The risk for preeclampsia at 36 weeks and at 12 weeks predicts intrapartum fetal compromise and spontaneous onset of labor

Key words: fetal compromise; fetal medicine foundation; parturition; placental dysfunction; preeclampsia screening; 12-week model; 36-week model

OBJCECTIVE: A complex relationship exists between placental and cardiovascular dysfunctions, gestation, spontaneous onset of labor (SL), intrapartum fetal compromise (FC), preeclampsia (PE), and other complications such as fetal growth restriction and postterm delivery. Placental and cardiovascular dysfunctions were associated with gestational age at SL and FC.[1−3] The Fetal Medicine Foundation (FMF) risk models for PE screening may be linked to the likelihood of SL and FC due to the nature of the included biomarkers and their relationship with placental and cardiovascular dysfunctions.[4,5] The objective was to quantify the hazard of SL and subsequent FC requiring cesarean delivery in pregnancies approaching term, using a two-stage survival analysis based on the FMF risk models for PE (36 weeks model alone or in combination with the 12 weeks model).

STUDY DESIGN: Secondary analysis of database from routine prospective assessment of risk for PE, conducted at the Fetal Medicine Research Centre, London, England. Recruitment occurred at 11^{+0} to 13^{+6} weeks of gestation (PE-12) and 35^{+0} to 36^{+6} weeks (PE-36). All patients had both PE-12 and PE-36 assessments and were classified into 5 categories according to the PE-36 risk: A: ≥1 in 2; B: ≥1:5 but <1:2; C: ≥1:20 but <1:5; D: ≥1:50 but <1:20; E: <1:50; and into 3 categories according to the PE-12 risk: high: >1:50; intermediate: 1:50 to 1:100; and low: <1:100. Enrollment coincided with PE-36 risk calculation (Supplemental Figure 1). Our previous studies described all additional aspects of methodology including ultrasound and laboratory methods, definition of outcomes and policy for Aspirin prophylaxis in the PE-12 high-risk group.[1−5]

Statistical analyses

Analyses assessed the association of SL and FC requiring cesarean delivery with PE risk estimated by FMF models (PE-12 and PE-36), accounting for all delivery outcomes: vaginal and cesarean (prelabor, due to FC, or other indications, serving as censors). The smoothed instantaneous hazard (SIH) assessed SL and FC risks (35−42 weeks), first for PE-12 and PE-36 separately, and then combined in a two-stage screening approach. Weibull regressions quantified PE-12 and PE-36 risk effects, calculating hazard ratios (HRs). Categories A and B were merged to increase sample size for FC analysis (Stata v16; StataCorp, 2019, College Station, TX).

RESULTS: Participants, descriptive data, and outcome data

The study included paired measurements at PE-12 and PE-36 from 9073 women with singleton pregnancies. The rate of FC was 4.6%, showing this distribution across PE risk categories. PE-36: A≥1 in 2 (n=22), B≥1 in 5 but <1 in 2 (n=125), C≥1 in 20 but <1 in 5 (n=1341), D≥1 in 50 but <1 in 20 (n=2829), E<1 in 50 (n=4756). PE-12: high risk: >1:50 (n=428), intermediate risk: 1:50 to 1:100 (n=512), and low risk: <1:100 (n=6413). There were 113 PE cases (1.2%), distributed across the FMF PE risk categories: PE-36 E: 16 (0.3%), D: 29 (1.0%), C: 33 (2.5%), B: 23 (18.4%), A: 12 (54.5%); PE-12 low risk: 63 (0.8%), intermediate risk: 17 (2.6%), and high risk: 33 (5.6%).

The estimated fetal weight percentiles at PE-36 decreased across risk categories E: 52 (SD, 25), D: 51 (SD, 26), C: 48 (SD, 27), B: 44 (SD, 30), and A: 24 (SD, 22); the overall mean was 51 (SD, 26); ($P<.001$). Participants' characteristics and descriptive data are in Supplemental Table 1, with PE screening and pregnancy outcomes in Supplemental Tables 2 and 3, respectively.

Spontaneous labor

Spontaneous labor distribution, stratified by PE-36 categories, was best fitted by a Weibull distribution, with increasing PE risk shifting the distribution leftward (Supplemental Figure 2). Stratification according to PE-12 confirmed that higher PE-risk categories were associated with a higher SIH for SL and earlier SL (not shown).[1] Stratification according to PE-36 risk categories produced SIH strata aligned with PE risk severity in the first 5 weeks (Supplemental Figure 3). Interestingly, category A showed an aberrant pattern with the highest SL hazard (5-fold increase vs category E, at 2 weeks), with all events occurring within 3 weeks (Supplemental Figure 3). This subgroup included 54.5% of PE cases, reinforcing the FMF model's predictive value. Incorporating PE-12 and PE-36 PE risks did not improve spontaneous labor discrimination. Weibull regression confirmed higher HRs for SL associated with higher PE risks at both PE-12 and PE-36, with stronger effects for PE-36 (Supplemental Tables 4 and 5, Supplemental Figure 4).

