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Planned delivery for pre-eclampsia between 34 and 37 weeks of gestation: the PHOENIX RCT

Lucy C Chappell, Peter Brocklehurst, Marcus Green, Pollyanna Hardy, Rachael Hunter, Alice Beardmore-Gray, Ursula Bowler, Anna Brockbank, Virginia Chiocchia, Alice Cox, Kate Duhig, Jessica Fleminger, Carolyn Gill, Melanie Greenland, Eleanor Hendy, Ann Kennedy, Paul Leeson, Louise Linsell, Fergus P McCarthy, Jamie O'Driscoll, Anna Placzek, Lucilla Poston, Stephen Robson, Pauline Rushby, Jane Sandall, Laura Scholtz, Paul T Seed, Jenie Sparkes, Kayleigh Stanbury, Sue Tohill, Basky Thilaganathan, John Townend, Edmund Juszcak, Neil Marlow and Andrew Shennan on behalf of the PHOENIX Study Group



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The PHOENIX RCT

Planned delivery for pre-eclampsia between 34 and 37 weeks of gestation: the PHOENIX RCT

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Abstract

The PHOENIX RCT

Planned delivery for pre-eclampsia between 34 and 37 weeks of gestation: the PHOENIX RCT

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Background: In women with late preterm pre-eclampsia (i.e. at 34⁺⁰ to 36⁺⁶ weeks' gestation), the optimal delivery time is unclear because limitation of maternal–fetal disease progression needs to be balanced against infant complications. The aim of this trial was to determine whether or not planned earlier initiation of delivery reduces maternal adverse outcomes without substantial worsening of perinatal or infant outcomes, compared with expectant management, in women with late preterm pre-eclampsia.

Methods: We undertook an individually randomised, triple non-masked controlled trial in 46 maternity units across England and Wales, with an embedded health economic evaluation, comparing planned

delivery and expectant management (usual care) in women with late preterm pre-eclampsia. The co-primary maternal outcome was a maternal morbidity composite or recorded systolic blood pressure of ≥ 160 mmHg (superiority hypothesis). The co-primary short-term perinatal outcome was a composite of perinatal deaths or neonatal unit admission (non-inferiority hypothesis). Analyses were by intention to treat, with an additional per-protocol analysis for the perinatal outcome. The primary 2-year infant neurodevelopmental outcome was measured using the PARCA-R (Parent Report of Children's Abilities-Revised) composite score. The planned sample size of the trial was 900 women; the trial is now completed. We undertook two linked substudies.

Results: Between 29 September 2014 and 10 December 2018, 901 women were recruited; 450 women [448 women (two withdrew consent) and 471 infants] were allocated to planned delivery and 451 women (451 women and 475 infants) were allocated to expectant management. The incidence of the co-primary maternal outcome was significantly lower in the planned delivery group [289 (65%) women] than in the expectant management group [338 (75%) women] (adjusted relative risk 0.86, 95% confidence interval 0.79 to 0.94; $p = 0.0005$). The incidence of the co-primary perinatal outcome was significantly higher in the planned delivery group [196 (42%) infants] than in the expectant management group [159 (34%) infants] (adjusted relative risk 1.26, 95% confidence interval 1.08 to 1.47; $p = 0.0034$), but indicators of neonatal morbidity were similar in both groups. At 2-year follow-up, the mean PARCA-R scores were 89.5 points (standard deviation 18.2 points) for the planned delivery group (290 infants) and 91.9 points (standard deviation 18.4 points) for the expectant management group (256 infants), both within the normal developmental range (adjusted mean difference -2.4 points, 95% confidence interval -5.4 to 0.5 points; non-inferiority $p = 0.147$). Planned delivery was significantly cost-saving ($-\pounds 2711$, 95% confidence interval $-\pounds 4840$ to $-\pounds 637$) compared with expectant management. There were 9 serious adverse events in the planned delivery group and 12 in the expectant management group.

Conclusion: In women with late preterm pre-eclampsia, planned delivery reduces short-term maternal morbidity compared with expectant management, with more neonatal unit admissions related to prematurity but no indicators of greater short-term neonatal morbidity (such as need for respiratory support). At 2-year follow-up, around 60% of parents reported follow-up scores. Average infant development was within the normal range for both groups; the small between-group mean difference in PARCA-R scores is unlikely to be clinically important. Planned delivery was significantly cost-saving to the health service. These findings should be discussed with women with late preterm pre-eclampsia to allow shared decision-making on timing of delivery.

