Validation of a preeclampsia early screening test in a Mexican population

Héctor Oviedo-Cruz,^{1*} Erika R. Carrasco-Blancas¹ and Marco A. Cortes-Martínez²

¹Department of Maternal-Fetal Medicine, Medical Center for Specialized Fetal Care, Hospital Español de México; ²Department of Biochemistry and Quality, Laboratorio CEMAFE S.A. de C.V. Mexico City, Mexico

Abstract

Background: No preeclampsia screening test has been validated in our country. **Objective:** To assess the fit and performance of the FMF 4.0 Bayesian algorithm in a Mexican population. **Method:** Cohort study in singleton pregnancies, according to the competing risks model for preeclampsia. A priori risk was calculated based on medical history. Mean blood pressure (MBP), uterine artery mean pulsatility index (UtAmPI) and pregnancy-associated plasma protein A (PAPP-A) were measured at 11-14 weeks of gestation using standardized methodology. The value of each marker was transformed into multiples of the median (MoM) by the original_a algorithm and by population-correction_b. Multivariate normal distribution and Bayes theorem were applied to obtain post-test probabilities. **Results:** There was 5.0% (40/807) of preeclampsia. Distributions in women without preeclampsia were MBP = 0.927_a vs. 0.991_b, UtAmPI = 0.895_a vs. 1.030_b and PAPP-A = 0.815_a vs. 0.963_b ($p < 0.001$). The AUC was 0.821_a vs. 0.823_b. For a detection rate of 69 %, cutoff points were 1 in 240_a and 1 in 120_b, with false positive rates of 31 %_a and 29 %_b. **Conclusions:** The model has to be adjusted to the target population.

KEY WORDS: Preeclampsia. Maternal serum screening tests. Doppler ultrasonography. Blood pressure. Prenatal care. Mexico.

Validación de un tamiz precoz de preeclampsia en una población mexicana

Resumen

Antecedentes: Ninguna prueba de tamiz de preeclampsia ha sido validada en nuestro país. **Objetivo:** Evaluar el ajuste y rendimiento del algoritmo bayesiano FMF 4.0 en una población mexicana. **Método:** Estudio de cohorte en embarazos de feto único, según el modelo de riesgos en competencia para preeclampsia. El riesgo a priori se calculó por historia clínica. La presión arterial media (PAM), el índice de pulsatilidad medio de la arteria uterina (IPmAUt) y la proteína plasmática A asociada al embarazo (PAPP-A) se midieron a las 11-14 semanas de gestación con metodología estandarizada. El valor de cada marcador se transformó en múltiplos de la mediana (MoM) por el algoritmo original_a y el corregido_b a la población. Se aplicaron la distribución normal multivariante y el teorema de Bayes para las probabilidades posprueba. **Resultados:** Hubo un 5.0% (40/807) de preeclampsia. Las distribuciones sin preeclampsia fueron PAM 0.927_a vs. 0.991_b, UtAmPI 0.895_a vs. 1.030_b y PAPP-A 0.815_a vs. 0.963_b ($p < 0.001$). El área bajo la curva fue 0.821_a vs. 0.823_b. Para una detección del 69%, los puntos de corte fueron 1 en 240_a y 1 en 120_b, a falsos positivos del 31%_a y 29%_b. **Conclusiones:** El modelo debe ajustarse a la población diana.

PALABRAS CLAVE: Preeclampsia. Pruebas de tamiz en suero materno. Ecografía Doppler. Presión arterial. Control prenatal. México.

Correspondence:

*Héctor Oviedo-Cruz

E-mail: HectorOC@cemafe.org.mx

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Introduction

Preeclampsia affects 2-8% of pregnancies in the world and is the main cause of both maternal and perinatal morbidity and mortality.¹ In Mexico, it is a cause of maternal death despite regular prenatal care.² Low doses of aspirin started at 16 weeks of gestation or earlier are an efficacious prophylaxis in high-risk pregnancies.³ Given that coverage by medical history is low,⁴ multiple marker tests were developed,⁵⁻⁷ with better performance than clinical practice guidelines.⁸ The effectiveness of prescribing prophylactic aspirin based on preeclampsia early screening has recently been proven,⁹ and even adopted by the International Federation of Gynecology and Obstetrics (FIGO).¹⁰

The performance of these tests has been suboptimal in populations other than those that originated the model,¹¹ except when the markers have been corrected for the target population.¹²

One of these algorithms, widely distributed because it is free-of-charge, is that of the UK London Fetal Medicine Foundation (FMF).^{5,6,13} Its most recent version, FMF 4.0 (2018),¹⁴ was released in March 2019, and there are at least 277 registered users in Mexico (<https://fetalmedicine.org/lists/map/certified/Ut>), but no Mexican population was included for its creation and neither has any validation been documented on it.

