Performance of the first-trimester Fetal Medicine Foundation competing risks model for preeclampsia prediction: an external validation study in Brazil

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BACKGROUND: The current version of the Fetal Medicine Foundation competing risks model for preeclampsia prediction has not been previously validated in Brazil.

OBJECTIVE: This study aimed (1) to validate the Fetal Medicine Foundation combined algorithm for the prediction of preterm preeclampsia in the Brazilian population and (2) to describe the accuracy and calibration of the Fetal Medicine Foundation algorithm when considering the prophylactic use of aspirin by clinical criteria.

STUDY DESIGN: This was a cohort study, including consecutive singleton pregnancies undergoing preeclampsia screening at 11 to 14 weeks of gestation, examining maternal characteristics, medical history, and biophysical markers between October 2010 and December 2018 in a university hospital in Brazil. Risks were calculated using the 2018 version of the algorithm available on the Fetal Medicine Foundation website, and cases were classified as low or high risk using a cutoff of 1/100 to evaluate predictive performance. Expected and observed cases with preeclampsia according to the Fetal Medicine Foundation—estimated risk range (≥1 in 10; 1 in 11 to 1 in 50; 1 in 51 to 1 in 100; 1 in 101 to 1 in 150; and <1 in 150) were compared. After identifying high-risk pregnant women who used aspirin, the treatment effect of 62% reduction in preterm preeclampsia identified in the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention trial was used to evaluate the predictive performance adjusted for the effect of aspirin. The number of potentially unpreventable cases in the group without aspirin use was estimated.

RESULTS: Among 2749 pregnancies, preterm preeclampsia occurred in 84 (3.1%). With a risk cutoff of 1/100, the screen-positive rate was 25.8%. The detection rate was 71.4%, with a false positive rate of 24.4%. The area under the curve was 0.818 (95% confidence interval, 0.773—0.863). In the risk range ≥1/10, there is an agreement between the number of expected cases and the number of observed cases, and in the other ranges, the predicted risk was lower than the observed rates. Accounting for the effect of aspirin resulted in an increase in detection rate and positive predictive values and a slight decrease in the false positive rate. With 27 cases of preterm preeclampsia in the high-risk group without aspirin use, we estimated that 16 of these cases of preterm preeclampsia would have been avoided if this group had received prophylaxis.

CONCLUSION: In a high-prevalence setting, the Fetal Medicine Foundation algorithm can identify women who are more likely to develop preterm preeclampsia. Not accounting for the effect of aspirin underestimates the screening performance.

Key words: algorithm, aspirin, clinical prediction model, preeclampsia, sensitivity and specificity, validation

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Why was this study conducted?

This study aimed to validate the current version of the Fetal Medicine Foundation algorithm for preterm preeclampsia (PE) prediction in the Brazilian population and to describe the accuracy of the FMF algorithm adjusted for the prophylactic use of aspirin by clinical criteria.

Key findings

Combined prediction of PE with multimarker algorithms was feasible in low- and middle-income countries and outperformed the use of clinical risk factors alone.

What does this add to what is known?

The study externally validates the current version of the FMF algorithm in the Brazilian population, accounting for the effect of treatment. It shows that proper evaluation of screening performance requires adjustment for the effect of aspirin.

Introduction

Preeclampsia (PE) is a major cause of maternal and perinatal morbidities and mortalities,[1] affecting 2% to 8% of pregnancies worldwide[2,3] and leading to considerable social and medical burdens.[4] Although the pathophysiology of this multifactorial disease is only partially understood,[5,6] recent advances have made early prediction and prevention possible,[7] such that prophylactic strategies, such as the use of low-dose aspirin (LDA), can be timely implemented in women identified as high risk.[8–10] The benefits are even more relevant in regions with a high disease prevalence.

Despite being an easy and low-cost strategy, the traditional approach that recommends LDA based on maternal characteristics and medical history performs poorly and is not cost-effective.[11] It underperforms as it detects only approximately 40% of preterm and 30% of all PE cases,[12,13] reducing the target population that benefits from the prophylactic intervention.

The Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial[8] concluded that among women identified as high-risk using an algorithm developed and previously validated by the Fetal Medicine Foundation (FMF), aspirin at a dose of 150 mg/day between 11 to 14 and 36 weeks of gestation reduces the risk of preterm PE by 62% (95% confidence interval [CI], 26%−80%).

