OBSTETRICS

Placental growth factor testing in the management of late preterm preeclampsia without severe features: a multicenter, randomized, controlled trial

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BACKGROUND: In women with late preterm preeclampsia, the optimal time for delivery remains a controversial topic, because of the fine balance between the maternal benefits from early delivery and the risks for prematurity. It remains challenging to define prognostic markers to identify women at highest risk for complications, in which case a selective, planned delivery may reduce the adverse maternal and perinatal outcomes.

OBJECTIVE: This trial aimed to determine whether using an algorithm based on the maternal levels of placental growth factor in women with late preterm preeclampsia to evaluate the best time for delivery reduced the progression to preeclampsia with severe features without increasing the adverse perinatal outcomes.

STUDY DESIGN: This parallel-group, open-label, multicenter, randomized controlled trial was conducted at 7 maternity units across Spain. We compared selective planned deliveries based on maternal levels of placental growth factor at admission (revealed group) and expectant management under usual care (concealed group) with individual randomization in singleton pregnancies with late preterm preeclampsia from 34 to 36+6 weeks' gestation. The coprimary maternal outcome was the progression to preeclampsia with severe features. The coprimary neonatal outcome was morbidity at infant hospital discharge with a noninferiority hypothesis (noninferiority margin of 10% difference in incidence). Analyses were conducted according to intention-to-treat.

RESULTS: Between January 1, 2016, and December 31, 2019, 178 women were recruited. Of those women, 88 were assigned to the revealed group and 90 were assigned to the concealed group. The data analysis was performed before the completion of the required sample size. The proportion of women with progression to preeclampsia with severe features was significantly lower in the revealed group than in the concealed group (adjusted relative risk, 0.5; 95% confidence interval, 0.33—0.76; P=.001). The proportion of infants with neonatal morbidity was not significantly different between groups (adjusted relative risk, 0.77; 95% confidence interval, 0.39—1.53; P=.45).

CONCLUSION: There is evidence to suggest that the use of an algorithm based on placental growth factor levels in women with late preterm preeclampsia leads to a lower rate of progression to preeclampsia with severe features and reduces maternal complications without worsening the neonatal outcomes. This trade-off should be discussed with women with late preterm preeclampsia to allow shared decision making about the timing of delivery.

Key words: biomarkers, blood pressure, infant, morbidity, newborn, prediction, preeclampsia, therapy

Introduction

Preeclampsia is a life-threatening, multisystem condition characterized by hypertension and end-organ dysfunction. It complicates 2% to 8% of pregnancies[1] and is a leading cause of maternal and neonatal morbidity and mortality. Management of preeclampsia is defined by a trade-off between the reduction in maternal complications by timely delivery and the minimization of risks for prematurity by expectant management. In women with late preterm preeclampsia (between 34 and 37 weeks' gestation), the optimal time for delivery remains a controversial topic, because the net benefit between reducing maternal and fetal risks by planned delivery and the secondary neonatal risks associated with prematurity is unclear.

A meta-analysis of individual patient data suggested that some women with late preterm preeclampsia may benefit from delivery before 37 weeks' gestation.[2] More recently, a randomized trial comparing expectant management with planned delivery in women with late preterm preeclampsia reported a 14% reduction in maternal morbidity but a 26% increase in the risk for neonatal intensive care unit (NICU) admission after planned delivery, suggesting that a more accurate measure to identify pregnancies at highest risk may maximize the benefits of an early planned delivery.[3]

The levels of maternal angiogenic factors, including placental growth factor (PlGF) and soluble FMS-like tyrosine kinase 1 (sFlt-1), have emerged as reliable predictors of complications in women with suspected preeclampsia.[4,5] PlGF exerts its biological function by binding to the Flt-1 receptor. In preeclampsia, the endothelial and placental dysfunction leads to increased levels of a circulating decoy receptor known as soluble Flt-1 (sFlt-1), which sequesters the circulating PlGF and prevents its biological function.[6] Evidence from randomized trials[7,8] in women with suspected preeclampsia suggests that determining

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AJOG at a Glance

Why was this study conducted?

The optimal time for delivery in women with late preterm preeclampsia without severe features is unclear. Using the maternal levels of placental growth factor (PlGF) as a prognostic marker for identifying women at high risk for complications and a selective planned delivery may reduce adverse maternal and perinatal outcomes.

Key findings

In women with late preterm preeclampsia without severe features, a planned delivery in those with low levels of PlGF and expectant management until 37 weeks' gestation in those with normal PlGF levels led to a reduction in the rate of progression to preeclampsia with severe features and maternal complications without worsening the neonatal outcomes.

What does this add to what is known?

Using an algorithm based on the maternal PlGF levels in women with late preterm preeclampsia to determine the optimal time for delivery led to a reduction in the rate of progression to preeclampsia with severe features without worsening the neonatal outcomes.

the concentration of circulating PlGF integrated within a management algorithm leads to an improved diagnosis of preeclampsia and a lower incidence of maternal morbidity. However, this evidence comes from studies in women with suspected, not confirmed, preeclampsia between 20 and 37 weeks' gestation and does not provide answers regarding the optimal time for delivery in women with late preterm preeclampsia without severe features.

This trial aimed to determine whether incorporating PlGF levels into the management algorithm for women with late preterm preeclampsia without severe features reduces the disease progression without increasing neonatal morbidity.

Material and Methods

Study design

We conducted a multicenter, open-label, parallel, randomized trial at 7 university hospitals in Spain (Supplemental Table 1). The trial was approved by the ethics committee of each participating center (HCB/2015/0363) in January 2016. The study protocol was entered in the ClinicalTrials.gov registry (https://clinicaltrials.gov/ct2/show/NCT02373839). The study met the Consolidated Standards for Reporting of Trial criteria for randomized trials.

