

1 **Placental growth factor testing in the management of late preterm pre-eclampsia**  
2 **without severe features: A multi-center, randomized, controlled trial**

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8

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1   **CONDENSATION**

2   In non-severe preeclampsia after 34 weeks, a selective planned delivery based on PIGF levels  
3   results in lower progression to severe features and reduces maternal complications without  
4   increasing neonatal morbidity.

5   **SHORT TITLE**

6   Placental growth factor testing in non-severe late preterm pre-eclampsia.

7   **AJOG AT A GLANCE**

8   **A) Why was the study conducted?**

9   The optimal time for delivery in women with late preterm pre-eclampsia without severe  
10  features is unclear. Maternal levels of placental growth factor as a prognostic marker  
11  identifying women with a high risk of complications and a selective planned delivery may  
12  reduce maternal and perinatal adverse outcomes.

13  **B) What are the key findings?**

14  In women with late preterm pre-eclampsia without severe features, planned delivery in  
15  those with low levels of PIGF and expectant management until 37 weeks gestation in those  
16  with normal PIGF levels resulted in a lower rate of progression to pre-eclampsia with severe  
17  features and of maternal complications, without worsening the neonatal outcomes.

18  **C) What does this study add to what is already known?**

19  Using an algorithm based on maternal levels of PIGF in women with late preterm pre-  
20  eclampsia to decide the best time of delivery results in a lower rate of progression to pre-  
21  eclampsia with severe features, without worsening the neonatal outcomes.

- 1 **KEYWORDS:** Biomarkers; Prediction; Pre-eclampsia; Therapy; Morbidity; Blood pressure;
- 2 Infant; Newborn

1 **ABSTRACT**

2 **Background** Because the optimal delivery time in late preterm pre-eclampsia is unclear, it  
3 remains challenging to define prognostic markers to identify women at the highest risk, in  
4 which the trade-off between maternal benefits and neonatal harms more clearly supports a  
5 timely planned delivery.

6 **Objective** This trial aimed to determine whether knowledge of the maternal levels of  
7 placental growth factor (PIGF) in women with late preterm pre-eclampsia reduced  
8 progression to pre-eclampsia with severe features after a planned selective delivery, without  
9 increasing perinatal adverse outcomes.

10 **Study Design** This parallel-group, open-label, multicenter, randomized controlled trial was  
11 conducted in seven maternity units across Spain. We compared selective planned delivery  
12 based on the maternal levels of PIGF at admission (revealed group) and expectant  
13 management under usual care (concealed group) with individual randomization in singleton  
14 pregnancies with late preterm pre-eclampsia from 34 to 36<sup>+6</sup> weeks gestation. The co-  
15 primary maternal outcome was the progression to pre-eclampsia with severe features. The  
16 co-primary neonatal outcome was morbidity up to infant hospital discharge with a non-  
17 inferiority hypothesis (non-inferiority margin of 10% difference in incidence). Analyses were  
18 conducted by the intention-to-treat method.

19 **Results** Between January 1, 2016, and December 31, 2019, 178 women were recruited. Of  
20 those women, 88 women were assigned to the revealed group and 90 were assigned to the  
21 concealed group. The data analysis was performed before the completion of the required  
22 sample size. The proportion of women with progression to pre-eclampsia with severe

1 features was significantly lower in the revealed group than in the concealed group (adjusted  
2 relative risk [RR], 0.5; 95% confidence interval [CI], 0.33–0.76;  $p=0.001$ ). The proportion of  
3 infants with neonatal morbidity was not significantly different between groups (adjusted RR,  
4 0.77; 95% CI, 0.39–1.53;  $p=0.45$ ).

5 **Conclusions** There is evidence to suggest that the use of an algorithm based on PIGF levels in  
6 women with late preterm pre-eclampsia results in a lower rate of progression to pre-  
7 eclampsia with severe features and reduces maternal complications, without worsening the  
8 neonatal outcomes. This trade-off should be discussed with women with late preterm pre-  
9 eclampsia to allow shared decision-making on the timing of delivery.

## 1 INTRODUCTION

2 Pre-eclampsia is a life-threatening, multi-system condition characterized by hypertension  
3 and end-organ dysfunction. It complicates 2-8% of pregnancies (1) and is a leading cause of  
4 maternal and neonatal morbidity and mortality. Management of pre-eclampsia is dictated  
5 by a trade-off between reducing the risks of maternal complications by timely delivery and  
6 minimizing the risks of prematurity by expectant management. In women with late preterm  
7 pre-eclampsia (between 34-37 weeks gestation), the optimal time for delivery is  
8 controversial because the net benefit between reducing maternal and fetal risks by planned  
9 delivery and the neonatal secondary risks of prematurity is unclear.

10 An individual patient data meta-analysis has suggested that some women with late preterm  
11 pre-eclampsia may benefit from delivery before 37 weeks (2). More recently, a randomized  
12 trial comparing expectant management with planned delivery in women with late preterm  
13 pre-eclampsia has reported a 14% reduction in maternal morbidity but a 26% increased risk  
14 of neonatal unit admission after planned delivery, suggesting that better identification of  
15 pregnancies with the highest risks may maximize the benefits of a planned early delivery (3).

16 Maternal levels of angiogenic factors, including placental growth factor (PlGF) and soluble  
17 fms-like tyrosine kinase 1 (sFlt-1), have emerged as reliable predictors of complications in  
18 women with suspected pre-eclampsia (4,5). PlGF exerts its biological function by binding to  
19 the Flt-1 receptor. In pre-eclampsia, the endothelial and placental dysfunction leads to  
20 increased levels of a circulating decoy receptor, known as soluble Flt-1 (sFlt-1), which  
21 sequesters the circulating PlGF and prevents its biological function (6). Evidence from

1 randomized trials (7,8) in women with suspected pre-eclampsia has suggested that  
2 measurement of circulating concentration of PIGF integrated with a management algorithm  
3 results in improved diagnosis of pre-eclampsia and a lower incidence of maternal morbidity.  
4 However, this evidence comes from studies in women with suspected, not confirmed, pre-  
5 eclampsia between 20-37 weeks gestation and does not provide answers as to when the  
6 optimal time for delivery is in women with late preterm pre-eclampsia without severe  
7 features.

8 This trial aimed to determine whether measuring PIGF levels in women with late preterm  
9 pre-eclampsia and planned early deliveries in those with lower levels reduced progression  
10 to pre-eclampsia with severe features and subsequent maternal adverse outcomes, without  
11 increasing neonatal adverse outcomes.