The purpose of this study is to evaluate the performance of the FMF 4.0¹⁴ algorithm in a Mexican population with and without correction for markers.

Materials and methods

A study was conducted in a cohort of perinatal studies.¹⁵ Recruitment was from January 2012 to December 2019, and approval by the scientific and bioethical committees of the study site was obtained, adhering to the Declaration of Helsinki of the World Medical Association for medical research involving human subjects.

The inclusion criteria were pregnancy with a single fetus with vitality and crown-rump length (CRL) between 45 and 84 mm (11^{+1} to 14^{+1} weeks of gestation), with complete data for the study and with the birth of a phenotypically normal newborn, alive or dead, with at least 24 weeks of gestation or more having been recorded. Pregnancies with chromosomal and non-chromosomal defects, as well as those with

spontaneous or induced abortion before 24 weeks were excluded.

Medical history

It was obtained by self-administered questionnaire, verified by interrogation and operationally coded according to the FMF.¹⁶

Maternal weight and height were obtained with standard analogue calibrated clinical scale and stadiometer.

Gestational age was established by CRL on ultrasonography according to the Robinson method corrected by Loughna et al.¹⁷

Mean blood pressure measurement

Standardized by FMF¹⁸ and adopted by FIGO,¹⁰ consistent with current international recommendations,¹⁹ it required the use of the single medium cuff provided with each device; those of other sizes are not available in the local market and brachial bias correction for maternal weight has been assumed.²⁰

The automatic electronic devices were of the Omron® brand (Japan), model HEM-7121, which meets the Food and Drug Administration (FDA) 510(k) requirement. The devices were periodically calibrated. The personnel in charge of the measurements was constantly trained and supervised.

Uterine artery mean pulsatility index measurement

Voluson (GE Healthcare Technologies®) ultrasound machines, models E10, E6, S8, 730 Expert, Logiq P5 and Logiq 3 Expert were used; all with multi-frequency transabdominal and transvaginal transducers, under constant preventive maintenance. The exams were carried out by two certified and periodically audited operators (fetalmedicine.org) following standardized methodology.²¹

Pregnancy-associated plasma protein A measurement

Automated, calibrated and controlled analyzers, based on ultrasensitive and FMF-approved immunoassays, were used, namely: BRAHMS Kryptor compact PLUS (ThermoFisher®) by time-resolved amplified cryptate emission, Cobas e411 (Roche®) by

electrochemiluminescence, and DELFIAxpress (PerkinElmer®) by time-resolved amplified europium emission.

The samples were peripheral venous blood (brachial) serum, with analyte stability²² and temporal validity²³ being ensured.

Outcomes of interest

The result of each pregnancy was obtained from the birth, death or delivery certificate, clinical record or patient anamnesis when she returned to the center for a new pregnancy. The records of women with pregnancy-associated hypertension were reviewed to classify preeclampsia or non-preeclampsia according to the International Society for the Study of Hypertension in Pregnancy (ISSHP).²⁴

Statistical analysis

The FMF 4.0¹⁴ algorithm was applied, based on the competing risks model²⁵ for preeclampsia. A priori risk was established based on medical history.¹⁶ The values of each marker were standardized in multiples of the median (MoM) both by the original algorithm¹⁴ (MoM_a) and by specific population medians (MoM_b); these data are in press (10.6084/m9.figshare.12268328, 10.6084/m9.figshare.12991322), except for PAPP-A.^{23,26} Expected MoMs configuration¹³ was centered at < 37 weeks, and the multivariate normal probability density functions of each marker and its combinations (scenarios) were calculated based on the $\log_{10}$ (MoM) of each model and the covariance matrices for each outcome. Likelihood ratios by scenario were obtained from the corresponding probability densities and applied to the a priori risk in order for Bayesian post-test probability to be obtained.

