OBSTETRICS

The 36-week preeclampsia risk by the Fetal Medicine Foundation algorithm is associated with fetal compromise following induction of labor

Antonio Farina, MD; Paolo I. Cavoretto, MD; Argyro Syngelaki, PhD; Danila Morano, MD; Stephen Adjahou, MD; Kypros H. Nicolaides, MD

BACKGROUND: Previous studies demonstrated that placental dysfunction leads to intrapartum fetal distress, particularly when an abnormal pattern of angiogenic markers is demonstrated at 36 weeks of gestation. The prediction of intrapartum fetal compromise is particularly important in patients undergoing induction of labor because of different indications for delivery, as this can be a useful in optimizing the method and timing of induction of labor.

OBJECTIVE: This study aimed to examine whether the risk of preeclampsia assessed using the Fetal Medicine Foundation algorithm (derived from a combination of maternal risk factors, mean arterial pressure, uterine arteries pulsatility index, placental growth factor, and soluble fms—like tyrosine kinase-1) is associated with the risk of intrapartum fetal compromise requiring cesarean delivery in a population of patients with singleton pregnancies undergoing induction of labor for various indications.

STUDY DESIGN: This was a retrospective analysis on prospectively collected data from women with singleton pregnancies who underwent routine assessments at 35 0/7 to 36 6/7 weeks of gestation at King's College Hospital (London, United Kingdom). The study outcome was the rate of fetal compromise requiring cesarean delivery, examined in relation to the risk of preeclampsia assessed at 36 weeks of gestation using the Fetal Medicine Foundation risk model. Patients who underwent spontaneous labor and prelabor cesarean deliveries were excluded. In addition, 5 risk categories for preeclampsia were created on the basis of the Fetal Medicine Foundation 36-week risk model: A ($\geq$1/2), B ($<$1/2- $\geq$1/5), C ($<$1/5- $\geq$1/20), D ($<$1/20-$\geq$1/50), and E ($<$1/50). Based on the reason for induction of labor, we created 5 categories: premature rupture of membranes, postterm pregnancy (>41 weeks of gestation), preeclampsia, fetal growth restriction (estimated fetal weight of <5th percentile), and preeclampsia and fetal growth restriction. A multinomial logistic regression was used to assess the risk of fetal compromise across the Fetal Medicine Foundation risk categories, accounting for all delivery outcomes (spontaneous or operative vaginal delivery and urgent cesarean delivery for fetal compromise, failure to progress, or other reasons) and allowing accurate and generalizable risk assessment of fetal compromise.

RESULTS: Of 45,375 pregnant women, 26,597 (58.6%) had spontaneous onset of labor, 6529 (14.0%) underwent elective prelabor cesarean delivery, which were excluded from the analysis. A total of 12,249 pregnant women were included, of which 182 had birth at $\leq$37 weeks of gestation and 1444 had fetal compromise (crude risk of 11.8%). The rate of vaginal delivery in the study population was 69.4%. The rates of fetal compromise in the 5 induction categories were 9.7% for premature rupture of membranes, 13.5% for postterm pregnancy, 14.8% for preeclampsia, 17.2% for fetal growth restriction, and 23.4% for preeclampsia and fetal growth restriction. Cases with intrapartum fetal compromise had a higher mean preeclampsia risk than cases without intrapartum fetal compromise (1/45 vs 1/81, respectively; $P<.001$). The risk of cesarean delivery for fetal compromise increased with (1) advancing gestational age (each week increase at 35—40 weeks: +1%; at 41—42 weeks: +5%), (2) nulliparity (+7%—10%) vs multiparity, (3) higher Fetal Medicine Foundation risk of preeclampsia (from the low-risk category of $<$1/50 to the high-risk category of $\geq$1/2: +18%; with greater effect for higher preeclampsia risk). In this study population, the rates of fetal compromise were lower with diagnoses of preeclampsia and rupture of membranes and higher with fetal growth restriction (alone or in combination with preeclampsia) and postterm pregnancy.

CONCLUSION: Our study highlights the clinical use of the Fetal Medicine Foundation 36-week PE risk model in determining the risk of fetal compromise requiring cesarean delivery after induction of labor. The same model can be combined with standard obstetric indications to induction of labour to establish the risk of fetal compromise requiring cesarean delivery. Therefore, the Fetal Medicine Foundation 36-week PE risk model can be used to optimize induction of labor.

Key words: angiogenic factors, fetal compromise, fetal distress, parturition, placental dysfunction, preeclampsia screening

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Introduction

Placental dysfunction accounts for at least part of intrapartum fetal compromise, frequently necessitating urgent delivery.[1] Nonreassuring fetal conditions may be detected through sudden changes in cardiotocographic monitoring or remarkable acute events during labor, such as abruption.[2,3] Fetal compromise typically necessitates operative or cesarean delivery and is associated with neonatal acidemia and other adverse outcomes. Predicting fetal compromise remains challenging, even though it largely depends on known risk factors, such as poor intrapartum placental function.[1,4]

Induction of labor (IOL) is a widely used procedure recommended for a series of conditions and complications, including preeclampsia (PE), fetal growth restriction (FGR), gestational diabetes mellitus (GDM), premature rupture of membranes (PROM), and

AJOG at a Glance

Why was this study conducted?

Intrapartum fetal compromise is associated with clinical/subclinical placental dysfunction. Therefore, this study aimed to explore the association between the risk of intrapartum fetal compromise and the risk of preeclampsia (PE) at 36 weeks of gestation after induction of labor (IOL).

Key findings

The Fetal Medicine Foundation (FMF) 36-week PE risk model was able to determine the risk of intrapartum fetal compromise after IOL for various indications. The risk of intrapartum fetal compromise was higher in nulliparas than in multiparas and was higher in postterm than in the preterm pregnancy. Moreover, the risk of intrapartum fetal compromise was associated with fetal growth restriction (alone or in combination with PE). In contrast, the risk of intrapartum fetal compromise was lower in patients with isolated PE or premature rupture of membranes.