Limitations: Limitations of the trial include the challenges of finding a perinatal outcome that adequately represented the potential risks of both groups and a maternal outcome that reflects the multiorgan manifestations of pre-eclampsia. The incidences of maternal and perinatal primary outcomes were higher than anticipated on the basis of previous studies, but this did not limit interpretation of the analysis. The trial was limited by a higher loss to follow-up rate than expected, meaning that the extent and direction of bias in outcomes (between responders and non-responders) is uncertain. A longer follow-up period (e.g. up to 5 years) would have enabled us to provide further evidence on long-term infant outcomes, but this runs the risk of greater attrition and increased expense.

Future work: We identified a number of further questions that could be prioritised through a formal scoping process, including uncertainties around disease-modifying interventions, prognostic factors, longer-term follow-up, the perspectives of women and their families, meta-analysis with other studies, effect of a similar intervention in other health-care settings, and clinical effectiveness and cost-effectiveness of other related policies around neonatal unit admission in late preterm birth.

Trial registration: The trial was prospectively registered as ISRCTN01879376.

Funding: This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in *Health Technology Assessment*; Vol. 27, No. 28. See the NIHR Journals Library website for further project information.

List of abbreviations

CI	confidence interval	PHOENIX	Pre-eclampsia in HOspital: Early iNduction or eXpectant management
HTA	Health Technology Assessment		
NICE	National Institute for Health and Care Excellence	PLGF	placental growth factor
NIHR	National Institute for Health and Care Research	PPI	patient and public involvement
PARCA-R	Parent Report of Children's Abilities-Revised	PREP-S	Prediction models for Risk of Early-onset Pre-eclampsia – Survival
PEACOCK	Prognostic indicators of severe disEAsE in women with late preterm pre-eClampsia tO guide decision-making on timing of delivery	QALY	quality-adjusted life-year
		SD	standard deviation

Plain language summary

Why did we do this trial?

We know that pre-eclampsia is a common condition and can cause serious illness in a pregnant woman or baby. It is unclear how we should best advise women about the timing of delivery if they develop the condition between 34 and 37 weeks of pregnancy. We wanted to compare planned early birth and usual clinical practice (that is, planning birth at 37 weeks of pregnancy, or sooner if needed for clinical reasons).

What did we do?

Between September 2014 and December 2018, 901 women with pre-eclampsia between 34 and 37 weeks of pregnancy agreed to take part. Half of the women were randomised to planning the birth of their babies within 48 hours and half were randomised to watching and waiting. During the study we collected pregnancy and birth information and health outcomes for the mother and the baby for 2 years after birth.

What did we find?

We found that planned early birth is better for these women, with fewer complications such as severely high blood pressure. We found that more babies in the planned birth group were admitted to the neonatal unit, mainly because they were premature, but they did not have more complications such as breathing problems and they did not stay longer in the unit than babies in the usual clinical practice group. At 2 years old, the babies in both groups had similar scores for development, with their average scores in the normal range.

What does this mean for women with pre-eclampsia?

Women with pre-eclampsia and their doctors will be able to make better decisions about the timing of delivery. Because the number of complications was reduced, and there was no difference in complications for the baby (though more babies were admitted to the neonatal unit), women and their doctors may use this information to share decision-making around timing of delivery.

SYNOPSIS

This report details the work undertaken to establish the clinical effectiveness and cost-effectiveness of prompt planned delivery of a baby between 34 and 37 weeks of gestation for women with mild to moderate pre-eclampsia compared with expectant care, together with linked studies. It arose from a call commissioned by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme, based on a research recommendation in the National Institute for Health and Care Excellence (NICE) 2010 clinical guideline on hypertension in pregnancy.¹

Clinical uncertainty

We presented the clinical uncertainty in a *BMJ* article,² highlighting the tension between optimising the maternal condition (typically by prompt planned delivery) and the unclear balance of benefits and risks for the baby. Preterm birth is known to be associated with short- and long-term morbidity, and expectant management may perpetuate growth restriction (with attendant neurodevelopmental impact) and increase the risk of urgent delivery (if the condition of the woman or fetus deteriorates) and stillbirth. Whereas other trials had evaluated a policy of planned delivery in women with a broader spectrum of pregnancy hypertension disorders, we proposed undertaking a trial in women with pre-eclampsia only, in the United Kingdom (UK) health-care setting, with a health economic evaluation.

