Planned delivery or expectant management in preeclampsia: an individual participant data meta-analysis

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OBJECTIVE: Pregnancy hypertension is a leading cause of maternal and perinatal mortality and morbidity. Between 34^{+0} and 36^{+6} weeks gestation, it is uncertain whether planned delivery could reduce maternal complications without serious neonatal consequences. In this individual participant data meta-analysis, we aimed to compare planned delivery to expectant management, focusing specifically on women with preeclampsia.

DATA SOURCES: We performed an electronic database search using a prespecified search strategy, including trials published between January 1, 2000 and December 18, 2021. We sought individual participant-level data from all eligible trials.

STUDY ELIGIBILITY CRITERIA: We included women with singleton or multifetal pregnancies with preeclampsia from 34 weeks gestation onward.

METHODS: The primary maternal outcome was a composite of maternal mortality or morbidity. The primary perinatal outcome was a composite of perinatal mortality or morbidity. We analyzed all the available data for each prespecified outcome on an intention-to-treat basis. For primary individual patient data analyses, we used a 1-stage fixed effects model.

RESULTS: We included 1790 participants from 6 trials in our analysis. Planned delivery from 34 weeks gestation onward significantly reduced the risk of maternal morbidity (2.6% vs 4.4%; adjusted risk ratio, 0.59; 95% confidence interval, 0.36—0.98) compared with expectant management. The primary composite perinatal outcome was increased by planned delivery (20.9% vs 17.1%; adjusted risk ratio, 1.22; 95% confidence interval, 1.01—1.47), driven by short-term neonatal respiratory morbidity. However, infants in the expectant management group were more likely to be born small for gestational age (7.8% vs 10.6%; risk ratio, 0.74; 95% confidence interval, 0.55—0.99).

CONCLUSION: Planned early delivery in women with late preterm preeclampsia 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 potential benefits and risks of prolonging a pregnancy complicated by preeclampsia should be discussed with women as part of a shared decision-making process.

Key words: expectant management, fetal growth restriction, infant outcomes, neonatal outcomes, obstetrics, planned delivery, preeclampsia, pregnancy hypertension, preterm birth, respiratory distress syndrome

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AJOG at a Glance

Why was this study conducted?

There is limited evidence regarding the optimal timing of delivery in late preterm preeclampsia, and single studies have not produced robust conclusions.

Key findings

Planned delivery from 34 weeks onward in women with preeclampsia significantly reduces maternal morbidity (adjusted risk ratio [RR], 0.59; 95% confidence interval [CI], 0.36−0.98) and the incidence of infants born small for gestational age (RR, 0.74; 95% CI, 0.55−0.99) but increases short-term neonatal respiratory morbidity (adjusted RR, 1.22; 95% CI, 1.01−1.47). The risk of short-term neonatal respiratory morbidity was lower in more recent trials where the use of antenatal steroids was higher.

What does this add to what is known?

This is the first individual patient data meta-analysis to evaluate planned delivery in women with preeclampsia at late preterm gestations. We have quantified the effect of planned delivery from 34 weeks onward on infant outcomes more precisely, demonstrating a reduction in the risk of infants being born small for gestational age but an increase in short-term neonatal respiratory morbidity. Evidence to guide clinical practice in this area is lacking. Our analysis provides more accurate information on the risks and benefits of planned delivery for preeclampsia without severe features from 34 weeks onward.

Introduction

Pregnancy hypertension is responsible for at least 27,800 maternal deaths[1] worldwide every year and 500,000 infant deaths,[2] including approximately 200,000 stillbirths.[3] Although the prevalence of preeclampsia varies throughout the world, it complicates between 2% and 3% of pregnancies in a high-income setting.[4] Estimates for low- and middle-income countries are higher, with up to 12% of pregnancies affected in these settings.[2] Delivery is the only definitive management for this progressive and unpredictable condition, and it is routinely recommended for all women with preeclampsia from 37 weeks gestation onward.[5] At gestations up to 34 weeks, if there are no immediate indications for delivery, expectant management is preferable because of the neonatal risks associated with early preterm birth.[5]

It is less clear whether a policy of expectant management in the late preterm period (34−37 weeks) should be pursued, although if severe features of preeclampsia develop or the woman reaches 37 weeks, delivery is indicated. However, there is uncertainty as to whether a policy of routine immediate delivery at this gestational window (34−37 weeks) could reduce maternal complications without serious neonatal consequences. Several studies have compared these 2 strategies in women with hypertensive disorders of pregnancy (including preeclampsia) from 34 weeks.[6−12] However, it has not been possible to draw firm conclusions from individual studies alone. Recent meta-analyses[13,14] and individual participant data (IPD) meta-analyses[15] of women with hypertensive disorders of pregnancy have shown that planned early delivery from 34 weeks gestation reduces maternal complications, but the neonatal impact remains unclear. These reviews generally grouped all hypertensive disorders of pregnancy together, combining women with chronic hypertension, gestational hypertension, and preeclampsia. However, the underlying pathophysiology of preeclampsia is distinct, with maternal endothelial dysfunction leading to multiorgan complications and potentially severe maternal and fetal outcomes. The optimal timing of delivery in preeclampsia may therefore differ compared with other hypertensive disorders of pregnancy, and the balance of risks and benefits for the infant should also be considered within the context of this rapidly progressive and unpredictable disease. A limited subgroup analysis conducted as part of the previous IPD meta-analysis[15] in women with all types of pregnancy hypertension identified women with preeclampsia as a population in whom planned delivery may confer significant benefit. The authors therefore highlighted a need to evaluate the impact of this intervention specifically in women with preeclampsia. Since this meta-analysis was published, a new trial has been reported,[6] enrolling more women with preeclampsia than all previously included trials combined. This enabled us to conduct an IPD meta-analysis evaluating the timing of delivery on a wider set of maternal and perinatal outcomes in this high-risk group of women with preeclampsia. A meta-analysis evaluating early delivery or expectant management for late preterm preeclampsia was recently published.[16] However, this study was limited by its inclusion of just 3 randomized controlled trials, only 2 of which were used to evaluate the coprimary outcome of neonatal intensive care unit admission. Our IPD meta-analysis is strengthened by its ability to harmonize data to overcome inconsistencies in outcome definitions between trials and to evaluate key outcomes such as neonatal morbidity, in more detail.

Objective

The objective of this study was to undertake an IPD meta-analysis focusing on women with preeclampsia alone. In women with preeclampsia from 34 weeks gestation onward, this study aimed to evaluate the effect of planned early delivery on maternal mortality or morbidity and perinatal mortality or morbidity compared with expectant management using IPD from randomized controlled trials. The use of IPD enabled us to target our review to women with late preterm preeclampsia and to perform subgroup analyses and adjustments that would not be possible with the use of aggregate data, for

example, using blood pressure values to reflect the severity of disease. This is clinically relevant, because the presence of additional risk factors in women with preeclampsia may alter management options.

Methods

Search strategy and study selection

We followed a protocol and statistical analysis plan published in the PROSPERO registry in accordance with PRISMA-IPD guidance.[17] We included studies that were randomized controlled trials comparing planned early delivery with expectant management in women presenting with preeclampsia from 34 weeks gestation onward. Cluster randomized trials or studies with a quasi-randomized design were excluded. To identify the eligible studies, we electronically searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE, and ClinicalTrials.gov using the search terms "pre-eclampsia" OR "preeclampsia" AND "delivery" OR "birth" with the limits "human" and "randomized controlled trial." The final search date was December 18, 2021. We did not restrict our search by language. We excluded trials published before the year 2000. This was because of changes in clinical practice, care of women with preeclampsia, and neonatal care over time such that the findings from earlier trials may be difficult to interpret. To ensure that the search was comprehensive, we also hand-searched the reference lists of the retrieved studies and any relevant reviews identified. Two independent review authors (A.B.G. and J.F.) assessed all the studies identified by the search strategy against the study-level inclusion criteria. Any disagreement was resolved through discussion or with a third review author (not required), if necessary.

Eligibility criteria

We included women with singleton or multifetal pregnancies presenting with preeclampsia or superimposed preeclampsia from 34 weeks gestation onward. The definition of preeclampsia or superimposed preeclampsia was that used by the study at the time. All the definitions used would now be encompassed by the current International Society for the Study of Hypertension in Pregnancy (ISSHP) 2018 diagnostic criteria.[18]

Data extraction

We sought participant-level data from the authors of all eligible trials. The available data were extracted from trial databases (provided via a data-sharing agreement) according to prespecified variables by 2 of the review authors (A.B.G. and P.S.). The data were recoded into a common format, and the definitions of key characteristics, diagnoses (eg, preeclampsia), and outcomes were harmonized. A final dataset was then produced and rechecked for accuracy and completeness.