What does this add to what is known?

The FMF 36-week PE risk model is clinically useful in determining the risk of fetal compromise after IOL. A combined approach utilizing the 36-week FMF PE risk and major delivery indications is strongly associated with intrapartum fetal compromise requiring cesarean delivery, after IOL. The FMF 36-week PE risk model proves to be clinically useful in optimizing labor induction.

other maternal and fetal abnormalities. Moreover, the application of IOL procedures is rapidly expanding as the publication of evidence that elective IOL at 39 weeks of gestation in uncomplicated singleton pregnancies reduces the risk of cesarean delivery, hypertensive disorders, maternal infection, and adverse perinatal outcomes, such as respiratory issues and neonatal intensive care admissions, without increasing maternal or perinatal complications.[5–7]

Objective

This study aimed to examine the risk of fetal compromise in pregnant women who underwent IOL for various indications, including PE, FGR (with and without PE), postterm pregnancy (>41 weeks of gestation), and PROM. The study hypothesis was that placental dysfunction assessed using the multivariate Fetal Medicine Foundation (FMF) algorithms, based on a combination of maternal risk factors, mean arterial pressure (MAP), mean uterine arteries pulsatility index (UtA-PI), placental growth factor (PlGF), and soluble fms–like tyrosine kinase-1 (sFlt-1), measured at 36 weeks of gestation, may be associated with fetal compromise leading to cesarean delivery in patients after IOL for different indications.

Materials and methods

Study design, setting, and participants

This was a retrospective analysis of prospectively collected data in a large cohort of patients who underwent routine assessment at 35 0/7 to 36 6/7 weeks of gestation at Kings College Hospital, London, England. In the same visit, the measurement of MAP and maternal serum sFlt-1 and PlGF concentration was performed as part of a research project. Women participating in the study, which was approved by the National Health Service Research Ethics Committee, gave written informed consent. This study was reported in agreement with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[8]

The inclusion criteria were singleton pregnancies undergoing IOL resulting in the live birth or stillbirth of neonates without major abnormalities. Patients who underwent spontaneous labor with intact membranes after PROM and those with elective cesarean delivery or stillbirth were excluded from the study.

Laboratory methods

The measurements of sFlt-1 and PlGF were performed with automated analyzers (BRAHMS KRYPTOR; Thermo Fisher Scientific, Hennigsdorf, Germany). The methods were described in a recent publication by our group.[1] Sample processing was performed following a standardized procedure, with timelines falling within the normal ranges recommended by the manufacturers.

Variables and outcomes

The primary outcome was fetal compromise in a population of pregnancies approaching early term (>35 weeks of gestation) after IOL for different indications. The risk of fetal compromise was stratified according to the FMF-derived risk of PE in different risk categories that represented the main study variable.

Fetal compromise was determined by the attending physicians based on specific case diagnoses, which included abnormalities in fetal heart rate detected through continuous cardiotocography in all cases (eg, bradycardia, prolonged or recurrent decelerations, and reduced beat-to-beat variability) with or without associated meconium-stained amniotic fluid.[4] Methods for IOL were according to the local protocol with vaginal or oral prostaglandins, oxytocin, amniorrhexis, and cervical ripening balloons as previously recommended.[9,10]

Risk assessment and strata

Risk assessment for PE was performed according to the FMF 36-week method using a competing-risk model with a combination of maternal factors, MAP, UtA-PI, PlGF, and sFlt-1 (triple test).[11–14] Data were stratified according to risks into the following groups: A (risk of >0.500; ≥1 in 2), B (risk of 0.200–0.499; ≥1 in 5 and<1 in 2), C (risk of 0.050–0.199; ≥1 in 20 and <1 in 5), D (risk of 0.020–0.049; ≥1 in 50 and <1 in 20), and E (risk of <0.020; <1 in 50).

Based on the reason for IOL, we created 5 categories: PROM; postterm pregnancy (>41 weeks of gestation), PE, FGR (defined as an estimated fetal weight of <5th percentile), and PE with associated FGR. The choice of 36 weeks of gestation was based on extensive research by the FMF, evaluating it as a potential period for general screening.[11–14]

Statistical methods

Data were presented descriptively for different strata of FMF PE risk and summarized by percentages for categorical variables and means and standard deviations or confidence intervals for continuous variables across these strata.

The distribution of FMF PE risk for the overall population was tested for normality after Log10 transformation. A multinomial logistic regression was used to assess the risk of cesarean delivery for fetal compromise having as the main independent predictor the 5 generated risks of PE categories, considering 4 possible outcomes: spontaneous delivery, cesarean delivery for fetal compromise, cesarean delivery for failure to progress (FTP), and cesarean delivery for other reasons. Considering the various nominal outcomes (and, thus, without a natural order), no proportionality assumption is required because each outcome category is treated as independent (even though, in practice, the categories are mutually exclusive). Furthermore, by including all possible outcomes in the analysis, this statistical approach allows for a more accurate and generalizable assessment of the risk of fetal compromise.

By excluding other possible outcomes from the analysis and reducing it to a binary logistic regression (cesarean delivery for fetal compromise vs cesarean delivery for other reasons), a simplification would be introduced that ignores the influence of the excluded outcomes, which could alter the relationships between the predictors and the odds. The odds ratios obtained from binary logistic regression may be overestimated or biased compared with those calculated using the multinomial model, particularly if the other outcomes have distributions that interact with the explanatory variables.

The vast majority of possible relevant covariates are already included in the PE risk calculation (ie, maternal age, height, weight, BMI, self-reported ethnic group, smoking habit, family history of PE, conception method, chronic hypertension, diabetes mellitus type I or II, systemic lupus erythematosus, antiphospholipid syndrome, parity, gestational age (GA) at examination, mean arterial pressure, serum sFLT-1, and PlGF). We only added covariates not accounted for in that calculation (ie, indication and GA at IOL), and we only reassessed the effect of parity given its utmost importance in the response to IOL.