Protocol

Full details of the proposed study and analysis plan were published as a protocol.³ It was prespecified that the findings of the main PHOENIX (Pre-eclampsia in HOspital: Early iNduction or eXpectant management) study would be divided into publication of the short-term results (up to discharge of the woman and baby from hospital) and subsequent publication of the long-term outcomes (assessed at 2 years after birth) of the women and the babies.

Short-term maternal and infant outcomes in the PHOENIX trial

The short-term trial results were published as a fast-track article in *The Lancet*.⁴ In this parallel-group, non-masked, multicentre, randomised controlled trial carried out in 46 maternity units across England and Wales, we compared planned delivery and expectant management (usual care), with individual randomisation, in women with late preterm pre-eclampsia at 34⁺⁰ to 36⁺⁶ weeks' gestation and a singleton or dichorionic diamniotic twin pregnancy. The co-primary maternal outcome was a composite of maternal morbidity or recorded systolic blood pressure of ≥ 160 mmHg with a superiority hypothesis. The co-primary perinatal outcome was a composite of perinatal deaths or neonatal unit admission up to infant hospital discharge with a non-inferiority hypothesis (non-inferiority margin of 10% difference in incidence). Analyses were by intention to treat, together with a per-protocol analysis for the perinatal outcome. The trial was prospectively registered with the ISRCTN (International Standard Randomised Controlled Trial Number) registry as ISRCTN01879376. Between 29 September 2014 and 10 December 2018, 901 women were recruited; 450 women [448 women (two withdrew consent) and 471 infants] were allocated to planned delivery and 451 women (451 women and 475 infants) were allocated to expectant management. The incidence of the co-primary maternal outcome was significantly lower in the planned delivery group [289 (65%) women] than in the expectant management group [338 (75%) women] [adjusted relative risk 0.86, 95% confidence interval (CI) 0.79 to 0.94; $p = 0.0005$]. The incidence of the co-primary perinatal outcome by intention to treat was significantly higher in the planned delivery group [196 (42%) infants] than in the expectant management group [159 (34%) infants] (adjusted relative risk 1.26, 95% CI 1.08 to 1.47; $p = 0.034$). The results from the per-protocol analysis

were similar. Expectant management prolonged pregnancy by an average of around 5 days (3 days by adjusted analysis), and 54% of women in the expectant management group needed expedited delivery for maternal or fetal indications. There were nine serious adverse events in the planned delivery group and 12 in the expectant management group. We concluded that there is strong evidence to suggest that planned delivery reduces maternal morbidity and severe hypertension compared with expectant management, with more neonatal unit admissions related to prematurity but no indicators of greater neonatal morbidity. We advised that this trade-off should be discussed with women with late preterm pre-eclampsia to allow shared decision-making on timing of delivery.

Secondary analysis of short-term PHOENIX outcomes

A secondary analysis of the study was undertaken to present results stratified by gestational age and to evaluate outcomes of induced labour in women with late preterm pre-eclampsia.⁵ We demonstrated that in women who started induction of labour, 63% of women delivered vaginally (56% at 34 weeks' gestation). Compared with expectant management, planned delivery was associated with higher rates of neonatal unit admission for prematurity (but lower proportions of small-for-gestational-age infants); length of neonatal unit stay and neonatal morbidity (including respiratory support) were similar across both trial groups at all gestational windows. Neonatal unit admission was more common among infants delivered at an earlier gestational age, small-for-gestational age infants and infants of women who developed severe pre-eclampsia. Documented neonatal morbidity at discharge and lengths of stay were similar between the trial groups at each gestational age (weeks), suggesting that these admissions may reflect clinicians' behaviour.

