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Short communication

Factors influencing perinatal outcomes in women with preterm preeclampsia: A secondary analysis of the PHOENIX trial

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ABSTRACT

This secondary analysis of the PHOENIX trial (evaluating planned delivery against expectant management in late preterm preeclampsia) demonstrates that in women who started induction of labour, 63% of women delivered vaginally (56% at 34 weeks' gestation). Compared to 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 intervention groups at all gestational windows. Neonatal unit admission was increased by earlier gestation at delivery, development of severe preeclampsia, and being small-for-gestational age.

1. Introduction

National guidance in the UK for women with late preterm preeclampsia recommends expectant management until 37 weeks' gestation, with intervention only if the woman develops severe preeclampsia or associated complications [1]. The PHOENIX (Planned early delivery or expectant management for late preterm preeclampsia) trial was a large, multicentre, randomised controlled trial comparing planned delivery with expectant management in 901 women with preeclampsia between 34 and 37 weeks' gestation [2]. This trial demonstrated that planned delivery reduced maternal morbidity and severe hypertension compared to expectant management. However, planned delivery was also found to be associated with an increase in neonatal unit admission related to prematurity, but with no evidence of greater neonatal morbidity. The aim of this planned secondary analysis was to evaluate the likelihood of successful vaginal delivery after induction of labour and to determine factors associated with neonatal unit admission, stratified by gestational age.

2. Methods

This was a planned secondary analysis of the PHOENIX trial (ISRCTN 01879376), and full details of the trial can be found within the protocol [3] and published short-term results [2]. Women aged 18 years and above with confirmed preeclampsia or superimposed preeclampsia [4] between 34^{+0} and 36^{+6} weeks' gestation were recruited from 46 maternity units across England and Wales. Participants were randomly allocated to planned delivery (within 48 h of randomisation to allow for corticosteroid administration and neonatal cot availability if necessary) or expectant management using a 1:1 ratio. The main trial results have been reported.[2] Action on Pre-eclampsia, the national patient support charity, advised on the design of this secondary analysis to ensure that relevant outcomes were studied.

Vaginal delivery after induction of labour was defined as spontaneous or assisted vaginal delivery after induction of labour. For evaluation of neonatal unit admission, all infants were included in this analysis. Infant characteristics were described by randomisation group and by week of gestational age at randomisation. Maternal and infant risk factors for neonatal unit admission were estimated using logistic

Abbreviations: ACS, antenatal corticosteroids; CS, Caesarean section; IUGR, Intrauterine growth restriction; SGA, Small-for-gestational age.

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Table 1
Mode of delivery and principal recorded indication for neonatal unit admission by gestation at randomisation and trial allocation.

	34 weeks		35 weeks		36 weeks	
	Planned delivery	**Expectant management**	**Planned delivery**	**Expectant management**	**Planned delivery**	**Expectant management**
Maternal outcomes	**N = 131**	**N = 135**	**N = 136**	**N = 131**	**N = 180**	**N = 184**
Mode of delivery						
Pre-labour caesarean section	47 (36%)	65 (48%)	56 (41%)	38 (29%)	37 (21%)	49 (27%)
Vaginal	46 (35%)	42 (31%)	44 (40%)	53 (40%)	102 (57%)	89 (48%)
Emergency caesarean section	38 (29%)	28 (21%)	26 (19%)	40 (31%)	41 (23%)	46 (25%)
Mode of delivery (following induction)						
Vaginal	46/83 (55%)	36/63 (57%)	54/81 (67%)	49/86 (57%)	100/142 (70%)	82/124 (66%)
Emergency caesarean section	37/83 (45%)	27/63 (43%)	27/81 (33%)	37/86 (43%)	42/142 (30%)	42/124 (34%)
Infant outcomes	**N = 136**	**N = 143**	**N = 148**	**N = 141**	**N = 187**	**N = 191**
Median (IQR) gestation at delivery (days)	243 (241–245)	247 (243–254)	250 (248–252)	256 (252–259)	258 (256–260)	260 (259–262)
Gestation at delivery ≥ 37 weeks	1 (<1%)	21 (15%)	4 (3%)	49 (37%)	77 (43%)	144 (78%)
Birthweight						
Median (IQR) birthweight (g)	2085 (1868–2403)	2171 (1971–2464)	2318 (2054–2690)	2400 (2140–2830)	2660 (2450–2915)	2720 (2473–3090)
Median (IQR) birthweight centile [7]	33 (15–60)	26 (11–46)	30 (14–59)	30 (12–59)	42 (20–65)	42 (18–74)
Birthweight less than tenth centile [7]	22 (16%)	35 (25%)	30 (20%)	32 (23%)	22 (12%)	28 (15%)
Neonatal unit admission						
Infants admitted to neonatal unit	96 (71%)	81 (57%)	66 (45%)	43 (31%)	34 (18%)	35 (18%)
Median (IQR) total days in neonatal unit	7 (3–12)	11 (4–15)	4 (2–10)	4 (1–8)	3 (1–8)	4 (1–7)
Principal indication for admission						
Prematurity	54/96 (56%)	29/81 (36%)	27/66 (41%)	10/43 (23%)	2/34 (6%)	1/35 (3%)
Respiratory disease	25/96 (26%)	19/81 (23%)	12/66 (18%)	10/43 (23%)	10/34 (29%)	12/35 (34%)
Hypoglycaemia	7/96 (7%)	12/81 (15%)	8/66 (12%)	11/43 (26%)	6/34 (18%)	8/35 (23%)
Jaundice	2/96 (2%)	4/81 (5%)	5/66 (8%)	4/43 (9%)	5/34 (15%)	3/35 (9%)
Infection suspected/ confirmed	1/96 (1%)	6/81 (7%)	4/66 (6%)	2/43 (5%)	4/34 (12%)	4/35 (11%)
IUGR/ SGA	3/96 (3%)	6/81 (7%)	4/66 (6%)	3/43 (7%)	1/34 (3%)	1/35 (3%)
Other	4/96 (4%)	5/81 (6%)	6/66 (9%)	3/43 (7%)	6/34 (18%)	6/35 (17%)
Neonatal morbidity (recorded at discharge)						
Need for respiratory support	24 (18%)	29 (20%)	11 (7%)	9 (6%)	10 (5%)	10 (5%)
Hypoglycaemia	34 (25%)	34 (24%)	24 (16%)	23 (16%)	22 (12%)	15 (8%)

