OBSTETRICS

Prospective evaluation of screening performance of first-trimester prediction models for preterm preeclampsia in an Asian population

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BACKGROUND: The administration of aspirin <16 weeks gestation to women who are at high risk for preeclampsia has been shown to reduce the rate of preterm preeclampsia by 65%. The traditional approach to identify such women who are at risk is based on risk factors from maternal characteristics, obstetrics, and medical history as recommended by the American College of Obstetricians and Gynecologists and the National Institute for Health and Care Excellence. An alternative approach to screening for preeclampsia has been developed by the Fetal Medicine Foundation. This approach allows the estimation of patient-specific risks of preeclampsia that requires delivery before a specified gestational age with the use of Bayes theorem-based model.

OBJECTIVE: The purpose of this study was to examine the diagnostic accuracy of the Fetal Medicine Foundation Bayes theorem-based model, the American College of Obstetricians and Gynecologists, and the National Institute for Health and Care Excellence recommendations for the prediction of preterm preeclampsia at $11-13^{+6}$ weeks gestation in a large Asian population

STUDY DESIGN: This was a prospective, nonintervention, multicenter study in 10,935 singleton pregnancies at $11-13^{+6}$ weeks gestation in 11 recruiting centers across 7 regions in Asia between December 2016 and June 2018. Maternal characteristics and medical, obstetric, and drug history were recorded. Mean arterial pressure and uterine artery pulsatility indices were measured according to standardized protocols. Maternal serum placental growth factor concentrations were measured by automated analyzers. The measured values of mean arterial pressure, uterine artery pulsatility index, and placental growth factor were converted into multiples of the median. The Fetal Medicine Foundation Bayes theorem-based model was used for the calculation of patient-specific risk of preeclampsia at <37 weeks gestation (preterm preeclampsia) and at any gestation (all preeclampsia) in each participant. The performance of screening for preterm preeclampsia and all preeclampsia by a combination of maternal factors, mean arterial pressure, uterine artery pulsatility index, and placental growth factor (triple test) was evaluated with the adjustment of aspirin use. We examined the predictive performance of the model by the use of receiver operating characteristic curve and calibration by measurements of calibration slope and calibration in the large. The detection rate of screening by the Fetal Medicine Foundation Bayes theorem-based model was compared with the model that was derived from the application of American College of Obstetricians and Gynecologists and National Institute for Health and Care Excellence recommendations.

RESULTS: There were 224 women (2.05%) who experienced preeclampsia, which included 73 cases (0.67%) of preterm preeclampsia. In pregnancies with preterm preeclampsia, the mean multiples of the median values of mean arterial pressure and uterine artery pulsatility index were significantly higher (mean arterial pressure, 1.099 vs 1.008 [$P<.001$]; uterine artery pulsatility index, 1.188 vs 1.063[$P=.006$]), and the mean placental growth factor multiples of the median was significantly lower (0.760 vs 1.100 [$P<.001$]) than in women without preeclampsia. The Fetal Medicine Foundation triple test achieved detection rates of 48.2%, 64.0%, 71.8%, and 75.8% at 5%, 10%, 15%, and 20% fixed false-positive rates, respectively, for the prediction of preterm preeclampsia. These were comparable with those of previously published data from the Fetal Medicine Foundation study. Screening that used the American College of Obstetricians and Gynecologists recommendations achieved detection rate of 54.6% at 20.4% false-positive rate. The detection rate with the use of National Institute for Health and Care Excellence guideline was 26.3% at 5.5% false-positive rate.

CONCLUSION: Based on a large number of women, this study has demonstrated that the Fetal Medicine Foundation Bayes theorem-based model is effective in the prediction of preterm preeclampsia in an Asian population and that this method of screening is superior to the approach recommended by American College of Obstetricians and Gynecologists and the National Institute for Health and Care Excellence . We have also shown that the Fetal Medicine Foundation prediction model can be implemented as part of routine prenatal care through the use of the existing infrastructure of routine prenatal care.

Key words: American College of Obstetricians and Gynecologists (ACOG), Asian population, aspirin, Bayes theorem, biomarker, detection rate, false-positive rate, Fetal Medicine Foundation (FMF), hypertension, MAP, multiples of the median (MoM), National Institute for Health and Care Excellence (NICE), placental growth factor (PlGF), prediction model, preeclampsia, pulsatility index, screening, UtA-PI, validation

Preeclampsia, which complicates 2–5% of pregnancies, is a major cause of maternal and perinatal morbidity and death.[1–14] The risk for such complications is particularly high when the disease is severe, which leads to preterm birth at <37 weeks gestation (preterm preeclampsia).[15,16] Evidence from the Combined Multimarker Screening and

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AJOG at a Glance

Why was this study conducted?