The FMF2012 algorithm,[14] with a different cutoff and early PE as outcome, has been previously evaluated in our population,[15] with crude parameters of screening performance underestimated by the treatment effect as some women received LDA based on clinical factors. To evaluate the true performance of prediction, estimates should be adjusted for the use of aspirin, as this effective intervention prevents PE in a high proportion of high-risk women, effectively converting true positives into false positives from screening.[16,17]

The updated algorithm is freely available on the FMF website since 2018,[18–20] allowing for the estimation of patient-specific risks for PE by combining maternal characteristics and history with biomarkers in the first trimester of pregnancy, and its performance has not yet been evaluated in the Brazilian population, with a higher PE prevalence than other populations in which the algorithm has been evaluated.[21–28] Before clinical implementation, this current version needs to be evaluated on a larger sample of our population, considering preterm PE as the primary outcome as it constitutes the main endpoint of prediction based on the FMF algorithm and prevention with LDA. This study aimed to validate the current version of the FMF algorithm for preterm PE prediction in the Brazilian population and to describe the accuracy of the FMF algorithm adjusted for the prophylactic use of LDA by clinical criteria.

Materials and Methods

Data for this cohort study were derived from the consecutive application of the currently available version of the FMF first-trimester screening model that reports the individual probabilities of major obstetrical syndromes, including PE. The study was conducted at the Maternity School of the Federal University of Rio de Janeiro, a not-for-profit teaching hospital. The local ethics committee approved the final study protocol (reference number: 4.859.359; July 2021). All participants provided written informed consent after counseling before undergoing first-trimester screening.

Study population

All singleton pregnancies undergoing first-trimester screening for PE using the previous version of the FMF algorithm between October 2010 and December 2018 were considered eligible for inclusion. Pregnancies with diagnosed chromosomal or structural fetal abnormality, miscarriage, or fetal death before 24 weeks of gestation were excluded.

We estimated that a sample size of 2762 with 78 events would be sufficient to externally validate the prediction model with a preterm PE prevalence of 3.0%[29] and an expected area under the curve of 0.80 (95% CI, 0.75−0.85).[30]

Screening procedure

Patients were scheduled for routine first-trimester screening at 11 0/7 to 13 6/7 weeks of gestation. This examination included recording maternal characteristics and medical history, obtained with a patient questionnaire, and anthropometric measures verified by a medical doctor on the day of the ultrasound examination. Continuous variables were maternal age, weight, height, interpregnancy interval, and gestational age (GA) of last birth. Categorical variables were self-reported place of birth, ethnicity, parity, maternal family history of PE, smoking during pregnancy, history of chronic hypertension, type 1 or type 2 diabetes mellitus, systemic lupus erythematosus, antiphospholipid syndrome, and method of conception (spontaneous, ovulation induction, or in vitro fertilization).

Following the measurement of fetal crown-rump length (CRL)[31] and the mean uterine artery pulsatility index (UtA-PI) on transabdominal color Doppler ultrasound by an FMF-certified doctor,[32] the mean arterial pressure (MAP) was measured with an automated device validated for use in pregnancy and calibrated at regular intervals using a standardized method.[33] All available data were entered posteriorly into the FMF online calculator of PE risk available at https://fetalmedicine.org/research/assess/preeclampsia/first-trimester, to calculate the current risk to be validated.

Predicted probabilities were calculated from maternal characteristics and biophysical markers (MAP and UtA-PI) and were presented as the risk of PE with delivery before 37 weeks of gestation. The cutoff value for positivity was 1/100. Because a cutoff of 1 in 150 was previously suggested to define the high-risk group that would benefit from prophylactic use of aspirin, the performance of screening with this cutoff value was also estimated.[19] Biochemical markers, such as placental growth factor and pregnancy-associated plasma protein A, were unavailable and, therefore, not used in the risk calculation.