Post-hoc study size and power analysis was performed. The performance metric was evaluated using a calibration plot to assess model accuracy and detect bias. Data were stratified into percentiles based on mean risks of fetal compromise estimated via multinomial logistic regression. For the analyses, SPSS Statistics for Windows (version 27.0; IBM Corporation, Armonk, NY) was used. Statistical significance was considered for a 2-sided α error of 0.05 and β error of 0.8.

Results

Participant, descriptive, and outcome data

Overall, 45,375 women with singleton pregnancies attended the routine assessment at 35 to 37 weeks of gestation, and 12,249 of these women had IOL and were included in the current study. Of 12,249 women, 182 (1.48%) delivered at <37 weeks of gestation, 1444 (11.8%) underwent cesarean delivery for fetal compromise (defined as abnormalities in fetal heart rate detected through continuous cardiotocography associated or not with meconium-stained amniotic fluid), 2243 (18.3%) had cesarean delivery for FTP, and 66 (0.5%) had cesarean delivery for other obstetrical indications.

Supplemental Figure 1 presents the flowchart of patient recruitment. The Table summarizes the maternal and pregnancy characteristics of 12,249 women in the study population, details of their screening marker result, and GA at delivery. There were 107 (0.9%), 391 (3.2%), 2514 (20.5%), 4178 (34.1%), and 5059 (41.3%) women in PE risk groups A, B, C, D, and E, respectively. The frequency and proportion of cases in each specific group of IOL are presented in the Supplemental Table.

The observed cases of PE in each PE risk category assessed by the FMF algorithm were as follows: 65 of 107 (69.7%) in group A, 157 of 391 (40.2%) in group B, 332 of 2514 (13.2%) in group C, 184 of 4178 (4.4%) in group D, and 57 of 5059 (1.1%) in group E. In the PE and PE + FGR groups, all cases had PE. In the FGR and PROM groups, none had PE. In the postterm pregnancy group, 2.4% were diagnosed with PE in the peripartum period after IOL for postterm pregnancy.

Main results

This study in patients after IOL showed a higher rate of fetal compromise than our recently published series on the subgroup with spontaneous onset of labor[1] from the same cohort (1444/12,249 [11.8%] vs 1167/23,831 [4.9%]; $P<.001$).

The rates of fetal compromise according to the different categories of indications for IOL were PROM (9.7%), postterm pregnancy (>41 weeks of gestation; 13.5%), PE (14.8%), FGR (17.2%), and PE and FGR (23.4%).

When plotting the risk of fetal compromise across the 5 PE risk categories (A, B, C, D, and E), we observed a substantial fetal compromise risk increase as the PE risk category increased. The rates of fetal compromise in each PE risk category assessed by the FMF algorithm were as follows: group A (high risk of PE of ≥1/2; 27/107 [25.2%]), group B (risk of PE of ≥1/5 to <1/2; 78/391 [19.9%]), group C (risk of PE of ≥1/20 to <1/5; 418/2514 [16.6%]), group D (risk of PE of ≥1/50 to <1/20; 547/4178 [13.0%]), and group E (low-risk of PE of <1/50; 378/5059 [7.5%]).

As expected, women with intrapartum fetal compromise had a higher mean PE risk than those without fetal compromise (1/45 vs 1/81, respectively;

TABLE
Characteristics of the cohort at 35 to 36 weeks' gestation and GA at delivery, by risk stratum (number (%) or mean (SD)

	Risk stratum for preeclampsia (N=12,249)				
Characteristic	A (≥1 in 2) n=107	B (<1 in 2 and ≥1 in 5) n=391	C (<1 in 5 and ≥1 in 20) n=2514	D (<1 in 20 and ≥1 in 50) n=4178	E (<1 in 50) n=5059
Maternal age (y)	33.2±6.5	32.8±6.4	32.6±6.1	31.9±5.6	32.2±5.3
Maternal weight (kg)	92.2±19.1	91.2±21.7	89.2±18.7	84.9±16.2	80.2±14.2
Maternal height (m)	164.1±6.6	163.8±7.2	164.3±6.4	165.1±6.7	166.4±6.6
Body mass index (kg/m^2)	34.21±6.65	33.88±7.25	33.00±6.32	31.10±5.38	28.95±4.81
GA (wk)	35.90±0.55	35.90±0.54	35.90±0.56	35.90±0.54	35.90±0.54
GA from dosage to induction of labor (wk)	2.00±1.27	2.77±1.45	3.67±1.52	4.15±1.50	4.23±1.50
Biomarkers					
Mean arterial pressure (MoM)	1.15±0.10	1.11±0.09	1.05±0.07	1.01±0.06	0.97±0.06
Placental growth factor (MoM)	0.38±1.12	0.62±0.85	1.16±1.23	1.50±1.33	1.63±1.31
Soluble fms–like tyrosine kinase (MoM)	3.09±1.80	2.19±1.41	1.40±1.01	1.11±0.77	1.03±0.69
Uterine artery Doppler pulsatility (MoM)	1.81±0.45	1.51±0.43	1.17±0.34	1.01±0.24	0.93±0.22
GA at delivery (wk)	37.98±1.25	38.75±1.39	39.62±1.41	40.07±1.40	40.17±1.40
Ethnic origin					
Black, n (%)	46 (43.0)	131 (33.5)	667 (26.5)	556 (13.3)	244 (4.8)
East Asian, n (%)	1 (15.9)	4 (12.3)	39 (4.0)	82 (0.4)	93 (0.1)
More than one, n (%)	1 (0.9)	6 (1.5)	63 (2.5)	143 (3.4)	156 (3.1)
South Asian, n (%)	14 (13.1)	43 (11.0)	207 (8.2)	294 (7.0)	222 (4.4)
White, n (%)	45 (42.1)	207 (52.9)	1538 (61.2)	3103 (74.3)	4344 (85.9)
Medical history					
Chronic hypertension, n (%)	17 (15.9)	48 (12.3)	100 (4.0)	16 (0.4)	4 (0.1)
Type 1 diabetes mellitus, n (%)	1 (0.9)	11 (2.8)	34 (1.4)	28 (0.7)	11 (0.2)
Type 2 diabetes mellitus, n (%)	10 (9.3)	15 (3.8)	89 (3.5)	36 (0.9)	6 (0.1)
SLE/APS, n (%)	2 (1.9)	4 (1.0)	16 (0.6)	11 (0.3)	6 (0.1)
Smoker, n (%)	4 (3.7)	12 (3.1)	82 (3.3)	187 (4.5)	312 (6.2)
Method of conception					
In vitro fertilization, n (%)	15 (14.0)	39 (10.0)	306 (12.2)	331 (7.9)	127 (2.5)
Ovulation induction, n (%)	2 (1.9)	4 (1.0)	16 (0.6)	24 (0.6)	34 (0.7)
Spontaneous, n (%)	90 (84.1)	348 (89.0)	2192 (87.2)	3823 (91.5)	4898 (96.8)
Parity					
Nulliparous, n (%)	67 (62.6)	274 (70.1)	1856 (73.8)	3054 (73.1)	1868 (36.9)
Parous: no history of preeclampsia, n (%)	26 (24.3)	70 (17.9)	499 (19.8)	1040 (24.9)	3180 (62.9)
Parous: history of preeclampsia, n (%)	14 (13.1)	47 (12.0)	159 (6.3)	84 (2.0)	11 (0.2)
Neonatal weight (g)	2635±511	2945±481	3298±520	3452±497	3510±508
Neonatal weight percentile	16±25	27±26	42±30	49±29	52±29