The purpose of this study was to determine and compare the predictive performance of the Fetal Medicine Foundation Bayes theorem-based model and the American College of Obstetricians and Gynecologists and the National Institute for Health and Care Excellence recommendations for the prediction of preterm preeclampsia at $11-13^{+6}$ weeks gestation in a large Asian population.

Key findings

The Fetal Medicine Foundation triple test with mean arterial pressure, uterine artery Doppler findings, and serum placental growth factor had detection rates of 48.2%, 64.0%, 71.8%, and 75.8% at 5%, 10%, 15%, and 20% fixed false-positive rates, respectively, for the prediction of preterm preeclampsia. Screening based on the American College of Obstetricians and Gynecologists recommendations achieved detection rate of 54.6% for preterm preeclampsia at 20.4% false-positive rate. Screening based on the National Institute for Health and Care Excellence guideline had detection rate of 26.3% at 5.5% false-positive rate.

What does this add to what is known?

The Fetal Medicine Foundation triple test has been validated successfully in the prediction of preterm preeclampsia in a large Asian population. This approach is superior to the American College of Obstetricians and Gynecologists and National Institute for Health and Care Excellence recommendations for the prediction of preeclampsia.

Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention trial (ASPRE) suggests that the risk of preterm preeclampsia can be reduced substantially by the prophylactic use of aspirin in high-risk women.[17] A systematic review and metaanalysis of 16 trials with a combined total of 18,907 participants, including the ASPRE trial, have reported that aspirin reduces the risk of preterm preeclampsia by 65%, provided the daily dose was $\geq$100 mg and onset of therapy was $<$16 weeks gestation.[18]

The traditional approach for the identification of the high-risk group that could benefit from aspirin is based on risk factors from maternal characteristics, obstetrics, and medical history as defined by professional bodies.[19–22] Specifically, the American College of Obstetricians and Gynecologists (ACOG) recommends to administer aspirin 81 mg daily beginning at 12–28 weeks gestation in women who have any 1 high-risk factor (history of preeclampsia in previous pregnancy, chronic hypertension, diabetes mellitus, renal disease, autoimmune disease) or any 2 moderate risk factors (first pregnancy, age $\geq$35 years, body mass index $>$30 kg/m^2, family history of preeclampsia, sociodemographic characteristics such as African American racial origin or low socioeconomic status, and personal history factors such as a previous low birthweight or small-for-gestational-age offspring, previous adverse pregnancy outcome, and interpregnancy interval $>$10 years).[22] Similarly, the National Institute for Care and Health Excellence (NICE) recommends to administer aspirin 75 mg daily beginning at 12 weeks gestation in women who have any 1 major factor (history of hypertensive disease in previous pregnancy, chronic kidney disease, autoimmune disease, diabetes mellitus, or chronic hypertension) or any 2 moderate factors (first pregnancy, age $\geq$40 years, interpregnancy interval $>$10 years, body mass index at first visit $\geq$35 kg/m^2, or family history of preeclampsia).[19]

Recent evidence has demonstrated that such approach to screening is insufficient for the prediction of preterm preeclampsia because the NICE recommendation achieves only a detection rate of 40%, for a 10% false-positive rate.[23] An alternative approach to screening for preeclampsia, which has been developed by the Fetal Medicine Foundation (FMF) and endorsed by the International Federation of Gynecology and Obstetrics, allows an estimation of patient-specific risks of preeclampsia that require delivery before a specified gestational age with the use of Bayes theorem to combine the a priori risk, which is based on maternal characteristics, obstetrics, and medical history, with the results of various combinations of biophysical and biochemical measurements.[14,24–26] Extensive research in the last decade has led to the identification of a number of biomarkers at $11-13^{+6}$ weeks gestation. The 3 that appear to be the most promising are mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and serum placental growth factor (PlGF).[14,27,28] The performance of screening of the FMF Bayes theorem-based approach for preterm preeclampsia appears to be superior to the traditional approach because it achieves a detection rate of 75% for 10% false-positive rate.[29,30] To date, the FMF first-trimester combined test has been validated in mixed-European,[23,31–39] British,[40] American,[41] Australian,[42] and Brazilian populations.[43]

The objective of the study was to examine and compare the performance of first-trimester screening for preterm preeclampsia by the FMF Bayes-theorem based method, the ACOG recommendations, and the NICE recommendations in a large Asian population.