## 1 MATERIAL AND METHODS

### 2 Study Design

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

### 9 Patients

10 Women of 18 years of age or older who presented with pre-eclampsia without severe  
11 features between 34<sup>+0</sup>-36<sup>+6</sup> weeks gestation with a singleton live fetus were invited to  
12 participate. Pre-eclampsia was defined by the presence of *de novo* hypertension (systolic  
13 blood pressure [BP] >140 mmHg and/or diastolic BP >90 mmHg, measured on two occasions  
14 at least 4 hours apart) after 20 weeks gestation accompanied by proteinuria (>300 mg/24  
15 hours or a urine protein/creatinine ratio > 0.3 mg/mmol) (9). Pre-eclampsia without severe  
16 features was defined when the following criteria were met upon recruitment: systolic BP  
17 <160 mmHg and diastolic BP <110 mmHg, platelet count >100x10<sup>9</sup>/L, blood concentrations  
18 of alanine and aspartate transaminase (AST) <70 IU/L, serum creatinine concentration <1.1  
19 mg/dL, lactate dehydrogenase (LDH) <700 IU/L, and absence of right upper-quadrant or  
20 epigastric pain, dyspnoea, and cerebral or visual disturbances (10). All participants provided  
21 individual written consent.

## 1 Randomization and masking

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

## 9 Procedures

10 After group allocation, a venous blood sample was obtained and immediately centrifuged for  
11 a minimum of 10 minutes at 2000 g. Serum samples were assayed within 2 hours for PlGF  
12 concentrations using the fully automated Elecsys assay on an electrochemiluminescence  
13 platform (Cobas Analyzers, Roche Diagnostics). In the revealed group, when PlGF  
14 concentrations were below the 5<sup>th</sup> centile (60 pg/mL) (11), planned delivery was  
15 recommended after completing a course of steroids for fetal lung maturation in women at  
16  $\leq 34^{+6}$  weeks gestation or within 48 hours in women at  $>35$  weeks' gestation. In the concealed  
17 group, the results were kept sequestered and were not available to participants, physicians,  
18 or outcome assessors. Management in the concealed group followed usual care, adhering to  
19 the Spanish Guidelines on Hypertensive Disorders in Pregnancy (9), and planned delivery was  
20 recommended at 37 weeks in the absence of severe features or within 48 hours if severity  
21 appeared. Research teams underwent standard assessments of safety and reported adverse

1 events and serious adverse events according to the standard governance procedures for a  
2 clinical trial.

### 3 Pre-specified Outcomes

4 The primary maternal outcome was the progression to pre-eclampsia with severe features,  
5 as defined by the criteria proposed by the American College of Obstetricians and  
6 Gynecologists, after study inclusion (10).

7 The primary neonatal outcome was neonatal morbidity, as assessed by the Morbidity  
8 Assessment Index for Newborns (MAIN) score (12). This score was designed to provide a  
9 numeric index of early neonatal outcomes reflecting prenatal care and adverse prenatal  
10 exposures in babies delivered after 28 weeks. The MAIN score comprises 47 binary items  
11 that describe 24 attributes of early neonatal morbidity. According to normative ranges, the  
12 score cut-off for neonatal morbidity is  $\geq 150$  (mild to severe morbidity). The template for the  
13 MAIN score is shown in Supplementary Table 2.

14 The pre-specified secondary maternal outcomes were a composite of maternal  
15 complications, including any of the following: (i) HELLP syndrome (LDH  $>700$  IU/L, AST at  
16 twice the normal value, and platelet count  $<100 \times 10^9/L$ ); (ii) central nervous system  
17 dysfunction (eclampsia, Glasgow Coma Score  $<13$  (13), stroke, reversible ischemic  
18 neurological deficit, or cortical blindness); (iii) hepatic dysfunction (international normalised ratio  
19 [INR]  $>1.2$  in the absence of disseminated intravascular coagulation, Model for End-stage  
20 Liver Disease [MELD] score  $>10$  (16), or hepatic hematoma or rupture); (iv) renal dysfunction  
21 (dialysis, serum creatinine concentration  $>150 \mu\text{mol/L}$ , or urine output  $<0.5 \text{ mL/kg/h}$  during

1 12 hours, according to the RIFLE criteria for renal insufficiency (16), or need for treatment  
2 with furosemide to maintain urine output  $>0.5$  mL/kg/h for 3 hours); (v) respiratory  
3 dysfunction (pulmonary edema, requirement of invasive or non-invasive mechanical  
4 ventilation, oxygen requirement  $>50\%$  concentration for longer than 1 hour, or severe  
5 breathing difficulty [no criteria for pulmonary edema but presence of dyspnea, crackles in  
6 pulmonary auscultation, and  $\text{SaO}_2 < 90\%$ ]); (vi) cardiovascular dysfunction (need for inotropic  
7 support, left ventricle failure, or myocardial infarction); (vii) placental abruption; or (viii)  
8 requirement of blood transfusion.

9 The pre-specified neonatal secondary outcomes included: birthweight and birthweight  
10 percentile, Apgar scores at 5 minutes after birth, neonatal acidosis (umbilical artery pH  $< 7.10$   
11 and base excess  $> -12$  mmol/L (17)), admission to a neonatal unit, and perinatal death (until  
12 28 days after birth).

### 13 Post-Hoc Changes from Initial Study Protocol

14 Before the commencement of the study, the intended provider of the PIGF analytical  
15 platform (Alere International) ceased marketing of the product (Alere Triage PIGF) and could  
16 not warrant its supply for the duration of the study. The clinically validated 5<sup>th</sup> centile  
17 threshold of PIGF levels recommended by the manufacturer of the Triage platform (Alere)  
18 (5) was converted into an Elecsys platform (Roche) threshold value of 60 pg/mL, according  
19 to published coefficients (11).

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

## 1 Post-Hoc Analyses

2 In addition to the pre-specified outcomes, we subsequently analyzed the time interval  
3 between randomization and diagnosis of pre-eclampsia with severe features.

## 4 Statistical Analysis

5 The baseline risk of progression to pre-eclampsia with severe features was estimated to be  
6 25% (18). Aiming at an alpha-risk of 5% and power of 80% and assuming a reduction of this  
7 risk to 12.5% (relative risk [RR], 0.5) as clinically relevant in the intervention group, a total of  
8 152 women per arm was estimated as needed (Pearson  $\chi^2$ ). With this sample size and  
9 assuming a 25% incidence of neonatal morbidity (5), 80% power could be achieved to detect  
10 a non-inferiority margin of no less than 10% (judged as clinically relevant).

