Planned delivery to improve postpartum cardiac function in women with preterm pre-eclampsia: the PHOEBE mechanisms of action study within the PHOENIX RCT

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Scientific summary

The PHOEBE RCT

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Scientific summary

Background

Pre-eclampsia affects 3–5% of pregnancies, complicating approximately 35,000 pregnancies in the UK every year. Cardiovascular disease is the leading cause of mortality in women in the UK. Hypertensive disorders of pregnancy, in particular preterm pre-eclampsia, have been shown to be associated with an increased risk of development of a wide range of cardiovascular diseases, with increases in incidences observed as soon as 1 year postpartum. The absolute risk that a woman with pre-eclampsia would develop a cardiovascular event including hypertension, ischaemic heart disease, stroke or venous thromboembolism when she reaches the age of 50–59 years is estimated to be 17.8%, compared with 8.3% in those without pre-eclampsia.

The Pre-eclampsia in HOspital: Early iNductIon or eXpectant management (PHOENIX) study, a multicentre, randomised controlled trial, recruited women with late preterm pre-eclampsia who were 34 weeks' gestation to less than 37 weeks' gestation and having a singleton or dichorionic diamniotic twin pregnancy. It demonstrated that initiation of planned delivery in the subsequent 48 hours after randomisation reduced severe maternal adverse outcomes with no difference in neonatal morbidity (but there were more neonatal unit admissions) compared with the current practice of expectant management until 37 weeks' gestation. This PHOENIX study provided a key opportunity to examine the mechanisms underlying cardiovascular dysfunction following a randomised intervention on timing of delivery. An associated editorial alongside the main trial publication questioned whether initiating delivery in late preterm pre-eclampsia rather than waiting until term might theoretically reduce the stress on the woman's cardiovasculature (Staff AC. Long-term cardiovascular health after stopping pre-eclampsia. *Lancet* 2019;**394**:1120–1). The editorial advised evaluating whether or not a change to active delivery of women with late preterm pre-eclampsia would also benefit maternal cardiovascular health in the long term.

We conducted a follow-up cardiovascular assessment of women eligible for the PHOENIX study to examine the hypothesis that planned delivery in women with preterm pre-eclampsia, with attendant myocardial ischaemia, may decrease the risk of the development of cardiovascular dysfunction following pregnancy.

Objectives

The main aim of this mechanistic study was to examine the effects of shortening pregnancy complicated by pre-eclampsia on cardiovascular function at 6 months postpartum by studying women enrolled in a randomised controlled trial of planned delivery compared with usual care (expectant management) and who had late preterm pre-eclampsia.

Methods

Study design and participants

In this parallel-group, non-masked, multicentre, randomised controlled trial, we compared cardiovascular function at 6 months postpartum in women with preterm pre-eclampsia who were managed by planned delivery against expectant management (usual care). This trial was carried out in 28 consultant-led maternity units in England and Wales. Participants who were eligible for the PHOENIX study were approached following their decision to participate. A pregnant woman was eligible if she was between

34^{+0} and 36^{+6} weeks' gestation, had a diagnosis of pre-eclampsia or superimposed pre-eclampsia [as defined by the International Society for the Study of Hypertension in Pregnancy (Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, *et al*. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertens* 2014;**4**:97–104)], with a singleton or dichorionic diamniotic twin pregnancy and at least one viable fetus, was aged ≥ 18 years, 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 her baby in the next 48 hours. There were no substantial changes to the published study design, methods or outcomes after the start of the trial. The trial was approved by the South Central – Hampshire B Research Ethics Committee (number 13/SC/0645).

Randomisation and masking

Participants were randomly assigned to planned delivery or expectant care in a 1 : 1 ratio, as previously described. When women declined participation in the PHOENIX study, participation in the PHOEBE study was offered and these women were included as a third, non-randomised expectant (usual-care) group. The intervention was not masked from women, clinicians or data collectors because of the nature of the intervention. Trial statisticians were also not masked to allocation. However, the trial echocardiographer (JOD) was blinded to allocation group in analysis of all echocardiograms.