Linked prognostic cohort study: the PEACOCK study

Two linked studies were undertaken, both addressing additional uncertainties around the main research question. In the first of these linked studies, funded by the NIHR HTA programme (15/59/06), we sought to establish a prognostic model to inform optimal timing of delivery in women with late preterm pre-eclampsia, comparing concentrations of placental growth factor (PIGF) with clinical and routinely collected blood and urinary parameters to determine clinically indicated need for delivery for pre-eclampsia (or related complications) within 7 days of assessment. The findings were published in a journal article⁶ and in the NIHR Journals Library.⁷ The PEACOCK (Prognostic indicators of severe disEase in women with late preterm pre-eClampsia tO guide decision-making on timing of delivery) study was a prospective cohort study nested within the PHOENIX trial. We undertook prospective recruitment of women in 36 maternity units across England and Wales between 34⁺⁰ and 36⁺⁶ weeks' gestation with a diagnosis of pre-eclampsia and in whom blood samples for PIGF testing were obtained, alongside clinical data, for use in the PREP-S (Prediction models for Risk of Early-onset Pre-eclampsia – Survival) model. The main outcome measure was clinically indicated need for delivery for pre-eclampsia within 7 days of assessment. For statistical analysis, both PREP-S score and PIGF concentration were assessed and compared using standard methods (sensitivity and specificity for PIGF thresholds of 100 pg/ml and <12 pg/ml; receiver operating characteristic areas for continuous measurements). The estimated probability of early delivery from PREP-S was compared with actual event rates among women with similar probabilities by calibration. Calibration using logistic regression was also used. Between 27 April 2016 and 24 December 2018, 501 women were recruited to the study. Although PIGF testing had high sensitivity (97.9%) for delivery within 7 days, the negative predictive value was only 71.4%, and the specificity was low (8.4%). The area under the curve for the clinical prediction model (PREP-S) and PIGF in this cohort in determining need for delivery within 7 days was 0.64 (standard error 0.03) and 0.60 (standard error 0.03), respectively, and 0.65 (standard error 0.03) in combination. We noted that a high proportion of women in this cohort already had low PIGF concentrations at the time of confirmed diagnosis, which reduced the ability of the biomarker to further predict adverse outcomes. We concluded that, in this group of women with late preterm pre-eclampsia, PIGF measurement is

not likely to add to the current clinical assessment to help plan care for late preterm pre-eclampsia regarding timing of delivery. Existing models developed in women with early-onset pre-eclampsia to predict complications cannot be used to predict clinically indicated need for delivery in women with late preterm pre-eclampsia.

Linked mechanism of action study: the PHOEBE study

In the second of these linked studies, funded by the NIHR Efficacy and Mechanism Evaluation (EME) programme (15/23/02), we evaluated the mechanism of action underlying the known association between pre-eclampsia and the development of cardiovascular disease, assessing whether or not planned delivery affected maternal echocardiographic measures of cardiac dysfunction and blood pressure 6 months after birth (the PHOEBE study). We published the findings in a journal article⁸ and in the NIHR Journals Library.⁹ In 28 maternity hospitals in England and Wales, we approached women who were eligible for the PHOENIX study and offered participation in the PHOEBE study. Additional post-partum follow-up included medical history, blood pressure assessment and echocardiography (at 6 months). All women had blood sampling performed at at least two time points from recruitment to 6-month follow-up for assessment of cardiac necrosis markers. The primary outcome was a composite of systolic and/or diastolic dysfunction (originally by 2009 guidelines,¹⁰ updated by 2016 guidelines,¹¹ with an amended definition of diastolic dysfunction). Analyses were by intention to treat together with a per-protocol analysis for the primary and secondary outcomes. Between 27 April 2016 and 30 November 2018, 623 women were found to be eligible, of whom 420 (67%) were recruited. 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 as part of usual care. The mean time from enrolment to delivery was 2.5 days [standard deviation (SD) 1.9 days] in the planned delivery group and 6.8 days (SD 5.3 days) in the expectant management group. There were no differences in the primary outcome between women in the planned delivery group and women in the expectant management group using either the 2009 definition (risk ratio 1.06, 95% CI 0.80 to 1.40) or the 2016 definition (risk ratio 0.78, 95% CI 0.33 to 1.86). Overall, 10% (31/321) of women had a left ventricular ejection fraction <55%, and 71% of the cohort remained hypertensive at 6 months post partum. No differences were observed between the two groups in cardiorespiratory outcomes prior to discharge from hospital or in systolic or diastolic blood pressure. Variables associated with the primary outcome (2009 definition) at 6 months post partum were maternal body mass index (adjusted odds ratio 1.33 per 5 kg/m², 95% CI 1.12 to 1.59 per 5 kg/m²) and maternal age (adjusted odds ratio 2.16 years, 95% CI 1.44 to 3.22 per 10 years). Limitations include changing definitions regarding systolic and/or diastolic dysfunction. We concluded that preterm pre-eclampsia results in persistence of hypertension in the majority of women with late preterm pre-eclampsia at 6 months post partum, and systolic dysfunction in 10%, and that pre-eclampsia should not be considered a self-limiting disease of pregnancy alone. This study underlined the importance of conceptualising pre-eclampsia as a disease with life-long cardiovascular implications.