Assessment of risk of bias

Two review authors (A.B.G. and J.F.) independently assessed the included trials for risk of bias using the Cochrane risk-of-bias tool.[19]

Outcomes

The primary maternal outcome was a composite of maternal mortality and severe maternal morbidity (adapted from a previously published composite derived by Delphi consensus).[20] The presence of severe maternal morbidity was defined as 1 or more of the following individual components: maternal death, eclampsia, stroke, pulmonary edema, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, acute renal insufficiency, and placental abruption. The primary perinatal outcome was a composite of perinatal mortality or morbidity. This was defined as any 1 of perinatal death, neonatal death, or neonatal morbidity. The selection of components was guided by recent recommendations for core outcome sets in preeclampsia.[21] Neonatal morbidity was defined as 1 or more of respiratory disease (any one of respiratory distress syndrome, need for respiratory support, neonatal unit admission for respiratory disease or bronchopulmonary dysplasia), central nervous system complications (any 1 of intraventricular hemorrhage, intracerebral hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, cerebral infarction, or convulsions), culture-proven sepsis, necrotizing enterocolitis, hypoglycemia requiring intravenous glucose or neonatal unit admission, or jaundice requiring neonatal unit admission. If data were missing (ie, not collected for a particular component) for either of the composite outcomes, we treated it as absent. The secondary maternal outcomes included severe postpartum hemorrhage, progression to severe hypertension, thromboembolic disease, hepatic dysfunction, onset of delivery, and admission to maternal intensive care unit. The secondary perinatal outcomes were gestational age at delivery, mode of delivery, birthweight, birthweight centile, baby sex, small for gestational age (<3rd centile or <10th centile), admission to neonatal unit, admission to neonatal intensive care unit, 5-minute Apgar score <7, and arterial pH <7.05.

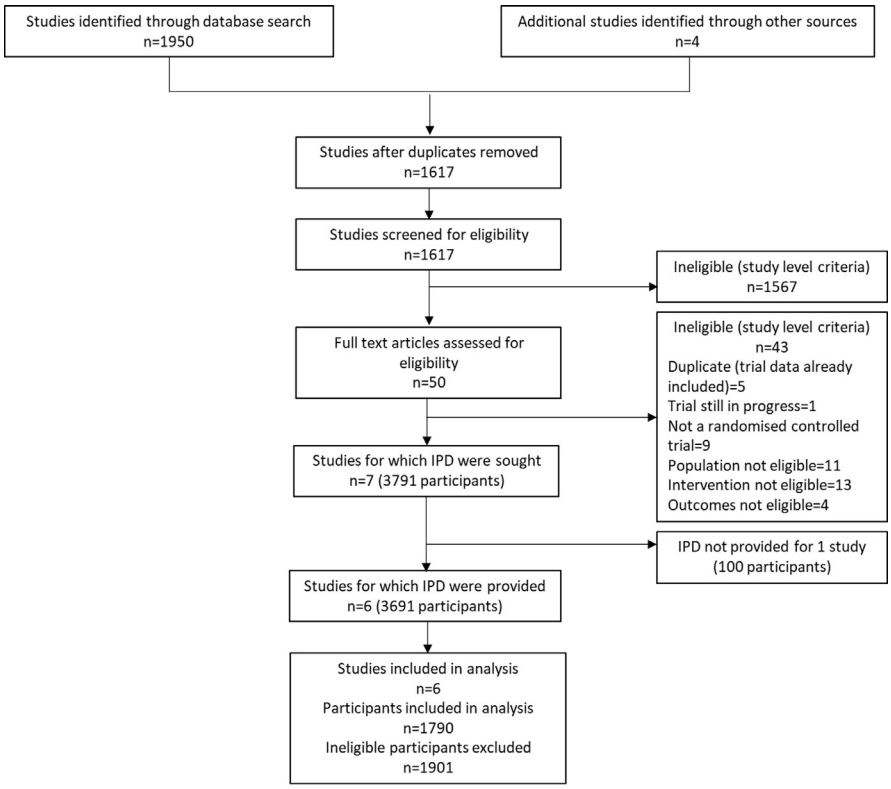
Data synthesis

We analyzed all available data for baseline maternal characteristics at enrolment, related process outcomes (such as time from randomization to delivery) and the data for each prespecified outcome on an intention-to-treat basis. In each study, all the outcomes of interest were either reported completely with <5% missingness or not reported at all. Under these circumstances, multiple imputation is not feasible or recommended, and we therefore analyzed all the outcomes without imputation. For primary IPD meta-analyses, we used a 1-stage fixed-effect model. Standard errors, confidence intervals (CIs), and *P* values were adjusted for clustering within studies. In addition, we used robust standard errors to correct for clustering of twin pregnancies by the mother for the perinatal outcomes.[22] We set out to calculate the odds ratios using multilevel models as originally outlined in the statistical analysis plan. However, this multilevel model structure did not converge, as there were not sufficient datapoints at each of the levels. We therefore performed a multivariate

analysis, calculating risk ratios for binary outcomes and mean differences for continuous outcomes using a simpler fixed-effects model. We also calculated unadjusted risk differences. A fixed-effects, 1-stage analysis such as this is appropriate where there are small studies with rare event numbers. We gave a separate intercept for each trial but assumed the same treatment effect (ie, we used fixed effects for each trial).

The numbers needed to treat or harm with 95% CIs were calculated for outcomes where a significant difference between the management groups was found. The analysis was adjusted for study, gestational age at randomization (34^{+0}–34^{+6} weeks, 35^{+0}–35^{+6} weeks, 36^{+0}–36^{+6} weeks, 37^{+0}–37^{+6} weeks, 38^{+0}–38^{+6} weeks, 39^{+0}–39^{+6} weeks, 40^{+0} weeks and above), severity of systolic hypertension at study entry (<150 vs ≥ 150 mm Hg), parity (primiparous vs multiparous), and number of fetuses (singleton vs all other). The severity of systolic hypertension at study entry was chosen, because it is an objective marker of disease severity consistently available across studies, and there is a known dose–response relationship between increasing blood pressure and adverse pregnancy outcomes.[23–25] We calculated and used the average value (or proportion for categorical variables) across all studies, where these prespecified adjustment variables were missing. We did not use multiple imputation methods, as they are not recommended in this scenario. Subgroup analysis was conducted if there were at least 10 events in each subgroup; this was also done using a 1-stage, fixed-effects model. The prespecified subgroups were study, gestational age at randomization, parity, singleton vs multifetal pregnancy, previous cesarean delivery, prerandomization diabetes of any type, superimposed preeclampsia, and suspected fetal growth restriction at enrolment. Because many of the subgroups concerned the same adjustment variables used for our main analysis (including some additional subgroups of clinical relevance), our subgroup analysis was unadjusted to better delineate the effect of these variables. Heterogeneity was assessed using I^2 (the proportion of the total variance of the outcome that is between studies rather than between subjects within studies) as part of the subgroup analysis. We have also presented values for tau.[2] No additional analyses were undertaken. This IPD meta-analysis was prospectively registered with PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020206425).

FIGURE 1
Flowchart summarizing search results



IPD, individual participant data.

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Results

Study selection

We identified 1617 references after duplicates were removed (Figure 1). A total of 1567 references were excluded after title screening, and 43 were excluded after abstract and full-text screening. Seven trials (3791 participants) were considered eligible for inclusion at study-level. One trial (100 participants) was subsequently excluded, as the trial authors did not respond to our request for participant-level data despite several attempts.[26] The only published data available from this trial were a conference abstract, and therefore we were not able to include any aggregate data for this trial. Six trials[6–11] with participant-level data were available. Following data extraction and review by 2 authors, 1901 participants were deemed ineligible for inclusion in this IPD meta-analysis principally because of women being enrolled with conditions other than preeclampsia or before 34 weeks gestation, with the reasons given for exclusion in Table 1. The remaining 1790 participants from 6 trials were therefore included in our analysis.

Study characteristics

A summary of characteristics of included studies, including details of the interventions, can be found in Table 1 and Supplementary Tables S1 and S2. Two trials (GRIT and DIGITAT) enrolled

TABLE 1
Characteristics of included studies

Study	Setting	Total participants enrolled (n)	Trial participants (inclusion criteria): Gestational age (wk)	Singleton or twin pregnancy	Diagnosis	Eligible for IPD (n)	Noneligible for IPD (n)
GRIT GRIT Study Group,[11] 2003	69 hospitals in 13 European countries	548 planned delivery n=296, expectant management=292	24^{+0} to 36^{+0}	Singleton or twin	Fetal compromise with an umbilical artery Doppler waveform recorded (including pregnancies complicated by preeclampsia)	15 planned delivery n=15, expectant management n=5	493 randomized before 34 wk; 40 no preeclampsia at study entry
HYPITAT Koopmans et al,[9] 2009	38 hospitals in The Netherlands	756 planned delivery n=377, expectant management=379	36^{+0} to 41^{+0}	Singleton	Gestational hypertension or preeclampsia without severe features[a]	246 planned delivery n=123, expectant management n=123	510 no preeclampsia at study entry
DIGITAT Boers et al,[10] 2010	52 hospitals in The Netherlands	650 planned delivery n=321, expectant management n=329	36^{+0} to 41^{+0}	Singleton	Suspected intrauterine growth restriction (including pregnancies complicated by preeclampsia)	45 planned delivery, n=18, expectant management n=27	605 no preeclampsia at study entry
Deliver or Deliberate Owens et al,[8] 2014	1 hospital in the United States	169 planned delivery n=97, expectant management n=86	34^{+0} to 36^{+6}	Singleton or twin	Preeclampsia (ACOG 2002 criteria) without any other maternal-fetal complications	165 planned delivery, n=93, expectant management n=72	4 randomized before 34 wk
HYPITAT II Broekhuijsen et al,[7] 2015	51 hospitals in The Netherlands	703 planned delivery n=352, expectant management, n=351	34^{+0} to 36^{+6}	Singleton or twin	Any hypertensive disorder of pregnancy without severe features[a]	420 planned delivery n=209, expectant management n=211	4 randomized before 34 wk; 283 no preeclampsia at study entry
PHOENIX Chappell et al,[6] 2019	46 hospitals in England and Wales	901 planned delivery n=450, expectant management n=451	34^{+0} to 36^{+6}	Singleton or twin	Preeclampsia (ISSHP 2014 criteria), not requiring immediate delivery	899 planned delivery, n=448, expectant management n=451	2 withdrew from trial

ACOG, American College of Obstetricians and Gynecologists; *IPD*, individual participant data; *ISSHP*, International Society for the Study of Hypertension in Pregnancy.