Methods

This was a prospective multicenter noninterventional cohort study in singleton pregnancies at $11-13^{+6}$ weeks gestation (fetal crown-to-rump measurement of 42–84 mm) in women who sought routine pregnancy care at 11 maternity or ultrasound diagnostic units across 7 regions in Asia between December 13, 2016 and June 30, 2018: Prince of Wales and Kwong Wah Hospitals (Hong Kong SAR), Japan Society for the Study of Hypertension in Pregnancy–affiliated hospitals (Japan), Nanjing Drum Tower Hospital (Nanjing, China), First Affiliated Hospital of Kunming Medical University (Kunming,

TABLE 1
Characteristics of the study populations in the outcome groups

Variable	No preeclampsia (n=10,711)	Preterm preeclampsia (n=73)	Term preeclampsia (n=151)	*P* value
Maternal age, y[a]	32.39 (29.19–35.73)	34.76 (30.29–37.47)	33.51 (29.29–36.55)	.005
Weight, kg[a]	54.5 (49.6–60.6)	56.4 (50.1–64.6)	57.4 (51.2–66.0)	<.001
Height, cm[a]	159 (155–163)	158 (154–161)	158 (154–160)	.01
Body mass index, kg/m^2[a]	21.50 (19.78–23.83)	22.51 (20.79–26.27)	23.44 (20.67–26.56)	<.001
Gestational age at screening, d[a]	88 (85–90)	88 (85–91)	88 (85–91)	.790
Racial origin, n (%)				.37
East Asian	10,390 (97)	71 (97.3)	148 (98.0)	
Afro-Caribbean	1 (0)	0	0	
White	20 (0.2)	1 (0.4)	0	
South Asian	300 (2.8)	1 (1.4)	3 (2)	
Method of conception, n (%)				<.001
Spontaneous	9,934 (92.7)	64 (87.7)	125 (82.8)	
Ovulation induction	163 (1.5)	0	3 (2.0)	
In vitro fertilization	614 (5.7)	9 (12.3)	23 (15.2)	
Smoking, n (%)	460 (4.3)	1 (1.4)	7 (4.6)	.458
Chronic hypertension, n (%)	43 (0.4)	9 (12.3)	7 (4.6)	<.001
Systemic lupus erythematosus/ antiphospholipid syndrome, n (%)	42 (0.4)	0	0	.643
Type I or II diabetes mellitus, n (%)	26 (0.24)	2 (2.74)	1 (0.66)	<.001
Parity, n (%)				<.001
Nulliparous	6,146 (57.4)	51 (69.9)	110 (72.8)	
Parous with previous preeclampsia	66 (0.6)	4 (5.5)	7 (4.6)	
Parous with no preeclampsia	4,499 (42)	18 (24.7)	34 (22.5)	
Family history of preeclampsia, n (%)	163 (1.5)	1 (1.4)	6 (4.0)	.053
Gestational age at delivery, d[a]	275 (269–281)	246 (232.5–253.8)	270 (263–277)	<.001
Birthweight, g[a]	3,140 (2875–3408)	2055 (1579–2475)	2940 (2720–3307)	<.001
Aspirin use, n (%)	418 (3.9)	11 (15.1)	14 (9.3)	<.001

[a] Data are presented as median (interquartile range).

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China), King Chulalongkorn Memorial Hospital (Bangkok, Thailand), Showa University Hospital (Tokyo, Japan), Taipei Chang Gung Memorial Hospital (Taipei, Taiwan), Mediscan (Chennai, India), National University Hospital (Singapore), Siriraj Hospital (Bangkok, Thailand) and KK Women's and Children's Hospital (Singapore).

Approval for the study was obtained from the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (CREC Ref. No. 2016.152) in Hong Kong and the Ethics Committee of each participating hospital in other regions. The study is registered with ClinicalTrials.gov (Identifier: NCT03554681).

Inclusion criteria for the study were ≥18 years old, singleton pregnancy, and live fetus at the 11–13^{+6} weeks gestation. All women who were unable to give a full informed consent because of any factor such as severe illness, learning difficulties, or significant mental illness or those for whom a major fetal abnormality was identified at the time of the screening scan were excluded from the study.