Two-year infant and maternal outcomes in the PHOENIX trial

We continued follow-up to 2 years post birth to evaluate the best time to initiate delivery in late preterm pre-eclampsia to optimise infant and maternal outcomes.¹² For this part of the trial, the primary long-term outcome was infant neurodevelopmental outcome at 2 years of age, using the Parent Report of Children's Abilities-Revised (PARCA-R) composite score. At the 2-year follow-up, the intention-to-treat analysis population included 276 women (290 infants) allocated to planned delivery and 251 women (256 infants) to expectant management. The mean composite standardised PARCA-R scores were 89.5 points (SD 18.2 points) in the planned delivery group and 91.9 points (SD 18.4 points) in the expectant management group, with an adjusted mean difference of -2.4 points (95% CI -5.4 to 0.5 points; non-inferiority $p = 0.147$). We concluded that, in infants of women with late preterm pre-eclampsia, average neurodevelopmental assessment at 2 years was within the normal range, regardless

of whether planned delivery or expectant management was pursued. Because of lower than anticipated levels of follow-up, there was limited power to demonstrate that these scores were not different, but the small between-group difference in PARCA-R scores was unlikely to be clinically important.¹²

Health economic evaluation

The objective of the health economic evaluation was to evaluate the 2-year cost-utility of planned delivery for women with late preterm pre-eclampsia at 34⁺⁰ to 36⁺⁶ weeks' gestation compared with expectant management from an NHS perspective.¹³ We undertook an economic evaluation alongside the multicentre randomised controlled trial (PHOENIX), using participant-level data. Women were individually randomised to planned delivery or expectant management. Resource use was collected from hospital records between randomisation and primary hospital discharge following birth. Women were followed up at 6 months and 2 years following birth, and we collected self-reported resource use for them and their infant(s) covering the previous 6 months. Women completed the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), at randomisation and follow-up. The main outcome measure was incremental cost per quality-adjusted life-year (QALY) gained. A total of 450 women were randomised to planned delivery and 451 to expectant management; 187 and 170 women, respectively, had complete data at 24 months. Planned delivery resulted in a significantly lower mean cost per woman and infant(s) over 2 years (–£2711, 95% CI –£4840 to –£637), with a mean incremental difference of 0.019 QALYs (95% CI –0.039 to 0.063 QALYs). Short- and long-term infant costs were not significantly different between the trial arms. We concluded that there is a high probability that planned delivery is cost-effective compared with expectant management. These results¹³ need to be considered alongside clinical outcomes and in the wider context of maternity care.

Patient and public involvement

Aim

The aim of patient and public involvement (PPI) in all aspects of the study was to ensure that the voices of pregnant women (and their wider families) were woven through the research, such that the results would be of direct benefit to them.

Methods

We worked with PPI representatives from grant preparation through to dissemination. Because the study arose from a commissioned call, we were aware that pregnant women had been involved through the NICE guideline committee and NIHR HTA prioritisation work, but we additionally worked with representatives (including those with lived experience) from Action on Pre-eclampsia (the patient support group) and Tommy's Charity (a national baby charity). This involvement extended across considerations around research design, development and iteration of participant information resources, research management and troubleshooting (as members of the Co-Investigator Group and Trial Steering Committee), interpretation of the data and writing and dissemination of the findings.

Results of patient and public involvement input

Examples of how PPI shaped the research included consideration of how to promote recruitment when it was slower than anticipated. Members of the central research team noted that women were often enthusiastic about participation, perceiving the clinical need for this uncertainty to be addressed, but that health-care professionals could act as gatekeepers to enrolment. We worked with site teams to support them, offering the trial to a greater proportion of eligible women, reinforcing that we had made the inclusion criteria as wide as possible for a pragmatic approach. We disseminated the information that around 55% of women who were approached agreed to take part and included positive quotations from women (about participation) in newsletters with the women's consent. This enabled a shift towards an inclusive approach to enrolment.

Discussion of patient and public involvement input

Pregnancy studies have had a long history of active PPI input, but for a trial on the timing of delivery this is particularly crucial, because the trade-off between maternal and infant benefits and risks is central to the research question. PPI input has been pivotal around appropriate representation of this balance, accurate depiction of the existing equipoise, and interpretation of the findings when, typically, benefits may not always go in the same direction for the woman and the baby. PPI has been only a positive and essential guiding influence.