Fetal compromise requiring cesarean after spontaneous labor

SIH increased over time, linking FC with advancing gestation. PE-36 risk independently correlated with FC, especially in high-risk categories (A+B, C). SIH rose rapidly

in these groups, with nearly all deliveries occurring within 4 weeks post-PE-36. (Supplemental Figure 5, panel A) PE-36 combined with PE-12 (>1:50) identified hidden high-risk subpopulations, especially in categories C and E (Supplemental Figure 5, Panel B). Further stratification of low-risk category E by PE-12 risk showed a proportional increase in SIH, as expected (Figure 1). Weibull regression confirmed higher HRs for increased PE risk at both PE-12 (likelihood ratio=71.24; $P<.001$; HR-intermediate risk: 2.562; $P<.001$); HR-high risk: 3.309; $P<.001$) and PE-36, with stronger effects and likelihood ratio at PE-36 (Supplemental Table 6 and Supplemental Figure 6).

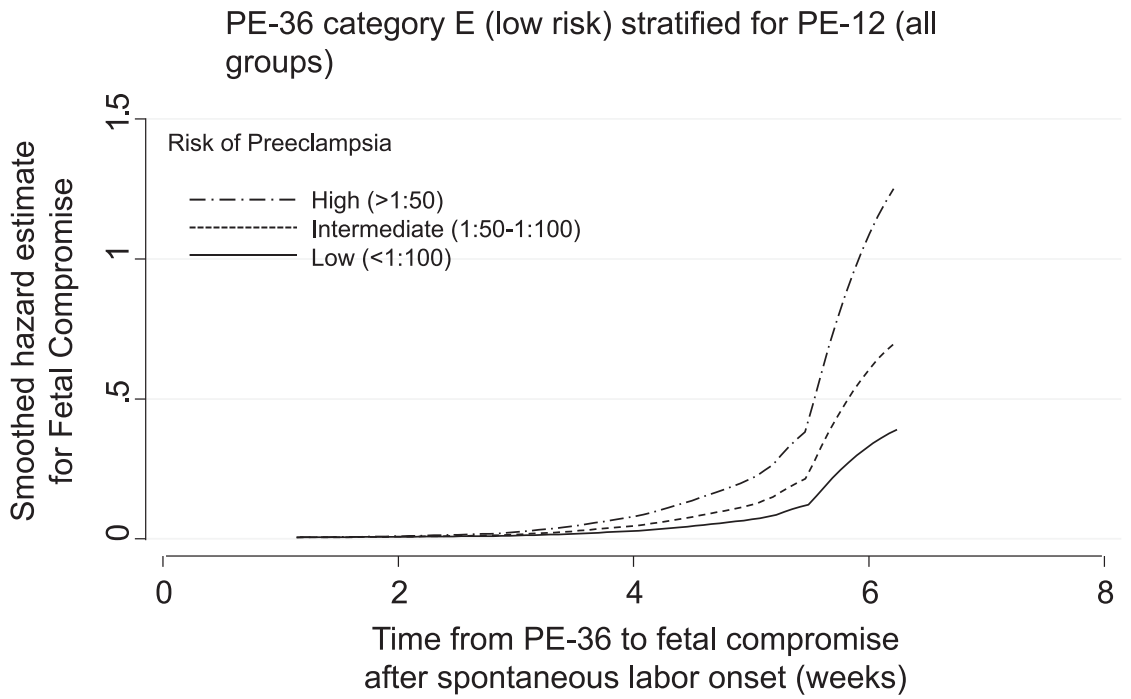
CONCLUSION: SL and FC requiring cesarean delivery are linked to placental-cardiovascular dysfunction, with FMF PE risk models (especially at PE-36) showing strong discrimination and added value from PE-12 integration to detect FC in low-risk cases. Integrating PE-12 and PE-36 underscores the importance of comprehensive risk assessments in guiding personalized perinatal care and identifying pregnancies needing closer monitoring, earlier delivery or tailored intrapartum management to reduce FC risks.

Clinical translation includes monitoring pregnancy at term, intrapartum care, and delivery timing, challenging the assumptions that week 40 is universally ideal for intensified surveillance, optimal for delivery, and that intrapartum management should be uniform rather than tailored on individual risks complications.

Firstly, high-risk cases at PE-36 show a rapid increase of SL hazard, indicating monitoring earlier than 40 weeks. Second, high-risk cases at PE-36 show higher FC hazard, requiring surveillance and specific, cautious intrapartum care (eg, measured oxytocin or neuraxial analgesia use, avoiding prolonged labor, favoring mechanical methods vs prostaglandin for labor induction). Cases with low risk at PE-36 but high risk at PE-12 also present rapid rise of FC hazard close to term requiring similar approach. Thirdly, based on the extent of placental-cardiovascular function (reflected by FMF PE risk models), each pregnancy may have an optimal and personalized timing for childbirth with maximization of fetal maturity and minimization of the risk of placental-cardiovascular dysfunction, as gestation progresses.

