L	5 (5–6)	5 (5–5)	5 (5–6)	5 (5–6)
>16 ng/L	12 (3.9)	2 (2.1)	5 (4.9)	5 (4.5)

AC indicates abdominal circumference; AFI, amniotic fluid index; AREDF; absent or reverse end diastolic flow; BP, blood pressure; EFW, estimated fetal weight; IQR, interquartile range; LMWH, low molecular weight heparin; and PI, pulsatility index.

*Minimization factors used to ensure balance at randomization.

†These are summary statistics for the mean of an individual's 2 BP readings.

‡LMWH received at any stage during pregnancy, including as thromboprophylaxis (eg, during hospital admission).

Table 3.   Primary and Secondary Outcomes at 6 Months Postpartum

Primary and secondary outcomes	Total cohort at 6 months follow-up (n=321)	Planned delivery (n=100)	Expectant management (randomized; n=107)	Effect measure, planned vs expectant randomized*	Expectant management (usual care nonrandomized; n=114)
	(%)	(%)	(%)	Risk ratio	
Primary outcome (2009 definition)					
Diastolic and systolic dysfunction postpartum	164 (51)	50/100 (50.0)	50/106 (47.2)	1.06 (0.80–1.40)	64 (56.1)
Systolic dysfunction (yes/no) defined as left ventricular ejection fraction <55%	31 (10)	8/98 (8.2)	11/102 (10.8)	0.76 (0.32–1.80)	12 (10.8)
Diastolic dysfunction sub-classification†		n=96	n=103		
Normal	157 (51)	48 (50.0)	57 (55.3)		52 (46.8)
Impaired myocardial relaxation with normal left ventricular end diastolic pressure (GRADE I)	27 (9)	10 (10.4)	8 (7.8)	1.40 (0.59–3.31)	9 (8.1)
Pseudonormal filling pattern (GRADE II)	123 (40)	37 (38.5)	37 (35.9)	1.11 (0.78–1.57)	49 (44.1)
Restrictive pattern (GRADE III)	3 (1)	1 (1.0)	1 (1.0)	1.18 (0.08 to 18.43)	1 (0.9)
Primary outcome (2016 definition)					
Diastolic and systolic dysfunction postpartum	31 (10)	8/100 (8.2)	11/107 (10.3)	0.78 (0.33 to 1.86)	12 (10.5)
Systolic dysfunction (yes/no) defined as LVEF <55%	31 (10)	8/98 (8.2)	11/102 (10.8)	0.76 (0.32 to 1.80)	12 (10.8)
Diastolic dysfunction (yes/no; >50%/≥3–4 positive)	5 (2)	1/100 (1.0)	0/107 (0.0)	NA	0 (0.0)
Average E/e′ >14	1 (1.0)	1/96 (1.0)	2/99 (2.0)	0.52 (0.05 to 5.59)	0 (0.0)
Septal e′ velocity <7 cm/s or Lateral e′ velocity <10 cm/s	45 (14.0)	15/96 (15.6)	13/103 (12.6)	1.24 (0.62 to 2.46)	17 (15.0)
Tricuspid regurgitant velocity >2.8 m/s	3 (0.9)	1/100 (1.0)	0/107 (0)	…	2 (1.8)
Left atrial volume index (>34 mL/m²)	13 (4.0)	4/98 (4.1)	3/106 (2.8)	1.44 (0.33 to 6.28)	6 (5.4)
Diastolic dysfunction criteria present		n=100	n=107		
0	257 (80.0)	82 (82.0)	90 (84.1)		89 (78.1)
1+	58 (18.0)	16 (16.0)	16 (15.0)	…	23 (20.2)
2+	5 (2.0)	1 (1.0)	1 (0.9)	…	2 (1.8)
≥3+	1 (0)	1 (1.0)	0 (0.0)	…	0 (0.0)
Secondary outcomes					
Hemodynamic		n=100	n=107		
Systolic blood pressure	123 (16)	124 (14)	123 (17)	1.48 (−2.88 to 5.85)	124 (15)
Diastolic blood pressure	76 (13)	76 (13)	75 (13)	−0.59 (−2.96 to 4.14)	76 (13)
Hypertension prevalence (on antihypertensive treatment±or systolic BP >140 ±diastolic BP >90	229 (71)	72 (72)	76 (71)	1.01 (0.85 to 1.20)	81 (71)
Biomarkers at 6 mo follow-up		n=92	n=100		
High sensitivity cTnI >16 ng/L	4 (1.4)	1 (1)	1 (1)	1.09 (0.07 to 17.13)	2 (2.0)
NT-proBNP >100 ng/L	38 (13.2)	10 (11)	15 (15)	0.72 (0.34 to 1.52)	13 (13.1)
MyC >87 ng/L	2 (0.7)	1 (1)	1 (1)	1.10 (0.07 to 17.31)	0 (0.0)