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

13 The analysis was based on originally assigned groups (intention-to-treat). Student's t-tests  
14 (or non-parametric Mann-Whitney U tests) and Pearson  $\chi^2$  tests (or Fisher's exact tests) were  
15 performed for univariate between-group comparisons of quantitative and qualitative  
16 variables, respectively. Primary outcomes were analyzed using logit regression with a robust  
17 variance estimator and were presented as adjusted RR or risk difference (RD) with the  
18 associated 95% confidence interval (CI). Gestational age at inclusion (34 vs. 35<sup>+</sup>) was treated  
19 as a fixed effect, and the site was treated as a random effect. Effect estimates were adjusted  
20 for the minimization factors by logit regression (expressed as adjusted RR or adjusted RD) or  
21 quantile regression (expressed as the adjusted difference of medians). Adjusted RRs and RDs

1 were computed by the margins-based post-estimation procedure described by Norton et al.  
2 (19).

3 The interval from randomization to the diagnosis of pre-eclampsia with severe features was  
4 graphed using the Kaplan-Meier method and was tested for differences in survival time by  
5 study group using the log-rank (Mantel-Cox) test and by calculating the hazard ratio.  
6 Statistical analyses were conducted using STATA software for Mac v15 (Stata Corp., College  
7 Station, Texas). A p-value <0.05 was considered statistically significant.

## 1 RESULTS

2 Between January 1, 2016, and December 31, 2019, 201 women were eligible and 178 (88.6%)  
3 were recruited across the seven maternity units (Supplementary Table 1). A total of 88  
4 women were assigned to the revealed group and 90 were assigned to the concealed group.  
5 For two women in the concealed group and one in the revealed group, the PIGF  
6 concentrations were not available because of technical problems with the analyzer. One of  
7 these women in the revealed group did not consent to further PIGF testing and asked for a  
8 planned delivery. In the remaining cases, the management complied with the allocated  
9 group. Figure 1 shows the flow of cases. Baseline characteristics were similar between the  
10 two groups, indicating well-balanced groups (Table 1). Of note, the mean gestational age at  
11 enrollment was 3 days higher in the concealed group than in the revealed group (35.4 vs.  
12 35.1;  $p=0.01$ ).

### 13 Progression to Severe Pre-eclampsia

14 The number of women with progression to pre-eclampsia with severe features was  
15 significantly lower in the revealed group (21.6%) than in the concealed group (42.2%);  
16 (adjusted RR, 0.5; 95% CI, 0.33–0.76;  $p=0.001$ ) (Table 2 and Figure 2). The necessary number  
17 of women for planned delivery subjected to PIGF values to reduce one instance of  
18 progression to preeclampsia with severe features was 4.8 (3-11.9). The mean elapsed days  
19 from inclusion to the diagnosis of pre-eclampsia with severe features was significantly lower  
20 in the concealed group than in the revealed group (13 [95% CI, 7.2-18.8] vs. 18.2 [95% CI,  
21 16.1-20.4]; Log-rank,  $p=0.0082$ ; HR, 0.49 [95% CI, 0.29-0.82]; Supplementary Figure 1). Table

1 4 shows the risk of progression to pre-eclampsia with severe features according to the study  
2 group and PIGF levels at recruitment.

### 3 Maternal Complications

4 A total of 13 (7.3%) women had a complication, which included: 4 cases of placental  
5 abruption, 2 cases of renal dysfunction, 2 cases of pulmonary edema, 3 cases of HELLP  
6 syndrome, and 3 cases requiring blood transfusions. The number of maternal complications  
7 was higher in the concealed group than in the revealed group (2.3% vs. 12.2%;  $p=0.01$ ). Other  
8 maternal and neonatal outcomes are depicted in Table 3.

9 There was a total of six serious adverse events, which consisted of two in the planned delivery  
10 group and four in the expectant management group (Supplementary Table 3). One serious  
11 adverse event in the concealed group was possibly related to the management protocol. All  
12 other serious adverse events were deemed unrelated to the intervention.

### 13 Neonatal Outcomes

14 The 95% CIs for the RDs of neonatal morbidity (-14.7—6.5%) excluded zero and did not  
15 contain the non-inferiority margin of 10%. Therefore, we can conclude that a revealed  
16 strategy is not inferior to a concealed strategy (expectant management) in determining  
17 neonatal outcomes (Supplementary Figure 2).

18 The mean MAIN score was not significantly different between the revealed and concealed  
19 groups (68.6 [SD, 158.5] vs. 76.8 [SD, 164.8];  $p=0.74$ ) and neither was the proportion of  
20 infants with neonatal morbidity (13.6% vs. 17.8%;  $p=0.45$ ; adjusted RR, 0.77; 95% CI, 0.39-

- 1 1.53;  $p=0.45$ ) (Table 2). Figure 3 shows the individual scores of neonatal morbidity according
- 2 to study group.

## 1 DISCUSSION

### 2 Main Findings

3 This is the first randomized controlled trial (RCT) comparing selective planned delivery based  
4 on maternal angiogenic factors versus expectant management until 37 weeks gestation in  
5 women with an established diagnosis of late preterm (>34 weeks) pre-eclampsia without  
6 severe features. We found that this strategy resulted in a reduced incidence of progression  
7 to pre-eclampsia with severe features and maternal complications, without higher rates of  
8 prematurity or neonatal morbidity.

### 9 Results in the Context of What is Known

10 On review of the literature, an individual patient data meta-analysis (2) including 870 women  
11 presenting with late preterm pre-eclampsia without severe features reported that planned  
12 delivery at the diagnosis of pre-eclampsia reduces the progression to HELLP syndrome or  
13 eclampsia (RR, 0.39; 95% CI, 0.15-0.98) compared to expectant management. However, the  
14 downside of this benefit was a 2-fold increased risk of neonatal respiratory distress syndrome  
15 (RR, 1.9; 95% CI, 1.1-3.6). Similarly, the Planned Early Delivery or Expectant Management for  
16 Late Preterm Pre-eclampsia (PHOENIX) trial (3) randomized 901 women with pre-eclampsia  
17 without severe features between 34 and 37 weeks gestation to either planned delivery or  
18 expectant management and also found a significant reduction in maternal complications  
19 with planned delivery (RR, 0.86; 95% CI, 0.79-0.94) at the cost of an approximate 25%  
20 increase in the number of infants requiring admission to the neonatal unit (RR, 1.26; 95% CI,  
21 1.08-1.47). In summary, available evidence shows improved maternal outcomes with a  
22 planned delivery but a higher risk of neonatal secondary risks of prematurity when

1 performed unselectively. Our study reinforces the findings of these previous reports  
2 regarding the improved maternal outcomes with a planned delivery but also considers the  
3 increased risk of adverse neonatal outcomes by using maternal PlGF levels to determine the  
4 appropriate delivery time.