Patients

Women aged 18 years and older who presented with preeclampsia without severe features between 34+0 to 36+6 weeks' gestation with a singleton live fetus were invited to participate. Preeclampsia was defined by the presence of de novo hypertension (systolic blood pressure [SBP] of >140 mm Hg and/or diastolic [DBP] of >90 mm Hg, measured on 2 occasions at least 4 hours apart) after 20 weeks' gestation accompanied by proteinuria (urine protein concentration of >300 mg/24 hours or a urine protein to creatinine ratio of >0.3 mg/mmol).[9] Preeclampsia without severe features was identified when the following criteria were met upon recruitment: SBP of <160 mm Hg and DBP of <110 mm Hg, platelet count of $>100\times10^9$/L, alanine and aspartate transaminase (AST) blood concentrations of <70 IU/L, serum creatinine concentration of <1.1 mg/dL, lactate dehydrogenase (LDH) concentration of <700 IU/L, and absence of right upper-quadrant or epigastric pain, dyspnea, and cerebral or visual disturbances.[10] All participants provided individual written consent.

Randomization and masking

Participants were randomly assigned to the revealed or concealed group in a 1:1 ratio using a probabilistic minimization algorithm to ensure an approximate balance of gestational age at inclusion (34 vs ≥35 completed weeks) and study site. The allocation sequence was sequestered internally by a clinical trials unit (CTU). After patients were enrolled, recruiting physicians obtained the allocation group from a web-based system. Owing to the nature of the intervention, it was not possible to blind the participants, managing professionals, or outcome assessors to the study group.

Procedures

After allocation, a venous blood sample was obtained and immediately centrifuged for a minimum of 10 minutes at 2000×g. Serum samples were assayed within 2 hours for PlGF concentrations using the fully automated Elecsys PlGF assay on an electrochemiluminescence platform (Cobas Analyzers, Roche Diagnostics, Rotkreuz, Switzerland). In the revealed group, when PlGF concentrations were below the fifth percentile (60 pg/mL),[11] planned delivery was recommended after completing a course of steroids for fetal lung maturation in women at ≤34+6 weeks' gestation or within 48 hours in women at >35 weeks' gestation. In the concealed group, the results were kept undisclosed and were not available to participants, physicians, or outcome assessors. Management in the concealed group followed usual care, adhering to the Spanish Guidelines on Hypertensive Disorders in Pregnancy,[9] and planned delivery was recommended at 37 weeks' gestation in the absence of severe features or within 48 hours if severity appeared. Research teams underwent standard assessments for safety and reported adverse events and serious adverse events according to the standard governance procedures for a clinical trial.

Prespecified outcomes

The primary maternal outcome was the progression to preeclampsia with severe features, as defined by the criteria proposed by the American College of Obstetricians and Gynecologists, after study inclusion.[10]

The primary neonatal outcome was neonatal morbidity, as determined by the morbidity assessment index for newborns (MAIN) score.[12] This score was designed to provide a numeric index of early neonatal outcomes reflecting prenatal care and adverse prenatal exposures in babies delivered after 28 weeks. The MAIN score comprises 47 binary items that describe 24 attributes of early neonatal morbidity. According to normative ranges, the score cutoff for neonatal morbidity is ≥150 (mild to severe morbidity). The template for the MAIN score is shown in Supplemental Table 2.

The prespecified secondary maternal outcomes were a composite of maternal complications including any of the following: (1) hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome (LDH >700 IU/L, AST concentration at twice the normal value, and platelet count $<100\times10^9$/L); (2) central nervous system dysfunction (eclampsia, Glasgow Coma Score of <13,[13] stroke, reversible ischemic neurologic deficit, or cortical blindness); (3) hepatic dysfunction (internal normalized ratio of >1.2 in the absence of disseminated intravascular coagulation, a Model for End-stage Liver Disease score of >10,[14,15] or hepatic hematoma or rupture); (4) renal dysfunction (dialysis, serum creatinine concentration of >150 μmol/L, urine output of <0.5 mL/kg/h during 12 hours according to the RIFLE criteria for renal insufficiency,[16] or need for treatment with furosemide to maintain urine output at >0.5 mL/kg/h for 3 hours); (5) respiratory dysfunction (pulmonary edema, requirement for invasive or noninvasive mechanical ventilation, oxygen requirement of >50% concentration for longer than 1 hour, or severe breathing difficulty [no criteria for pulmonary edema but presence of dyspnea, crackles in pulmonary auscultation, and O_2 saturation of <90%]); (6) cardiovascular dysfunction (need for inotropic support, left ventricle failure, or myocardial infarction); (7) placental abruption; or (8) requirement for blood transfusion.

The prespecified neonatal secondary outcomes included birthweight and birthweight percentile, Apgar score at 5 minutes after birth, neonatal acidosis (umbilical artery pH of <7.10 and base excess of >−12 mmol/L[17]), admission to a neonatal unit, and perinatal death (by 28 days after birth).

Post hoc changes from initial study protocol

Before the beginning of the study, the intended provider of the PlGF analytical platform (Alere Triage assay) ceased the marketing of the product (Triage PlGF Test [Alere, San Diego, CA]) and could not warrant its supply for the duration of the study. The clinically validated fifth percentile threshold level of PlGF recommended by the manufacturer of the Triage platform (Alere)[5] was converted into an Elecsys platform (Roche Diagnostics) threshold value of 60 pg/mL according to published coefficients.[11]

The trial was stopped before the completion of the required sample size.

Post hoc analyses

In addition to the prespecified outcomes, we subsequently analyzed the time interval between randomization and diagnosis of preeclampsia with severe features.