MoM distribution in women without preeclampsia was audited according to FMF criteria (<https://fetal-medicine.org/research/audit/>). MoM regression lines by weeks of gestation to preeclampsia-associated delivery were compared with the hypothetical model^{13,14} using Student's t-test for coefficients.²⁷

Post-test performance by scenarios of each model was evaluated using ROC curves.²⁸

As a pilot test, the performance of the American College of Obstetricians and Gynecologists (ACOG)²⁹ and the UK National Institute for Excellence in Health and Care (NICE)³⁰ guidelines was calculated and plotted.

Representativeness of post-test probabilities of each model was explored by inspection of their calibration curves.³¹

Normality, linearity and homoscedasticity assumptions were tested in order to decide whether to apply parametric or non-parametric statistics or to transform the variables for analysis.

The level of significance was $\alpha = 0.05$ for statistical tests (degree of significance [p]).

Sample size was based on both a statistical power³² for the minimal area reported under the ROC curve: 0.733¹⁴ (596 observations), and a frequency of 5.4% for preeclampsia in Mexico City,³³ and a sensitivity of 65.6% for the test in a population other than that which originated it;¹² $n = 741$ was calculated³² with 40 preeclampsia incidences.

The database was created using the Astraia® (Germany) and Excel® (USA) programs (available upon reasonable request to the corresponding author). Statistical analysis was carried out using the Excel® (USA) and MATLAB® (USA) programs with valid licenses; the programming codes are the property of the laboratory.

Results

The incidence of preeclampsia was 40/807 (5.0%; 95% confidence interval [CI]: 3.6-6.3). There were 29/40 (73%) births < 37 weeks due to preeclampsia and 118/767 (15%) without preeclampsia ($p < 0.001$, Fisher's exact test). The characteristics of the sample are shown in table 1.

The distribution of markers in cases without preeclampsia is illustrated in figure 1. Central values of the original model were located beyond ± 0.2 standard deviations (SD) of hypothetical values:

$$MBP = 0.927 MoM_a = -0.9 SD$$

$$mPI = 0.895 MoM_a = -0.4 SD$$

$$PAPP-A = 0.815 MoM_a = 0.4 DE$$

Central values of the corrected_b model for local population were within an optimal ± 0.1 SD of the hypothetical model:

$$MBP = 0.991 MoM_b = -0.1 SD$$

$$mPI = 1.030 MoM_b = +0.1 SD$$

$$PAPP-A = 0.963 MoM_b = -0.1 SD.$$

MoMs distribution by gestational age at delivery due to preeclampsia is depicted in figure 2 with the hypothetical regression lines and those of the sample for both the original_a and corrected_b models. The MBP line was parallel ($p = 0.226$) but significantly lower than the hypothetical line in the

Table 1. Maternal and gestational characteristics in the study groups

Variables	No preeclampsia	Preeclampsia	p-value
Maternal age (years) [†]	33.0 (30.0; 35.9)	34.4 (31.0; 39.0)	0.032*
Maternal weight (kg) [†]	61.4 (55.4; 68.6)	63.6 (58.8; 74.2)	0.060
Maternal height (cm) [†]	160.0 (156.0; 164.0)	161.5 (159.0; 164.6)	0.101
Body mass index [†]	23.9 (21.8; 26.8)	24.0 (23.2; 39.0)	0.134
Gestational age (weeks) [†]	12.7 (12.3; 13.3)	12.7 (12.1; 13.2)	0.568
Ethnicity [‡]			
Caucasian/Hispanic	674 (87.9)	34 (85.0)	0.619
Afro-Caribbean	3 (0.4)	0 (0.0)	1.000
South Asian	2 (0.3)	0 (0.0)	1.000
East Asian	16 (2.1)	0 (0.0)	1.000
Other, mixed	72 (9.4)	6 (15.0)	0.265
Conception [‡]			
Spontaneous	686 (89.4)	31 (77.5)	0.034*
<i>In vitro</i> fertilization	46 (6.0)	9 (22.5)	0.001*
Ovulation inducer drugs	35 (4.6)	0 (0.0)	0.410
Smoking habit [‡]			
Smoker	16 (2.1)	1 (2.5)	0.582
Former smoker	83 (10.8)	4 (10.0)	1.000
Non-smoker	668 (87.1)	35 (87.5)	1.000
Parity [‡]			
Nulliparous	562 (73.3)	32 (80.0)	0.462
Parity without PE	195 (25.4)	1 (2.5)	< 0.001*
Parity with previous PE	10 (1.3)	7 (17.5)	< 0.001*
Medical history ^{‡,§}			
Chronic hypertension	6 (0.8)	2 (5.0)	0.056
Systemic lupus erythematosus	1 (0.1)	0 (0.0)	1.000
Anti-phospholipid syndrome	6 (0.8)	0 (0.0)	
Family history of PE [‡]	9 (1.2)	4 (10.0)	0.003*

Comparisons between study groups were made using the chi-square test or Fisher's exact test for categorical variables and Mann-Whitney's U-test for continuous variables.