Following the hospital's protocol, from 2013, the use of LDA at a daily dose of 100 mg, at night, for PE prophylaxis was recommended before 16 weeks of gestation based on local clinical guidelines if 1 major risk factor (previous hypertensive disorder of pregnancy, chronic hypertension, type 1 or type 2 diabetes mellitus, chronic kidney disease, or autoimmune disease) or at least 2 moderate risk factors (nulliparity, maternal age ≥40 years, body mass index at booking of ≥35 kg/m^2, interpregnancy interval of >10 years, or family history of PE) were present.[34] During the study period, the screening results did not dictate clinical management, which became routine in 2019.

Physician compliance with the local protocol was calculated as the prescription rate of aspirin prophylaxis to high-risk women with the aforementioned clinical criteria. Adherence to aspirin prophylaxis was not directly evaluated. Nevertheless, the files contain records of dates and GA at which LDA was initiated and ceased. At each antenatal visit, women were asked if LDA was being taken regularly as prescribed.

Outcome measures

Data on pregnancy outcomes were collected from hospital records. GA at birth was calculated on the basis of the last menstrual period or the CRL measurement performed at the routine 11- to 13-week ultrasound scan when the difference between the 2 was >7 days.[31]

PE was defined according to the International Society for the Study of Hypertension in Pregnancy[35] definition and classified according to GA at delivery: PE at <34 weeks of gestation or early PE (with delivery before 34 weeks of gestation), PE at <37 weeks of gestation or preterm PE (with delivery before 37 weeks of gestation), and total PE (including all cases of PE). The primary outcomes of the study were preterm PE and screening performance.

Pregnancies lost to follow-up were stratified according to the GA of the last recorded clinical information. Pregnancies lost to follow-up before 37 weeks of gestation were excluded from all analyses, whereas patients lost to follow-up after 37 weeks of gestation were only excluded from analyses related to term PE but kept in the analysis of preterm PE, as the presence or absence of this outcome could be ascertained.

Statistical analysis

Continuous variables were described as mean and standard deviation or median and interquartile range (IQR), depending on the distribution, and compared between the groups with independent samples *t* tests when normally distributed and the Wilcoxon rank-sum test when nonnormally distributed. The normality of the distributions was verified by inspection of histograms. Categorical variables were presented as absolute numbers and percentages and compared between the groups using the chi-square or Fisher exact test, as appropriate. Associations of $\log_{10}$UtA-PI and $\log_{10}$MAP values with GA at birth in the PE and non-PE groups were analyzed with linear regression models.[14]

Screening performance was accessed by calculating sensitivity, specificity, and the receiver operating characteristic (ROC) curve. Model calibration was investigated by inspecting the calibration plot of observed rates of preterm PE concerning predicted probabilities. Expected and observed cases with PE according to the estimated risk range (≥1 in 10; 1 in 11 to 1 in 50; 1 in 51 to 1 in 100; 1 in 101 to 1 in 150; and <1 in 150) were compared using chi-square tests.

Participants were classified as low risk and high risk according to the current FMF algorithm and stratified according to the use of LDA, which was prescribed on the basis of clinical criteria according to local protocol. The rates of preterm and term PEs were compared among groups.

To obtain accurate estimates of the algorithm performance, as proposed by Wright and Nicolaides,[16] the aspirin treatment effect was accounted for in patients classified as high risk by the FMF algorithm and with aspirin intake. The expected and avoidable number of cases of PE at <37 weeks of gestation that would occur had LDA not been used was simulated. This is because aspirin prophylaxis may have effectively converted women who would otherwise experience PE into false-positive screening results, given that LDA reduces the risk of preterm PE by more than 60% (adjusted odds ratio, 0.38; 95% CI, 0.20 −0.74), as observed in the ASPRE trial.[8]

Sensitivity, specificity, and false-positive rate (FPR) with corresponding 95% CIs from the PE cases simulated above were recalculated and presented in a new scenario based on a risk reduction of 62% noticed in the ASPRE trial.

To avoid potential criticism of bias against the method recommended by local guidelines, we assumed that the effect of 100 mg was similar to that of higher drug doses.[36]

The statistical software Stata (Stata Statistical Software: Release 13; 2013; StataCorp, College Station, TX) was used for data analyses, and *P* values of <.05 were considered statistically significant.