Data are median (IQR) or n (%) unless otherwise stated. IQR: interquartile range. IUGR: intrauterine growth restriction. SGA: Small for gestational age.

regression, expressed as odds ratios with 95% confidence intervals as appropriate. Randomisation group was included as a potential factor (with all infants analysed according to the group into which their mother was allocated). Significant predictors including trial allocation, severe maternal hypertension, severe preeclampsia, gestation at delivery, small-for-gestational age, mode of delivery and administration of antenatal corticosteroids were adjusted for, and the adjusted estimates were considered primary with regards to inference.

Table 2
Effect of maternal and infant characteristics on neonatal unit admission. N = all infants unless otherwise stated.

	Number of infants (N)	**Neonatal unit admission (n, %)**	**Unadjusted odds ratio (95% CI)**	**Adjusted odds ratio* (95% CI)**
Trial allocation				
Planned delivery (vs expectant management)	471	196 (42%)	1.43 (1.10–1.86)	0.98 (0.70–1.35)
Maternal characteristics				
Maternal diabetes (pre- and gestational) (vs none)	163	66 (40%)	1.16 (0.82–1.63)	–
Maternal severe hypertension before delivery (≥160 mmHg) (vs none)	611	249 (41%)	1.47 (1.11–1.96)	0.52 (0.26–1.04)
Progression to severe preeclampsia (vs none)	655	270 (41%)	1.68 (1.25–2.27)	**2.35 (1.14–4.79)**
Infant characteristics				
SGA (<10th centile)	169	94 (56%)	2.47 (1.76–3.47)	**3.11 (2.12–4.58)**
Twin pregnancy (vs singleton)	94	32 (34%)	0.87 (0.55–1.36)	–
Gestation at delivery				
≥37 weeks	296	50 (17%)	Referent	–
36 weeks	297	87 (29%)	2.04 (1.38–3.04)	**2.09 (1.36–3.23)**
35 weeks	215	106 (49%)	2.78 (3.21–7.22)	**4.65 (2.91–7.52)**
34 weeks	136	112 (82%)	22.96 (13.66–39.97)	**25.52 (14.06–47.92)**
Delivery				
ACS given (vs ACS not given)	575	260 (45%)	2.43 (1.83–3.25)	0.96 (0.67–1.39)
Mode of delivery				
Vaginal delivery	394	113 (29%)	Referent	–
Pre-labour CS	322	150 (47%)	2.17 (1.59–2.96)	1.36 (0.94–1.98)
Emergency CS	228	92 (40%)	1.68 (1.19–2.37)	1.40 (0.94–2.08)

*Estimates calculated using multivariable logistic regression, adjusted for variables that were significant on univariable analysis (shown in unadjusted odds ratio column): trial allocation, maternal severe hypertension, progression to severe preeclampsia, SGA, gestation at delivery, ACS given, mode of delivery. SGA: Small for gestational age. ACS: antenatal corticosteroids. CS: Caesarean section.

All statistical analyses were performed using R, version 4.0.3.