Statistical analysis

The baseline risk for progression to preeclampsia with severe features was estimated to be 25%.[18] Aiming for an alpha risk of 5% and power of 80% and assuming a reduction of this risk to 12.5% (relative risk [RR], 0.5) as clinically relevant in the intervention group, an estimated total of 152 women per arm was required to fulfil these criteria (Pearson chi-square test). With this sample size and assuming a 25% incidence of neonatal morbidity,[5] 80% power could be achieved to detect a noninferiority margin of no less than 10% (judged as clinically relevant).

During the study, all the participating centers were subjected to auditing by external personnel from the CTU to ensure integrity and protocol adherence.

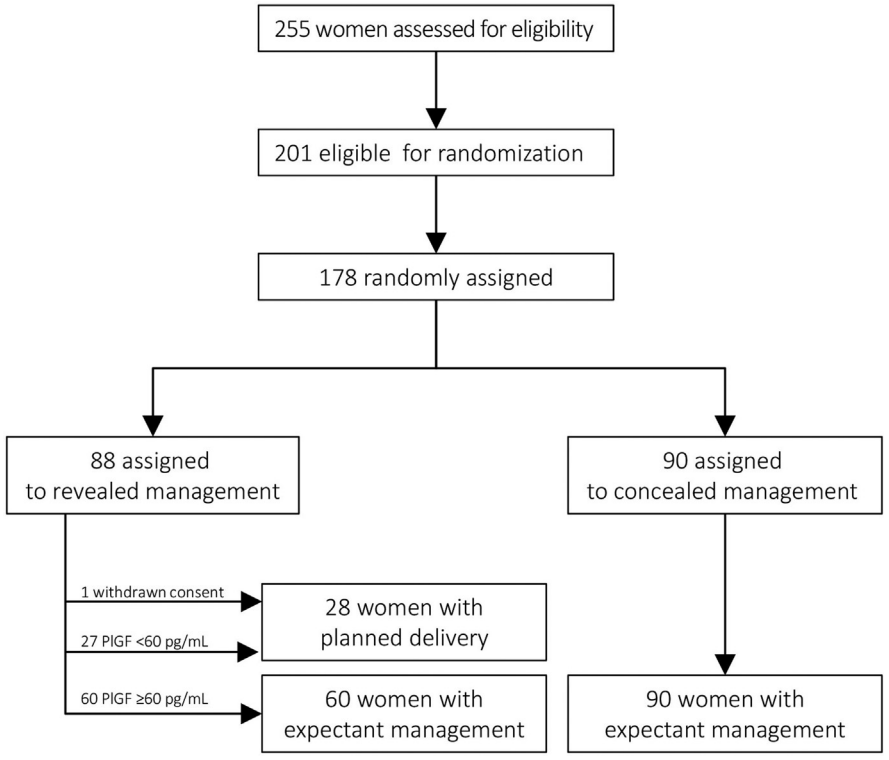
The analysis was based on the original assigned groups (intention-to-treat). Student's *t* tests (or nonparametric Mann-Whitney *U* tests) and Pearson chi-square tests (or Fisher exact tests) were performed for univariate between-group comparisons of the quantitative and qualitative variables, respectively. Primary outcomes were analyzed using logistic regressions with a robust variance estimator and were presented as the adjusted RR or risk difference (RD) with the associated 95% confidence interval (CI). Gestational age at inclusion (34 vs ≥35 weeks) was treated as a fixed effect, and the site was treated as a random effect. Effect estimates were adjusted for the minimization factors by logistic regressions (expressed as adjusted RR or adjusted RD) or quantile regressions (expressed as the adjusted difference of medians). Adjusted RRs and RDs were computed by the margins-based, post-estimation procedure described by Norton et al.[19]

The interval from randomization to the diagnosis of preeclampsia with severe features was graphed using the Kaplan-Meier method and was evaluated for differences in survival time by study group using the log-rank (Mantel-Cox) test and by calculating the hazard ratio. Statistical analyses were conducted using STATA software for Mac version 15 (Stata Corp, College Station, TX). A *P* value of <.05 was considered statistically significant.

Results

Between January 1, 2016, and December 31, 2019, 201 women were eligible and 178 (88.6%) were recruited across the 7 maternity units (Supplemental Table 1). A total of 88 women were assigned to the revealed group and 90 were assigned to the concealed group. For 2 women in the concealed group and 1 in the revealed group, the PlGF concentrations were not available because of technical problems with the analyzer. One of these women in the revealed group did not consent to further PlGF testing and asked for a planned delivery. In the remaining cases, the management corresponded with the allocated group. The Figure shows the flow of cases. Baseline characteristics were similar between the 2 groups, indicating well-balanced groups (Table 1). Of note, the mean gestational age at enrolment was 3 days later in the

FIGURE
Trial profile



PlGF, placentral growth factor.

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concealed group than in the revealed group (35.4 vs 35.1; *P*=.01).

Progression to severe preeclampsia

The number of women who progressed to preeclampsia with severe features was significantly lower in the revealed group (21.6%) than in the concealed group (42.2%) (adjusted RR, 0.5; 95% CI, 0.33−0.76; *P*=.001) (Table 2, Supplemental Figure 1). Table 3 shows the risk for progression to preeclampsia with severe features according to the study group and PlGF levels at recruitment. In the concealed group, 56.4% of women with abnormal PlGF levels progressed to severe disease, whereas 32.7% of those with normal values progressed to severe disease presentation. One instance of progression to preeclampsia with severe features was averted for each of 4.8 women who delivered because of abnormal PlGF values (number needed to treat, 4.8; 95% CI, 3−11.9). The mean elapsed time from inclusion to the diagnosis of preeclampsia with severe features was significantly lower in the concealed group than in the revealed group (13 days; 95% CI, 7.2−18.8 vs 18.2 days; 95% CI, 16.1−20.4; log-rank, *P*=.0082; hazard ratio, 0.49; 95% CI, 0.29−0.82) (Supplemental Figure 2).