*Statistically significant.

[†]Median (IQR).

[‡]n (%).

[§]There were no pregnant women with diabetes mellitus in any of the study groups.

PE: preeclampsia.

Figure 1. Distribution of multiples of the median (MoM) of the markers transformed into base 10 log within the group without preeclampsia ($n = 767$); in box-and-whiskers plots, the original model¹⁴ and local population-corrected model (white box); all pairs were significantly different ($p < 0.001$, Student's *t*-test).

PI: pulsatility index; PAPP-A: pregnancy-associated plasma protein A.

Figure 2. Distribution of multiples of the median (MoM) by gestational age at birth due to preeclampsia (o). Regression line of the sample (---) vs. hypothetical line¹³ (···). The horizontal line (—) refers to 1.0 MoM. The original MoM model in upper panel (A, B and C); the population-co-corrected model in lower panel (D, E and F).

PAPP-A: pregnancy-associated plasma protein A.

original_a model ($p = 0.001$); in contrast, the corrected_b model line was not significantly different from the hypothetical line (slope $p = 0.406$ and intersection $p = 0.744$). Uterine arteries mean PI line in the original_a model showed a steeper slope that was statistically marginal ($p = 0.062$); but not its intersection ($p = 0.318$). In the uterine arteries mean PI corrected_b model, no significant difference was found (slope $p = 0.188$ and intersection $p = 0.617$). PAPP-A lines in both models were significantly different in terms of slope and intersection ($p < 0.001$).

The ROC curves by marker and their combinations are illustrated in figure 3 both for preeclampsia <

37 weeks and for global preeclampsia; each model separately with the ACOG²⁹ and NICE³⁰ criteria comparative pilot test. Relevant ROC curves cutoff points are shown in table 2.

Total combined test calibration lines, for each model separately, are illustrated in figure 4.

Discussion

Until now, there was no information on the performance of the FMF 4.0¹⁴ algorithm in our country. Analysis by markers and their combinations is particularly valuable, given that their availability varies in our institutions.

Figure 3. ROC curves for preeclampsia < 37 weeks (left) and global preeclampsia (right), original model¹⁴ and model corrected for local Mexican population (bottom). MBP: mean blood pressure; PI: uterine arteries mean pulsatility index; PAPP-A: pregnancy-associated plasma protein A; ACOG: American College of Obstetricians and Gynecologists;²⁹ NICE: UK National Institute for Health and Care Excellence.³⁰

Another key contribution of our study was to prove that the original_a FMF-2018¹⁴ medians model of the algorithm under study is not valid for our population. The authors advise against the use of this calculator in Mexico without correction for population, unless it is temporary (see below). Correction for biochemical markers is possible in first-trimester aneuploidy screening computer packages,²⁶ but not for MBP or uterine arteries mean PI. We have chosen to generate our application with the corrected_b medians (see above); its external validity will be limited by the standardization of processes and regional differences in the country.

The MBP corrected_b model was the one that showed the best reproducibility with regard to what was expected¹³ and to what has been reported by others.¹²

Given this validity demonstration and the simplicity of the method, this line of research should be expanded.

The corrected_b PAPP-A model had a steeper-than-expected slope towards very early preeclampsia;¹³ given that the correction was with a different methodology than that for MBP, investigating the development of a local model is justified.