APS, antiphospholipid syndrome; *GA*, gestational age; *MoM*, multiple of the median; *SLE*, systemic lupus erythematosus.
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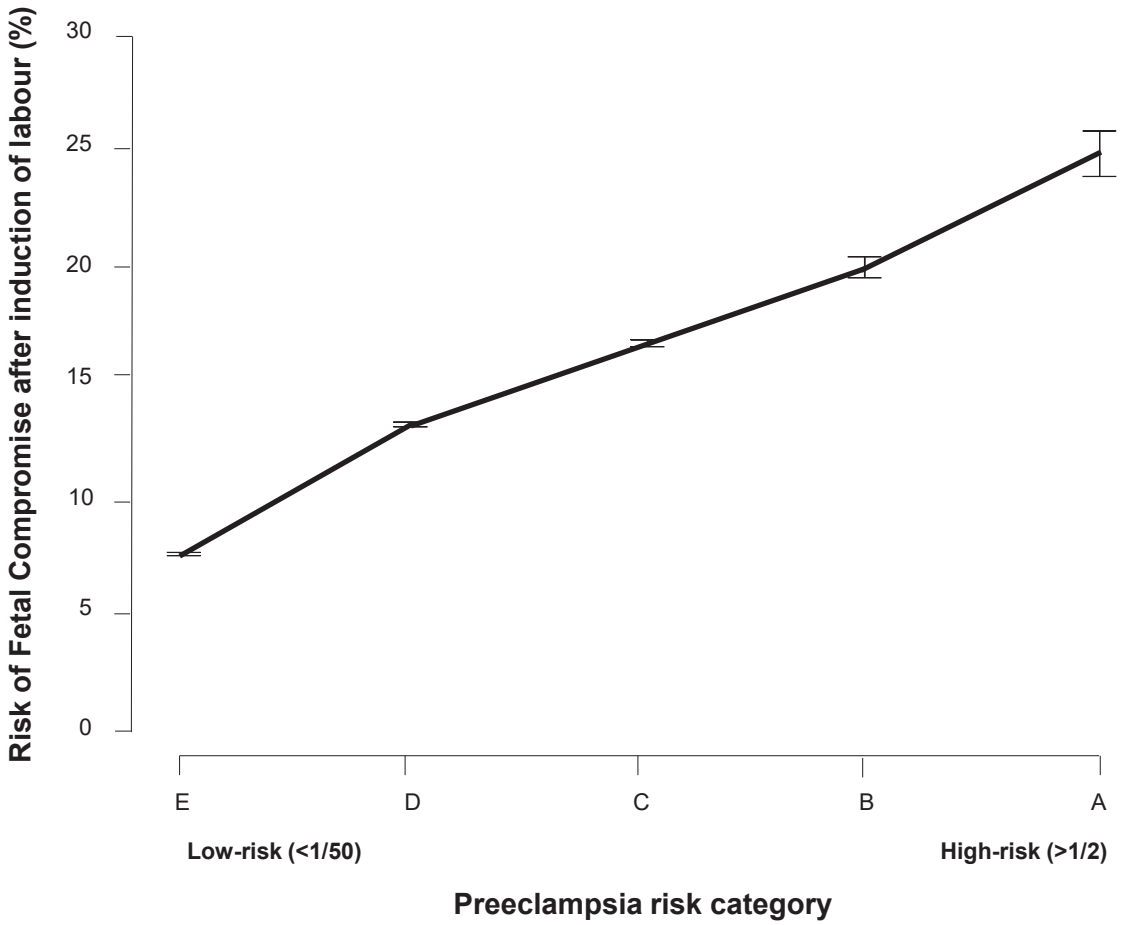
$P<.001$). Increasing risk of PE, from the low-risk E category (<1/50) to the high-risk A category (≥1/2), was associated with an 18% risk increase for cesarean delivery because of fetal compromise. Specifically, the risk of fetal compromise increased from 7.5% in the lowest risk category (group E) to 25.2% in the highest risk category (group A), indicating a 3-fold increase in risk across these categories (Figure 1). The most remarkable increase (6%–7%) occurred when moving from category E to category D and from category B to category A.

Nulliparity was associated with an extra risk of fetal compromise across the PE risk categories compared with pluriparity, ranging from 5% (6% vs 11%) for category E to 10% (19% vs 29%) for category A ($P<.001$; Figure 2).