[a] Preeclampsia defined as a diastolic blood pressure of 90 mm Hg or higher measured on 2 occasions at least 6 hours apart, combined with proteinuria.

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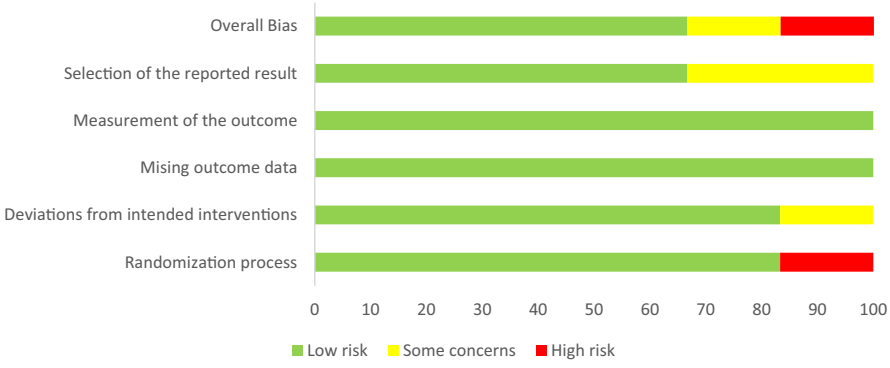
women with suspected fetal growth restriction on ultrasound, including those with pregnancies complicated by preeclampsia, over a wide gestational age range. The HYPITAT and HYPITAT II trials enrolled women with any hypertensive disorder of pregnancy from 36^{+0} and 34^{+0} weeks gestation onward, respectively. The PHOENIX trial and Deliver or Deliberate trial focused specifically on women with preeclampsia (without severe features) between 34^{+0} and 36^{+6} weeks gestation. None of the trials enrolled women with severe features of preeclampsia or any other indications for immediate delivery. This was stated in each of their inclusion criteria (Table 1), with severe features defined in accordance with the relevant guidelines at the time (primarily American College of Obstetricians and Gynecologists or ISSHP criteria). These are consistent with current definitions.[27] For the purposes of this IPD meta-analysis, we selected only those participants who met our eligibility criteria as described in the section above.

FIGURE 2
Risk of bias (using Cochrane RoB 2 tool) presented as percentage across all included studies



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Risk of bias of included studies

The results of our risk of bias assessment using the Cochrane Risk of Bias 2 tool can be found in Figures 2 and 3. The PHOENIX and HYPITAT trials were prospectively registered in a clinical trials registry (before enrolment of the first participants). The GRIT, DIGITAT, Deliver or Deliberate, and HYPITAT II trials were retrospectively registered. Four of the included trials were assessed as being at a low risk of bias. The HYPITAT II trial had some concerns because of minor discrepancies between the published protocol and final paper. The Deliver or Deliberate trial

FIGURE 3
Risk of bias summary (using Cochrane RoB 2 tool) about each risk of bias domain for each included study

	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
GRIT *GRIT Study Group* (2003)	+	+	+	+	+	+
HYPITAT I *Koopmans* (2009)	+	+	+	+	+	+
DIGITAT *Boers* (2010)	+	+	+	+	+	+
Deliver or Deliberate *Owens* (2014)	-	!	+	+	!	-
HYPITAT II *Broekhuijsen* (2015)	+	+	+	+	!	!
PHOENIX *Chappell* (2019)	+	+	+	+	+	+

Key
- - High risk
- ! Some concerns
- + Low risk

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was judged to be at a high risk of bias. This was primarily because of limited reporting regarding the randomization process and an imbalance in the final analysis population suggesting postrandomization exclusions. Supplementary Tables S3 and S4 describe the missing data for each maternal and perinatal variable by study. Missing data were usually because of the outcome not being collected, with very few cases of missing data because of incomplete reporting or exclusion.

Synthesis of results

The baseline maternal characteristics at enrolment were similar across the planned delivery and expectant management groups (Table 2). Importantly, the proportion of women with suspected fetal growth restriction and severe hypertension at enrolment (Table 2) was balanced between the 2 management groups as expected with randomization. None of the trials enrolled women with severe features of preeclampsia. However, we acknowledge that some participants may have transiently had high blood pressure readings before enrolment. This alone would not be an indication for delivery.[18] The difference in median time between the 2 groups from randomization to delivery was 4.0 (95% CI, 3.0−4.0) days. One-stage meta-analysis found that planned delivery from 34 weeks gestation onward significantly reduced the risk of major maternal morbidity (2.6% vs 4.4%; adjusted risk ratio [aRR], 0.59; 95% CI, 0.36−0.98; *P*=.041) compared with expectant management (Table 3). This direction of effect was also consistent across the secondary maternal outcomes (Table 4), with a significant reduction in postrandomization severe hypertension (risk ratio [RR], 0.80; 95% CI, 0.73−0.87). The primary composite perinatal outcome of perinatal mortality (stillbirth or early neonatal death) or morbidity was increased by planned delivery (20.9% vs 17.1%; aRR, 1.22; 95% CI, 1.01−1.47; *P*=.040). This result was driven by a significant increase in neonatal respiratory disease (RR, 1.41; 95% CI, 1.05−1.90) (Table 5). Neonatal unit admission was also increased among infants born to mothers in the planned delivery arm (RR, 1.21; 95% CI, 1.08−1.36) (Table 6). However, infants in the planned delivery group were less likely to be born small for gestational age, both <3rd centile (RR, 0.74; 95% CI, 0.55−0.99) and <10th centile (RR, 0.82; 95% CI, 0.70−0.97). As expected, given the nature of the intervention, there was an adjusted mean difference of −0.61 weeks in the gestational age at delivery between infants in the planned delivery and expectant management groups and an adjusted mean difference of −127.28 g in birthweight between the 2 groups (Table 6). There was no significant difference in vaginal delivery between the planned delivery and expectant management groups. The observed difference in the primary perinatal outcome between the allocated groups was largely driven by a difference in respiratory distress syndrome, seen mainly in infants from trials conducted earlier in the time period (the HYPITAT II trial between 2009 and 2013 and the Deliver or Deliberate trial between 2002 and 2008). The individual components of the respiratory disease composite outcome by study are shown in Supplementary Table S5. Overall, there were small numbers of central nervous system complications (individual components of this composite outcome by study are shown in Supplementary Table S6), with babies from the earlier HYPITAT II and GRIT trials (conducted between 1993 and 2001) contributing to most of the cases. The subgroup analyses (Figures 4 and 5) were consistent with the main results. Higher degrees of heterogeneity were seen when analyzed by study and by twin or singleton pregnancy. Subgroup analysis was only undertaken if there were 10 or more events in each subgroup, which meant that the overall effect by study was different to that reported for the overall IPD meta-analysis because of the exclusion of certain trials from the subgroup analysis. A summary of findings and the numbers need to treat and harm are presented in supplementary tables S9 and S10.

TABLE 2
Baseline maternal characteristics at enrolment

Characteristic	n	Planned delivery n=901	n	Expectant management n=889
Maternal age (y; mean [SD])	901	29.56 (6.32)	889	29.97 (6.12)
White European ethnicity	891	618 (69.4)	884	624 (70.6)
No previous births	891	564 (63.3)	884	555 (62.8)
Singleton pregnancy	901	866 (96.1)	889	843 (94.8)
Previous cesarean delivery	780	99 (12.7)	785	101 (12.9)
Prerandomization diabetes	780	94 (12.1)	785	88 (11.2)
Suspected fetal growth restriction	808	124 (15.3)	817	132 (16.2)
Systolic blood pressure≥160 mm Hg	810	227 (28.0)	818	221 (27.0)
Systolic blood pressure≥150 mm Hg	810	442 (54.6)	818	433 (52.9)
Diagnosis of superimposed preeclampsia	675	100 (14.8)	689	113 (16.4)

SD, standard deviation.