5 It is also worth noting that, compared to the PHOENIX study, our study found lower maternal  
6 risks (32% vs. 69% developed severe hypertension and 7.3% vs. 18.2% had a complication).  
7 In line with the milder risks found in our study, there were two additional trials that  
8 compared planned delivery with expectant management in women with pre-eclampsia  
9 without severe features between 34 and 37 weeks gestation. In the Immediate Delivery  
10 Versus Expectant Monitoring for Hypertensive Disorders of Pregnancy Between 34 and 37  
11 Weeks of Gestation (HYPITAT-II) study (18), among 897 women with non-severe  
12 hypertensive disorders (46% of them with pre-eclampsia), only 1.5% developed HELLP  
13 syndrome and 0.7% had other maternal complications. Similarly, in a smaller series of 169  
14 women with non-severe pre-eclampsia, Owens et al. (20) found that 19.5% developed severe  
15 pre-eclampsia, 11.7% developed severe hypertension, and 0.6% HELLP syndrome.

#### 16 Clinical Implications

17 It remains challenging to define prognostic markers to identify women with late preterm  
18 pre-eclampsia who are at the highest risk of developing severe features while considering  
19 the trade-off between the maternal benefits and neonatal harms of a planned delivery. Our  
20 findings suggest that selective planned deliveries in women with disturbed angiogenic  
21 profiles reduce the progression to pre-eclampsia with severe features, without affecting

1 neonatal morbidity and without a net reduction in the gestational age at delivery.  
2 Determining why the planned delivery strategy did not result in earlier gestational ages at  
3 delivery would be interesting. A plausible reason could be because the overall median  
4 gestational age at delivery was 259 days in the revealed group, but the median gestational  
5 age at delivery was 10 days earlier in the 20% of women with PIGF levels <60 pg/mL and was  
6 2 days later in the remaining 80% of women with normal PIGF values, thus resulting in no net  
7 effect of planned delivery based on PIGF values. This suggests that planned delivery based  
8 on PIGF levels prevents the occurrence of pre-eclampsia with severe features in women with  
9 low PIGF values and allowssafe expectant management for those with normal values. Even  
10 though our study was not primarily intended to demonstrate an effect of planned delivery in  
11 maternal complications secondary to pre-eclampsia, we also found that a reductionin the  
12 most conservative limit of the CI was 26%.

13 In our study, maternal corticosteroids were administrated to all women with an indication of  
14 delivery before 35 weeks gestation(26% of the total). In the PHOENIX study, the proportion  
15 of women that were given corticosteroids was even larger (60%), which probably reflected  
16 their national guidelines recommendingmaternal corticosteroids for planned preterm births  
17 until 35<sup>+6</sup> weeks gestation. This couldexplain the lack of difference in neonatal morbidity  
18 between planned deliveries and expectant management observed in both studies. This  
19 should be considered before translating these findings to other settings.

20 Research Implications

1 A larger trial with a sample size powered to detect differences in hard maternal outcomes,  
2 such as maternal mortality or permanent morbidity, would further support our findings.  
3 Including centers from middle- or low-income countries, where late pre-eclampsia is a larger  
4 contributor to stillbirths and other adverse perinatal and neonatal outcomes (21), may  
5 improve the external validity of our study.

### 6 Strengths and Limitations

7 We acknowledge some limitations of our study. First, we could not complete the intended  
8 sample size. Some participating centers had concerns about the equipoise between planned  
9 delivery and expectant management after the publication of the results of the PHOENIX  
10 study, and the compliance with the non-maleficence principle of expectant management in  
11 the concealed group was questioned. As a result, the consortium decided to finish the study  
12 before completion. Our study is still powered to detect differences in the rate of progression  
13 to pre-eclampsia with severe features (the maternal primary outcome) and maternal  
14 complications. Even though we aimed to capture overall neonatal morbidity by using a  
15 standardized score, we acknowledge that the sample size of the study renders it  
16 underpowered to evaluate the effect of the intervention on individual components of this  
17 morbidity. Second, the intended PIGF analyzer (Alere PIGF triage) had to be replaced because  
18 it was discontinued, and we had to transform the intended PIGF 5<sup>th</sup>-centile cut-off to its  
19 equivalent in the Roche Elecsys platform according to the published transforming  
20 coefficients. This resulted in a cut-off of 60 pg/mL, which differed from the validated cut-off  
21 of 38 for the sFlt-1/PIGF ratio (4). However, this cut-off was derived from women with  
22 suspected pre-eclampsia between 24 and 37 weeks gestation and not in women with an

1 already established diagnosis of pre-eclampsia presenting after 34 weeks. We opted not to  
2 modify our protocol by incorporating the sFlt-1 or the sFlt-1/PlGF ratio in the management,  
3 which was also provided by the Roche Elecsys system. Third, we admit that progression to  
4 pre-eclampsia with severe features is an indirect health outcome and that the occurrence of  
5 maternal complications may represent a better outcome.

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

### 17 Conclusions

18 In conclusion, our trial demonstrates that a strategy of selective planned delivery based on  
19 the maternal levels of PlGF at admission reduces progression to severe features maternal  
20 complications in women presenting with pre-eclampsia without severe features after 34  
21 weeks gestation, without relevantly increasing neonatal morbidity.

## 1 ACKNOWLEDGMENTS

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1 **Table 1** Maternal demographic and pregnancy characteristics at baseline and randomization