Based on the indications for IOL and the univariate unstratified risk of fetal compromise, the study population was divided into 5 groups with progressively increasing rates of fetal compromise: 9.7% for PROM, 13.5% for postterm pregnancy (>41 weeks of gestation), 14.8% for PE, 17.2% for FGR, and 23.4% for PE and FGR. In the stratification of PE risk categories across groups of indications for IOL (Figure 3), we identified that both PROM (group 1) and PE (group 3) exhibited a similar risk of fetal compromise, ranging from 6% to 20% for both (from PE risk category E to category A). In contrast, the other 3 groups, that is, postterm pregnancy (group 2), FGR (group 4), and PE with associated FGR (group 5), showed a different risk profile, the risk of fetal compromise being approximately 10% in category E and approximately 30% in category A. Postterm pregnancy was associated with the higher risk of fetal compromise (32%), followed by FGR and PE with associated FGR (29%). Finally, the risk of fetal compromise increased by approximately 1% at 35 to 40 weeks of gestation and by 5% at 41 to 42 weeks of gestation for each additional week of gestation at IOL.

The calibration plot of the entire dataset showed a slight and consistent

FIGURE 1
Mean risk of cesarean delivery for fetal compromise by preeclampsia risk categories



The references are provided with 95%conficence intervals. FMF preeclampsia risk categories: (A [>1/2], B [1/2–1/5], C [1/5–1/20], D [1/20–1/50], and E [<1/50]).

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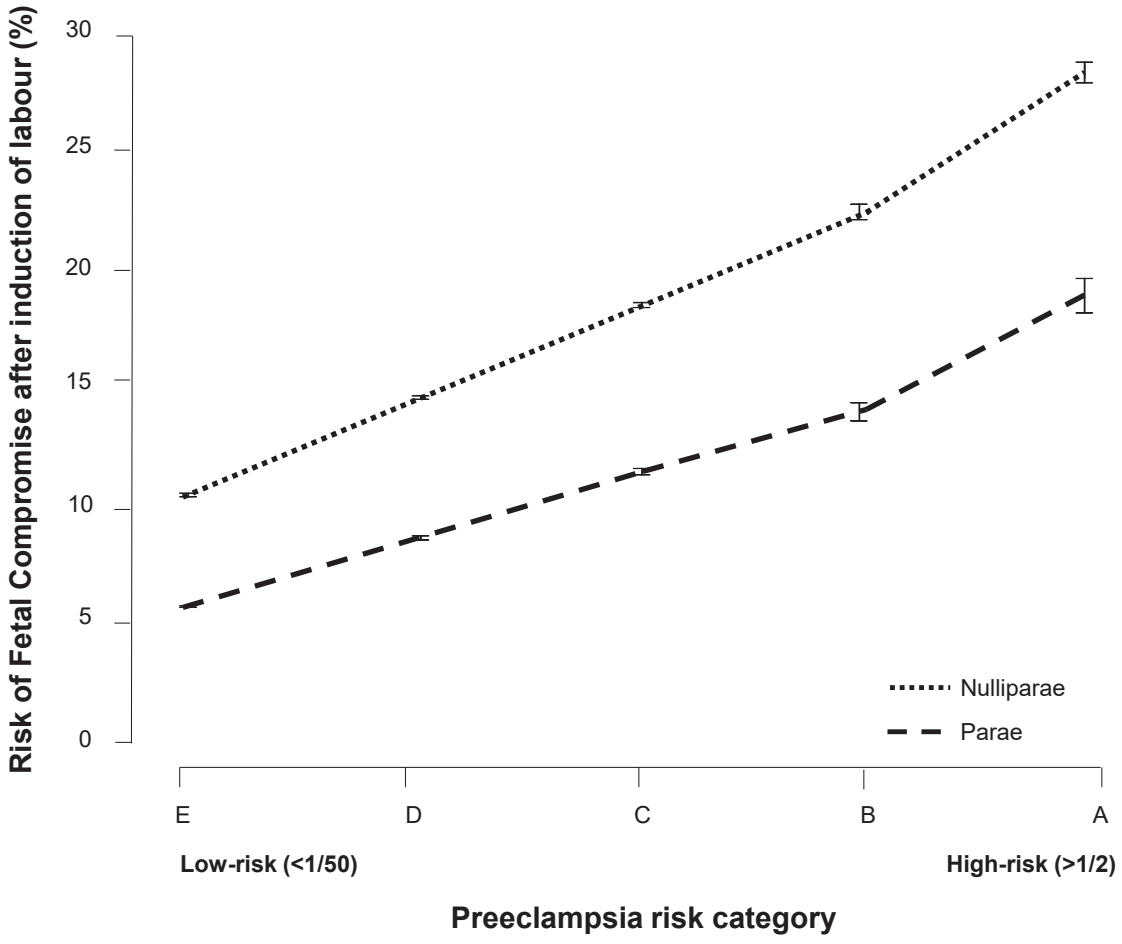
FIGURE 2
Mean risk of cesarean delivery for fetal compromise by preeclampsia risk categories and parity



The references are provided with 95%conficence intervals. FMF preeclampsia risk categories: (A [>1/2], B [1/2—1/5], C [1/5—1/20], D [1/20—1/50], and E [<1/50]).

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overestimation of the estimated risk compared with the expected values across all deciles into which the dataset was divided (Supplemental Figure 2). The study power was optimal in most groups (Supplemental Table).