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Comment

Principal findings

In this IPD meta-analysis, we show that planned early delivery from 34 weeks gestation onward in women with preeclampsia significantly reduces adverse maternal outcomes and the number of infants born small for gestational age. This was balanced against an increase in the composite perinatal outcome driven by short-term neonatal respiratory morbidity; there was no significant

impact of gestational age on this primary outcome. These results indicate clinically important maternal benefits, and in particular, a reduction in severe hypertension and HELLP syndrome among women allocated to planned delivery. Importantly, the intervention did not increase the risk of cesarean delivery. Information on medical comorbidities was not consistently available across all studies. However, other than singleton or twin pregnancy subgroup analysis for the primary perinatal outcome, there was no significant test of interaction for any pre-enrolment characteristics such that we could not predefine a particular group of pregnant women in whom the impact of the intervention might be different. Most of the participants included in this analysis were classified as White European, which should be taken into account when considering the generalizability of these findings to other populations.

The differences in the incidence of respiratory disease between the management groups was mainly seen among infants born to women from 2 trials, namely HYPITAT II[7] and Deliver or Deliberate,[8] conducted earlier in the time period considered for this meta-analysis. In HYPITAT II, only 8.6% of women randomized to planned delivery received antenatal corticosteroids. Steroid use was not reported in the Deliver or Deliberate trial, though planned delivery took place within 12 hours of randomization, leaving little time for optimal steroid administration. In comparison, 65% of the women in the PHOENIX trial[6] allocated to planned delivery received antenatal corticosteroids; this likely influences the much lower incidence of adverse respiratory outcomes among infants in this trial, with no difference between the 2 management groups. Although we acknowledge that our analysis was not specifically powered to address this question, it is likely that the difference in administration of steroids observed between different time epochs and trial settings explains our perinatal findings. This suggests that appropriately timed antenatal corticosteroid administration mitigates the short-term risk of respiratory complications for infants of women with preeclampsia, as previously demonstrated by a large systematic review.[28] Antenatal corticosteroids have also been shown to reduce infant intraventricular hemorrhage,[28] which is a rare

TABLE 3
Primary maternal outcome

Outcome	Planned delivery n=891	Expectant management n=884	Effect size[a]
Primary composite maternal outcome n (%)	23 (2.6)	39 (4.4)	aRR,[b] 0.59; (0.36–0.98) *P* value=.041
			Unadjusted risk difference (%) −1.8% (−3.5 to −0.1)
Individual components			
Maternal death	0/891 (0.0)	1/884 (0.1)[c]	—
Eclampsia	3/891 (0.3)	6/884 (0.7)	RR, 0.50 (0.12–1.98)
Stroke	0/559 (0.0)	0/550 (0.0)	—
Pulmonary edema	1/798 (0.1)	4/812 (0.5)	RR, 0.25 (0.03–2.27)
HELLP syndrome	12/891 (1.3)	23/884 (2.6)	RR, 0.52 (0.26–1.03)
Renal insufficiency	4/768 (0.5)	6/761 (0.8)	RR, 0.66 (0.19–2.33)
Placental abruption	4/768 (0.5)	4/812 (0.5)	RR, 1.02 (0.26–4.05)

aRR, adjusted risk ratio; *HELLP*, hemolysis, elevated liver enzymes, low platelet count syndrome; *RR*, risk ratio.

[a] Effect sizes are RRs (95% CIs) unless stated otherwise; [b] aRR for study, gestational age at randomization, singleton pregnancy, parity, and severity of hypertension at study entry. Presented as unadjusted RR where the model failed to converge; [c] This death was considered unrelated to trial allocation by the original study authors.

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TABLE 4
Secondary maternal outcomes

Outcome	Planned delivery n=891	Expectant management n=884	Effect size[a]
Postrandomization severe hypertension	396/780 (50.8)	498/785 (63.4)	RR,[b] 0.80 (0.73– 0.87)
Hepatic dysfunction	72/891 (8.1)	96/884 (10.9)	aRR, 0.76 (0.57–1.01)
Thromboembolic disease	1/798 (0.1)	1/812 (0.1)	—
Severe postpartum hemorrhage	87/891 (9.8)	98/884 (11.1)	aRR, 0.88 (0.68–1.15)
Prelabor cesarean delivery	156/797 (19.6)	180/811 (22.2)	RR, 0.88 (0.73–1.07)
Intensive care unit admission	9/589 (1.5)	19/601 (3.2)	aRR, 0.48 (0.22–1.07)
Time from randomization to delivery (d), Median (IQR)	2.0 (1.0–3.0) n=890[c]	6.0 (3.0–10.0) n=883[c]	Difference (95% CI) 4.0 (3.0–4.0)

aRR, adjusted risk ratio; *CI*, confidence interval; *IQR*, interquartile range; *RR*, risk ratio.

[a] Effect sizes are RRs (95% CIs) unless stated otherwise; [b] aRR for study, gestational age at randomization, singleton pregnancy, parity, and severity of hypertension at study entry. Presented as unadjusted RR where model failed to converge; [c] One woman (from each group) excluded because of missing gestational age at delivery.

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TABLE 5
Primary perinatal outcome

Outcome	Planned delivery n = 936	Expectant management n = 935	Effect size[a]
Composite primary perinatal outcome	196 (20.9%)	160 (17.1%)	aRR,[b] 1.22 (1.01–1.47) *P*=.040
			Unadjusted risk difference (%) 3.83 (0.17–7.48)
Individual components	**Planned delivery**	**Expectant management**	**RR**
Stillbirth	0/936 (0.0)	0/935 (0.0)	—
Neonatal death	1/936 (0.1)	0/935 (0.0)	RR, 1.00 (1.00–1.00)
Respiratory disease	95/936 (10.1)	66/935 (7.1)	RR, 1.41 (1.05–1.90)
Central nervous system complications	11/936 (1.2)	4/935 (0.4)	RR, 2.65 (0.90–7.83)
Neonatal sepsis	3/489 (0.6)	2/502 (0.4)	RR, 1.54 (0.26–9.20)
Necrotizing enterocolitis	3/936 (0.3)	0/935 (0.0)	RR, 1.00 (1.00–1.00)
Hypoglycemia	86/692 (12.4)	86/708 (12.1)	RR, 1.03 (0.77–1.37)
Jaundice	19/612 (3.1)	13/625 (2.1)	RR, 1.56 (0.78–3.11)

aRR, adjusted risk ratio; *RR*, risk ratio.

[a] Effect sizes are RRs (95% CIs) unless stated otherwise; [b] aRR for study, gestational age at randomization, singleton pregnancy, parity, and severity of hypertension at study entry. Presented as unadjusted RR where model failed to converge.

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outcome in infants at this late preterm gestation, providing further potential benefit in ameliorating the risk of central nervous system complications at this gestational age. Although some authors have raised concerns over the association between maternal antenatal corticosteroid treatment and childhood behavioral disorders in term-born children (on the basis of a population-based study[29]), the most recent Cochrane systematic review of randomized controlled trials reported that antenatal corticosteroids probably lead to a reduction in developmental delay in childhood (RR, 0.51; 95% CI, 0.27–0.97).[28]

The rates of other serious neonatal complications such as sepsis and necrotizing enterocolitis were low, as expected in this population. The relatively high rates of neonatal admission across both groups highlights the additional care that this high-risk population of infants may require irrespective of the timing of delivery. In addition, infants born to mothers in the expectant management group were significantly more likely to be born small for gestational age. As low birthweight is a risk factor for long-term neurodevelopmental delay[30,31] and has been shown to be a more important predictor of long-term infant outcomes than gestational age at delivery,[32] avoidance of ongoing growth restriction may influence management choices. Use of ultrasound to accurately evaluate gestational age and presence of growth restriction should therefore be an integral part of assessment of a woman with preeclampsia. Although the average difference between the 2 groups was 4 days, the third quartile was 10 days. It remains difficult to identify the women (and infants) who are most likely to require delivery within the following 7 days using clinical risk factor or biomarker prognostication,[33] but for a progressive and unpredictable condition such as preeclampsia, this degree of pregnancy prolongation could be associated with a biologically plausible and clinical relevant difference in fetal growth restriction and neonatal outcomes. An increased awareness that expectant management increases the risk of a small for gestational age infant, most likely by perpetuating growth restriction within an adverse intrauterine environment, may lower the threshold for considering planned delivery from 34 weeks onward. These findings raise interesting questions regarding the influence of expectant management on fetal growth restriction and the impact that this may have on the infant, which should be addressed by future research.