Maternal complications

A total of 13 (7.3%) women had a complication, which included 4 cases of placental abruption, 2 cases of renal dysfunction, 2 cases of pulmonary edema, 3 cases of HELLP syndrome, and 3 cases requiring blood transfusions. The number of maternal complications was higher in the concealed group than in the revealed group (12.2% vs 2.3%; *P*=.01). Other maternal and neonatal outcomes are depicted in Table 4.

There were 6 serious adverse events, which consisted of 2 in the planned delivery group and 4 in the expectant management group (Supplemental Table 3). One serious adverse event in the concealed group was possibly related to the management protocol. All other serious adverse events were deemed unrelated to the intervention.

Neonatal outcomes

The mean MAIN score was not significantly different between the revealed and concealed groups (68.6; standard deviations [SD], 158.5 vs 76.8; SD, 164.8; *P*=.74) and neither was the proportion of infants with neonatal morbidity (13.6% vs 17.8%; *P*=.45; adjusted RR, 0.77; 95% CI, 0.39−1.53; *P*=.45) (Table 2). Supplemental Figure 3 shows the individual scores for neonatal morbidity according to the study group.

The 95% CIs for the RDs in neonatal morbidity (−14.7% to 6.5%) excluded zero and did not contain the noninferiority margin of 10%. Therefore, we can conclude that a revealed strategy is not inferior to a concealed strategy (expectant management) in determining the neonatal outcomes (Supplemental Figure 4).

Discussion

Main findings

This randomized controlled trial compared selective planned delivery based on maternal angiogenic factors with expectant management until 37 weeks' gestation in women with an established diagnosis of late preterm (>34 weeks' gestation) preeclampsia without severe features. We found that this strategy led to a reduction in the incidence of progression to preeclampsia with severe features and maternal complications without an increase in the rates of prematurity or neonatal morbidity.

Results in the context of what is known

On reviewing the literature, we found that a meta-analysis of individual patient data[2] that included 870 women presenting with late preterm preeclampsia without severe features reported that planned delivery at the diagnosis of preeclampsia reduced the progression to HELLP syndrome or eclampsia (RR, 0.39; 95% CI, 0.15−0.98) when compared with expectant management.

TABLE 1
Maternal demographic and pregnancy characteristics at baseline and randomization

Baseline characteristics	Revealed (n=88)	Concealed (n=90)	*P* value[a]
Maternal age (y), mean (SD)	33 (6.4)	33 (6.6)	.999
Body mass index (kg/m^2), mean (SD) [rank]	28 (6.2) [17.4–47.8]	27 (5.1) [15.4–39.2]	.241
Low educational level,[b] n (%)	21 (23.9)	17 (18.9)	.417
White—European ethnicity, n (%)	45 (51.1)	51 (56.7)	.455
Smoking, n (%)	4 (4.5)	8 (8.9)	.243
Chronic hypertension, n (%)	9 (10.2)	9 (10)	.965
Renal disease, n (%)	2 (2.3)	1 (1.1)	.619[c]
Pregestational diabetes, n (%)	5 (5.7)	5 (5.6)	.999[c]
Autoimmune disease, n (%)	0	1 (1.1)	.999[c]
Nulliparity, n (%)	47 (53.4)	46 (51.1)	.759
Previous preeclampsia, n (%)	10 (11.4)	17 (18.9)	.165
Previous intrauterine growth restriction, n (%)	4 (4.5)	8 (8.9)	.243
Previous stillbirth, n (%)	4 (4.5)	1 (1.1)	.169
Low-dose aspirin prophylaxis, n (%)	18 (20.5)	19 (21.1)	.923
Perinatal characteristics at randomization			
GA at diagnosis of preeclampsia (wk), mean (SD)	34.4 (1.5)	34.7 (1.1)	.129
GA at enrolment (wk), mean (SD)	35.1 (0.8)	35.4 (0.8)	.01
GA at enrolment (completed wk), n (%)			
34 wk	35 (39.8)	33 (36.7)	.671
≥35 wk	53 (60.2)	57 (63.3)	
Systolic blood pressure (mm Hg), mean (SD)	145.3 (10.8)	143.4 (9.8)	.221
Diastolic blood pressure (mm Hg), mean (SD)	92.2 (5.5)	91.9 (8.8)	.786
Urinary protein-creatinine ratio recorded, n (%)	56 (63.6)	62 (68.9)	.456
Urinary protein-creatinine ratio (mg/mg), median (IQR)	0.51 (0.33–1.04)	0.68 (0.38–2.97)	.368[d]
24-h urinary protein excretion recorded, n (%)	66 (75)	71 (78.9)	.538
24-h urinary protein excretion (mg/24 h), median (IQR)	491 (368–1010)	520 (389–1370)	.451[d]
PlGF (pg/mL), median (IQR)[e]	90.6 (101)	78.2 (92)	.155[d]
PlGF<60 pg/mL, n (%)	18 (20.5)	19 (21.1)	.923
Estimated fetal weight[f] (g), mean (SD)	2421 (491)	2345 (504)	.285
Estimated fetal weight percentile, mean (SD)	41 (33.6)	45.3 (34.1)	.398
Estimated fetal weight percentile <tenth percentile,[g] n (%)	24 (27.3)	19 (21)	.327
Abnormal uterine artery Doppler,[h] n (%)	41 (46.6)	41 (45.6)	.894
Abnormal umbilical artery Doppler,[i] n (%)	32 (36.4)	29 (32.2)	.556

Data are presented as n (%), mean (standard deviation [SD]), or median (interquartile range [IQR]).

GA, gestational age; *PlGF*, placental growth factor.