Results

Characteristics of the study population

The FMF first-trimester combined screening test was performed in 2904 singleton pregnancies. Among those, 59 (2.0%) were early lost to follow-up. We excluded 96 cases (3.3%) because of fetal aneuploidies or major fetal abnormalities (57 [1.9%]) or because of miscarriage, termination of pregnancy, or fetal death before 24 weeks of gestation (39 [1.3%]). The final sample included 2749 pregnancies. There were 84 women (3.1%; 95% CI, 2.5%−3.8%) who developed preterm PE, including 31 women (1.1%; 95% CI, 0.8%−1.6%) who developed early PE.

There were 129 cases (4.7%) of late loss to follow-up, which were not included in the denominator for the prevalence estimates cases of term PE (185/2620 [7.1%]; 95% CI, 6.4%−8.4%).

According to the clinical criteria, there were 702 women (25.0%) with 1 major risk factor or 2 moderate risk factors, and 55 preterm PE cases (65.0%) occurred in this high-risk group. LDA use was recorded in 341 women (11.7%) in the overall sample and 321 women (11.7%) in the final study sample, and LDA was prescribed to 267 women (38.0%) with high-risk clinical criteria.

Table 1 presents the maternal characteristics in the studied groups, according to the outcome.

Overall, the median UtA-PI was 1.01 MoM (IQR, 0.81−1.23), and the median MAP was 0.99 MoM (IQR, 0.93−1.06). The 90th percentile of preterm PE risk was 1 in 32.

Linear regression analysis (Figure 1) of biophysical markers showed that UtA-PI and MAP deviate from normal and are inversely related to the GA at delivery in cases with PE but cross the expected 1.0 MoM value line at term.

The screening performance for preterm PE with ROC curve analysis without adjustment for the effect of aspirin is illustrated in Figure 2. Using a cutoff of 1 in 100, there were 709 screen-positive cases (25.8%; 95% CI, 24.2%−27.4%), reaching a detection rate (DR) of 60 in 84 cases (71.4%; 95% CI, 60.5%−80.8%) and FPR of 24.4% (95% CI, 22.7%−26.0%) for the prediction of preterm PE.

The calibration curve in Figure 3 graphically expresses the number of expected and observed cases with a slope value of <1. In contrast, Table 2 compares the number of expected and observed cases in ranges of FMF risk according to the probability reported by the algorithm. In the highest risk range (≥1 in 10), there is agreement between the number of expected cases and those observed. In the other ranges, the expected cases are fewer than those observed. The difference was significant between 1 in 11 and 1 in 50, 1 in 51 and 1 in 100, and <1 in 150.

Tables S1 and S2 present the outcomes observed in subgroups stratified by high risk and low risk with the 2 predefined cutoffs and stratification according to aspirin use. With 1 in 100 as the cutoff, the occurrence of 27 cases of PE in the FMF high-risk subgroup that did not use LDA, it can be inferred that 16 cases of preterm PE would have been avoided if this group had used prophylaxis.

In addition, we observed that, among 225 participants with chronic hypertension, preterm PE occurred only in the group classified as high risk, with 17 cases in the subgroup that used LDA and 5 cases in the subgroup without the use of LDA. There were 39 women with chronic hypertension in the FMF low-risk group, and there was no preterm PE case in this group, irrespective of LDA use.

When evaluating the values of FMF risk and the incidence of preterm PE in the 4 subgroups, there was a gradient of estimated and observed risks, as the subgroups using LDA had the highest rates of the disease compared with the subgroups without LDA use (Tables S1 and S2).

PE rates and test performance measures are displayed in Table S3 according to cutoffs of >1 in 100 and >1 in 150. The observed scenario corresponds to what happened, and the simulated scenario enacts what could have happened regarding the number of cases of preterm PE had LDA not been used by a portion of the sample. Even with only 33 high-risk women using LDA, we estimated that 31 more cases could have occurred if none had used LDA. As a result of adjustment for treatment effect, an improvement in performance measures was observed, with an increase in the DR from 71% to 79% with a cutoff of 1 in 100 and in positive predictive values and a slight decrease in the FPR from 24.4% to 23.5%.

Comment

Principal findings

In this Brazilian validation study of the current FMF competing risks algorithm combining maternal characteristics with biophysical markers, the DRs of preterm PE were similar to those observed in the landmark Screening programme for pre-eclampsia (SPREE) study,[22] despite a higher FPR. The predictive model effectively identified women in whom preterm PE disease will develop.