Comparison with existing literature

In the United States, current guidelines recommend planned early delivery in women with late preterm preeclampsia with severe features[34] but advise expectant management in women without severe features up to 37 weeks gestation. The guidelines acknowledge that this latter recommendation is based on limited and inconsistent evidence.[27-] Current United Kingdom[35] and international[18] guidelines provide similar recommendations but again note the uncertainty in clinical practice around thresholds for intervention and the limited evidence base. Many reviews, including a recent Cochrane review, have therefore called for evidence focusing on optimal timing of delivery in different types of pregnancy hypertensive disease. Our findings confirm clear maternal benefits associated with planned early delivery in women with preeclampsia from 34 weeks gestation onward and provide a greater understanding of the perinatal benefits and risks, including factors (such as antenatal steroid use) that mitigate these. Our analysis extends the current evidence base and quantifies the benefit–risk balance specific to women with preeclampsia in the late preterm period. The important lack of increased risk in operative delivery is in keeping with other recent clinical studies comparing induction of labor with expectant management[36–38]; women and clinicians may perceive similar rates of vaginal delivery in both groups as important to their decision-making. The perinatal results are consistent with interpretation by a systematic review evaluating planned early delivery for suspected fetal compromise that

highlighted an increased short-term risk of respiratory complications and neonatal unit admission.[39] However, the varying use of antenatal corticosteroids across the different trials included in our analysis should be considered when interpreting these results. Planned subgroup analysis showed that there was no difference in the primary perinatal outcome in the most recent trial,[6] where most of the women allocated to planned delivery received antenatal corticosteroids. Given that the universal administration of antenatal corticosteroids is not routinely recommended for women considered at risk of late preterm birth,[40] demonstrating benefit in certain clinical scenarios such as planned delivery for preeclampsia may guide clinical practice. Furthermore, we have demonstrated an increased risk of small for gestational age births associated with expectant management, a finding that is consistent with similar studies and is known to be associated with longer term impaired neurodevelopmental outcomes.[30,31] In addition, on the basis of the largest and most recent trial in this population,[6] clinicians and women should be aware that there is an average prolongation of pregnancy of around 3 days only with expectant management, with 74% progressing to severe preeclampsia (compared with 64% with planned delivery) and 55% requiring expedited delivery before 37 weeks gestation. The high proportion of women who were delivered early is in keeping with an expectant management strategy and highlights the rapidly progressive nature of preeclampsia often resulting in a constellation of maternal and fetal complications.

Data from this IPD meta-analysis (which included the trial discussed above) supported this finding with a difference in median time from randomization to delivery of only 4 days between the 2 management groups. This study therefore strengthens the current evidence supporting a policy of considering planned early delivery for maternal benefit in late preterm preeclampsia. Planned delivery has been shown to be cost-saving in the UK National Health Service setting compared with expectant management (£1478 per woman) when the total maternal and infant costs were considered, but the decision-making should reflect clinical and health economic factors together.

TABLE 6
Secondary perinatal outcomes

Outcome	Planned delivery n=936	Expectant management n=935	Adjusted mean difference (CI)
Gestational age at delivery (wk; mean [SD])	36.2 (1.4) n=934	36.9 (1.5) n=934	−0.61 (−0.67 to −0.55)
Birthweight (g; mean [SD])	2561 (563.7) n=934	2681 (615.0) n=934	−127.28 (−171.0 to −83.5)
Birthweight centile (mean [SD])	41.0 (30.8) n=934	40.4 (33.2) n=933	−0.42 (−3.14 to 2.29)
			Effect size[a]
Small for gestational age (<10th centile)	198/934 (21.2)	241/933 (25.8)	RR,[b] 0.82 (0.70–0.97)
Small for gestational age (<3rd centile)	73/934 (7.8)	99/993 (10.6)	RR, 0.74 (0.55–0.99)
Neonatal unit admission	395/831 (47.5)	336/858 (39.2)	RR, 1.21 (1.08–1.36)
Neonatal intensive care unit admission	56/926 (6.0)	43/930 (4.6)	aRR, 1.20 (0.83–1.74)
5-min Apgar score<7	30/936 (3.2)	25/935 (2.7)	aRR, 1.20 (0.71–2.01)
Umbilical artery pH<7.05	17/926 (1.8)	19/930 (2.0)	aRR, 0.85 (0.45–1.61)
Vaginal delivery	377/713 (52.9)	349/702 (49.7)	RR, 1.06 (0.96–1.18)

aRR, adjuted risk ratio; *CI*, confidence interval; *RR*, risk ratio; *SD*, standard deviation.

[a] Effect sizes are RRs (95% CIs) unless stated otherwise; [b] aRR for study, gestational age at randomization, singleton pregnancy, parity, and severity of hypertension at study entry. Presented as unadjusted RR where the model failed to converge.

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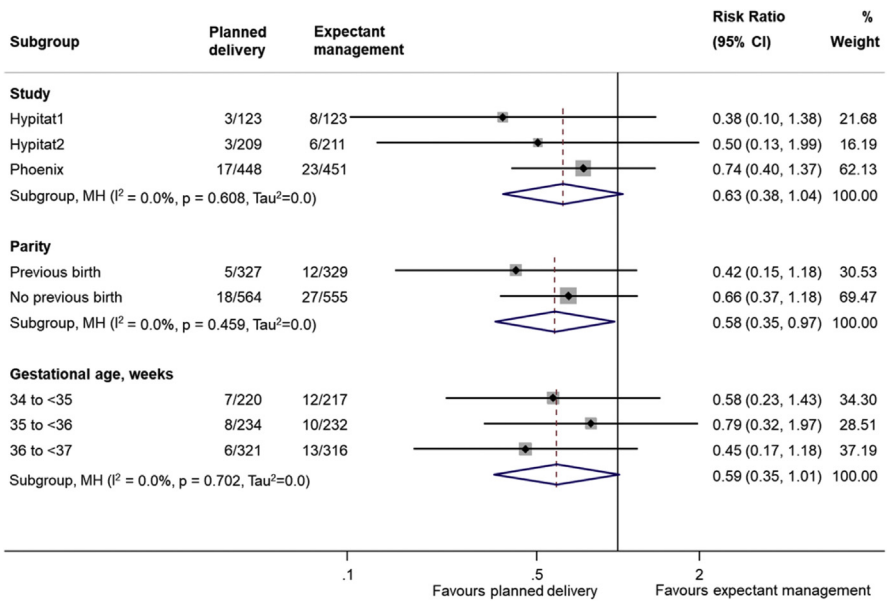
Strengths and limitations

Following guidance on the use of IPD meta-analysis,[41] we did not adopt an overly restrictive approach when selecting trials for inclusion, and this study is therefore strengthened by the inclusion of several large, well-conducted randomized clinical trials, most of which were assessed as being at a low risk of bias. For most outcomes, heterogeneity between studies was low, though some important differences have been highlighted above. Furthermore, the use of a 1-stage IPD meta-analysis approach allows the relative influence of multiple trial and participant characteristics on any intervention effect to be considered simultaneously.[41] We had full access to the trial data and were able to include all the eligible participants for most of the studies. We were able to include complete data for most of our outcomes of interest but were limited by differences in outcome reporting between trials such that data were not available for every variable. This low missingness for most of the variables and broad consistency between trials means that we have confidence in our results. The limitations include changes in clinical practice during the time period of the trials included such that external factors (such as uptake of antenatal corticosteroid use) may impact the main outcomes directly. Certain perinatal outcomes such as bronchopulmonary dysplasia, cerebral infarction, and intracerebral hemorrhage were not collected across a large proportion of included studies likely because of the rarity of these outcomes and the availability of more objective

FIGURE 4
Primary maternal outcome: subgroup analysis (unadjusted)



Weights and between-subgroup heterogeneity test are from the MH model. Prespecified subgroup analysis only performed if there were ≥10 events in each subgroup, and subgroups without analysis therefore are shown in Supplementary table S7.

CI, confidence interval; *MH*, Mantel–Haenszel.

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measures. Ideally, all trials should include longer term follow-up of the women and infants, but retention within a study can be challenging and expensive to undertake. We were not able to report the indications for delivery, as this information was not consistently available across the included trials. However, given the randomized nature of the data, we would not expect significant differences between the 2 management groups at baseline. The PHOENIX trial reported indications for delivery for both the management groups. In the planned delivery group, 99% of women had allocation to planned delivery arm as their recorded indication for delivery, consistent with trial procedures. Women in the expectant management group were delivered more frequently for both maternal and fetal indications, with over 50% requiring expedited delivery, compared with the planned delivery group.