[a] Student's *t* tests (or Mann-Whitney *U* tests[d]) or Pearson chi-square tests were used to determine significance; [b] Less than secondary school; [c] Fisher exact test; [d] Mann-Whitney *U* test was used to determine significance; [e] Missing values in 3 patients; [f] Hadlock formula was used to determine the values[20]; [g] Determined according to Spanish standards[21]; [h] Pulsatility index of >95th percentile[22]; [i] Pulsatile index >95th percentile.[23]

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TABLE 2
Primary maternal and neonatal outcomes

Outcomes	Revealed group	Concealed group	Effect measure	Adjusted effect measure[a]
Progression to preeclampsia with severe features	19/88 (21.6%)	38/90 (42.2%)	RR, 0.51 (0.33−0.8)	RR, 0.5 (0.33−0.76)
RD	—	—	0.21 (0.07−0.33)	0.22 (0.09−0.34)
Neonatal morbidity[b]	12/88 (13.6%)	16/90 (17.8%)	RR, 0.77 (0.39−1.53)	0.77 (0.39−1.53)
RD	—	—	−0.041 (−0.15 to 0.066)	−0.041 (−0.15 to 0.07)

MAIN, morbidity assessment index for newborns; *RD*, relative difference; *RR*, relative risk.

[a] Adjusted by minimization factors (gestational age at inclusion [34 vs ≥35 completed weeks] and site); [b] MAIN score of ≥150.

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However, the disadvantage was a 2-fold increase in the risk for neonatal respiratory distress syndrome (RR, 1.9; 95% CI, 1.1−3.6). Similarly, in the planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX) trial,[3] 901 women with preeclampsia without severe features between 34 and 37 weeks' gestation were randomized to either planned delivery or expectant management and in this trial, there was also a significant reduction in maternal complications with planned delivery (RR, 0.86; 95% CI, 0.79−0.94) at the cost of a 25% increase in the number of infants requiring admission to the NICU (RR, 1.26; 95% CI, 1.08−1.47). In summary, the available evidence shows improved maternal outcomes with a planned delivery but a higher risk for secondary neonatal outcomes owing to prematurity when performed unselectively. Our study reinforces the findings of these previous reports regarding the improved maternal outcomes with a planned delivery, but also considers the increased risk for adverse neonatal outcomes by using maternal PlGF levels to determine the appropriate delivery time.

It is also worth noting that when compared with the PHOENIX study, the maternal risks were lower in our study (32% vs 69% developed severe hypertension and 7.3% vs 18.2% had a complication). In line with the milder risks found in our study, 2 additional trials compared planned delivery with expectant management in women with preeclampsia without severe features between 34 and 37 weeks' gestation. In the immediate delivery vs expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II) study,[18] among 897 women with nonsevere hypertensive disorders (46% of them with preeclampsia), only 1.5% developed HELLP syndrome and 0.7% had other maternal complications. Similarly, in a smaller series of 169 women with nonsevere preeclampsia, Owens et al[25] found that 19.5% developed severe preeclampsia, 11.7% developed severe hypertension, and 0.6% HELLP syndrome.

TABLE 3
Primary maternal outcome by study group and placental growth factor levels at recruitment

Group	Outcome		PlGF <60 pg/mL	PlGF ≥60 pg/mL	*P* value[a]
Revealed	Progression to preeclampsia with severe features	No	19 (70.4)	49 (81.7)	.186
		Yes	8 (29.6)	11 (18.3)	
	Total		27	60	
Concealed	Progression to preeclampsia with severe features	No	17 (43.6)	33 (67.3)	.032
		Yes	22 (56.4)	16 (32.7)	
	Total		39	49	
Overall	Progression to preeclampsia with severe features	No	36 (54.5)	82 (75.2)	.004
		Yes	30 (45.5)	27 (24.8)	
	Total		66	109	

Data are expressed as number (percentage) unless indicated otherwise. As per the protocol, the analysis was conducted on 175 women with placental growth factor levels measured at admission.

PlGF, placental growth factor.

[a] Pearson chi-square was used to determine significance.

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TABLE 4
Secondary maternal and neonatal outcomes

Outcomes	Revealed (n=88)	Concealed (n=90)	Adjusted effect measure[a] (95% CI)
Maternal complication (nonexclusive), n (%)	2 (2.3)	11 (12.2)	0.19 (0.05–0.74)
Placental abruption, n	1	3	—
Renal dysfunction, n	1	1	—
Pulmonary edema, n	0	2	—
HELLP syndrome, n	0	3	—
Need for transfusion of blood products, n	0	3	—
Median days of maternal admission	5	5	0 (−1.1 to 1.1)
Admission to high-dependency unit, n (%)	24 (27.3)	29 (32.2)	0.85 (0.54–1.33)
Severe hypertension, n (%)	11 (12.5)	15 (16.7)	0.75 (0.36–1.54)
Need for magnesium sulfate, n (%)	18 (20.5)	26 (28.9)	0.71 (0.42–1.2)
Spontaneous delivery, n (%)	0	0	—
Cesarean delivery, n (%)	47 (53.4)	47 (52.2)	1.02 (0.77–1.35)
Cesarean delivery for fetal distress, n (%)	10 (11.4)	9 (10)	1.14 (0.48–2.7)
Median gestational age at delivery (d)	259	259	0 (−3 to 3)
Median birthweight (g)	2540	2550	−10 (−244 to 225)
Median birthweight percentile	18	19	1 (−19 to 22)
Birthweight less than tenth percentile, n (%)	33 (37.5)	33 (36.7)	1.02 (0.7–1.5)
Birthweight less than third percentile, n (%)	22 (25)	24 (26.7)	0.94 (0.57–1.54)
Placental maternal hypoperfusion,[b] n (%)	37 (60.7)	41 (71.9)	0.84 (0.65–1.09)
Placental fetal hypoperfusion,[b] n (%)	14 (23)	7 (12.3)	2.26 (1.01–5.1)
Admission to neonatal unit, n (%)	10 (11.4)	16 (17.8)	0.64 (0.31–1.33)
Prematurity, n (%)	41 (46.6)	41 (45.6)	1.02 (0.74–1.4)
Maternal corticosteroids	24 (27.3)	22 (24.4)	1.13 (0.69–1.84)
Neonatal respiratory complication, n (%)	7 (7.9)	6 (6.7)	1.19 (0.4–3.4)
Transient tachypnea, n	5	6	
Respiratory distress syndrome, n	2	0	
Median stay in the neonatal unit (d)	7	5	2 (−4 to 10)
5-min Apgar score of <7, n (%)	5 (5.7)	7 (7.8)	0.73 (0.24–2.21)
Median umbilical artery pH[c]	7.25	7.23	0.02 (−0.01 to 0.04)
Metabolic acidosis,[c] n (%)	5 (6.8)[b]	7 (9.2)[c]	0.73 (0.24–2.2)
Perinatal deaths	0	0	—