Reflections and critical perspective

The active involvement of Action on Pre-eclampsia (the patient support group) has been vital at all stages. This has enabled contribution from the Action on Pre-eclampsia Chief Executive Officer, Marcus Green, who combines indirect lived experience (as a partner of a woman with pre-eclampsia) with a powerful conduit to many other voices for whom he constantly advocates. The study has also had involvement of others with lived experience, but we noted that sometimes women transition through various phases of their lives and may choose to be involved for varying durations (not always for the entire length of the study). This has led Action on Pre-eclampsia to set up a research involvement panel, so that those with lived experience can contribute in the way that best suits them.

Equality, diversity and inclusion

The study enrolled 901 pregnant women in the main PHOENIX trial from 46 maternity units in England and Wales. A total of 30% of women were from non-White ethnic minority groups and 70% of women were from White ethnic groups [following Office for National Statistics (ONS) ethnic group descriptors]. In ONS data on live births in 2018¹⁴ (the most recent year of recruitment into the PHOENIX trial), 72% of women were from a White ethnic group, suggesting that the women recruited were broadly representative of the wider pregnancy population. The mean age of pregnant women in the PHOENIX trial was within the most common age category reported by the ONS in 2018.¹⁵

We are not aware of any published data on ethnicity groupings specifically for women with late preterm pre-eclampsia (between 34⁺⁰ and 36⁺⁶ weeks' gestation) in the UK between 2014 and 2018 to ascertain whether or not our participants were representative of the wider population. However, our wide geographical diversity of maternity units, inclusive approach to recruitment and enrolment of a similar proportion of women from non-White ethnic minority groups is in keeping with the wider pregnancy population characteristics and suggests that our research teams enabled participation by a diverse group of women and that our findings are generalisable.

Implication for practice/decision-makers

This study adds considerably to the body of literature on planned delivery in late preterm pre-eclampsia, more than doubling the number of women enrolled in similar studies to date. The results show that women with late preterm pre-eclampsia should be informed of the benefits and risks of planned delivery compared with expectant management, specifically including the following:

- Expectant management will prolong pregnancy by an average of 3–5 days.
- Around 54% of women managed expectantly will need expedited delivery for maternal or fetal indications, with a 74% chance of progressing to severe pre-eclampsia (compared with 64% of women progressing to severe pre-eclampsia with planned delivery).
- Planned delivery significantly reduces maternal complications, including severe high blood pressure.
- Planned delivery is associated with more babies being admitted to the neonatal unit because of prematurity, but with no clinically relevant differences in neonatal morbidity, suggesting that this may be a precautionary measure.

- At 2 years after birth, infants in both groups have development scores in the normal range.
- Planned delivery is around £2700 cheaper for the health service, mainly because of shorter stays in the neonatal unit and fewer complications for the women, with no overall difference in neonatal unit admission costs between the groups.

Since publication of the trial, an individual patient data meta-analysis has been undertaken to compare planned delivery with expectant management, focusing specifically on women with pre-eclampsia after 34 weeks' gestation. This concluded that planned early delivery provides clear maternal benefits and may reduce the risk of the infant being born small for gestational age, with a possible increase in short-term neonatal respiratory morbidity. The article reiterated that potential benefits and risks of prolonging a pregnancy complicated by pre-eclampsia should be discussed with women as part of a shared decision-making process.¹⁶

Research recommendations

We identified the following questions for future research, and have indicated the area of research to which they relate. We suggest that a more formal process of scoping and prioritisation is undertaken to determine how these are best taken forward in the wider context of pregnancy research and ongoing work in this area.

Further interventions

- What other disease-modifying medications or interventions may ameliorate the disease process of pre-eclampsia or its long-term effects for the woman or infant?

Prognostic factors

- What antenatal clinical factors or biomarkers best determine need for delivery in women with late preterm pre-eclampsia?
- What antenatal clinical factors are associated with longer-term infant outcomes (e.g. at 2 years)?

Longer-term follow-up

- What are the longer-term outcomes (e.g. at 5 and 10 years) for women and infants after late preterm pre-eclampsia?

Women and families' perspectives

- What do women and their families consider most important when undertaking shared decision-making around timing of delivery in late preterm pre-eclampsia?
- How can we best support women and their families when diagnosed with late preterm pre-eclampsia antenatally and beyond?