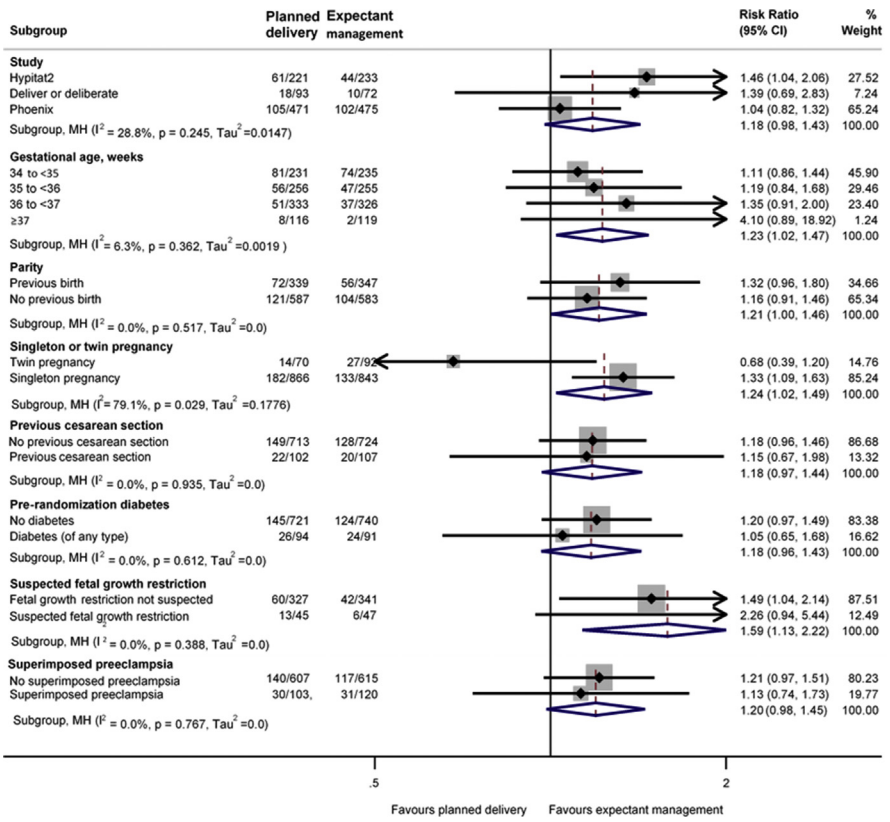
Clinical implications

Delivery is already known to improve maternal outcomes in preeclampsia. However, this review quantifies the effect, specific to gestation, on outcomes and addresses the balance between maternal and fetal effects. We also addressed the question specifically in women who have preeclampsia without severe features. By synthesizing and presenting the available data on this topic, we aim to provide as much information as possible on the balance of risks and benefits associated with each management strategy so that women and their caregivers can make fully informed decisions. For clinicians who already have a low threshold for planned delivery in women with late preterm preeclampsia, this meta-analysis provides new evidence that could support this approach. Other clinicians may consider that although maternal benefit of planned delivery is clear, there is a trade-off with short-term perinatal morbidity. However, this may be ameliorated by judicial use of antenatal corticosteroids.

Conclusions

This meta-analysis of IPD from 6 randomized controlled trials synthesizes the available evidence pertaining to timing of delivery in late preterm preeclampsia. We have clearly demonstrated that planned delivery in women with preeclampsia from 34 weeks onward provides maternal benefit with no increased risk of operative delivery compared with expectant management. Planned delivery reduces the likelihood of infants being born small for gestational age but increases short-term respiratory morbidity. The administration of antenatal corticosteroids was observed to reduce this risk such that perinatal morbidity was no different between the groups in the most recent trial; the potential benefits of antenatal corticosteroids should be discussed with women undergoing late preterm delivery. Further research is needed to identify the optimal methods of determining the women and infants who are at the greatest risk of adverse outcomes, enabling the stratification of surveillance and targeted intervention. A similar need for accurate prognostic strategies has been identified for planning delivery in pregnancies with suspected fetal compromise[39] and preterm prelabor rupture of membranes[42], as the challenges are common across these scenarios. Longer-term infant outcome data (including infants born with and without growth restriction) from large randomized controlled trials are also needed, as outcomes cannot be extrapolated from population-level databases comparing delivery at preterm gestations with term gestations in healthy pregnancies. There is also a need to establish the most clinically meaningful neonatal outcomes to measure when conducting preeclampsia trials, particularly those focused on timing of delivery. The impact of the intervention is likely to be very different in low-resource settings, where most of the maternal and perinatal disease

FIGURE 5
Primary perinatal outcome: subgroup analysis (unadjusted)



Weights and between-subgroup heterogeneity test are from the MH model. Prespecified subgroup analysis only performed if there were ≥10 events in each subgroup, and subgroups without analysis therefore are shown in Supplementary table S8.

CI, confidence interval; *MH*, Mantel—Haenszel.

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burden associated with preeclampsia lies.[43] Because antenatal stillbirth is much more common in these settings,[44,45] it is possible that early delivery in women with preeclampsia in low- and middle-income countries may reduce not just adverse maternal outcomes but fetal and perinatal deaths associated with severe maternal disease. However, this must also be balanced against the resource constraints in these environments. A multicenter randomized controlled trial evaluating this is currently underway[46] and may shed further light on this clinical dilemma in a different context. Our findings provide further information to guide women and clinicians in a high-income setting, who must consider the balance of benefits and risks associated with planned delivery for women and their infants with late preterm preeclampsia. In line with recent recommendations,[47] we recommend that clinicians discuss the trade-off with earlier delivery (better for maternal outcomes but with increased admissions to the neonatal unit) with women, fully supporting them to understand their options and consider both management strategies. ■

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REFERENCES

1. Wang W, Xie X, Yuan T, et al. Epidemiological trends of maternal hypertensive disorders of pregnancy at the global, regional, and national levels: a population-based study. BMC Pregnancy Childbirth 2021;21:364.
2. Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. Int J Gynecol Obstet 2019;145:1–33.
3. Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet 2016;387:587–603.
4. Roberts CL, Ford JB, Algert CS, et al. Population-based trends in pregnancy hypertension and pre-eclampsia: an international comparative study. BMJ Open 2011;1:e000101.
5. World Health Organization. WHO recommendations for prevention and treatment of preeclampsia and eclampsia. 2011. Available at: http://apps.who.int/iris/bitstream/10665/44703/1/9789241548335_eng.pdf. Accessed December 30, 2021.
6. Chappell LC, Brocklehurst P, Green ME, et al. Planned early delivery or expectant management for late preterm pre-eclampsia (phoenix): a randomised controlled trial. Lancet 2019;394:1181–90.
7. Broekhuijsen K, van Baaren GJ, van Pampus MG, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (hypitat-ii): an open-label, randomised controlled trial. Lancet 2015;385:2492–501.
8. Owens MY, Thigpen B, Parrish MR, et al. Management of preeclampsia when diagnosed between 34-37 weeks gestation: deliver now or deliberate until 37 weeks? J Miss State Med Assoc 2014;55:208–11.
9. Koopmans CM, Bijlenga D, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (hypitat): a multicentre, open-label randomised controlled trial. Lancet 2009;374:979–88.
10. Boers KE, Vijgen SM, Bijlenga D, et al. Induction versus expectant monitoring for intra-uterine growth restriction at term: randomised equivalence trial (digitat). BMJ 2010;341:c7087.
11. GRIT Study Group. A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and bayesian interpretation. BJOG 2003;110:27–32.
12. Thornton JG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M; GRIT study group. Infant wellbeing at 2 years of age in the growth restriction intervention trial (grit): multicentred randomised controlled trial. Lancet 2004;364:513–20.
13. Cluver C, Novikova N, Koopmans CM, West HM. Planned early delivery versus expectant management for hypertensive disorders