Comment

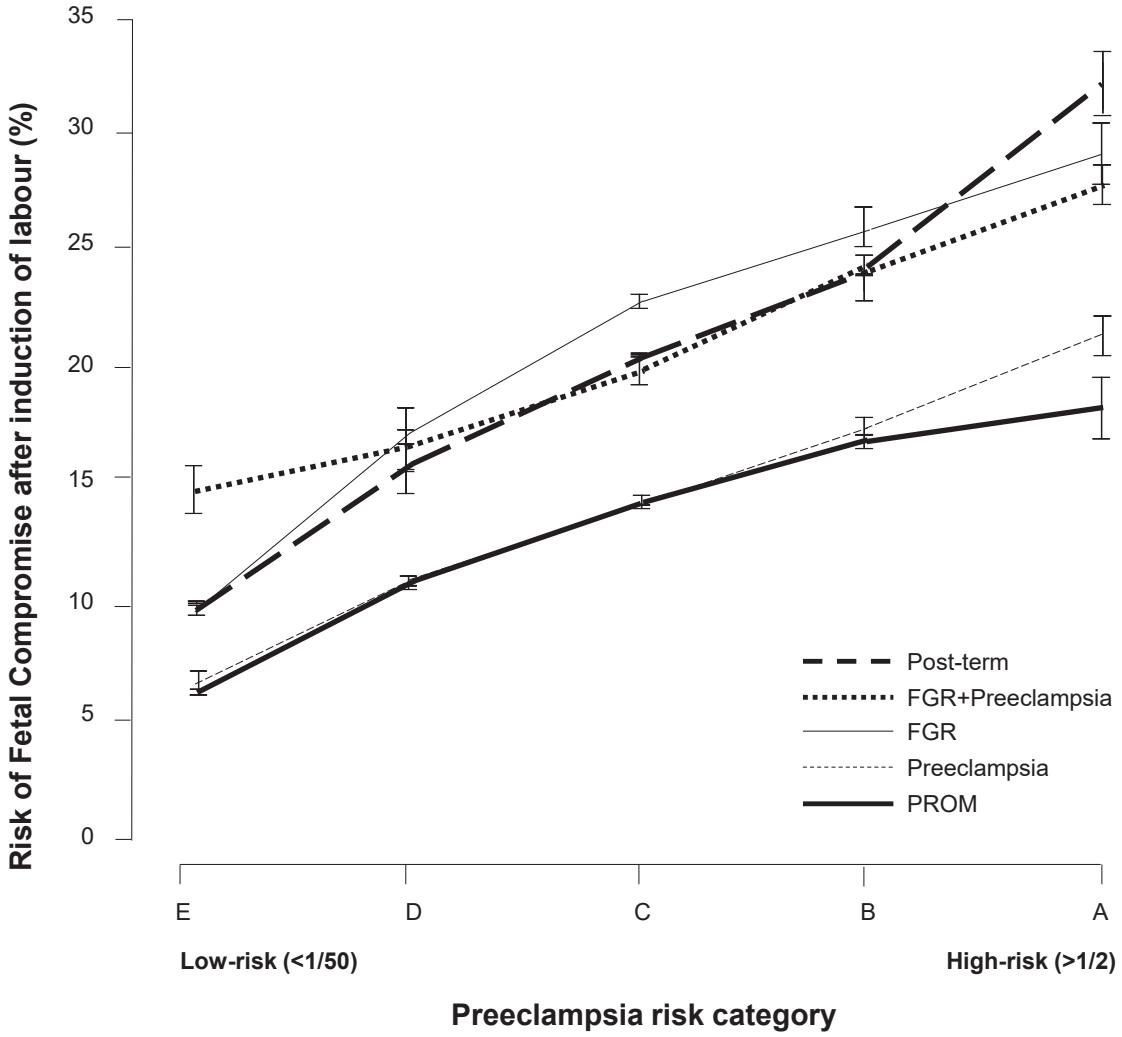
Main findings

This study examined pregnant women who underwent IOL for various obstetrical indications after routine PE screening at 36 weeks of gestation using the FMF protocol. It showed a crude fetal compromise risk of approximately 12% and a vaginal delivery rate of 69%, along with 2 key findings. First, the risk of fetal compromise after IOL increases progressively and consistently with increasing estimated risk of PE, with a relevant effect of multiparity in mitigating fetal compromise risk and increasing GA in aggravating fetal compromise risk. Second, the indication for IOL is a central factor affecting the risk of fetal compromise across FMF PE risk categories, with lower risk in PROM and PE groups and higher risk in FGR (with or without associated PE) and postterm pregnancy. Here, the lowest estimated risk of fetal compromise was approximately 5% in pregnancies with a PE risk of <1/50 in the categories PROM and PE, and the highest estimated risk of fetal compromise was approximately 30% in pregnancies with PE risk of >1/2 in the categories postterm pregnancy and FGR (with or without PE). There was an average 5% risk increase for fetal compromise across categories of increasing PE risk (from the low risk of <1/50 to the high risk of >1/2).

Interpretation in the context of what is known

This study confirmed that subclinical forms of placental insufficiency during pregnancy are linked to future fetal compromise observed during labor after IOL procedures. This concept was supported by different findings of this study.

FIGURE 3
Mean risk of cesarean delivery for fetal compromise by preeclampsia risk categories and subgroups of indications to labour induction



The references are provided with 95% confidence intervals. FMF preeclampsia risk categories: (A [>1/2], B [1/2—1/5], C [1/5—1/20], D [1/20—1/50], and E [<1/50]).

FGR, fetal growth restriction.

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First, increasing PE risk assessed at 36 weeks of gestation using the FMF method related to increasing degree of placental dysfunction and reliably associated with increasing rates of fetal compromise. This is consistent with previous work showing a relevant association of increased sFlt-1/PlGF levels at 36 weeks of gestation with fetal compromise[1] and with evidence showing presence of placental lesions of maternal vascular malperfusion in obstetrical syndromes related to abnormal concentrations of sFlt-1 and PlGF.[15] Second, the indications for IOL were also correlated with fetal compromise with a consistent progression from classes associated with a lower degree of placental insufficiency (PROM and term pregnancy, frequently mild PE) to classes with a more severe degree of placental dysfunction (FGR with or without PE and postterm pregnancy).[15,16]