Future research on individualized antenatal surveillance, intrapartum care, and delivery timing with risk-specific protocols will assess whether anticipated monitoring, induction of labor, and specific intrapartum care may improve

FIGURE 1
Smoothed hazard of cesarean for fetal compromise by PE-36 and PE-12 risks



A high risk of PE at PE-12 increases the hazard at PE-36 in the low-risk category.

FMF, Fetal Medicine Foundation; PE, preeclampsia.

maternal-fetal outcomes in cases with higher PE risk reducing the likelihood of adverse events, as gestation advances. ■

Paolo I. Cavoretto, MD
Department of Obstetrics and Gynaecology
IRCCS San Raffaele Scientific Institute
Milan, Italy
Vita-Salute San Raffaele University
Milan, Italy

Antonio Farina, MD
Obstetric Unit
IRCCS Azienda Ospedaliero-Universitaria di Bologna
Bologna, Italy
Department of Medical and Surgical Sciences (DIMEC)
Alma Mater Studiorum
University of Bologna
Bologna, Italy
antonio.farina@unibo.it

Argyro Syngelaki, PhD
Fetal Medicine Research Institute
King's College Hospital
London, UK

Filippos Solonos, MD
Fetal Medicine Research Institute
King's College Hospital
London, UK

Kypros H. Nicolaides, MD
Fetal Medicine Research Institute
King's College Hospital
London, UK

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This study was conducted in accordance with the ethical standards for human research established by the Declaration of Helsinki. The original data collection received approval from the London-Surrey Borders Research Ethics Committee.

The authors report no conflict of interest.

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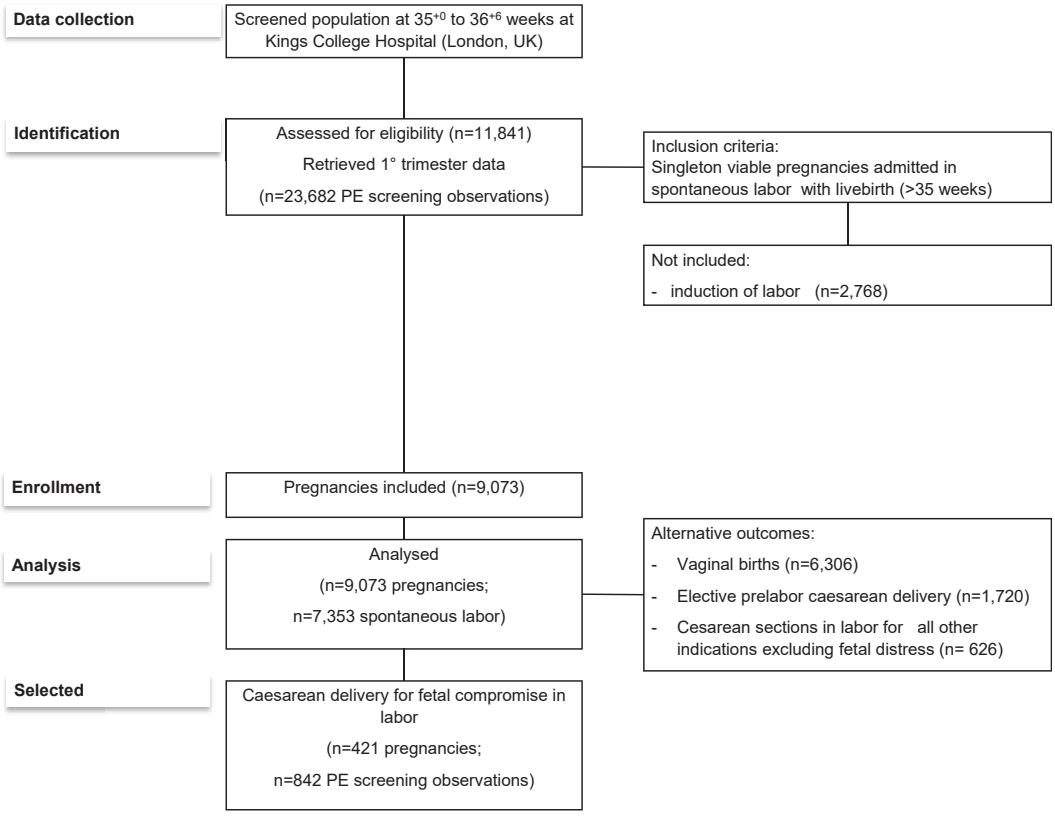
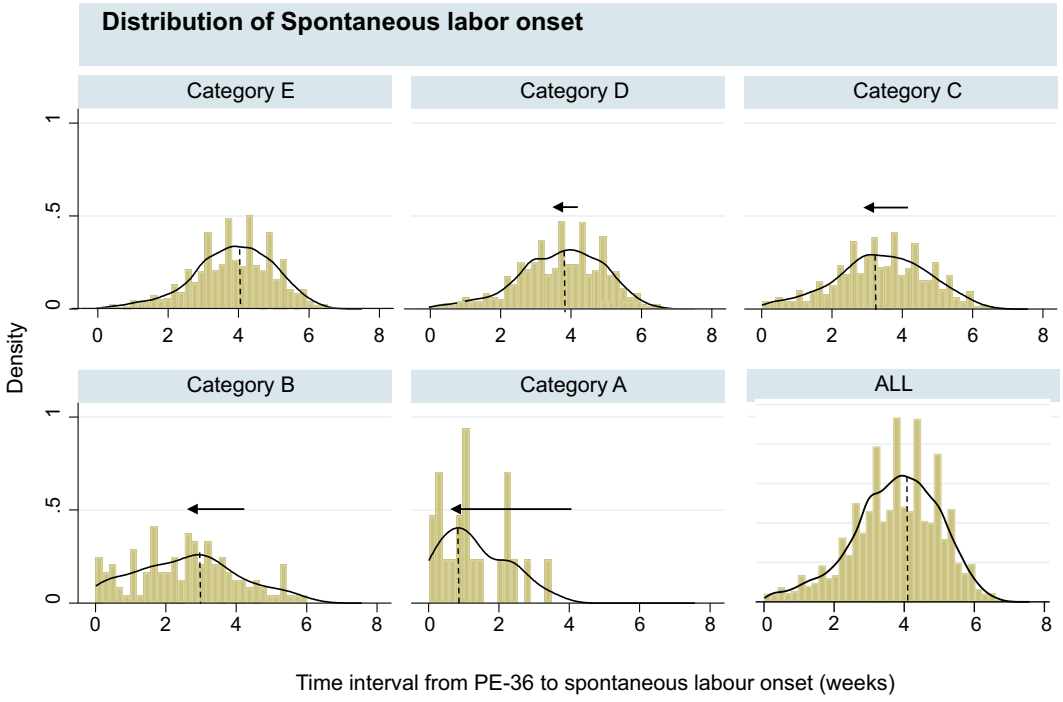
SUPPLEMENTAL FIGURE 1
STROBE flow chart of patients screening, selection and recruitment