The FMF 4.0¹⁴ version does not have a predetermined cutoff point, leaving this decision to the end user. A useful contribution of our study was the ROC characteristic, which allows selecting the cutoff point by scenario and according to the goals in centers similar to ours. Based on the ROC table, it can even be proposed, as a temporary solution to the lack of

Table 2. Performance of the markers for preeclampsia < 37 weeks and global preeclampsia and their combinations according to the original model¹⁴ and local population-corrected model

Preeclampsia < 37 weeks		Detection	False +				
ACOG		62 (46-78)	45 (28-61)				
NICE		28 (13-42)	14 (3-26)				
Screening method	Area under the curve	Cutoff point					
		1 in 60		1 in 120		1 in 240	
		Detection	False +	Detection	False +	Detection	False +
History (a priori)	0.671 (0.570-0.772)	34 (19-50)	11 (6-16)	52 (35-68)	28 (21-35)	90 (80-100)	74 (67-81)
Original model							
History +							
+ Mean blood pressure	0.765 (0.680-0.850)	28 (13-42)	8 (3-12)	48 (32-65)	17 (11-23)	66 (50-81)	30 (22-37)
+ Uterine arteries mean PI	0.672 (0.571-0.773)	28 (13-42)	9 (5-14)	59 (42-75)	31 (23-38)	72 (58-87)	52 (44-60)
+ PAPP-A	0.659 (0.556-0.762)	38 (22-54)	19 (13-26)	62 (46-78)	40 (32-48)	86 (75-98)	71 (64-79)
+ Mean blood pressure + uterine arteries mean PI	0.793 (0.714-0.872)	24 (10-38)	6 (2-10)	38 (22-54)	13 (7-18)	72 (58-87)	27 (20-34)
+ Uterine arteries mean PI + PAPP-A	0.651 (0.547-0.755)	31 (16-46)	17 (11-23)	62 (46-78)	35 (27-43)	76 (62-90)	58 (50-67)
+ Mean blood pressure + PAPP-A	0.746 (0.658-0.834)	34 (19-50)	14 (8-19)	52 (35-68)	25 (18-32)	76 (62-90)	35 (27-43)
+ Mean blood pressure + uterine arteries mean PI + PAPP-A	0.755 (0.668-0.842)	28 (13-42)	8 (4-13)	52 (35-68)	20 (14-27)	69 (54-84)	31 (24-39)
Population-corrected model							
History +							
+ Mean blood pressure	0.765 (0.680-0.850)	45 (28-61)	15 (9-21)	59 (42-75)	25 (18-33)	90 (80-100)	47 (39-56)
+ Uterine arteries mean PI	0.660 (0.557-0.763)	34 (19-50)	14 (9-20)	62 (46-78)	38 (30-46)	76 (62-90)	60 (52-68)
+ PAPP-A	0.695 (0.598-0.792)	38 (22-54)	10 (5-15)	59 (42-75)	33 (25-41)	86 (75-98)	68 (60-75)
+ Mean blood pressure + uterine arteries mean PI	0.784 (0.704-0.864)	45 (28-61)	14 (9-20)	72 (58-87)	31 (23-38)	86 (75-98)	46 (38-54)
+ Uterine arteries mean PI + PAPP-A	0.676 (0.576-0.776)	38 (22-54)	16 (10-22)	69 (54-84)	37 (29-45)	79 (66-93)	59 (51-67)
+ Mean blood pressure + PAPP-A	0.777 (0.695-0.859)	48 (32-65)	18 (12-24)	66 (50-81)	26 (19-33)	93 (85-100)	49 (41-57)
+ Mean blood pressure + uterine arteries mean PI + PAPP-A	0.785 (0.705-0.865)	52 (35-68)	18 (12-24)	69 (54-84)	29 (21-36)	93 (85-100)	43 (35-51)
Global preeclampsia		Detection	False +				
ACOG		60 (44-76)	40 (24-56)				
NICE		25 (11-39)	9 (0-19)				
Screening method	Area under the curve	Cutoff point					
		1 in 60		1 in 120		1 in 240	
		Detection	False +	Detection	False +	Detection	False +
History (a priori)	0.726 (0.659-0.793)	35 (22-48)	5 (4-6)	53 (38-67)	21 (18-23)	93 (85-100)	69 (67-72)
Original model							
History +							
+ Mean blood pressure	0.801 (0.747-0.855)	30 (17-43)	4 (3-5)	50 (36-64)	9 (8-11)	65 (52-78)	23 (20-26)
+ Uterine arteries mean PI	0.737 (0.671-0.803)	33 (19-46)	5 (4-7)	58 (44-71)	17 (15-19)	73 (60-85)	46 (43-49)
+ PAPP-A	0.732 (0.666-0.798)	40 (26-54)	9 (7-11)	60 (46-74)	27 (24-30)	85 (75-95)	64 (61-67)
+ Mean blood pressure + uterine arteries mean PI	0.887 (0.852-0.922)	20 (9-31)	3 (2-4)	43 (29-56)	8 (6-10)	70 (57-83)	17 (15-19)
+ Uterine arteries mean PI + PAPP-A	0.742 (0.677-0.807)	33 (19-46)	8 (6-10)	63 (49-76)	22 (19-24)	78 (66-89)	50 (46-53)
+ Mean blood pressure + PAPP-A	0.799 (0.745-0.853)	35 (22-48)	5 (4-7)	50 (36-64)	13 (11-15)	73 (60-85)	27 (24-30)
+ Mean blood pressure + uterine arteries mean PI + PAPP-A	0.821 (0.771-0.871)	23 (11-34)	4 (3-5)	55 (41-69)	10 (8-12)	68 (54-81)	20 (18-23)