from 34 weeks gestation to term. Cochrane Database Syst Rev 2017;1:CD009273.
14. Wang Y, Hao M, Sampson S, Xia J. Elective delivery versus expectant management for pre-eclampsia: a meta-analysis of RCTs. Arch Gynecol Obstet 2017;295:607–22.
15. Bernardes TP, Zwertbroek EF, Broekhuijsen K, et al. Delivery or expectant management for prevention of adverse maternal and neonatal outcomes in hypertensive disorders of pregnancy: an individual participant data meta-analysis. Ultrasound Obstet Gynecol 2019;53:443–53.
16. Chatzakis C, Liberis A, Zavlanos A, et al. Early delivery or expectant management for late preterm preeclampsia: a meta-analysis of randomized controlled trials. Acta Obstet Gynecol Scand 2021;100:1392–400.
17. Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the prisma-ipd statement. JAMA 2015;313:1657–65.
18. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: Isshp classification, diagnosis, and management recommendations for international practice. Hypertension 2018;72:24–43.
19. Sterne JAC, Savović J, Page MJ, et al. Rob 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
20. von Dadelszen P, Payne B, Li J, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullpiers model. Lancet 2011;377:219–27.
21. Duffy J, Cairns AE, Richards-Doran D, et al. A core outcome set for pre-eclampsia research: an international consensus development study. BJOG 2020;127:1516–26.
22. Williams RL. A note on robust variance estimation for cluster-correlated data. Biometrics 2000;56:645–6.
23. Bone JN, Magee LA, Singer J, et al. Blood pressure thresholds in pregnancy for identifying maternal and infant risk: a secondary analysis of community-level interventions for pre-eclampsia (clip) trial data. Lancet Glob Health 2021;9:e1119–28.
24. Magee LA, von Dadelszen P, Singer J, et al. The chips randomized controlled trial (control of hypertension in pregnancy study): is severe hypertension just an elevated blood pressure? Hypertension 2016;68:1153–9.
25. Reddy M, Rolnik DL, Harris K, et al. Challenging the definition of hypertension in pregnancy: a retrospective cohort study. Am J Obstet Gynecol 2020;222:606.e1–21.
26. Roos A, Thakar R, Sultan A, de Leeuw J, Paulus A. The impact of pelvic floor surgery on female sexual function: a mixed quantitative and qualitative study. BJOG 2014;121:92–101.
27. Gestational hypertension and preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol 2020;135:e237–60.
28. McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2020;12:CD004454.
29. Räikkönen K, Gissler M, Kajantie E. Associations between maternal antenatal corticosteroid treatment and mental and behavioral disorders in children. JAMA 2020;323:1924–33.
30. Figueras F, Eixarch E, Meler E, et al. Small-for-gestational-age fetuses with normal umbilical artery doppler have suboptimal perinatal and neurodevelopmental outcome. Eur J Obstet Gynecol Reprod Biol 2008;136:34–8.
31. van Wyk L, Boers KE, van der Post JA, et al. Effects on (neuro)developmental and behavioral outcome at 2 years of age of induced labor compared with expectant management in intrauterine growth-restricted infants: long-term outcomes of the digitat trial. Am J Obstet Gynecol 2012;206:406.e1–7.
32. Zwertbroek EF, Zwertbroek J, Broekhuijsen K, et al. Neonatal developmental and behavioral outcomes of immediate delivery versus expectant monitoring in mild hypertensive disorders of pregnancy: 5-year outcomes of the hypitat ii trial. Eur J Obstet Gynecol Reprod Biol 2020;244:172–9.
33. Duhig KE, Seed PT, Placzek A, et al. Prognostic indicators of severe disease in late preterm pre-eclampsia to guide decision making on timing of delivery: the peacock study. Pregnancy Hypertens 2021;24:90–5.
34. ACOG committee opinion no. 764: medically indicated late-preterm and early-term deliveries. Obstet Gynecol 2019;133:e151–5.
35. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. 2019. Available at: https://www.nice.org.uk/guidance/ng133. Accessed December 30, 2021.
36. Grobman WA, Rice MM, Reddy UM, et al. Labor induction versus expectant management in low-risk nulliparous women. N Engl J Med 2018;379:513–23.
37. Roland C, Warshak CR, DeFranco EA. Success of labor induction for pre-eclampsia at preterm and term gestational ages. J Perinatol 2017;37:636–40.
38. Mishanina E, Rogozinska E, Thatthi T, Uddin-Khan R, Khan KS, Meads C. Use of labour induction and risk of cesarean delivery: a systematic review and meta-analysis. CMAJ 2014;186:665–73.
39. Stock SJ, Bricker L, Norman JE, West HM. Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes. Cochrane Database Syst Rev 2016;7:CD008968.
40. Norman J, Shennan A, Jacobsson B, Stock SJ; FIGO Working Group for Preterm Birth. Figo good practice recommendations on the use of prenatal corticosteroids to improve outcomes and minimize harm in babies born preterm. Int J Gynaecol Obstet 2021;155:26–30.
41. Tierney JF, Vale C, Riley R, et al. Individual participant data (ipd) meta-analyses of randomised controlled trials: guidance on their use. PLoS Med 2015;12:e1001855.
42. Bond DM, Middleton P, Levett KM, et al. Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. Cochrane Database Syst Rev 2017;3:CD004735.
43. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol 2009;33:130–7.
44. Nathan HL, Seed PT, Hezelgrave NL, et al. Early warning system hypertension thresholds to predict adverse outcomes in pre-eclampsia: a prospective cohort study. Preg Hypertens 2018;12:183–8.
45. Blencowe H, Cousens S, Jassir FB, et al. National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: a systematic analysis. Lancet Glob Health 2016;4:e98–108.
46. Beardmore-Gray A, Vousden N, Charantimath U, et al. Planned early delivery versus expectant management to reduce adverse pregnancy outcomes in pre-eclampsia in a low- and middle-income setting: study protocol for a randomised controlled trial (cradle-4 trial). Trials 2020;21:960.
47. National Institute for Health Research. Care and decision-making in pregnancy: research reveals the supt women need. 2022. Available at: https://evidence.nihr.ac.uk/collection/care-decision-making-pregnancy-research-reveals-support-women-need/. Accessed December 30, 2021.

SUPPLEMENTARY TABLE S1
Additional study characteristics

Study	Funding source	Conflict of interest	Study design	Enrolment dates	Intervention	Antenatal corticosteroid (ACS) use
GRIT *GRIT Study Group* (2003)	MRC, European Union Concerted Action, Princess Beatrix Foundation	Nil	Randomized controlled trial	November 1993-March 2001	Delivery initiated within 48h of randomization	Pre-randomization ACS given in 70% of immediate delivery group and 69% of expectant management group. Post-randomization ACS use not reported
HYPITAT *Koopmans* (2009)	ZonMw	Nil	Randomized controlled trial	October 2005-March 2008	Delivery initiated within 24h of randomization	Not reported
DIGITAT *Boers* (2010)	ZonMw	Nil	Randomized controlled trial	November 2004-November 2008	Delivery initiated within 48h of randomization	Not reported
Deliver or Deliberate *Owens* (2014)	Division of Maternal-Fetal Medicine in the Dept. of OBGYN at the University of Mississippi Medical Center	Nil	Randomized controlled trial	March 2002-June 2008	Delivery initiated within 12h of randomization	Not reported
HYPITAT II *Broekhuijsen* (2015)	ZonMw	Nil	Randomized controlled trial	March 1st 2009-Feb 21st 2013	Delivery initiated within 24h of randomization	Pre-randomization ACS given in 7.5% of immediate delivery group and 8% of expectant management group. Post-randomization ACS use 1% across both groups
PHOENIX *Chappell* (2019)	NIHR Health technology assessment programme	Nil	Randomized controlled trial	Sept 29th 2014-Dec 10th 2018	Delivery initiated within 48h of randomization	Post- randomization ACS given in 65% of immediate delivery group and 55% of expectant management group

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SUPPLEMENTARY TABLE S2

Additional study characteristics

Study	Short-term primary outcome	Short-term secondary outcomes
GRIT *GRIT Study Group* (2003)	Infant survival up to hospital discharge	Mode of delivery, surrogate outcomes for fetal morbidity: birthweight, sex, Apgar score <7 at 5 minutes, cord pH <7.0, ventilation >24hrs, necrotizing enterocolitis, neonatal convulsions, GMH/IVH, PVL/VM, stillbirth, neonatal death, death >28 days
HYPITAT *Koopmans* (2009)	Composite measure of poor maternal outcomes defined as: maternal mortality, maternal morbidity (eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease, or placental abruption), progression to severe disease and major PPH up to maternal hospital discharge and 6 weeks after birth	Mode of delivery, neonatal mortality, and neonatal morbidity (composite outcome consisting of a 5 minute Apgar score <7, umbilical artery pH <7.05 or admission to a neonatal intensive care unit)
DIGITAT *Boers* (2010)	Composite measure of adverse neonatal outcome (defined as death before hospital discharge, 5 minute Apgar score <7, umbilical artery pH <7.05, or admission to the neonatal intensive care unit)	Operative delivery (vaginal instrumental delivery or caesarean section), length of stay in the NICU or neonatal ward, length of stay in the maternal hospital and maternal morbidity (PPH >1000ml, gestational hypertension or pre-eclampsia, pulmonary oedema, thromboembolism, or any other serious event)
Deliver or Deliberate *Owens* (2014)	Maternal mortality, maternal morbidity, and progression of PE with the appearance of severe features as defined by the American College of Obstetricians and Gynecologists (ACOG)	Onset of labor, progression to severe pre-eclampsia, postpartum complications (HELLP syndrome, eclampsia), total hospital length of stay (LOS) post delivery (days), total hospital LOS (days), birthweight, small for gestational age, arterial umbilical cord pH, NICU admission, asphyxia, respiratory distress syndrome, transient tachypnoea of the new-born, apnea, NICU LOS (days)
HYPITAT II *Broekhuijsen* (2015)	*Maternal:* composite of adverse maternal outcomes (thromboembolic disease, pulmonary oedema, eclampsia, HELLP syndrome, placental abruption, or maternal death) up to maternal final discharge from hospital and 6 weeks after birth. *Neonatal:* Respiratory distress syndrome (RDS), defined as need for supplementary oxygen for more than 24h combined with radiographic findings typical for RDS up to infant final discharge from hospital	Instrumental vaginal delivery, caesarean section, 5-minute Apgar score of less than 7, umbilical artery pH of less than 7.05, admission to a NICU, death before discharge, suspected or confirmed neonatal infection or sepsis, hypoglycemia necessitating intravenous glucose, transient tachypnoea of the new-born, meconium aspiration syndrome, pneumothorax or pneumomediastinum, necrotizing enterocolitis, IVH, PVL and convulsions
PHOENIX *Chappell* (2019)	*Maternal:* composite of maternal morbidity of fullPIERS[20] outcomes, with the addition of recorded systolic BP of at least 160mmHg post randomization, up to primary maternal hospital discharge *Perinatal:* composite of neonatal deaths within 7 days of delivery and perinatal deaths or neonatal unit admissions before infant primary hospital discharge	Individual components of the composite primary outcome, use of antihypertensive drugs, progression to severe pre-eclampsia (systolic BP of at least 160mmHg, platelet count <100, abnormal liver function enzymes - ALT or AST >70), time and mode of onset, confirmed thromboembolic disease, confirmed sepsis, primary and additional indications for delivery; and placental abruption. Stillbirth, NND within 7 days of delivery, NND before hospital discharge, admissions to NNU, number of nights in each category of care, total number of nights in hospital, BW, BW centile, BW less than 10th or 3rd centile, GA at delivery, Apgar score at 5 min after birth, umbilical arterial and venous pH at birth, need for supplementary oxygen before discharge, number of days required, need for respiratory support, other indications and main diagnoses resulting in NNU admission and health resource use outcomes

ALT, alanine aminotransferase; *AST*, aspartate transaminase; *BW*, birthweight; *GA*, gestational age; *GMH*, Germinal matrix hemorrhage; *HELLP syndrome*, Hemolysis, elevated liver enzymes, low platelet count syndrome; *IVH*, intraventricular hemorrhage; *NICU*, neonatal intensive care unit; *NND*, neonatal death; *NNU*, neonatal unit, *PPH*, post-partum hemorrhage; *PVL*, Periventricular leukomalacia; *VM*, ventriculomegaly.