FMF, Fetal Medicine Foundation; *PE*, preeclampsia; *STROBE*, Strengthening the Reporting of Observational Studies in Epidemiology.

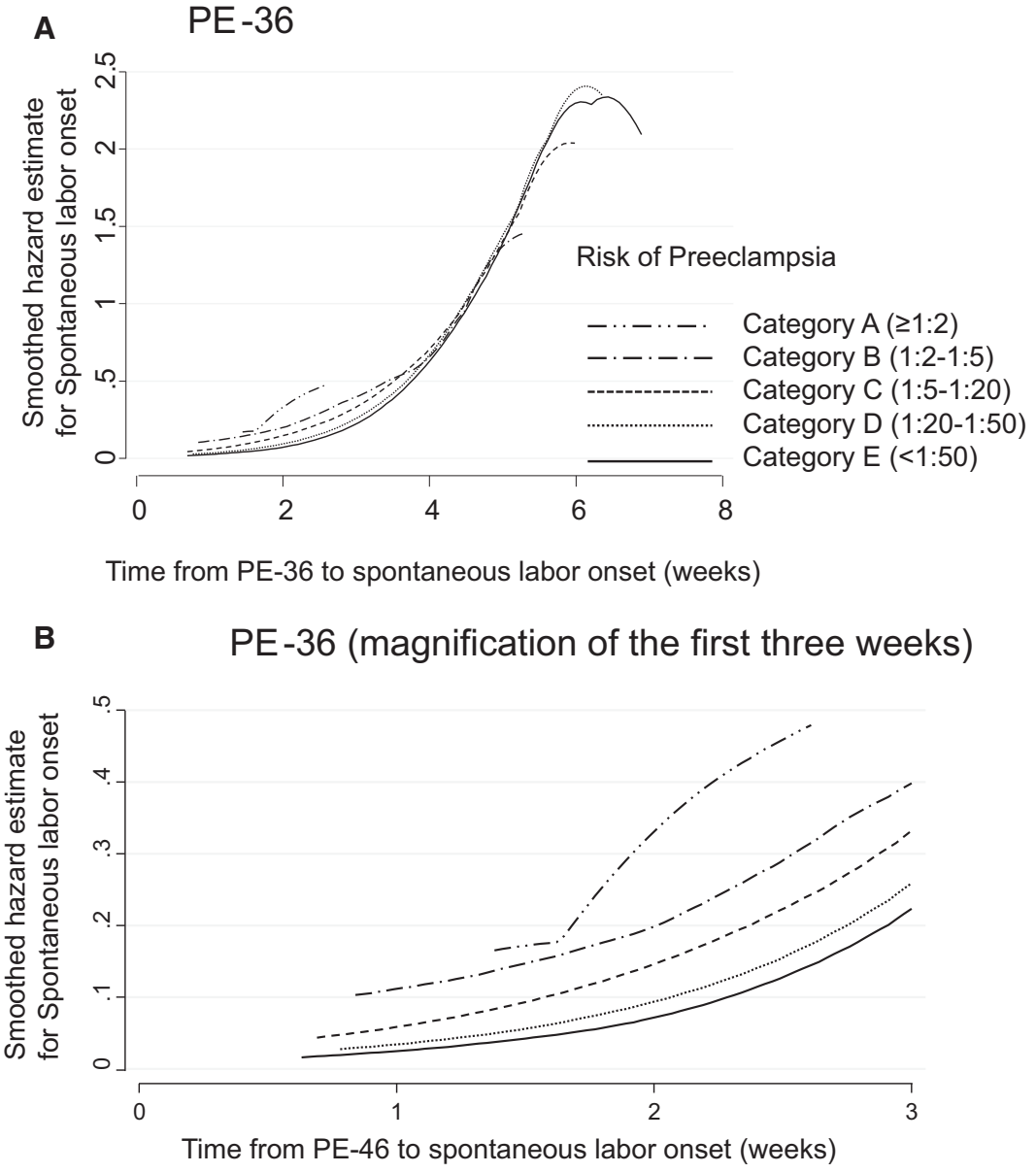
SUPPLEMENTAL FIGURE 2
Density distribution across time after PE-36 screening