Meta-analysis with other similar studies

- What are the maternal and infant outcomes after planned delivery for late preterm pre-eclampsia (compared with expectant management) when included with other studies in an individual patient data meta-analysis?

Intervention in other health-care settings

- How does the impact of planned delivery compared with expectant management in late preterm pre-eclampsia differ across varied health-care settings (e.g. in low- and middle-income countries)?

Wider clinical uncertainties

- What is the clinical effectiveness and cost-effectiveness of a policy of promoting postnatal mother-baby care together wherever possible compared with a routine admission policy to the neonatal unit based on infant gestational age or weight thresholds?

Conclusion

In women with late preterm pre-eclampsia, planned delivery reduces short-term maternal morbidity (including severe hypertension) compared with expectant management, with more neonatal unit admissions related to prematurity but no indicators of greater short-term neonatal morbidity. At 2-year follow-up, average infant development was within the normal range for both groups; the small between-group mean difference in PARCA-R scores is unlikely to be clinically important. Planned delivery was significantly cost-saving to the health service. These findings should be discussed with women with late preterm pre-eclampsia to allow shared decision-making on timing of delivery.

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Rachael Hunter (<https://orcid.org/0000-0002-7447-8934>) was a member of the co-investigator group and undertook the health economic analyses.

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Ethics statement

The trial was approved by the South Central – Hampshire B Research Ethics Committee (13/SC/0645) on 19 December 2013.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

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Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.

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Planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial

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Abstract

Background

In women with late preterm pre-eclampsia, the optimal time to initiate delivery is unclear because limitation of maternal disease progression needs to be balanced against infant complications. The aim of this trial was to determine whether planned earlier initiation of delivery reduces maternal adverse outcomes without substantial worsening of neonatal or infant outcomes, compared with expectant management (usual care) in women with late preterm pre-eclampsia.

Methods

In this parallel-group, non-masked, multicentre, randomised controlled trial done in 46 maternity units across England and Wales, we compared planned delivery versus expectant management (usual care) with individual randomisation in women with late preterm pre-eclampsia from 34 to <37 weeks' gestation and a singleton or dichorionic diamniotic twin pregnancy. The co-primary maternal outcome was a composite of maternal morbidity or recorded systolic blood pressure of at least 160 mm Hg with a superiority hypothesis. The co-primary perinatal outcome was a composite of perinatal deaths or neonatal unit admission up to infant hospital discharge with a non-inferiority hypothesis (non-inferiority margin of 10% difference in incidence). Analyses were by intention to treat, together with a per-protocol analysis for the perinatal outcome. The trial was prospectively registered with the ISRCTN registry, ISRCTN01879376. The trial is closed to recruitment but follow-up is ongoing.

Findings

Between 29 September 2014 and 10 December 2018, 901 women were recruited. Four hundred fifty women (448 women and 471 infants analysed) were allocated to planned delivery and 451 women (451 women and 475 infants analysed) to expectant management. The incidence of the co-primary maternal outcome was significantly lower in the planned delivery group [289 (65%) women] compared with the expectant management group [338 (75%) women; adjusted relative risk 0.86, 95% CI 0.79 to 0.94; $p = 0.0005$]. The incidence of the co-primary perinatal outcome by intention to treat was significantly higher in the planned delivery group [196 (42%) infants] compared with the expectant management group [159 (34%) infants; 1.26, 1.08 to 1.47; $p = 0.0034$]. The results from the per-protocol analysis were similar. There were 9 serious adverse events in the planned delivery group and 12 in the expectant management group.

Interpretation

There is strong evidence to suggest that planned delivery reduces maternal morbidity and severe hypertension compared with expectant management, with more neonatal unit admissions related to prematurity but no indicators of greater neonatal morbidity. This trade-off should be discussed with women with late preterm pre-eclampsia to allow shared decision making on timing of delivery.

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Cost-utility analysis of planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX)

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Abstract

Aim

There is currently limited evidence on the costs associated with late preterm pre-eclampsia beyond antenatal care and post-natal discharge from hospital. The aim of this analysis is to evaluate the 24-month cost-utility of planned delivery for women with late preterm pre-eclampsia at 34⁺⁰ and 36⁺⁶ weeks' gestation compared to expectant management from an English National Health Service perspective using participant-level data from the PHOENIX trial.