(Continued)

Table 2. Performance of the markers for preeclampsia < 37 weeks and global preeclampsia and their combinations according to the original model¹⁴ and local population-corrected model (*Continued*)

Population-corrected model							
History +							
+ Mean blood pressure	0.808 (0.756-0.860)	48 (33-62)	8 (7-10)	60 (46-74)	20 (18-23)	88 (78-97)	43 (40-46)
+ Uterine arteries mean PI	0.728 (0.661-0.795)	38 (24-51)	8 (6-9)	60 (46-74)	26 (23-29)	80 (69-91)	57 (54-61)
+ PAPP-A	0.747 (0.683-0.822)	38 (24-51)	5 (4-7)	58 (44-71)	20 (18-23)	83 (72-93)	61 (58-64)
+ Mean blood pressure + uterine arteries mean PI	0.812 (0.760-0.864)	45 (31-59)	9 (8-11)	68 (54-81)	21 (18-24)	85 (75-95)	40 (37-43)
+ Uterine arteries mean PI + PAPP-A	0.747 (0.683-0.811)	40 (26-54)	8 (7-10)	68 (54-81)	25 (23-28)	80 (69-91)	54 (51-57)
+ Mean blood pressure + PAPP-A	0.825 (0.776-0.874)	45 (31-59)	9 (7-11)	65 (52-78)	20 (17-22)	90 (82-98)	42 (38-45)
+ Mean blood pressure + uterine arteries mean PI + PAPP-A	0.823 (0.752-0.894)	53 (38-67)	10 (8-12)	65 (52-78)	20 (17-22)	90 (82-98)	39 (36-43)

ACOG: American College of Obstetricians and Gynecologists; NICE: UK National Institute for Health and Care Excellence; PI: pulsatility index; PAPP-A: pregnancy-associated plasma protein A.

Figure 4. Calibration curves for preeclampsia < 37 weeks combined screening. Calibration lines (---) for preeclampsia screening by history + mean blood pressure + uterine arteries mean pulsatility index + pregnancy-associated plasma protein A: original model¹⁴ (A) and corrected model (B) for multiples of the median (MoM) of Mexican local population (right). The diagonal line indicates the ideal scenario.

correction for population, a higher cutoff point for each scenario.

The comparative pilot test with ACOG²⁹ and NICE³⁰ guidelines vs. multivariate Bayesian model was similar to findings reported by others, with lower performance than the FMF¹¹ algorithm, but specific research on the subjects is required.

Sample characteristics, false positive rates and the calibration curve are consistent with sample bias for high-risk pregnancies. The study design was based on the competing risks model;^{25,34} therefore, preeclampsia-free births were not necessarily normal, had various medical or obstetric

indications, with up to 15% of prematurity observed in this sample of a larger cohort. This explains higher false positive rates for the expected detection rates of the test;¹²⁻¹⁴ thus, population composition should also be considered for selecting practical cutoff points.

An essential achievement of our study was the programming code that was specifically created, as a result of the theoretical and practical mastery of the algorithm. With this and the follow-up of the cohort, generating a local competing risks model for preeclampsia and other adverse perinatal outcomes will be possible.

Conclusions

The use of the FMF 4.0¹⁴ calculator in Mexico without correction for target population markers is advised against. Coding an application with local medians and, better yet, developing an own competing risks model for preeclampsia is recommended.

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Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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