Note the leftward shift of the curves across increasing PE risk categories.

FMF, Fetal Medicine Foundation; *PE*, preeclampsia.

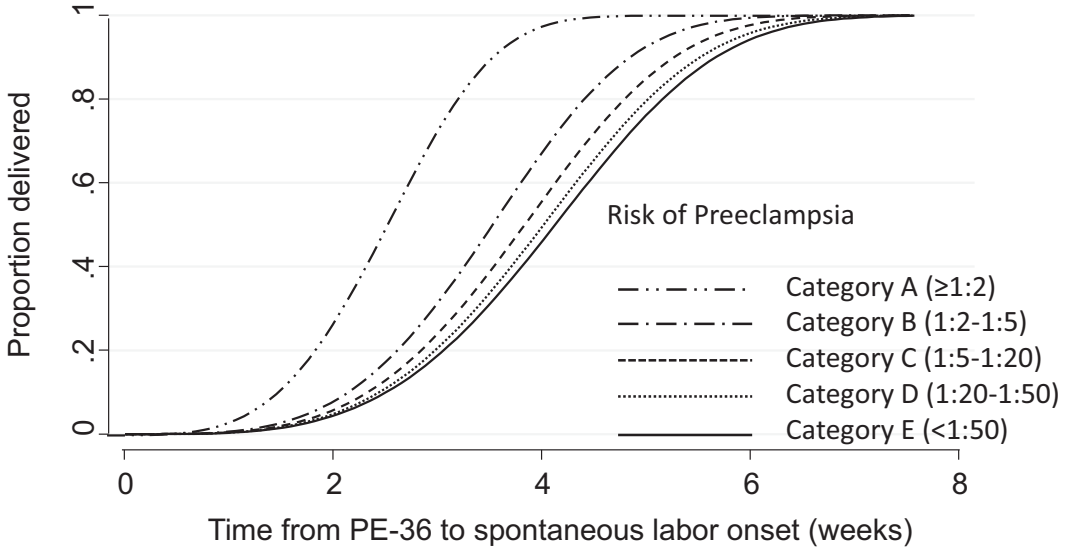
SUPPLEMENTAL FIGURE 3
Smoothed instantaneous hazard of spontaneous labor by PE-36 risk category



Smoothed instantaneous hazard for spontaneous labor onset is shown in the 5 categories at FMF PE-36 screening. The higher the risk of PE, the higher the smoothed instantaneous hazard of spontaneous onset of birth, implying earlier spontaneous birth.

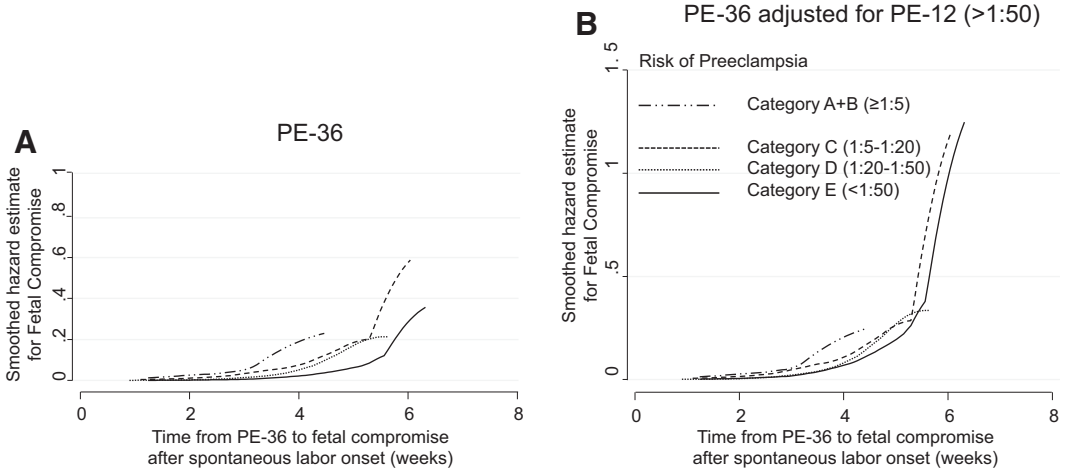
A, Main graph. **B**, Magnification of the first 3 weeks. *FMF*, Fetal Medicine Foundation; *PE*, preeclampsia.