As not every echocardiography parameter was available on each examination, individual denominators are shown where applicable. E/A: <0.73; 0.73–2.33; >2.33; DT: >194 ms; 138–194 ms; <138 ms; and IVRT; >83 ms; 51–83 ms; <51 ms. E/e′ indicates ratio of the peak early mitral inflow velocity (E) over the early diastolic mitral annular velocity (e′); and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Effect measure adjusted for gestational age at study entry.

†Graded I–III using the median value from the classification of the variables E/A (early to late diastole peak transmitral velocity ratio), deceleration time (DT) of E wave and isovolumetric relaxation time (IVRT) into the following groups.

women following pregnancy. We prespecified use of the independent definition of systolic and diastolic dysfunction for this particular patient group as defined by Melchiorre et al, adapted from recommendations of the American Society of Echocardiography/European Association of Cardiovascular Imaging[11] with adjustments for age, the higher circulating volume in pregnancy and the acute nature of preeclampsia in an otherwise previously normal cardiovascular system.[23] Newer nonpregnant specific definitions (American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines 2016)[28] result in lower prevalence of diastolic dysfunction but cardiovascular morbidity is still evident and prevalent. There was a relatively short difference of a median 4 days in those managed with planned delivery compared with women managed expectantly, and it is

Table 4. Secondary Outcomes at Discharge Following Delivery and 6 Month Follow-Up

Secondary outcomes	All recruited women (n=321)	Randomized planned delivery (n=100)	Randomized expectant management (n=108)	Effect measure	Expectant management (usual care nonrandomized; n=114)
Cardiorespiratory outcomes before discharge from hospital					
Positive inotropic support	0 (0.0)	0 (0.0)	0 (0.0)	…	0 (0.0)
Infusion of a third parenteral antihypertensive drug	1 (0.3)	0 (0.0)	0 (0.0)	…	1 (0.9)
Myocardial ischemia or infarction	1 (0.3)	1 (1.0)	0 (0.0)	…	0 (0.0)
SpO_2 <90%	1 (0.3)	1 (1.0)	0 (0.0)	…	0 (0.0)
≥50% FiO_2 for >1 h	0 (0.0)	0 (0.0)	0 (0.0)	…	0 (0.0)
Intubation (other than for caesarean section)	0 (0.0)	0 (0.0)	0 (0.0)	…	0 (0.0)
Pulmonary edema	0 (0.0)	0 (0.0)	0 (0.0)	…	0 (0.0)
Time from enrolment to delivery (mean; SD)	5.7 (5.0)	2.5 (1.9)	6.8 (5.3)	MD, −3.83 (−5.61 to −2.06)	7.6 (5.3)
Gestational age at delivery, wk	36.2 (1.0)	35.9 (0.8)	36.4 (1.0)	MD, −0.55 (−0.80 to −0.29)	36.4 (1.1)
Highest Systolic BP enrolment to delivery (mean; SD)	162 (16)	156 (17)	164 (15)	MD, −8.06 (−12.47 to −3.65)	164 (15)
Highest diastolic BP enrolment to delivery (mean; SD)	96 (11)	94 (10)	97 (13)	MD, −3.16 (−6.27 to −0.04)	98 (10)
Highest systolic BP delivery to hospital discharge (mean; SD)	156 (16)	154 (15)	157 (17)	MD, −3.58 (−7.99 to 0.83)	157 (16)
Highest diastolic BP delivery to hospital discharge (mean; SD)	92 (13)	90 (13)	93 (14)	MD, −3.09 (−6.84 to 0.66)	93 (12)
Birth centile* (median, IQR)	23.8 (8.3,54.3)	29.7 (10.0, 58.0)	17.4 (8.3, 50.6)	MedD, 6.34 (−0.98 to 13.67)	23.7 (5.6, 57.2)
Birth centile <10th centile	105 (30.3)	27 (24.5)	35 (29.7)	RR, 0.83 (0.54 to 1.27)	43 (36.4)
Birth centile <third centile	31 (9)	7 (6.4)	9 (7.6)	RR, 0.83 (0.32−2.16)	15 (12.7)
BMI 6 mo follow-up (n, %)					
Normal	66 (21)	22 (22)	26 (24)	NA	18 (16)
Overweight	94 (29)	30 (30)	31 (29)		33 (29)
Obese	160 (50)	48 (48)	50 (47)		62 (55)
Breast feeding at 6 mo follow-up (yes; n, %)	81 (25)	21 (21)	19 (18)	N/A	41 (36)