The performance of the FMF algorithm for predicting preterm PE was adjusted for the treatment effect in women who used LDA. With this adjustment, the sensitivity increased from 81.0% to 86.0% with a cutoff of 1 in 150 and from 71.0% to 79.0% with a cutoff of 1 in 100. Given that the result of the algorithm did not dictate prophylaxis, many women who developed PE were classified as low risk by traditional methods, leading to potentially avoidable cases. Such findings emphasize the importance of using LDA in women identified as high risk using better screening strategies than risk factor−based prediction. Moreover, despite the difference noted between the expected and observed number of cases, there is a positive relationship between higher probabilities and higher prevalence. This reflects the differences

TABLE 1
Comparison of maternal characteristics, medical history, biomarkers, and delivery according to observed outcomes

Characteristics	No PE (n=2351)	PE at <37 wk (n=84)	*P* value	PE at >37 wk (n=185)	*P* value
Birthplace			.309		.003
Southeast	1743 (74.1)	67 (80.0)		154 (83.2)	
Other regions	591 (25.1)	17 (20.0)		28 (15.1)	
Foreigner	8 (0.4)	0 (0)		2 (1.09)	
Maternal age (y)	28 (23–33)	31 (26–37)	<.001[a]	30 (24–35)	.01[a]
Maternal weight (kg)	66.0 (58.0–76.0)	69.0 (61.0–81.0)	.045[a]	73.6 (61.5–86.6)	.000[a]
Maternal height (cm)	161 (156–165)	160 (156–164)	.22	161 (157–165)	.92
CRL (mm)	64.00 (58.00–70.00)	64.00 (58.00–71.00)	.888	62.00 (55.00–69.75)	.21
GA (wk)	12.6 (12.1–13.1)	12.6 (12.1–13.3)	.888	12.6 (12.1–13.0)	.316
Ethnicity			.241		.333
White	905 (38.5)	29 (34.5)		61 (33.0)	
Indigenous	2 (0.1)	0 (0)		0 (0)	
Mixed	979 (41.6)	33 (39.3)		82 (44.3)	
Black	464 (19.7)	22 (26.2)		42 (22.7)	
East Asian	1 (0.04)	0 (0)		0 (0)	
Parity			<.001[a]		<.001[a]
Nulliparous	1200 (51.0)	42 (50.0)		90 (48.0)	
Parous without previous PE	1043 (44.4)	26 (30.9)		70 (38.0)	
Parous with previous PE	108 (4.6)	16 (19.0)		25 (14.0)	
Gestation of last birth (wk)	39.0 (38.0–40.0)	37.1 (34.0–38.6)	<.001[a]	39.0 (38.0–39.7)	.541
Interpregnancy interval (y)	6.1 (3.2–9.8)	7.3 (3.1–9.5)	.541	8.1 (3.7–12.2)	.01[a]
Smoking	114 (4.8)	4 (4.8)	1.000	14(8.0)	.104
Family (maternal) history of PE	167 (7.1)	6 (7.1)	.989	19(10.0)	.112
Assisted conception			.012[a]		.009[a]
Ovulation drugs	8 (0.3)	1 (1.2)		0 (0)	
IVF	0 (0)	1 (1.2)		2 (1.0)	
Chronic hypertension	159 (6.8)	22 (26.2)	<.001[a]	40 (21.6)	<.001[a]
Type 1 diabetes mellitus	50 (2.1)	13 (15.5)	<.001[a]	12 (3.3)	.001[a]
Type 2 diabetes mellitus	34 (145)	11 (13.1)	<.001[a]	7 (3.8)	.001[a]
Diet only	4 (0.2)	1 (1.2)		1 (0.5)	
Insulin	23 (1.0)	8 (9.5)		4 (2.1)	
Metformin	7 (0.3)	2 (2.4)		2 (1.1)	
SLE or APS	1 (0.04)	0 (0)	1.000	0 (0)	1.000
UtA-PI	1.70 (1.35–2.03)	1.87 (1.39–2.31)	.019[a]	1.58 (1.27–2.05)	.069
UtA-PI (MoM)	1.01 (0.81–1.22)	1.13 (0.84–1.35)	.015[a]	0.98 (0.77–1.23)	.254
MAP	85 (79–91)	96 (88–106)	<.001[a]	92 (86–99)	<.001[a]
MAP (MoM)	0.98 (0.93–1.05)	1.07 (1.0–1.17)	<.001[a]	1.03 (0.96–1.09)	<.001[a]
Positive FMF risk >1 in 150	734 (31.2)	68 (80.9)	<.001[a]	108 (58.4)	<.001[a]