[a] Adjusted by minimization factors (gestational age at inclusion [34 vs ≥35 completed weeks] and site); [b] Available for 61 and 57 pregnancies, respectively. Placental lesions were classified as arising from the placental vascular maternal side or fetal side according to Redline's classification[24]; [c] Available for 74 and 76 infants, respectively.

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Clinical implications

It remains challenging to define prognostic markers to identify women with late preterm preeclampsia who are at the highest risk for developing severe features while considering the trade-off between the maternal benefits and neonatal harms of a planned delivery. Our findings suggest that selective planned deliveries in women with disturbed angiogenic profiles reduced preeclampsia progression with severe features without affecting neonatal morbidity and without a net reduction in the gestational age at delivery. Determining why the planned delivery strategy did not lead to earlier gestational ages at delivery would be interesting. A plausible reason could be that the overall median gestational age at delivery was 259 days in the revealed group, but that

the median gestational age at delivery was 10 days earlier in the 20% of women with PlGF levels of <60 pg/mL and was 2 days later in the remaining 80% of women with normal PlGF values, thus resulting in no net effect of planned delivery based on PlGF values on the gestational age. This suggests that planned delivery based on PlGF levels prevents the progression to preeclampsia with severe features in women with low PlGF values and allows safe expectant management for those with normal values. Although our study was not primarily intended to demonstrate the effect of planned delivery on maternal complications secondary to preeclampsia, we also found that a reduction in the most conservative limit of the CI was 26%.

In our study, maternal corticosteroids were administrated to all women with an indication for delivery before 35 weeks' gestation (26% of the total). In the PHOENIX study, the proportion of women that were given corticosteroids was even higher (60%), which probably reflected their national guidelines recommending maternal corticosteroids for planned preterm births until 35+6 weeks gestation. This could explain the lack of difference in neonatal morbidity between planned deliveries and expectant management observed in both studies and this should be considered before translating these findings to other settings.

Research implications

A larger trial with a sample size powered to detect differences in severe maternal outcomes, such as maternal mortality or permanent morbidity, would further support our findings. Including centers from middle- or low-income countries, in which late preterm preeclampsia is a larger contributor to stillbirths and other adverse perinatal and neonatal outcomes,[26] may improve our study's external validity.

Strengths and limitations

We acknowledge some limitations of our study. First, we could not complete the intended sample size. Some participating centers had concerns about the equipoise between planned delivery and expectant management after the publication of the results of the PHOENIX study, and the compliance with the nonmaleficence principle of expectant management in the concealed group was questioned. As a result, the consortium decided to finish the study before completion. Nonetheless, our study is still powered to detect differences in the rate of progression to preeclampsia with severe features (the primary maternal outcome) and maternal complications. Although we aimed to capture the overall neonatal morbidity by using a standardized score, we acknowledge that the sample size of the study renders it underpowered to evaluate the effect of the intervention on individual components of this morbidity. Second, the intended PlGF analyzer (Alere PlGF Triage) had to be replaced because it was discontinued, and we had to transform the intended PlGF fifth percentile cutoff to its equivalent value in the Roche Elecsys platform according to the published transforming coefficients. This resulted in a cutoff of 60 pg/mL, which differed from the validated cutoff of 38 for the sFlt-1 to PlGF ratio.[4] However, this cutoff was derived from women with suspected preeclampsia between 24 and 37 weeks' gestation and not in women with an already established diagnosis of preeclampsia presenting after 34 weeks. We chose not to modify our protocol by incorporating the sFlt-1 concentration or the sFlt-1 to PlGF ratio in the management, which was also provided by the Roche Elecsys system. Third, we acknowledge that progression to preeclampsia with severe features is an indirect health outcome and that the occurrence of maternal complications may represent a better outcome.

The randomized design made the study robust against selection bias. However, detection bias was still possible because masking participating clinicians and women was unfeasible. Every primary maternal outcome was double checked by the principal investigator at each site and the coprimary neonatal outcome was independently recorded by the attending neonatologists. Performance bias was unlikely because the management of women in the concealed group and those in the revealed group with normal PlGF values adhered to the standard-of-care recommendations. We could not completely exclude the possibility that women in the expectant management group more closely self-monitored their blood pressure, making the detection of severe hypertension more likely. However, in addition to this outcome, maternal complications were increased in this group, which reinforces the existence of a worse preeclampsia course.