Beardmore-Gray. Timing of delivery in late preterm preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTARY TABLE S3
Missing maternal variables

	HYPITAT n=246	HYPITAT II n=420	DIGITAT n=45	Deliver or Deliberate n=165	GRIT n=15	PHOENIX n=899
Maternal death	0	0	0	0	15	0
Eclampsia	0	0	0	0	15	0
Stroke	246	420	0	0	15	0
Pulmonary oedema	0	0	0	165	15	0
HELLP syndrome	0	0	0	0	15	0
Renal insufficiency	246	0	0	0	15	0
Placental abruption	0	0	0	165	15	0
Post-randomization severe hypertension	0	0	45	165	15	0
Hepatic dysfunction	0	0	0	0	15	0
Thromboembolic disease	0	0	0	165	15	0
Severe postpartum hemorrhage	0	0	0	0	15	0
Pre-labor caesarean section	0	0	0	165	15	2[a]
Intensive care unit admission	0	420	0	165	15	0

HELLP syndrome, Hemolysis, elevated liver enzymes, low platelet count syndrome.

[a] Data missing/excluded. All other missing variables were not collected.

Beardmore-Gray. Timing of delivery in late preterm preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTARY TABLE S4
Missing perinatal variables

	HYPITAT n=246	HYPITAT II n=454	DIGITAT n=45	Deliver or Deliberate n=165	GRIT n=15	PHOENIX n=946
Stillbirth	0	0	0	0	0	0
Neonatal death	0	0	0	0	0	0
Respiratory distress syndrome	0	0	0	0	15	946
Need for respiratory support	0	454	0	0	0	0
Neonatal unit admission for respiratory disease	246	454	45	165	15	0
Bronchopulmonary dysplasia	246	454	45	0	15	946
Cerebral infarction	246	454	45	165	15	946
Hypoxic ischemic encephalopathy	246	0	45	165	15	0
Intra-cerebral hemorrhage	246	454	45	165	15	946
Intra-ventricular hemorrhage	0	0	0	0	0	0
Convulsions	0	0	0	165	0	0
Peri-ventricular leukomalacia	0	0	0	165	15	0
Neonatal sepsis	246	454	0	165	15	0
Necrotizing enterocolitis	0	0	0	0	0	0
Jaundice	0	454	0	165	15	0
Hypoglycemia	246	0	45	165	15	0
Gestational age at delivery	1[a]	0	0	0	0	2[a]
Mode of delivery	0	454	0	0	0	2[a]
Birthweight	0	1[a]	0	0	0	2[a]
Sex	0	0	0	0	0	2[a]
Neonatal unit admission	0	0	0	165	15	2[a]
Neonatal intensive care unit admission	0	0	0	0	15	0
5 -minute Apgar score less than 7	0	0	0	0	0	0
Arterial pH less than 7.05	0	0	0	0	15	0

[a] Data missing/excluded. All other missing variables were not collected.

Beardmore-Gray. Timing of delivery in late preterm preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTARY TABLE S5

Perinatal respiratory disease

	HYPITAT n=246		HYPITAT II n=454		DIGITAT n=45		Deliver or Deliberate n=165		GRIT n=15		PHOENIX n=946	
	PD[a] n=123	EM[a] n=123	PD n=221	EM n=223	PD n=18	EM n=27	PD n=93	EM n=72	PD n=10	EM n=5	PD n=471	EM n=475
Respiratory disease (composite)	**1**	**1**	**14**	**3**	**1**	**0**	**18**	**10**	**1**	**0**	**60**	**52**
Individual components:												
Respiratory distress syndrome	0	1	14	3	0	0	10	6	-	-	-	-
Need for respiratory support	1	0	-	-	1	0	12	6	1	0	40	41
Bronchopulmonary dysplasia	-	-	-	-	-	-	0	0	-	-	-	-
Neonatal unit admission for respiratory disease	-	-	-	-	-	-	-	-	-	-	47	39

[a] PD denotes planned delivery arm; EM denotes expectant management arm. Dash (-) indicates outcome not collected by study.

Beardmore-Gray. Timing of delivery in late preterm preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTARY TABLE S6

Perinatal central nervous system complications

	HYPITAT n=246		HYPITAT II n=454		DIGITAT n=45		Deliver or Deliberate n=165		GRIT n=15		PHOENIX n=946	
	PD[a] n=123	EM[a] n=123	PD n=221	EM n=223	PD n=18	EM n=27	PD n=93	EM n=72	PD n=10	EM n=5	PD n=471	EM n=475
Central nervous system complications (composite)	**0**	**1**	**6**	**3**	**0**	**0**	**0**	**0**	**3**	**0**	**2**	**0**
Individual components:												
Cerebral infarction	-	-	-	-	-	-	-	-	-	-	-	-
Hypoxic ischemic encephalopathy	-	-	0	0	-	-	-	-	-	-	0	0
Intracerebral hemorrhage	-	-	-	-	-	-	-	-	-	-	-	-
Intraventricular hemorrhage	0	0	2	0	0	0	0	0	3	0	2	0
Convulsions	0	1	2	1	0	0	-	-	0	0	0	0
Periventricular leukomalacia	0	0	4	2	0	0	-	-	-	-	0	0

[a] PD denotes planned delivery arm; EM denotes expectant management arm. Dash (-) indicates outcome not collected by study.

Beardmore-Gray. Timing of delivery in late preterm preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTARY TABLE S7

Primary maternal outcome in excluded subgroups (descriptive only)

Subgroup	Planned delivery	Expectant management
Study		
DIGITAT	0/18	1/27
Deliver or deliberate	0/93	1/72
GRIT	No maternal data	No maternal data
Gestational age at randomization		
Gestational age $\geq$ 37 weeks	2/119	4/119
Singleton or twin pregnancy		
Twin pregnancy	1/35	1/46
Singleton pregnancy	22/856	38/838
Previous caesarean section		
No previous caesarean section	22/681	35/684
Previous caesarean section	1/99	2/101
Pre-randomization diabetes		
No diabetes	22/686	33/697
Diabetes (of any type)	1/94	4/88
Suspected fetal growth restriction		
Fetal growth restriction not suspected	20/683	37/685
Suspected fetal growth restriction	3/115	1/127
Superimposed pre-eclampsia		
No superimposed pre-eclampsia	18/575	29/576
Superimposed pre-eclampsia	2/100	1/113

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SUPPLEMENTARY TABLE S8

Primary perinatal outcome in excluded subgroups (descriptive only)

Subgroup	Planned delivery	Expectant management
Study		
HYPITAT	5/123	2/123
DIGITAT	4/18	2/27
GRIT	3/10	0/5

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SUPPLEMENTARY TABLE S9
Summary of findings

Planned delivery compared with expectant management for women with late preterm pre-eclampsia without severe features

Population: Pregnant women with a confirmed diagnosis of pre-eclampsia from 34 weeks' gestation onwards, not requiring immediate delivery

Setting: Multicenter trials across different high-income countries in Europe and U.S.A.

Intervention: Planned delivery within 48 hours of randomization

Comparison: Usual care — expectant management

Outcomes	Relative effect (95% CI)	Number of participants (studies)
Maternal[a]		
Eclampsia	RR 0.50 (0.12 to 1.98)	1,775 (5 studies)
HELLP syndrome	RR 0.52 (0.26 to 1.03)	1,775 (5 studies)
Renal insufficiency	RR 0.66 (0.19 to 2.33)	1,529 (4 studies)
Placental abruption	RR 1.02 (0.26 to 4.05)	1,610 (4 studies)
Perinatal[a]		
Respiratory disease	RR 1.41 (1.05 to 1.90)	1,871 (6 studies)
Hypoglycaemia	RR 1.03 (0.77 to 1.37)	1,400 (2 studies)
Jaundice	RR 1.56 (0.78 to 3.11)	1,237 (3 studies)

HELLP syndrome: Hemolysis, elevated liver enzymes, low platelet count syndrome.

[a] Outcomes selected as most prevalent

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SUPPLEMENTARY TABLE S10
Numbers needed to treat and harm

Outcome	Number needed to treat/harm (95% CI)
Primary maternal	NNT 54.6 (28.3 to 816)
Primary perinatal	NNH 26.1 (13.5 to 363.5)

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