The FMF competing risk models for PE screening in the first, second or third trimester were established by a series of publications and encompass biomarkers related to placental dysfunction or senescence.[11—14,17—22] Both the early model at 12 weeks of gestation and the late model at 36 weeks of gestation were the subject of previous studies showing earlier onset of spontaneous labor and earlier delivery for medical indications, confirming a strong association between PE risk and placental dysfunction.[23,24] Therefore, it is scientifically sound to hypothesize that cases with better placental function would be capable of

providing a greater extent of oxygen delivery to the fetus during labor, whereas those with suboptimal placental function (either clinically evident or subclinical) are exposed to progressively increasing risks of fetal compromise in labor as contractions during labor intermittently interrupt oxygen delivery, effectively acting as a stress test that deteriorates acid-base status in clinically evident placental dysfunction (ie, higher risks of PE, FGR with or without PE, and postterm pregnancy) or may reveal subclinical forms of placental dysfunction (ie, lower risks of PE, PROM, and PE with no FGR).[4]

Strengths and limitations

The main strength of this work is the evaluation of a large population recruited in a narrow gestational window at a single center, assessing the effect of subclinical placental insufficiency (based on FMF risk of PE at 36 weeks of gestation) as an initiator of spontaneous labor and intrapartum fetal compromise requiring cesarean delivery after IOL. A further strength is that this study presents a major clinical translation being able to direct the management of IOL in specific clinical conditions, representing the basis for future prospective studies aimed at improving pregnancy outcomes.

There are some limitations in this study. The retrospective design inherently reduced its strength and reproducibility. Although adjustments were made for the available covariates and the available outcomes, unaccounted confounding factors may still exist, particularly those related to clinical management during labor, including labor duration, which can be influenced by various variables. In particular, variables that could not be examined were the use of epidural analgesia, which was linked to intrapartum fetal compromise, particularly when associated with reduced fetal growth,[25] and the method of IOL that may also be associated with different degrees of uterine contractility and fetal tolerance to labor.[9,26]

Although the definition of fetal compromise was standardized (abnormal cardiotocography [CTG] with or without associated meconium-stained amniotic fluid), individual clinician reassessment and evaluation were performed on a case-by-case basis. This variability is a common limitation in studies based on real-life clinical scenarios.

Finally, not all fetal compromise cases are related to placental dysfunction. Unfortunately, the breakdown of fetal compromise types was not analyzed because of the lack of data.

Implications for clinical practice and future research

This study showed that the risk of PE by the FMF model at 36 weeks of gestation presents a further clinical value besides the capability of predicting PE, being clinically useful to tailor follow-up of pregnancies close to term or at term, because of the strong association with fetal compromise. This knowledge may be used to define methods of IOL favoring mechanical methods as opposed to pharmacologic methods (ie, prostaglandins) in cases at higher risk of fetal compromise to avoid exceeding the threshold for fetal compensation promoted by excessive and uncontrolled uterine contractions.[27]

In addition, this knowledge may be used to define individualized and patient-specific timing for elective IOL concerning the risk of pregnancy complications, including PE and fetal compromise. For instance, conservative management postponing IOL may be reconsidered toward earlier IOL in preterm PROM or in pregnancies at term, when the biomarker profile is suggestive of a high risk of fetal compromise, which is expected to increase with advancing gestation as shown in our study. This would allow for a move toward individualization of care, and future research will assess this hypothesis as opposed to the use of predefined and indiscriminate GA thresholds for labor induction.

A recent randomized trial using sildenafil citrate to improve fetal or uteroplacental perfusion in labor (ie, placental function) demonstrated a reduction of operative births for intrapartum fetal compromise in a high-risk population.[28] Future studies with prospective design will need to assess the extent to which this or other therapeutic approaches may yield improved results if applied in cases with greater risk of fetal compromise, as shown by our method. Moreover, future research may assess the value of the 36-week assessment for defining optimal birth timing, including the prediction of success of IOL.

Finally, given the results of this study, there is a sound rationale for testing the risk of fetal compromise within multivariate strategies for fetal compromise in labor, given its considerable association with placental dysfunction. This approach may integrate other established methods of screening, such as repeat uterine artery Doppler for pulsatility index measurement, first-trimester screening for preterm PE, and equally important intrapartum variables, such as cardiotocographic traces and clinical variables that may occur at a later stage to be used prospectively in the labor ward.[17,29,30]

Conclusion

Our study suggests that categorizing PE risk using the FMF 36-week competing-risk prediction model is clinically useful for estimating the patient-specific risk of cesarean delivery for fetal compromise after IOL considering all possible outcomes. Factors, such as GA at the time of IOL, presence of fetal growth impairment, and parity, extensively influence the risk of fetal compromise. This knowledge represents a step toward creating an effective prediction model for intrapartum fetal compromise and will favor immediate clinical translation for optimization of obstetrical management of pregnancies approaching term and potential prevention of maternal-fetal risks and will promote future research. ■

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Author and article information

From the Obstetric Unit, Istituto di Ricovero e Cura a Carattere Scientifico Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy (Farina); Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy (Farina); Department of Obstetrics and Gynaecology, Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Scientific Institute, Milan, Italy (Cavoretto); Vita-Salute San Raffaele University, Milan, Italy (Cavoretto); Fetal Medicine Research Institute, King's College Hospital, London, United

Kingdom (Syngelaki, Adjahou, and Nicolaides); and Department of Obstetrics and Gynecology, Sant'Anna University Hospital, Cona, Ferrara, Italy (Morano).