Conclusions

Our trial demonstrates that a strategy of selective planned delivery based on maternal PlGF levels at admission reduces progression to severe maternal complications in women presenting with preeclampsia without severe features after 34 weeks' gestation without markedly increasing the neonatal morbidity. ■

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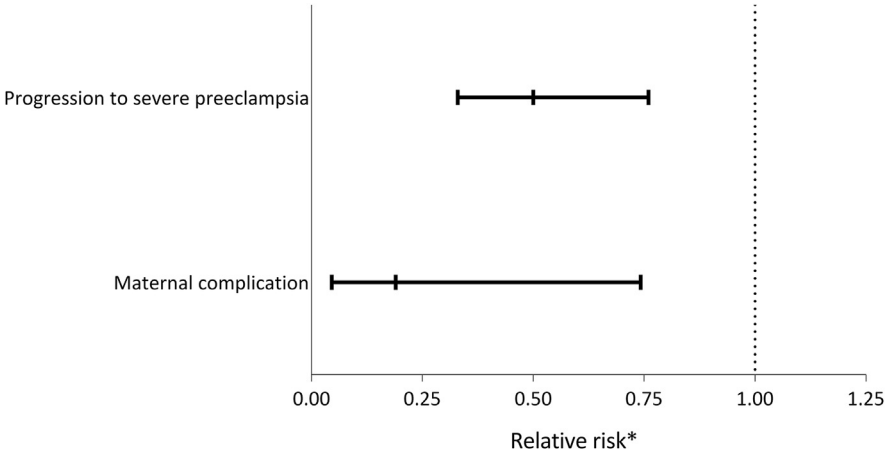
SUPPLEMENTAL FIGURE 1
Adjusted relative risks



Adjusted relative risks of progression to preeclampsia with severe features (primary maternal outcome) and maternal complications (secondary maternal outcome) of revealed vs concealed groups. The *asterisk* symbol indicates adjustment by minimization factor (gestational age at inclusion [34 vs 35+ completed weeks] and site).

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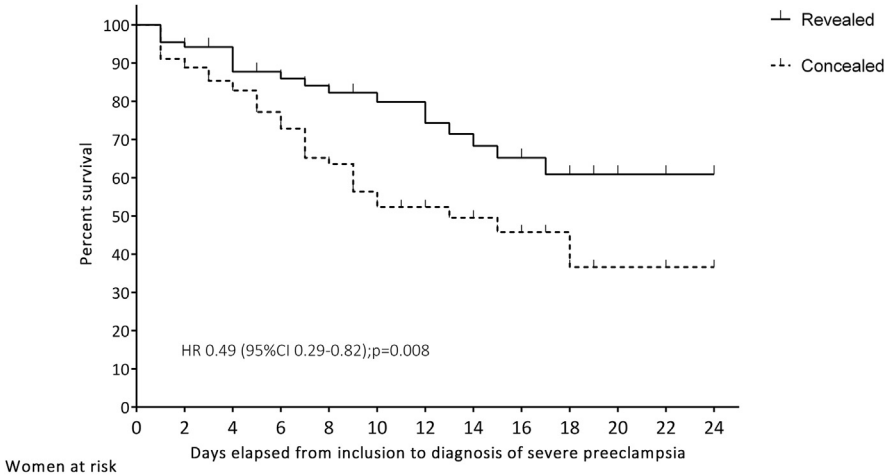
SUPPLEMENTAL FIGURE 2
Kaplan-Meier survival estimate



Women at risk

Revealed	88	76	58	50	44	34	29	23	19	12	8	5	3
Concealed	90	80	68	53	40	28	21	17	11	5	5	3	2

Time to severe preeclampsia development by trial arm.

HR, hazard ratio.

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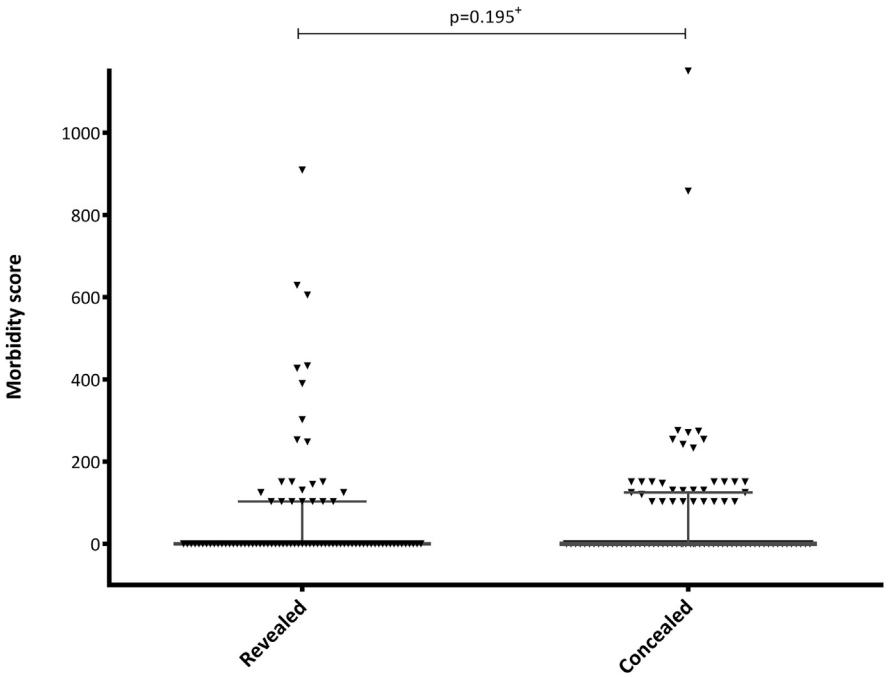
SUPPLEMENTAL FIGURE 3
MAIN scores according to group



+Mann-Whitney *U* test was used to determine significance.

MAIN, morbidity assessment index for newborns.