	Revealed (n=88)	Concealed (n=90)	p*
<b>Baseline characteristics</b>			
Maternal age [years]; mean (SD)	33 (6.4)	33 (6.6)	0.999
Body mass index [kg/m <sup>2</sup> ]; mean (SD) [rank]	28 (6.2) [17.4-47.8]	27 (5.1) [15.4-39.2]	0.241
Low educational level <sup>1</sup> ; n (%)	21 (23.9)	17 (18.9)	0.417
White-European ethnicity; n (%)	45 (51.1)	51 (56.7)	0.455
Smoking; n (%)	4 (4.5)	8 (8.9)	0.243
Chronic hypertension; n (%)	9 (10.2)	9 (10)	0.965
Renal disease; n (%)	2 (2.3)	1 (1.1)	0.619 <sup>§</sup>
Pre-gestational diabetes; n (%)	5 (5.7)	5 (5.6)	0.999 <sup>§</sup>
Autoimmune disease; n (%)	0	1 (1.1)	0.999 <sup>§</sup>
Nulliparity; n (%)	47 (53.4)	46 (51.1)	0.759
Previous preeclampsia; n (%)	10 (11.4)	17 (18.9)	0.165
Previous fetal growth restriction; n (%)	4 (4.5)	8 (8.9)	0.243
Previous stillbirth; n (%)	4 (4.5)	1 (1.1)	0.169
Low-dose aspirin prophylaxis; n (%)	18 (20.5)	19 (21.1)	0.923
<b>Perinatal characteristics at randomization</b>			
GA at diagnosis of pre-eclampsia [weeks]; mean (SD)	34.4 (1.5)	34.7 (1.1)	0.129
GA at enrolment (weeks); mean (SD)	35.1 (0.8)	35.4 (0.8)	0.01
GA at enrolment (completed weeks)			
34 weeks; n (%)	35 (39.8)	33 (36.7)	0.671
35+ weeks; n (%)	53 (60.2)	57 (63.3)	
Systolic blood pressure [mmHg]; mean (SD)	145.3 (10.8)	143.4 (9.8)	0.221
Diastolic blood pressure [mmHg]; mean (SD)	92.2 (5.5)	91.9 (8.8)	0.786
Urinary protein-creatinine ratio recorded; n (%)	56 (63.6)	62 (68.9)	0.456
Urinary protein-creatinine ratio (mg/mg); median (IQR)	0.51 (0.33-1.04)	0.68 (0.38- 2.97)	0.368 <sup>*</sup>
24-h urinary protein excretion recorded; n (%)	66 (75)	71 (78.9)	0.538
24-h urinary protein excretion (mg/24 h); median (IQR)	491 (368- 1010)	520 (389- 1370)	0.451 <sup>*</sup>
PlGF [pg/mL]; median (IQR) <sup>2</sup>	90.6 (101)	78.2 (92)	0.155 <sup>†</sup>
PlGF<60 pg/mL; n(%)	18 (20.5)	19 (21.1)	0.923
Estimated fetal weight <sup>3</sup> (g); mean (SD)	2421 (491)	2345 (504)	0.285
Estimated fetal weight percentile; mean (SD)	41 (33.6)	45.3 (34.1)	0.398
Estimated fetal weight percentile <10 <sup>th</sup> percentile <sup>4</sup> ; n (%)	24 (27.3)	19 (21)	0.327
Abnormal uterine artery Doppler <sup>5</sup> ; n (%)	41 (46.6)	41 (45.6)	0.894
Abnormal umbilical artery Doppler <sup>6</sup> ; n (%)	32 (36.4)	29 (32.2)	0.556

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

3 PlGF: placental growth factor; GA: gestational age

4 \* Student's t- (or Mann-Whitney U<sup>§</sup>) or Pearson  $\chi^2$  (or Fisher's exact) tests.5 <sup>1</sup> Less than secondary school; <sup>2</sup> Missing values in three patients; <sup>3</sup> Hadlock formula (22); <sup>4</sup> Spanish standards(23); <sup>5</sup> Pulsatility index >95<sup>th</sup>6 percentile (24); <sup>6</sup> Pulsatility index >95<sup>th</sup> percentile (25)

7

1 **Table 2** Primary maternal and neonatal outcomes

	<b>Revealed group</b>	<b>Concealed group</b>	<b>Effect measure</b>	<b>Adjusted effect measure*</b>
<b>Progression to severe pre-eclampsia</b>	19/88 (21.6%)	38/90 (42.2%)	RR 0.51 (0.33-0.8)	0.5 (0.33-0.76)
Risk difference			RD 0.21 (0.07-0.33)	0.22 (0.09-0.34)
<b>Neonatal morbidity</b>	12/88 (13.6%)	16/90 (17.8%)	RR 0.77 (0.39-1.53)	0.77 (0.39-1.53)
Risk difference			RD -0.041 (-0.15 to 0.066)	-0.041 (-0.15 to 0.07)

2

3

\*Adjusted by minimization factors [gestational age at inclusion (34 vs. 35+ completed weeks) and site]

1 **Table 3** Secondary maternal and neonatal outcomes

	Revealed (n=88)	Concealed (n=90)	Adjusted effect measure* (95% CI)
Maternal complication (non-exclusive); 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 (-1.1-1.1)
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 sulphate; n (%)	18 (20.5)	26 (28.9)	0.71 (0.42-1.2)
Spontaneous delivery; n (%)	0	0	-
Cesarean section; n (%)	47 (53.4)	47 (52.2)	1.02 (0.77-1.35)
Cesarean section for fetal distress; n (%)	10 (11.4)	9 (10)	1.14 (0.48-2.7)
Median gestational age at delivery, days	259	259	0 (-3-3)
Median birthweight, g	2540	2550	-10 (-244-225)
Median birthweight percentile	18	19	1 (-19-22)
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 <sup>1</sup> ; n (%)	37 (60.7)	41 (71.9)	0.84 (0.65-1.09)
Placental foetal hypoperfusion <sup>1</sup> ; 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, days	7	5	2 (-4-10)
5-min Apgar <7; n (%)	5 (5.7)	7 (7.8)	0.73 (0.24-2.21)
Median umbilical artery pH <sup>2</sup>	7.25	7.23	0.02 (-0.01-0.04)
Metabolic acidosis <sup>2</sup> ; n (%)	5 (6.8) <sup>1</sup>	7 (9.2) <sup>2</sup>	0.73 (0.24-2.2)
Perinatal deaths	0	0	-

2 \*Adjusted by minimization factors [gestational age at inclusion (34 vs. 35+ completed weeks) and site]

3 <sup>1</sup> Available in 61 and 57 pregnancies, respectively; <sup>2</sup> Available in 74 and 76 infants, respectively

- 1 **Table 4** Primary maternal outcome by study group and PIGF levels at recruitment (per protocol  
 2 analysis on 175 women with PIGF levels at admission)

			PIGF <60 pg/mL	PIGF ≥60 pg/mL	p*
<b>Revealed</b>	Progression to severe pre-eclampsia	No	19 (70.4%)	49 (81.7%)	0.186
		Yes	8 (29.6%)	11 (18.3%)	
	Total		27	60	
<b>Concealed</b>	Progression to severe pre-eclampsia	No	17 (43.6%)	33 (67.3%)	0.032
		Yes	22 (56.4%)	16 (32.7%)	
	Total		39	49	
<b>Overall</b>	Progression to severe pre-eclampsia	No	36 (54.5%)	82 (75.2%)	0.004
		Yes	30 (45.5%)	27 (24.8%)	
	Total		66	109	

3

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\*Pearson  $\chi^2$

1 **FIGURE LEGENDS**

2

3 **Figure 1** Trial profile.