Procedures

Women were approached about participating in the PHOENIX study. Regardless of their participation in the PHOENIX study, site research teams approached women to confirm their eligibility and to provide 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. 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, which was performed within an 8-week window. At this assessment, a brief medical history was recorded, blood pressure was assessed, and venepuncture and echocardiography were undertaken. Echocardiography was performed locally in accordance with a standard operating procedure circulated by the research team. Anonymised echocardiography discs were then sent to the lead echocardiographer (JOD), who analysed each echocardiogram without knowledge of trial allocation and entered results into the web-based trial database. Every tenth echocardiogram was second read, again masked to trial allocation, by an echocardiographer at the University of Oxford and the findings were compared by the trial lead cardiologist (PL) to ensure consistency. When echocardiography assessment demonstrated potentially concerning features that may have an impact on clinical care, the findings were escalated and reviewed by the lead cardiologist (PL) and communicated back to the lead clinician at the recruiting site with a clinical recommendation for 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, originally classified in 2009 and updated prior to study completion in 2016. Secondary outcomes included systolic blood pressure and diastolic blood pressure at 6 months postpartum, together with the cardiovascular components of the fullPIERS (Preeclampsia Integrated Estimate of RiSk) composite maternal morbidity outcome, which was adapted from the fullPIERS prediction of adverse events in pre-eclampsia study. The cardiovascular components from the maternal morbidity composite outcome in the PHOENIX study included severe hypertension post randomisation (systolic blood pressure ≥ 160 mmHg on at least one occasion), positive inotropic support, infusion of a third parenteral antihypertensive drug, myocardial ischaemia or infarction, oxygen saturation (SpO_2) < 90%, ≥ 50% fraction of inspired oxygen for > 1 hour, intubation (other than for caesarean section) and pulmonary oedema.

Echocardiographic assessment

All participants were studied by standard two-dimensional and Doppler transthoracic echocardiography at rest. Women were studied in the left lateral decubitus position and data were acquired at end-expiration from standard parasternal/apical views using a GE Vivid (GE Medical Systems Ltd, Chalfont St Giles, UK) or Philips (Philips Electronics UK, Farnborough, UK) scanner. For each acquisition, three cardiac cycles of non-compressed data were stored in cine-loop format and analysed by one investigator (JOD), who was masked to the group allocation, with a second read as described above. Cardiac indices were normalised for body surface area, height and end-diastolic left ventricle long- or short-axis lengths, as appropriate. Tissue Doppler imaging, strain and strain rate indices are given as absolute values. Details of measurements of heart remodelling, systolic and diastolic dysfunction are also described.

Myocardial necrosis assessment

Participants were also consented to at least two blood sampling time points, most commonly performed at initial recruitment and the 6-month postpartum assessment. These samples were analysed for markers of myocardial necrosis/ischaemia: highly sensitive cardiac troponin-Is. High-sensitivity troponin-Is concentration in patients with stable cardiovascular disease identify those at increased risk of future myocardial infarction and other ischaemic cardiac outcomes (McQueen MJ, Kavsak PA, Xu L, Shestakovska O, Yusuf S. Predicting myocardial infarction and other serious cardiac outcomes using high-sensitivity cardiac troponin T in a high-risk stable population. *Clin Biochem* 2013;**46**:5–9). A sex-specific level of > 16 ng/l of high-sensitivity troponins was considered to be an elevated level in women. Cardiac myosin-binding protein C was also measured at 6 months postpartum using Singulex's (Alameda, CA, USA) Single Molecule Counting Technology SMC™, a quantitative fluorescent sandwich immunoassay technique. The level of a third biomarker, N-terminal pro-brain natriuretic peptide (a marker used in the assessment of patients with heart failure), was also assessed at 6 months postpartum.

Statistical analysis

Assuming an anticipated incidence of 70% of women with preterm pre-eclampsia having evidence of systolic and/or diastolic dysfunction at 6 months postpartum, a sample size of 322 women was 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 two-sided 5% significance level and 90% power. With a 20% loss of women at follow-up, the overall target for recruitment was 404 women (202 per group). The primary analysis for all maternal outcomes was by intention to treat, with participants analysed in the groups to which they were assigned regardless of protocol non-compliances. Risk ratios were estimated for binary outcomes with associated 95% confidence intervals. Simple and multiple regression analysis were used to assess the influence of early pregnancy factors, including blood pressure, demographic variables (maternal age, body mass index), pregnancy characteristics (parity, gestation at delivery, gestation at onset and severity of pre-eclampsia), on indices of cardiac function and remodelling, as detailed above (see *Outcomes*). All of the conventional echocardiographic indices were adjusted for body surface area and all of the tissue Doppler velocity and deformation indices to the end-diastolic left or right ventricle long-axis length. Prespecified subgroup analyses were carried out for co-primary outcomes in view of the changes to definitions of systolic and diastolic dysfunction over the study period. Data analyses were carried out with Stata/SE® (StataCorp LP, College Station, TX, USA) version 15.1.

Results

Between 27 April 2016 and 30 November 2018, 623 women were found to be eligible, of whom 420 (67%) were recruited, across 28 maternity units in England and Wales. A total of 133 women were allocated to planned delivery, 137 women were allocated to expectant management and a further 150 received non-randomised expectant management.