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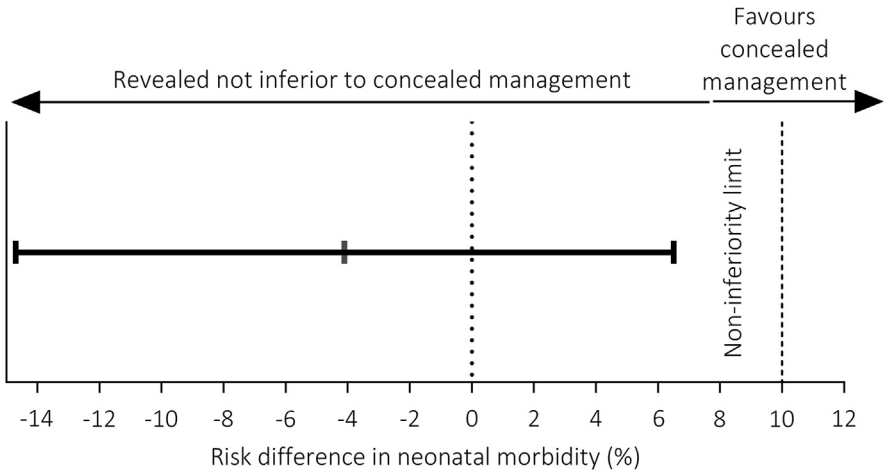
SUPPLEMENTAL FIGURE 4
Risk difference in neonatal morbidity



Risk difference in neonatal morbidity (MAIN score of ≥150) with the limit of the noninferiority hypothesis displayed.

MAIN, morbidity assessment index for newborns.

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SUPPLEMENTAL TABLE 1
Recruitment by center

Center	Revealed (n=88)	Concealed (n=90)
Hospital Clínic de Barcelona (Catalonia)	33 (37.5)	34 (36.8)
Hospital Universitario 12 de Octubre (Madrid)	26 (29.5)	25 (27.8)
Hospital Universitari i Politècnic La Fe (Valencia)	13 (14.8)	11 (12.2)
Hospital Universitario Cruces (Basque Country)	7 (8)	9 (10)
Hospital General de l'Hospitalet (Catalonia)	4 (4.5)	5 (5.1)
Hospital Sant Joan de Déu Barcelona (Catalonia)	3 (3.4)	4 (4.4)
Hospital Universitari Dexeus (Catalonia)	2 (2.3)	2 (2.2)

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SUPPLEMENTAL TABLE 2
Morbidity assessment index for newborns score table with morbidity items and their corresponding scale values

Time after birth	Item	Morbidity attribute		Scale
Within 24 h of birth	1	Cord blood pH of ≤7.10		151
	2	Resuscitation at birth: intubation		127
	3	Meconium: meconium below cords		155
	4	Apgar score 5 min	score 4–7	125
	5		score 1–3	162
	6		score <1	193
	7	Apgar score 10 min	score 4–7	154
	8		score 1–3	183
	9	Altered color:[a] dusky or central cyanosis		145
	10	Respiratory rate/min[a]	<30 or >60 at 3–24 h	131
	11		>100 between 3–24 h	140
Within 7 d of birth	12	Heart rate/min[a]	160–200 beat	120
	13		>200 beat	183
	14		<100 beat	157
	15	Hypotonia[a]	Present beyond 120 h of age	129
	16		Present at 1–120 h of age	156
	17	Flaccidity[a] present at 1–120 h		154
	18	Apnea[a]	Apnea corrected by oxygen	115
	19		Apnea corrected by resuscitation	140
	20	Bleeding disorder	Thrombocytopenia with or without bleeding disorder	147
	21		Need for transfusion owing to anemia or item 20	170
	22	Mean systolic BP (mm Hg)[a] 28–32 wk: <30 or 32–42 wk: <40		136
	23	Urine output[a] low (<2 mL/kg/h)		141
	24	Seizures	Tremors or single seizure	137
	25		Multiple seizures	155

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SUPPLEMENTAL TABLE 2

Morbidity assessment index for newborns score table with morbidity items and their corresponding scale values

(continued)

Time after birth	Item	Morbidity attribute		Scale
	26		If >2 drugs used for seizures	183
	27	Level of consciousness[a]	Drowsy or lethargic	137
	28		Stupor or obtundation or coma	187
	29	Oral feeding difficulties[a]	Poor sucking within 24 h	81
	30		Poor sucking at 24 h–7 d	98
	31		Poor sucking beyond 7 d	119
	32		Persistent vomiting	136
	33	Assisted ventilation:[a] assisted ventilation beyond 24 h		117
	34	Mechanical ventilation[a]	Mechanical ventilation within 24 h	130
	35		Mechanical ventilation at 24 h–7 d	135
	36		Mechanical ventilation beyond 7 d	162
	37	Birth trauma	Bone fracture—long bone or clavicle or skull	176
	38		Nerve injury (facial or peripheral)	183
	39		Subdural or intracerebral hematoma	179
	40	Hypoglycemia (lowest level): blood glucose <2.2 mmol/L		151
	41	Hyperbilirubinemia, mmol/L (peak level)	Serum bilirubin >250 (phototherapy)	103
	42		Serum bilirubin >340 (exchange transfusion)	179
	43	Bacterial culture	Blood positive	162
	44		CSF positive	187
	45	Intraventricular hemorrhage	Grade 1 or 2	152
	46		Grade 3 or 4	186
	47	Cardiopulmonary resuscitation any time before discharge		162

Circle all items that apply between birth and discharge from the hospital or up to 7 days of life, whichever is earlier. MAIN score is the sum of the scale values of all checked items.

Adapted from Verma et al.[12]

[a] More than 2 consecutive readings.

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SUPPLEMENTAL TABLE 3
Description of adverse events according to group allocation

	Revealed (n=88)	Concealed (n=90)
Adverse events	15	24
Severity		
Mild	8	10
Moderate	4	9
Severe	0	2
Potentially life-threatening	2	2
Causality		
Not related	12	16
Unlikely related	3	3
Possible related	0	3
Probably related	0	2
Outcome		
Ad integrum recovery	12	20
Partial recovery	1	0
Not resolved	0	0
Death	0	0
Unknown	0	3
System organ class (nonexclusively)		
Hematological	3	10
Biochemical	3	4
Cardiovascular	2	4
Gastrointestinal	0	4
Neurologic	8	10
Infectious	2	1
Systemic	2	0
Ophthalmologic	0	2

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