4

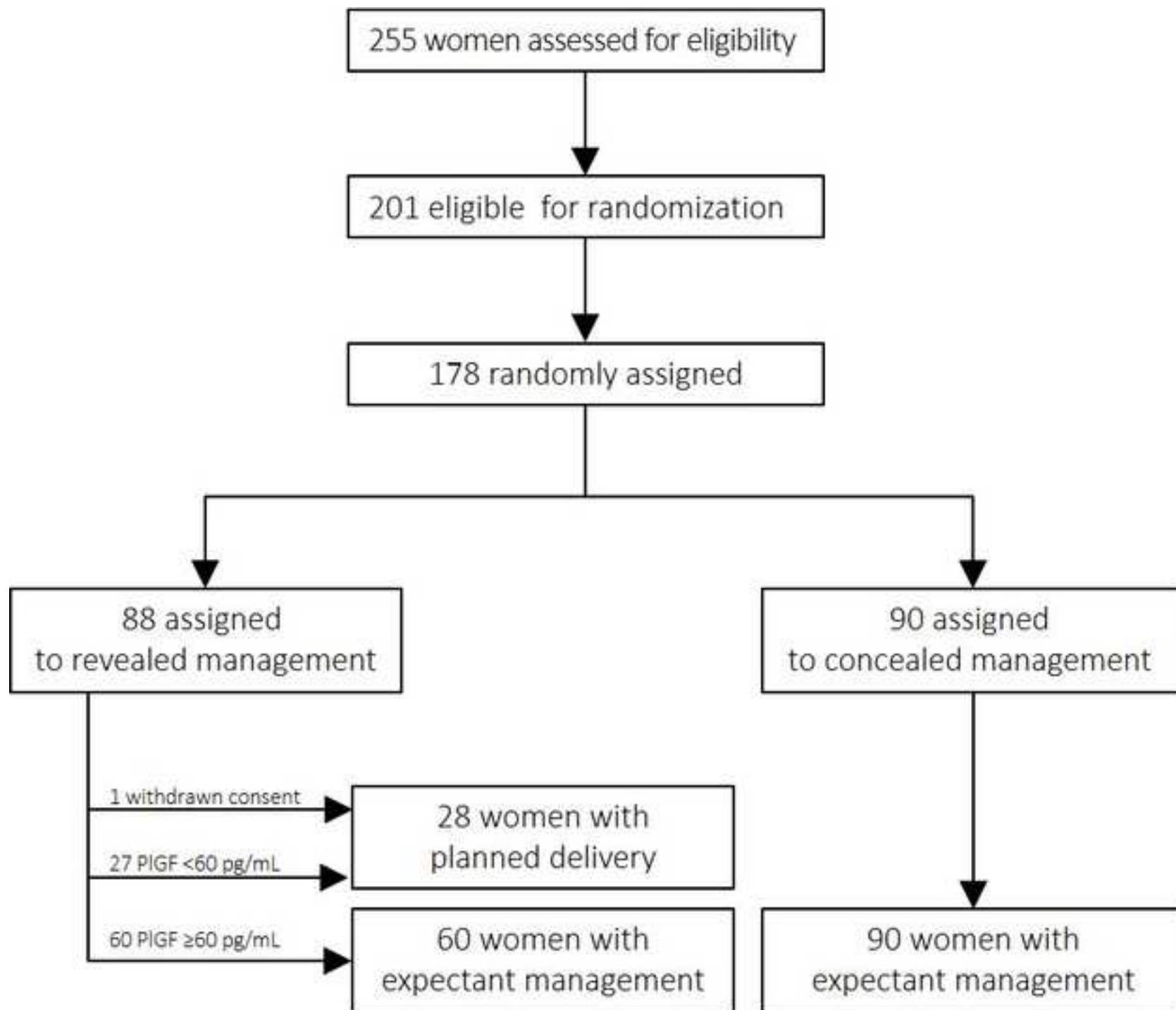
5 **Figure 2** Adjusted\* relative risks of progression to severe preeclampsia (primary maternal  
6 outcome) and maternal complications (secondary maternal outcome) of revealed vs.  
7 concealed groups.

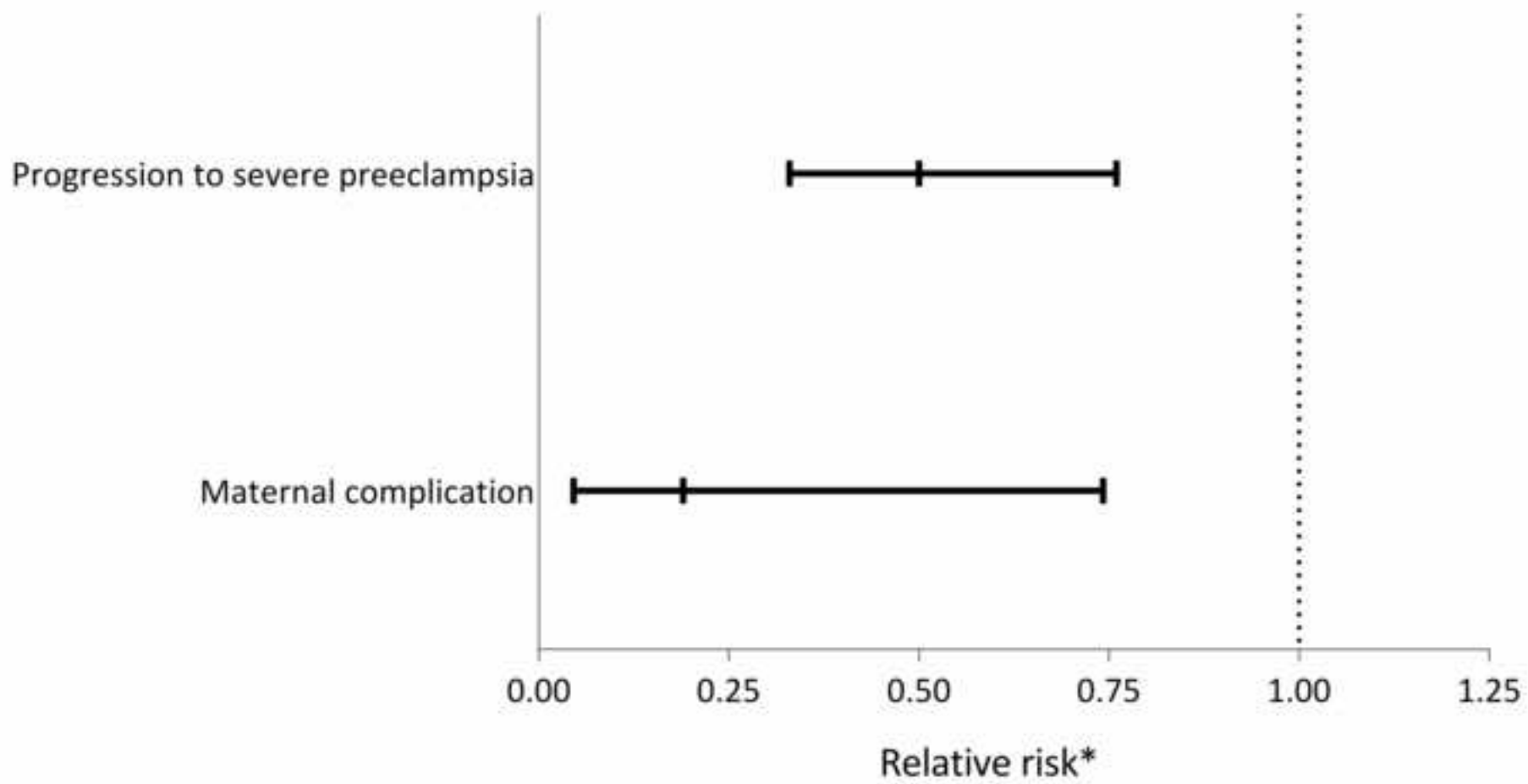
8 \*Adjusted by minimization factor [gestational age at inclusion (34 vs. 35+ completed weeks)  
9 and site]