SUPPLEMENTAL FIGURE 4
Weibull regression curves showing the failure rates for spontaneous labor after PE-36



FMF, Fetal Medicine Foundation; *PE*, preeclampsia.

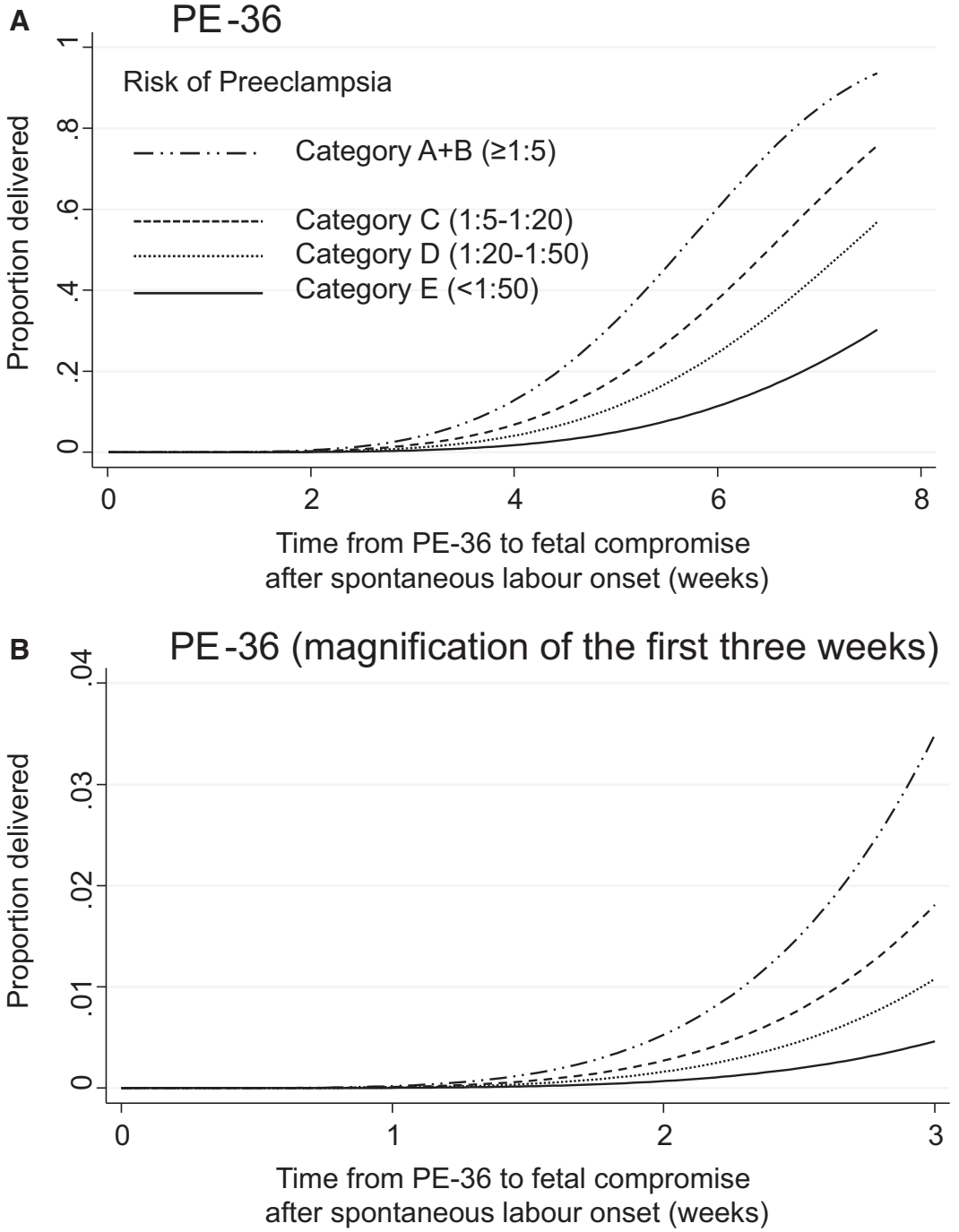
SUPPLEMENTAL FIGURE 5
Smoothed instantaneous hazard of fetal compromise by PE-36 (alone or combined with PE-12)



A, Smoothed Instantaneous hazard based on PE-36 alone. **B**, Smoothed Instantaneous hazard based on PE-36 reassessed by high risk at PE-12.

FMF, Fetal Medicine Foundation; *PE*, preeclampsia.