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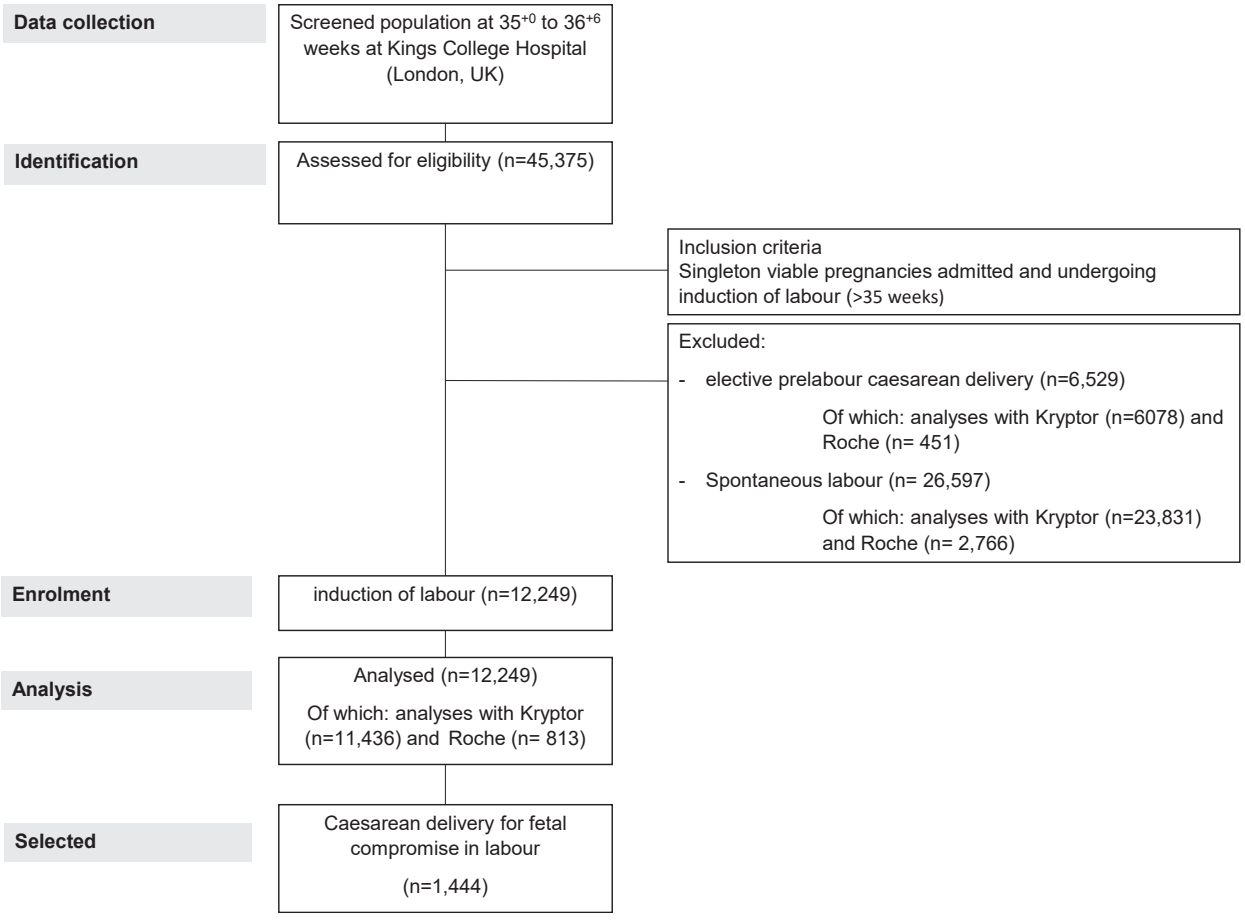
Corresponding author: Antonio Farina, MD. antonio.farina@unibo.it

SUPPLEMENTAL FIGURE 1
Flowchart of the study design and patients' recruitment



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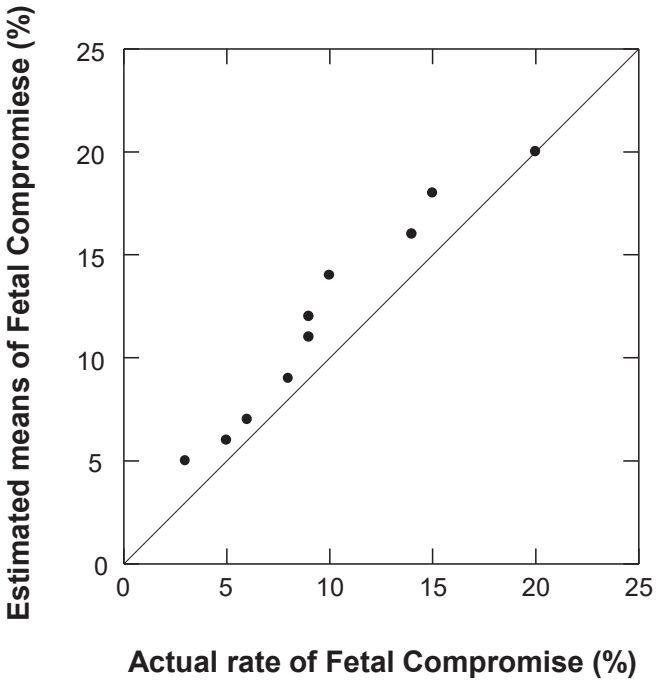
SUPPLEMENTAL FIGURE 2
Calibration plot based on the predicted risk



The whole dataset was grouped into 10 equally sized bins (deciles) based on the predicted risk.

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SUPPLEMENTAL TABLE
Frequency and proportion of cases in each specific group of induction of labor and post hoc statistical power given the rate of fetal compromise in the study population of 11.8% (n = 1444)

	Frequency	Proportion	Statistical power population	Statistical power groups	Rate of fetal compromise	No. of cases of fetal compromise	Fetal compromise group vs reference group
Variable	n	%	%	%	%	n	n/N (%)
Group 1: PROM	6940	56.7	100.0	100.0	9.7	672	772/5309 (14.5)
Group 2: postterm pregnancy	3597	29.4	87.1	100.0	13.5	485	959/8652 (5.6)
Group 3: PE	586	4.8	60.4	66.1	14.8	87	1357/11,663 (11.6)
Group 4: FGR	1002	8.2	99.8	100.0	17.1	171	1273/11,247 (11.3)
Group 5: PE + FGR	124	1.0	94.0	100.0	23.4	29	1415/12,125 (11.7)
Total	12,249	100	—	—	—	—	—

Postterm pregnancy indicates a pregnancy >41 0/7 weeks of gestation. Statistical power population: uses as a reference group the whole group of 12,249 cases vs the one in analysis; Statistical power group: uses as a reference group the combination of the other 4 groups vs the one in analysis.

PE, preeclampsia; *PROM*, premature rupture of membranes; *FGR*, fetal growth restriction.

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