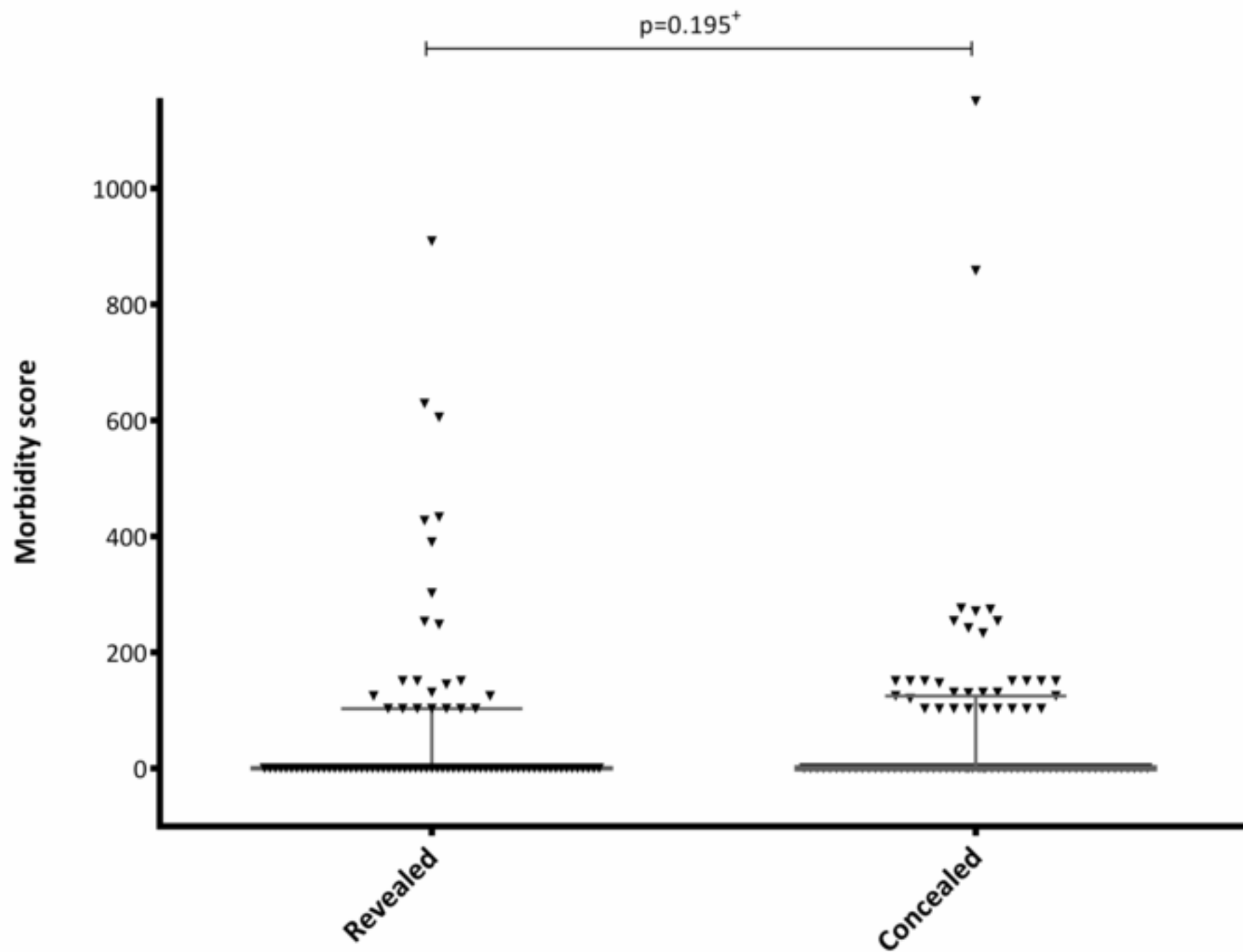
10

11 **Figure 3:** Morbidity Assessment Index for Newborns (MAIN) scores by group.