SUPPLEMENTAL FIGURE 6
Weibull regression curves showing the failure rate for fetal compromise after PE-36



Panel A shows the whole graph and panel B shows a magnification of the first 3 weeks.

FMF, Fetal Medicine Foundation; *PE*, preeclampsia.

SUPPLEMENTAL TABLE 1

Summary of patients' characteristics of the 9073 patients included in the study according to the 4 groups of delivery outcomes

	CD fetal compromise N = 421 N (%) or mean (SD)	CD other indications N = 626 N (%) or mean (SD)	Vaginal births N = 6306 N (%) or mean (SD)	CD pre labour N = 1720 N (%) or mean (SD)	*P*-value χ^2 or ANOVA
Maternal Age (years)	31.81 (5.25)	33.24 (4.98)	31.87 (5.19)	34.60 (5.01)	<0.001
Ethnic groups					<0.001
Black	98 (23.3)	76 (12.1)	787 (12.5)	194 (11.3)	
East Asian	11 (2.6)	19 (3.0)	151 (2.4)	34 (2.0)	
Mixed	18 (4.3)	25 (4.0)	193 (3.1)	55 (3.2)	
South Asian	23 (5.5)	42 (6.7)	303 (4.8)	87 (5.1)	
White	271 (64.4)	464 (74.1)	4872 (73.3)	1350 (78.5)	
Conception Method					<0.001
In vitro fertilization	19 (4.5)	39 (6.2)	167 (2.6)	168 (9.8)	
Ovulation drugs	2 (0.5)	3 (0.5)	22 (0.3)	8 (0.5)	
Natural	400 (95.0)	584 (93.3)	6117 (97.0)	1544 (89.8)	
Cigarette smoking	26 (6.2)	18 (2.9)	335 (5.3)	67 (3.9)	<0.005
Diabetes Mellitus					<0.001
Diabetes mellitus type 1	0 (0.0)	1 (0.2)	4 (0.1)	20 (1.2)	
Diabetes mellitus type 2	3 (0.4)	11 (1.0)	32 (0.4)	11 (0.6)	
SLE/APS	2 (0.5)	2 (0.3)	11 (0.2)	10 (0.6)	0.031
Chronic hypertension	6 (1.4)	10 (1.6)	30 (0.5)	34 (2.0)	<0.001
Nulliparous	304 (72.2)	388 (62.0)	2831 (44.9)	541 (31.5)	<0.001
Previous PE	9 (2.1)	14 (2.2)	92 (1.5)	103 (6.0)	<0.001
Previous SGA	23 (5.5)	40 (6.4)	476 (7.5)	142 (8.3)	<0.001
Aspirin prophylaxis	99 (25.9)	117 (18.7)	714 (11.3)	313 (18.2)	<0.001

CD, caesarean delivery; *PE*, preeclampsia; *SGA*, small for gestational age; *SLE/APS*, systemic lupus erythematosus, antiphospholipid antibody syndrome.

SUPPLEMENTAL TABLE 2

Summary of PE screening results of the 9073 patients included in the study according to the 4 groups of delivery outcomes

	CD fetal compromise N = 421 Mean (SD)	CD other indications N = 626 Mean (SD)	Vaginal births N = 6306 Mean (SD)	CD pre labour N = 1720 Mean (SD)	*P*-value ANOVA
12-weeks PE screening variables					
GA 12-week screening (wks)	12.7 (0.60)	12.76 (0.56)	12.76 (0.57)	12.78 (0.56)	0.478
Crown-rump length (mm)	64.54 (8.22)	64.27 (7.62)	64.28 (7.85)	64.59 (7.67)	0.497
Weight (kg)	69.74 (13,96)	68.73 (14,84)	68.43 (14,13)	72.45 (15,78)	<0.001
Height (cm)	163 (6.10)	163 (6.80)	165 (6.35)	164 (6.60)	<0.001
UtA-PI MoMs	1.06 (0.32)	1.03 (0.30)	1.05 (0.31)	1.02 (0.32)	0.006
MAP MoMs	1.00 (0.08)	0.99 (0.08)	1.00 (0.70)	1.00 (0.80)	0.335
PlGF MoMs	1.12 (0.55)	1.19 (3.09)	1.11 (0.61)	1.07 (0.53)	0.058
FMF-12 weeks PE risk	0.00966 (0.017)	0.01017 (0.038)	0.00519 (0.014)	0.00963 (0.033)	<0.001
36-weeks PE screening variables					
GA 36-weeks screening (wks)	35.98 (0.51)	35.94 (0.50)	36.03 (0.49)	35.09 (0.52)	<0.001
Weight (kg)	80.7 (13.6)	80.2 (14.9)	79.2 (13.9)	83.0 (14.3)	<0.001
Estimated fetal weight (grams)	2807 (227)	2812 (237)	2762 (226)	2815 (286)	<0.001
Estimated fetal weight centile	57 (25)	58 (25)	50 (26)	57 (28)	<0.001
UtA-PI MoMs	1.05 (0.32)	1.05 (0.31)	1.04 (0.28)	1.04 (0.31)	0.645
MAP MoMs	1.00 (0.07)	1.00 (0.08)	1.00 (0.08)	1.00 (0.08)	0.104
PlGF MoMs	1.45 (1.25)	1.458 (1.35)	1.35 (1.19)	1.44 (1.38)	0.003
sFlt-1 MoMs	1.16 (0.67)	1.16 (0.64)	1.13 (0.70)	1.14 (0.71)	0.887
FMF 36-weeks PE risk	0.047 (0.06)	0.038 (0.05)	0.029 (0.04)	0.044 (0.09)	<0.001