(continued)

TABLE 1
Comparison of maternal characteristics, medical history, biomarkers, and delivery according to observed outcomes *(continued)*

Characteristics	No PE (n=2351)	PE at <37 wk (n=84)	*P* value	PE at >37 wk (n=185)	*P* value
Positive FMF risk >1 in 100	533 (22.7)	60 (71.4)	<.001[a]	92 (49.7)	<.001[a]
GA at birth (wk)	39.3 (38.4–40.3)	34.7 (32.9–36.0)	<.001[a]	38.4 (38.0–39.3)	<.001[a]
Birthweight (g)	3255 (2945–3550)	2360 (1597–2995)	<.001[a]	3175 (2780–3455)	.003[a]

Data are presented as number (percentage) or median (interquartile range), unless otherwise indicated. Comparison between studied subgroups were performed using the chi-square test or Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

APS, antiphospholipid syndrome; *CRL*, crown-rump length; *GA*, gestational age; *IVF*, in vitro fertilization; *MAP*, mean arterial pressure; *MoM*, multiple of the median; *PE*, preeclampsia; *UtA-PI*, uterine artery pulsatility index; *SLE*, systemic lupus erythematosus

[a] *P*<.05.

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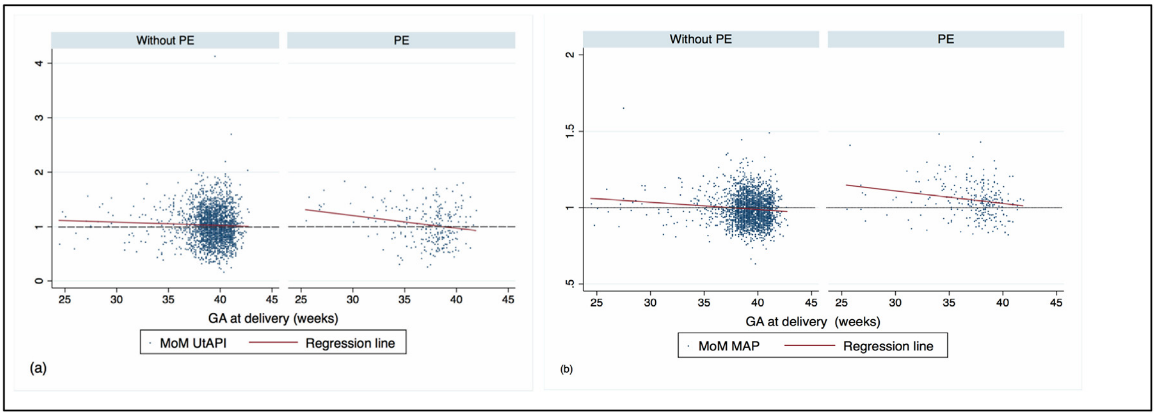
between the local prevalence of preterm PE of 3.1% and the 0.8% of the reference United Kingdom population.[22]

Results in the context of what is known

Preterm and term PE incidences of 3.1% and 7.1%, respectively, in this sample are higher than all PE rates observed in the internal and external validations of PE predictive models.[21–28] The number of participants with chronic hypertension was higher, in both absolute and relative values, than that presented in the 2 arms of the ASPRE trial,[8] reinforcing chronic hypertension as the independent factor with the most significant effect on the occurrence of PE. This sample had a higher proportion of Black women contributing 26% and 23% of preterm and term PE cases, respectively. However, there was no significant difference in the association of race and color with preterm PE, which contradicts the SPREE study in which 16% of pregnant women of African Caribbean origin constituted 37% and 30% of preterm and term PE cases, respectively.[22] Another Brazilian study did not identify a greater risk of PE in women classified as Black.[26] Unsurprisingly, MoM values of UtA-PI and MAP discriminate between normal and preterm PE cases. According to expectations, those medians were nearly 1.0 MoM, in contrast with other studies[37] where UtA-PI was lower than expected, which was previously described as a problem.[37,38]