3. Results

Of 901 women recruited, 897 women were included in this analysis (2 withdrew consent and there were missing data for this analysis for 2 women), of which 447 were randomised to planned delivery and 450 to expectant management. Baseline characteristics for these women are presented in Supplementary Table 1. 579 of these women underwent induction of labour and 367 of these (63%) had a vaginal delivery. Rates of vaginal (assisted or spontaneous) delivery were similar in the planned delivery (200/304; 66%) and expectant management (167/275; 61%) groups (adjusted Risk Ratio (aRR) 1.08, 95% CI 0.96–1.22). In the trial, 56.1% of women undergoing induction of labour at 34 weeks, 61.6% at 35 weeks and 68.4% at 36 weeks delivered vaginally. Vaginal delivery rates were similar between those allocated to planned delivery or expectant management when stratified by gestational weeks at enrolment (Table 1).

In women randomised to planned delivery, a higher proportion of infants were admitted to the neonatal unit at 34 (71% vs 57%) and 35 (45% vs 31%) weeks, compared with those women allocated to expectant management, though not at 36 weeks (both 18%). Median birthweight centile was greater in infants born to women randomised to planned delivery at 34 weeks (33 vs 26), but not at 35 or 36 weeks. Across all gestations, planned delivery was associated with fewer babies born small-for-gestational age (<10th centile) compared to those allocated to expectant management (16% vs 25% at 34 weeks, 20% vs 23% at 35 weeks, 12% vs 15% at 36 weeks). Neonatal unit length of stay, need for respiratory support and hypoglycaemia (assessed through recording at discharge) were similar between planned delivery and expectant management groups, at all gestational ages. Predictors at delivery for neonatal unit admission included progression to severe preeclampsia (adjusted Odds Ratio (aOR) 2.35, 95% CI 1.14–4.58), being small-for-gestational age (aOR 3.11, 95% CI 2.12–4.58) or increasing prematurity (36 weeks aOR 2.09, 95% CI 1.36–3.23; 35 weeks aOR 4.65, 95% CI 2.91–7.52; 34 weeks aOR 25.52, 95% CI 14.06–47.92) (Table 2). Delivery by caesarean section was not associated with an increase in neonatal unit admission compared with vaginal delivery (pre-labour caesarean section aOR 1.36, 95% CI 0.94–1.98, emergency caesarean section aOR 1.40, 95% CI 0.94–2.08).

4. Discussion

In women with late preterm preeclampsia, 63% of women delivered vaginally after induction of labour. Even at 34 weeks' gestation, more than half of the women induced delivered vaginally. Infants in the planned delivery group were more likely to be admitted to the neonatal unit at 34 and 35 weeks' gestation (compared to those managed expectantly), but the indication for admission for these infants was most frequently attributed to prematurity itself, rather than indicators of morbidity. Documented neonatal morbidity at discharge and lengths of stay were similar between the groups, suggesting that these admissions may reflect clinicians' behaviour.

Neonatal unit admission was increased by some factors more common in the planned delivery group, such as earlier gestation at delivery, and by some factors more common in the expectant management group, including development of severe preeclampsia, and being small-for-gestational age. This demonstrates the need to balance the benefits and risks of continuing the pregnancy in a preeclamptic environment, with associated maternal and perinatal sequelae, compared to earlier delivery by a few days and potential increased neonatal unit admission, without additional short-term morbidity.

This was a prespecified secondary analysis of a large multicentre trial, hence the findings are generalisable. Limitations include reporting of secondary, descriptive outcomes from the main trial data.

These findings are supported by other studies in the literature. In a retrospective cohort study of women with preterm preeclampsia in a broader gestational window (23–36 weeks' gestation), a 67% vaginal delivery rate was reported [5]. Another large retrospective cohort demonstrated a reduced risk of neonatal complications (particularly self-limiting respiratory conditions of transient tachypnoea and respiratory distress) with induction when compared to planned caesarean section in women with preeclampsia beyond 34 weeks' gestation [6].

This secondary analysis adds to the findings of the main trial, and to other existing literature, to better inform counselling and shared decision-making regarding timing and mode of delivery in this high-risk group, stratified by gestational age. The risks and benefits of different delivery strategies can now be tailored to an individual woman's gestation, particularly around provision of information that there do not appear to be clinically important differences in indicators of neonatal morbidity (such as need for respiratory support) across this gestational age range. There is still a trade off between increased rates of neonatal unit admission (though of shorter median length) at 34 weeks' gestation with planned delivery versus lower rates of small-for-gestational age infants with this management strategy. Further studies should consider how we improve discrimination of those women and babies at higher risk of adverse outcome in late preterm preeclampsia, for more targeted and individualised care.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2021.10.002.

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