Methods

Women between 34⁺⁰ and 36⁺⁶ weeks' gestation in 46 maternity units in England and Wales were individually randomised to planned delivery or expectant management. Resource use was collected from hospital records between randomisation and primary hospital discharge following birth. Women were followed up at 6 months and 24 months following birth and self-reported resource use for themselves and their infant(s) covering the previous 6 months. Women completed the EQ-5D-5L at randomisation and follow-up.

Results

A total of 450 women were randomised to planned delivery, 451 to expectant management: 187 and 170 women, respectively, had complete data at 24 months. Planned delivery resulted in a significantly lower mean cost per woman and infant(s) over 24 months [–£2711, 95% confidence interval (CI) –4840 to –637], with a mean incremental difference in QALYs of 0.019 (95% CI –0.039 to 0.063). Short-term and 24-month infant costs were not significantly different between the intervention arms. There is a 99% probability that planned delivery is cost-effective at all thresholds below £37,000 per QALY gained.

Conclusion

There is a high probability that planned delivery is cost-effective compared to expectant management. These results need to be considered alongside clinical outcomes and in the wider context of maternity care.

Trial registration

ISRCTN registry ISRCTN01879376. Registered 25 November 2013.

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Two-year follow-up of infant and maternal outcomes after planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial

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Abstract

Objective

We evaluated the best time to initiate delivery in late preterm pre-eclampsia in order to optimise long-term infant and maternal outcomes.

Design

Parallel-group, non-masked, randomised controlled trial.

Setting

46 UK maternity units.

Population

Women with pre-eclampsia between 34⁺⁰ and 36⁺⁶ weeks' gestation, without severe disease, were randomised to planned delivery or expectant management.

Primary long-term outcome

Infant neurodevelopmental outcome at 2 years of age, using the PARCA-R (Parent Report of Children's Abilities-Revised) composite score.

Results

Between 29 September 2014 and 10 December 2018, 901 women were enrolled in the trial, with 450 allocated to planned delivery and 451 to expectant management. At 2-year follow-up, the intention-to-treat analysis population included 276 women (290 infants) allocated to planned delivery and 251 women (256 infants) to expectant management. The mean composite standardised PARCA-R scores were 89.5 [standard deviation (SD) 18.2] in the planned delivery group and 91.9 (SD 18.4) in the expectant management group, with an adjusted mean difference of -2.4 (95% CI -5.4 to 0.5) points.

Conclusion

In infants of women with late preterm pre-eclampsia, average neurodevelopmental assessment at 2 years lies within the normal range, regardless of whether planned delivery or expectant management is pursued. Because of lower than anticipated follow-up, there was limited power to demonstrate these scores were not different, but the small between-group difference in PARCA-R scores is unlikely to be clinically important.

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Prognostic indicators of severe disease in late preterm pre-eclampsia to guide decision making on timing of delivery: the PEACOCK study

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Abstract

Objective

To assess the diagnostic performance of angiogenic biomarkers in determining need for delivery in seven days in women with late preterm preeclampsia.

Study design

In a prospective observational cohort study in 36 maternity units across England and Wales, we studied the diagnostic accuracy of placental growth factor (PlGF) and sFlt-1 in determining the risk of complications requiring delivery in late preterm (34⁺⁰ to 36⁺⁶ weeks' gestation) preeclampsia. Angiogenic biomarkers were measured using the Quidel (PlGF) and Roche (sFlt-1 : PlGF ratio) assays. Additional clinical data was obtained for use within the established 'Prediction of complications in early-onset pre-eclampsia' (PREP)-S prognostic model. Biomarkers were assessed using standard methods (sensitivity, specificity, Receiver Operator Curve areas). Estimated probability of early delivery from PREP-S was compared to actual event rates.

Main outcome measures

Clinically indicated need for delivery for pre-eclampsia within seven days.

Results

PlGF (Quidel) testing had high sensitivity (97.9%) for delivery within seven days, but negative predictive value was only 71.4%, with low specificity (8.4%), with similar results from sFlt-1/PlGF assay. The area under the curve for PlGF was 0.60 (SE 0.03), and 0.65 (0.03), and 0.64 (0.03) for PREP-S in combination with PlGF, and sFlt-1 : PlGF, respectively.

Conclusions

Angiogenic biomarkers do not add to clinical assessment to help determine need for delivery for women with late preterm pre-eclampsia. Existing models developed in women with early-onset pre-eclampsia to predict complications cannot be used to predict clinically indicated need for delivery in women with late preterm pre-eclampsia.

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