12 + Mann-Whitney U test







**Supplementary 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%)

Supplementary table 2: MAIN score morbidity items with their scales values

	Item	Morbidity attribute	Scale	
Within 24h of birth	1	Cord blood pH $\leq 7.10$	151	
	2	Resuscitation at birth: Intubation	127	
	3	Meconium: Meconium below cords	155	
	4	Apgar score 5min:	score 4-7	125
	5		score 1-3	162
	6		score <1	193
	7	Apgar score 10min:	score 4-7	154
	8		score 1-3	183
	9	Altered colour* Dusky / Central cyanosis		145
	10	Respiratory rate/min*	<30 or >60 at 3-24h	131
	11		>100 between 3-24h	140
Within 7 days of birth	12	Heart rate/min*	160-200 beat	120
	13		>200 beat	183
	14		<100 beat	157
	15	Hypotonia*	Present beyond 120 h of age	129
	16		Present at 1-120 h of age	156
	17	Flaccidity* Present at 1-120 h		154
	18	Apnea*	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 due to anemia or item 20	170
	22	Systolic BP (mean, mmHg)* 28-32 weeks: <30 / 32-42 weeks: <40		136
	23	Urine output* Low (<2ml/kg/h)		141
	24	Seizures	Tremors/single seizure	137
	25		Multiple seizures	155
	26		If >2 drugs used for seizures	183
	27	Level of consciousness*	Drowsy / Lethargic	137
	28		Stupor / Obtundation / Coma	187
	29	Oral feeding difficulties*	Poor sucking within 24h	81
	30		Poor sucking at 24h – 7 days	98
	31		Poor sucking beyond 7 days	119
	32		Persistent vomiting	136
	33	Assisted ventilation* Assisted ventilation beyond 24h		117
	34	Mechanical ventilation*	Mechanical ventilation within 24h	130
	35		Mechanical ventilation at 24h – 7 days	135
	36		Mechanical ventilation beyond 7 days	162
	37	Birth trauma	Bone fracture – long bone / clavicle /skull	176
	38		Nerve injury (facial / peripheral)	183
39	Subdural or intracerebral haematoma		179	
40	Hypoglycaemia (lowest level): Blood glucose <2.2 mmol/l		151	
41	Hyperbilirubinaemia, 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 seven days of life, whichever is earlier. **MAIN score is the summatory of the scale values of all checked items.**  
 \*>2 consecutive readings

Adapted from: A.Verma et al. Performance profile of an outcome measure: morbidity assessment index for newborns. J Epidemiol Community Health. 2005;59:420-426.

**Supplementary table 3:** Description of adverse events by allocation

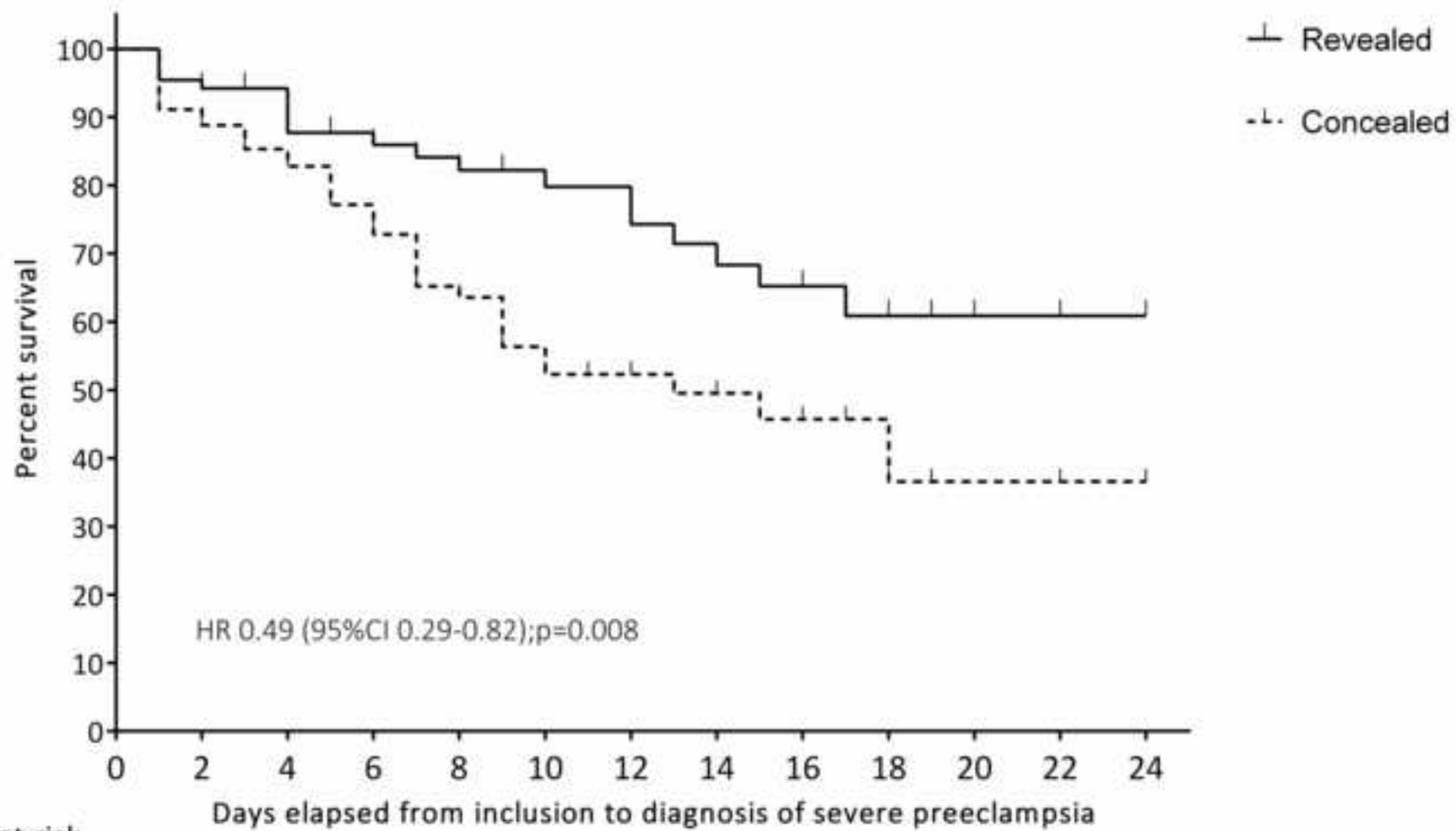
	Revealed (n=88)	Concealed (n=90)
<b>Adverse events</b>	15	24
<b>Severity</b>		
Mild	8	10
Moderate	4	9
Severe	0	2
Potentially life-threatening	2	2
<b>Causality</b>		
Not related	12	16
Unlikely related	3	3
Possible related	0	3
Probably related	0	2
<b>Outcome</b>		
Ad integrum recovery	12	20
Partial recovery	1	0
Not resolved	0	0
Death	0	0
Unknown	0	3
<b>System Organ Class (non-exclusively)</b>		
Hematological	3	10
Biochemical	3	4
Cardiovascular	2	4
Gastrointestinal	0	4
Neurological	8	10
Infectious	2	1
Systemic	2	0
Ophtalmologic	0	2

**SUPPLEMENTARY FIGURE LEGENDS**

**Supplementary figure 1:** Kaplan-Meier survival estimate for time to severe preeclampsia development by trial arm.

HR: Hazard Ratio

**Supplementary figure 2:** Risk difference in neonatal morbidity (Morbidity Assessment Index for Newborns [MAIN] score  $\geq 150$ ) with the limit of the non-inferiority hypothesis displayed.



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