BMI indicates body mass index; MD, mean difference; MedD, median difference; and RR, risk ratio.
*Calculated using INTERGROWTH centiles.[51]

likely that this difference may not have been sufficiently long to result in detectable differences in cardiovascular function 6 months postpartum. Approximately, one-third of the women recruited for this study had been eligible for, but declined participation in the main PHOENIX trial, and as a result were included as a nonrandomized expectant management (usual care) group. Results across all groups were very similar. We did not recruit women with a healthy pregnancy, as our primary research question was whether shortening of pregnancy after diagnosis of preterm preeclampsia altered the prevalence of cardiovascular dysfunction 6 months postpartum.

We considered sources of possible bias for our trial. Selection bias into the trial was unlikely due to the randomization process, which included robust allocation sequence concealment such that determining next allocation was not possible. Performance and detection bias were possible because it was not possible to mask participating clinicians or women, nor data collectors because timing of delivery was contained within maternity records where morbidity was recorded. However, the trial echocardiographer was masked to randomization groups and each echocardiogram was, therefore, read independent of knowledge of trial allocation. There was expected attrition to 6 month follow-up of around 20% in both groups, but data completeness of pregnancy outcomes was high (over 99%). The study was originally powered for an analysis of 322 women comprised of 161 women in 2 treatment groups. However, it became apparent that a group of eligible women chose not to consent to the main randomized comparison in the PHOENIX trial but would consent for the observational PHOEBE (also known as PHOENIX-3) study, with all women in this group following usual care, which was expectant management. The aims of the PHOEBE study were primarily to explore the mechanism behind the effect of the intervention (earlier timing of delivery) and to provide an understanding of postpartum cardiovascular dysfunction after preterm preeclampsia. We acknowledge that we were underpowered for examining the effect of the intervention. The primary outcome event rate was also lower than expected by both 2009 and 2016 guidelines. For the

Table 5. Effect of Baseline Characteristics on the Development of Cardiovascular Dysfunction (2009 and 2016 Definition) at 6 Months Postpartum (All 321 Women)

Maternal baseline characteristics	2009 Definition Unadjusted odds ratios (95% CI)	2009 Definition Adjusted odds ratios (95% CI)**	2016 Definition Unadjusted odds ratios (95% CI)
At enrolment variables			
Systolic blood pressure (per 10 mm Hg)	1.000 (0.999–1.002)	1.000 (0.998–1.002)	0.999 (0.996–1.001)
Diastolic blood pressure (per 10 mm Hg)	1.001 (0.998–1.003)	1.001 (0.999–1.003)	0.999 (0.996–1.003)
Height (per 10 cm)	1.042 (0.768–1.414)	1.010 (0.736–1.386)	1.157 (0.688–1.949)
Weight (per 1 kg)	1.016 (1.004–1.027)	1.000 (0.969–1.031)	1.005 (0.988–1.023)
BMI (per 5 kg/m²)	1.294 (1.091–1.534)	1.334 (1.118–1.592)†	1.058 (0.815–1.373)
Age (per 10 y)	2.034 (1.375–3.008)	2.156 (1.444–3.217)†	1.161 (0.621–2.172)
Smoking status: current	1.797 (0.648–4.983)	1.773 (0.624–5.037)	1.310 (0.284–6.054)
CTnI at enrolment, >16 ng/L	0.993 (0.313–3.150)	1.044 (0.322–3.380)	1.8 (0.203–15.921)
Post enrolment variables			
Time from study recruitment to delivery	0.873 (0.636–1.197)	0.986 (0.709–1.373)	0.958 (0.567–1.617)
Highest systolic blood pressure enrolment to delivery (per 10 mm Hg)	1.000 (0.999–1.002)	1.000 (0.999–1.002)	0.999 (0.997–1.001)
Highest diastolic blood pressure enrolment to delivery (per 10 mm Hg)	1.001 (0.999–1.003)	1.001 (0.999–1.003)	1.002 (0.998–1.005)
Adverse maternal event (dichotomous)*	1.148 (0.701–1.881)	1.155 (0.688–1.940)	0.677 (0.310–1.480)
Gestational age at delivery	0.993 (0.963–1.024)	0.990 (0.958–1.023)	1.018 (0.705–1.471)