CD, caesarean delivery; *FMF*, Fetal Medicine Foundation; *GA*, gestational age; *MAP*, mean arterial pressure; *PlGF*, placental growth factor; *UtA-PI*, uterine artery pulsatility index.

SUPPLEMENTAL TABLE 3

Pregnancy outcomes of the 9073 patients included in the study according to the 4 groups of delivery outcomes

	CD fetal compromise N = 421 N (%) or mean (SD)	CD other indications N = 626 N (%) or mean (SD)	Vaginal births N = 6306 N (%) or mean (SD)	CD pre labour N = 1720 N (%) or mean (SD)	*P*-value χ^2 or ANOVA
GA at birth (weeks)	40.2 (1.2)	39.7 (1.4)	40.0 (1.1)	39.0 (0.8)	<0.001
Interval (36-w to birth)	5.0 (3.7)	4.1 (3.3)	3.8 (2.8)	3.9 (2.8)	<0.001
Birthweight (grams)	3241 (455)	3462 (475)	3435 (435)	3398 (485)	0.005
Birthweight (centile)	45 (28)	53 (28)	49 (27)	54 (30)	<0.001
Preeclampsia	10 (2.4)	8 (1.3)	48 (0.8)	47 (2.7)	<0.001
SGA (3–10 centile)	42 (10)	41 (6.5)	409 (6.5)	99 (5.8)	<0.001
FGR<3 centile	12 (2.9)	13 (2.1)	171 (2.7)	59 (3.4)	<0.01
AGA (from 10 to 90 centile)	338 (80.3)	511 (81.6)	5285 (83.8)	1317 (76.6)	<0.01
LGA>90 centile	24 (5.7)	47 (7.5)	330 (5.2)	162 (9.4)	<0.001
Macrosomia>97 centile	5 (1.2)	14 (2.2)	111 (1.8)	83 (4.8)	<0.001

CD, caesarean delivery; *GA*, gestational age; *LGA*, large for gestational age; *SGA*, small for gestational age.

SUPPLEMENTAL TABLE 4

Output of the Weibull regression models for spontaneous labor onset stratified according to PE-12 screening categories

Variable	Hazard ratio	Standard error	Z-score	95% CI lower	95%CI higher	*P*-value
Constant	0.003	0.0002	143.1	1.31	1.34	<0.001
Low-risk: <1:100	1.00					
Intermediate-risk: 1:50–1:100	1.12	0.05	2.49	1.02	1.23	0.013
High-risk: >1:50	1.17	0.05	3.11	1.06	1.29	0.002
Shape parameter (k)	3.77	0.03		3.70	3.84	

The likelihood ratio of the model was 14.3 ($P<0.001$).

SUPPLEMENTAL TABLE 5

Output of the Weibull regression models for spontaneous labor onset stratified according to PE-36 screening categories

Variable	Hazard ratio	Standard error	Z-score	95% CI lower	95%CI higher	*P*-value
Constant	0.0032	0.0001	−100.4	0.0029	0.0036	<0.001
Category E: <1 in 50	1.00					
Category D: ≥1 in 50 but<1 in 20	1.11	0.03	3.89	1.05	1.66	<0.001
Category C: ≥1 in 20 but<1 in 5	1.32	0.04	7.97	1.23	1.41	<0.001
Category B: ≥1 in 5 but<1 in 2	1.81	0.21	5.22	1.45	2.26	<0.001
Category A: ≥1 in 2	5.43	2.43	3.78	2.26	13.1	<0.001
Shape parameter (k)	3.78	0.03		3.72	3.85	

The likelihood ratio of the model was 90.3 ($P<0.001$).

SUPPLEMENTAL TABLE 6

Output of Weibull regression for fetal compromise stratified according to PE-36 screening categories (merging category A and B)

Variable	Hazard ratio	Standard error	Z-score	95% CI lower	95%CI higher	*P*-value
Constant	0.00003	7.62 e−6	−36.83	0.00002	0.00005	<0.001
Category E: <1 in 50	1.00					
Category D: ≥1 in 50 but<1 in 20	2.33	0.27	7.35	1.86	2.93	<0.001
Category C: ≥1 in 20 but<1 in 5	3.93	0.51	10.56	3.05	5.07	<0.001
Category A+B≥1 in 5	7.65	2.40	6.49	4.14	14.15	<0.001
Shape parameter (k)	4.70	0.17		4.37	5.04	

The likelihood ratio of the model was 90.3 ($P<0.001$).