Effective treatment, known as the "treatment paradox," underestimates screening performance by converting true-positive screening results into false-positive screening results, as aspirin may prevent many cases of preterm PE.[16,39] The effect of aspirin was arithmetically considered,[16] in contrast with other approaches using Markov chain Monte Carlo simulations.[21,27] This adjustment

FIGURE 1
Scatter diagram and regression lines of UtA-PI and MAP distributions according to GA (weeks) at delivery



A, UtA-PI according to GA. **B,** MAP distributions according to GA. The β indicates the slope of the sample regression line in (**A**) without PE (−0.0026; *P*=.089) and with PE (−0.009; *P*=.006*) and in (B) without PE (−0.00193; *P*<.001) and with PE (−0.00325; *P*=.001)

GA, gestational age; *MAP*, mean arterial pressure; *MoM*, multiple of the median; *PE*, preeclampsia; *UtA-PI*, uterine artery pulsatility index.

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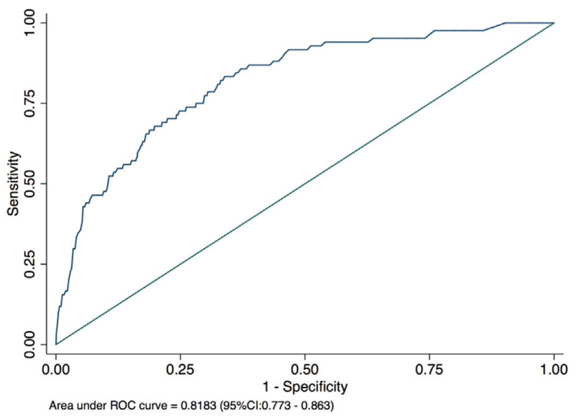
FIGURE 2
ROC curve for the prediction of preterm preeclampsia



ROC, receiver operating characteristic.

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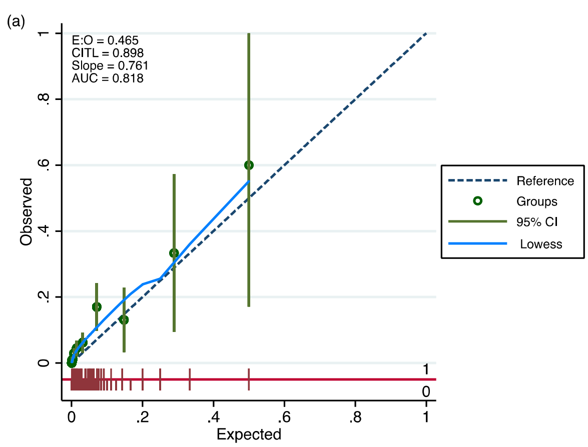
FIGURE 3
Calibration plot comparing observed and predicted risks of preterm PE in all samples



AUC, area under the curve; *CI*, confidence interval; *CTIL*, calibration in the large; *FMF*, Fetal Medicine Foundation; *PE*, preeclampsia.

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resulted in improved performance consistent with studies that previously validated the FMF algorithm.[21–28]

Despite the high rate of PE, even in the group with prophylactic LDA use, we verified in a previous study using propensity score analysis that LDA did not have a causal association with the observed higher rates of preterm PE, suggesting confounding bias by indication.[17]

Clinical and research implications

Despite the expected probabilities of preterm PE being lower than those observed, the ability to identify women who developed the disease was well documented. The adjustment for the treatment effect enabled quantifying the number of cases avoided and operationalized dialogues with managers to update, multiply, and implement PE screening and targeted prophylaxis protocols in this and other centers. Considering the population's characteristics and the study's findings, we have since increased the dose from 100 to 150 mg/day as another strategy to mitigate PE rates in the assisted population, in line with recent evidence.[8,40] This approach provides a window to evaluate the effects on PE rates in a time series analysis.