BMI indicates body mass index; and CTnI, cardiac troponin.

*Adverse maternal event is defined using the PHOENIX study protocol as a composite of maternal morbidity adapted from the fullPIERS model for prediction of preeclampsia adverse events (von Dadelszen et al, *Lancet* 2011) which will include central nervous system, cardio-respiratory, hematological, hepatic, and renal outcomes together with placental abruption, intensive care unit admission as well as confirmed severe systolic hypertension (≥160 mm Hg). In the PHOEBE study the clinical event does not include confirmed severe systolic hypertension.

† indicates $p<0.05$.

evaluation of the effect of the intervention, the 2 randomized groups were compared (as described in the Statistical Analysis Plan). As there was no signal of a significant effect in the secondary outcomes, it would suggest that we had not missed an important difference in the primary outcome (likely to be related to the much shorter separation in time between randomization and initiation of delivery between the 2 groups than anticipated). In light of this, we also combined all women recruited to provide an overall cohort of 321 women in which to complete the prognostic assessment (presented in Table 5) and to present a detailed cardiovascular assessment on a large prospective cohort of women with preterm preeclampsia. We chose 6 months as a generally accepted timepoint that pregnancy changes have resolved and underlying cardiovascular changes could not be attributed to pregnancy alone. This figure was also based on others' work showing that persistent cardiovascular changes are present as early as 6 months postpartum.[23] Maternal and neonatal outcomes before discharge from hospital between those randomized to immediate or expectant management are presented in Table S4 and do not differ significantly. In our original cohort, 12% had preexisting chronic hypertension. At the 6 month follow-up, 71% of women were classified as having chronic hypertension not explained by other factors other than exposure to preterm preeclampsia. 241 (75%) of women were not breast feeding and 81 (25%) of women continued to breast-feed (including as part of mixed feeding) at 6 months postpartum. Exploratory analysis demonstrated that our primary outcome was unaffected by breast-feeding status (odds ratio, 1.20 [0.78–1.87]; $P=0.43$). At the 6 month follow-up, 79% of women were classified as overweight or obese, but hypertension was seen across all weight groups. The occurrence of chronic hypertension at 6 months was not dependent on the body mass index category. The occurrence of chronic hypertension at 6 months was not dependent on the body mass index category. The proportion of women with chronic hypertension 6 months postpartum was similar across the 3 main weight categories as follows; normal weight 71% (47/66); overweight 60% (57/94); and obese 57% (91/160).

A recent systematic review summarized 36 studies of maternal cardiovascular function involving 815 women at time of disease with preeclampsia, demonstrated that increased vascular resistance and LV mass were the most consistent findings in preeclampsia.[33] Differentiating features of a pregnancy complicated by preeclampsia from normal pregnancy include LV wall thickness of ≥1.0 cm, exaggerated reduction in early diastole/atrial contraction, and lateral e′ of <14 cm/s, markers of diastolic dysfunction. Reduced stroke volume, diastolic dysfunction, and LV remodeling are most marked in severe

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and early-onset preeclampsia.[23,31,34] Our finding of cardiovascular dysfunction and persistent hypertension in the majority of women following preterm preeclampsia is in keeping with other single-center observational studies.[35–44] However, none were multicenter nor designed to examine different maternal delivery strategies. Our finding of 71% of women with preterm preeclampsia remaining hypertensive 6 months postpartum is higher than reported in larger population based cohorts, highlighting high levels of presumed undiagnosed hypertension.[45] As the PHOENIX trial has now reported, it is unlikely that the opportunity will arise for other investigators to examine whether timing of delivery impacts cardiovascular function using such a randomized approach. Developing accurate validated prognostic tools to best identify those at highest risk of cardiovascular dysfunction remains challenging, and postpartum intervention strategies must now be explored to reduce this cardiovascular burden of disease.