For the intention-to-treat analysis, data from 100 women in the planned delivery group and from 107 women in the expectant management group were included. Follow-up to the 6-month postpartum assessments continued until 20 June 2019. Thirty-three (25%) women were lost to follow-up in the planned delivery group and 30 (22%) in the expectant management group. Baseline characteristics appeared similar between the two groups, with groups well balanced on minimisation factors.

There were no differences in the primary outcome between women in the planned delivery group (50%) compared with those in the expectant management group (47.2%) using either the 2009 (risk ratio 1.06, 95% confidence interval 0.80 to 1.40) or the 2016 definition (8.0% vs. 10.3%; risk ratio 0.78, 95% confidence interval 0.33 to 1.86). No between-group differences were observed in 2009 diastolic dysfunction grade 1 (risk ratio 1.40, 95% confidence interval 0.59 to 3.31), grade 2 (risk ratio 1.11, 95% confidence interval 0.78 to 1.57) or grade 3 (risk ratio 1.18, 95% confidence interval 0.08 to 18.43) diastolic dysfunction subclassifications nor in 2016 diastolic dysfunction classification. Overall, 10% (31/321) of women had a left ventricular ejection fraction < 55% 6 months postpartum. Similarly, using the more recent 2016 classification for systolic and diastolic dysfunction, no differences were observed in systolic (risk ratio 0.76, 95% confidence interval 0.32 to 1.80) or any of the diastolic dysfunction parameters. Hypertension prevalence, defined as on antihypertensive treatment or systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg at 6 months postpartum, was similar between those managed with planned delivery and those expectantly managed (risk ratio 1.01, 95% confidence interval 0.85 to 1.20) but, overall, was present in 71% of the cohort. No significant differences were observed in any of the cardiac parameters including geometric and haemodynamic parameters, left ventricular global cardiac parameters, myocardial mechanics and left ventricular basal or apical parameters between those women with planned delivery and those who were expectantly managed.

The only variables that were predictive of systolic and/or diastolic dysfunction at 6 months postpartum were maternal body mass index (adjusted odds ratio 1.33 per 5 kg/m^2, 95% confidence interval 1.12 to 1.59 per 5 kg/m^2) and maternal age (adjusted odds ratio 2.16, 95% confidence interval 1.44 to 3.22 per 10 years). The interval from study enrolment to delivery was not associated with development of the primary outcome. All women in the planned delivery group received the trial intervention, although this was not always initiated within 48 hours as intended. Of women allocated to the planned delivery group, 105 (78%) out of 133 had delivery initiated within 48 hours.

Overall, 8% ($n = 25$) of 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, with 88% of those with systolic and/or diastolic dysfunction not requiring clinical escalation.

Conclusions

In this randomised controlled trial of women with late preterm pre-eclampsia, planned delivery did not reduce cardiovascular dysfunction at 6 months postpartum. The adverse cardiovascular sequelae of preterm pre-eclampsia are substantial; 10% of women with preterm pre-eclampsia had a left ventricular ejection fraction < 55%, 71% remained hypertensive and 49% of women had evidence of impaired diastolic dysfunction of undetermined long-term clinical importance at 6 months postpartum. Women in the planned delivery group had a median 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 a higher age at enrolment predicted the occurrence of postpartum systolic and/or diastolic dysfunction.

Our finding of 71% of women with preterm pre-eclampsia remaining hypertensive 6 months postpartum is higher than reported in larger population-based cohorts, highlighting high levels of presumed undiagnosed hypertension. 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.

Our study confirms that pre-eclampsia is associated with substantial postpartum cardiovascular dysfunction, not influenced by expectant management or planned delivery. Pre-eclampsia should not be considered a self-limiting disease of pregnancy alone. This research improves our understanding of the mechanistic processes linking pre-eclampsia with maternal cardiovascular impairment. The evidence suggests that expectant management of preterm pre-eclampsia does not worsen postpartum cardiovascular dysfunction and women can be reassured that prolongation of a pregnancy affected by preterm pre-eclampsia will not further worsen their cardiovascular health. The study informs counselling of women with pre-eclampsia around future risks and also identifies the postpartum period as a critical area to target in future intervention studies. 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.

Recommendations for research

1. What postnatal interventions are effective in reducing cardiovascular dysfunction following preterm pre-eclampsia?
2. How can biomarker discovery improve prediction of cardiovascular dysfunction following adverse pregnancy outcomes?

Trial registration

This trial is registered as ISRCTN01879376.

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