About 60 years ago, because of the little progress in the pathophysiology, interpretation, treatment, and prevention of the so-called toxemias of pregnancy, the "immediate and remote prognoses of PE or eclampsia disturbed and kept the competent people apprehensive."[42] To date, in the post-ASPRE era, as we are competent in the execution, interpretation, and application of a

TABLE 2
Number of expected and observed cases by Fetal Medicine Foundation risk range

Variable	Estimated risk (range)	Mean risk	Total cases	Expected number	Observed number	Observed risk	*P* value
High risk	≥1 in 10	1 in 5	75	14.5	14	1 in 5	>.999
	1 in 11 to 1 in 50	1 in 24	345	14.3	33	1 in 11	.004[a]
	1 in 51 to 1 in 100	1 in 72	293	4.0	13	1 in 23	.026[a]
	1 in 101 to 1 in 150	1 in 122	232	1.9	8	1 in 29	.055
Low risk	<1 in 150	1 in 435	1804	5.0	16	1 in 112	.007[a]

[a] *P*<.05.

Rezende. Validation of preterm preeclampsia screening in Brazil. Am J Obstet Gynecol Glob Rep 2024.

feasible, valid, patient-specific screening method and the availability of effective prophylaxis, doing nothing is no longer an option.

Strengths and limitations

The greatest strength of this study is that the FMF algorithm for PE prediction in the first trimester of pregnancy effectively identifies high-risk pregnancies, allowing for adequate targeted prophylaxis. The Maternity School of the Federal University of Rio de Janeiro hosted the pioneering initiative in a public hospital of prediction and prevention routines for all women attending first-trimester ultrasound in Brazil. It was duly published in its clinical protocols,[34,40] which serve as a reference for other regional and national centers. To the best of our knowledge, this is the largest Brazilian validation of the current FMF algorithm for predicting preterm PE and the only one accounting for the effect of treatment locally when assessing screening performance. We consecutively included all pregnancies undergoing routine first-trimester screening over 8 years, reflecting real-world use of a predictive algorithm.

We recognize that one of the limitations of the study was that it was unicentric. Nevertheless, it included pregnant women from all regions of Brazil. There was no specific adjustment of the biomarkers (MAP and UtA-PI MoM values) for the characteristics of the Brazilian population, but we used the algorithm as available. The development and internal validation of a predictive PE model in a prospective and contemporary cohort, with pregnant women assisted in Brazil, could correct the expected biomarkers (MoM values) to adjust, customize, and calibrate the model for the Brazilian population. However, in the post-ASPRE era, the potential use of aspirin by patients classified as high risk from such a cohort makes modeling difficult. There is no reason to postpone the implementation of first-trimester PE screening, followed by aspirin prophylaxis in high-risk cases, as this would delay the necessary reduction in the incidence and complications of PE. The full performance of the FMF algorithm could be limited in low- and middle-income settings, when biochemical markers could not be included as universal screening, because of budget restrictions. Although we account for the treatment effect, it is necessary to consider that the sample may not have achieved the mean result of 62% risk reduction for preterm PE in cases exposed to aspirin. A high prevalence of PE was observed in the subgroups using aspirin because of confounding by indication.[17] The DR of the algorithm in predicting preterm PE was as high as that of the landmark SPREE study,[22] in line with a high screen-positive rate. This is inevitable in regions with high disease prevalence, using Bayesian models, where the predicted risks depend largely on the previous risk based on maternal characteristics and history. Moreover, we found some features that have been seen to be associated with a lesser effect of LDA in the prevention of preterm PE,[41] such as (1) high prevalence of chronic hypertension, (2) mean maternal weight of 76 kg, (3) adherence to aspirin not directly measured, (4) dose of 100 mg instead of 150 mg, and (5) indication based on clinical criteria. These reflections do not compromise the validity of the results and guided us to modify our clinical protocols.[40]

Conclusions

In a high PE prevalence scenario, the FMF algorithm effectively identifies women more likely to develop preterm PE. Not accounting for the effect of aspirin underestimates the screening performance. ■

CRediT authorship contribution statement

Karina Bilda de Castro Rezende: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Rita G. Bornia:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis. **Daniel L. Rolnik:** Writing – review & editing, Writing – original draft, Visualization, Methodology. **Joffre Amim:** Writing – review & editing, Writing – original draft, Visualization, Supervision. **Luiza P. Ladeira:** Writing – review & editing, Writing – original draft, Visualization, Investigation. **Valentina M.G. Teixeira:** Writing – review & editing, Writing – original draft, Visualization, Investigation. **Antonio Jose L.A. da Cunha:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization. ■

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xagr.2024.100346.

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