We have demonstrated that the burden of postpartum cardiovascular dysfunction following preterm preeclampsia in these women is high. In low resource health care settings where under-detected comorbidities including chronic hypertension are high and cases of fulminant eclampsia prevalent (incidence 1.4%),[46] the burden of cardiovascular morbidity is likely much higher. Recent US data suggest stagnation in the improvements in incidence and mortality of cardiovascular disease, specifically among younger women.[47] It is imperative that we understand the mechanisms that contribute to worsening risk factor profiles in young women to reduce future cardiovascular morbidity and mortality.

Two decades of research have documented an association between preeclampsia and major cardiovascular disorders in later life.[2,3,48,49] Despite this body of evidence, usual practice after a pregnancy complicated by preterm preeclampsia is for no specific follow-up. It is recognized by the Joint British Societies that include the British Cardiac Society, Heart UK, and the British Hypertension Society that pregnancy and infancy are good opportunities for education and intervention.[50] Furthermore, they endorse intensive risk factor lowering in individuals with high-risk factors that cause cardiovascular disease. Women with preterm preeclampsia are at increased risk for cardiovascular disease later in life. This study has provided mechanistic information on how subsequent clinical cardiovascular events may be mediated through impaired cardiac function identifiable at 6 months after preterm preeclampsia and highlights the postpartum period as an opportunity for early intervention before sustained and irreversible damage. There is increasing interest in the role of lifestyle interventions and therapeutic (eg, with angiotensin-converting enzyme inhibitors) to reduce subsequent cardiovascular risk. This study provides a body of evidence for postpartum cardiac functional impairment and demonstrates the need for further research into early intervention, particularly relating to novel therapeutic pathways.

PERSPECTIVES

In conclusion, our study confirms that late preterm preeclampsia is associated with substantial postpartum cardiovascular dysfunction. The relatively short delay in those expectantly managed (compared with planned delivery) does not worsen this cardiovascular dysfunction. Further follow-up would be useful to understand the longer term cardiovascular implications of these findings and whether these parameters relate to hypertension, age, or increased body mass index. Preeclampsia should not be considered a self-limiting disease of pregnancy alone. This research improves our understanding of the mechanistic processes linking preeclampsia with maternal cardiovascular impairment. Earlier delivery does not improve or worsen postpartum cardiovascular dysfunction, and women can be reassured that prolongation of a pregnancy affected by preterm preeclampsia will not further worsen their cardiovascular health. The study informs counseling of women with preeclampsia around future risks and also identifies the postpartum period now as a critical area to target in future intervention studies.

Affiliations

From the Department of Women and Children's Health (F.P.M., P.T.S., C.G., J.S., L.P., A.H.S., L.C.C.) and Cardiovascular Division (M.M.), King's College London, London, United Kingdom; Department of Obstetrics and Gynaecology, The IN-FANT Research Centre, University College Cork, Cork University Maternity Hospital, Ireland (F.P.M.); School of Psychology and Life Science, Canterbury Christ Church University, Kent, United Kingdom (J.M.O.); Department of Cardiology, St George's University Hospitals National Health Service Foundation Trust, London, United Kingdom (J.M.O.); National Perinatal Epidemiology Unit (NPEU), Nuffield Department of Population Health (A.P.) and Oxford Cardiovascular Clinical Research Facility, Radcliffe Department of Medicine (P.L.), University of Oxford; and Fetal Medicine Unit, St George's University Hospitals National Health Service Foundation Trust and Molecular & Clinical Sciences Research Institute, St George's University of London, United Kingdom (B.T.).

for the detection of cMyC as a biomarker of myocardial injury. The other authors report no conflicts.

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