Procedures

Training for all research procedures was provided to all investigators before the commencement of the study. The principal investigator of this study (L.C.P.) visited all the participating sites for study protocol demonstration and hands-on training for the measurement of MAP and UtA-PI. Consistency in data collection was maintained throughout the study period.

All eligible women were given written information about the study, and those who agreed to participate provided written informed consent. Gestational age was determined from the measurement of the fetal crown-rump length.[44] Maternal characteristics and medical, obstetric, and drug histories were recorded[19,20,26]; maternal weight and height were measured. MAP was measured by validated automated devices (BP3AQ1 Microlife, Taipei, Taiwan) according to a standardized protocol.[14,45,46] Transabdominal color Doppler ultrasound imaging was used to identify uterine artery; pulsed-wave Doppler imaging was used to measure the left and right UtA-PI according to a standardized protocol, and the average value was recorded.[14,47] Serum PlGF concentrations were measured by 1 of 3 automated analyzers: AutoDELFIA or DELFIA Xpress system (PlGF 1-2-3 kits; PerkinElmer Inc, Waltham, MA), B·R·A·H·M·S KRYPTOR analyzer (ThermoFisher Scientific, Hennigsdorf, Germany), or Cobas e411 system (Roche Diagnostics, Mannheim, Germany). All operators undertaking the Doppler studies had received the appropriate Certificate of Competence from the FMF.[48]

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with preexisting or pregnancy-associated hypertension were examined to determine the diagnosis of preeclampsia. This was based on the definitions of the International Society for the Study of Hypertension in Pregnancy and the ACOG.[20,49] Specifically, dedicated researchers (P.C., L.C.P.) determined the accuracy of preeclampsia diagnosis, which was determined by the investigators at all the sites. For cases with unclear diagnosis, the principal investigator of the study was consulted. Preterm preeclampsia and term preeclampsia were defined as preeclampsia with delivery at <37 and ≥ 37 weeks gestation, respectively.[20,49]

Sample size

The target number of subjects in this study was 10,000. Published studies that assessed the screening performance of the first-trimester combined test in the prediction of preterm preeclampsia indicated an area under the receiver operating characteristic curve (AUROC) of 0.90.[29] To achieve the AUROC of 0.90 with the FMF triple test, assuming a standard deviation of the AUROC is 0.05, then a minimum of 60 cases of preterm preeclampsia would be required for an alpha of 5% and a power of 80%. The reported incidence of preterm preeclampsia in Asia is 0.6%.[50] To obtain 60 cases of preterm preeclampsia, we would need to recruit 10,000 women.

Statistical analysis

Asian-specific biomarker multiples of the median (MoM) formulae were determined by multivariate regression analysis of factors among gestational age and maternal characteristics, which included maternal age, weight, height, racial origin (East Asian vs South Asian), method of conception, smoking, chronic hypertension, preexisting diabetes mellitus, systemic lupus erythematosus/antiphospholipid syndrome, parity, history of preeclampsia, and family history of preeclampsia. The measured values of MAP, UtA-PI, and PlGF were converted into MoMs, with adjustment for characteristics that were found to provide a substantive contribution to the $\log_{10}$ transformed value that included maternal factors in the previous history model.[51] In addition, PlGF values were adjusted for the analyzer that had been used.

Patient-specific risks of delivery with preeclampsia at <37 weeks gestation (preterm preeclampsia) and at any gestation (all preeclampsia) were calculated with the FMF Bayes theorem-based model to combine the previous distribution of the gestational age at delivery with preeclampsia, which was obtained from maternal characteristics and medical history, with the MoM values of MAP, UtA-PI, and PlGF (triple test).[52-54] The performance of screening for preterm preeclampsia and all preeclampsia by the history-derived previous risk and the triple test was assessed. We examined the predictive performance of the model (1) by the ability of the model to discriminate between the preeclampsia and no preeclampsia groups and (2) by calibration, which assesses agreement between predicted risks and outcomes (for a well-calibrated model, among those women with a risk of "1 in n," the incidence should be "1 in n").[39]

Discrimination was assessed by the AUROC curve (this indicates perfect discrimination if the value is 1 and no discrimination beyond chance if the value is 0.5) and the detection rate at fixed false-positive rates of 5%, 10%, 15% and 20%. Calibration was assessed visually through a figure that showed that the observed incidence against that predicted from risk for preterm preeclampsia by the FMF triple test. The plot was produced by grouping the data into bins according to risk. The observed incidence in each group was then plotted against the incidence predicted by the model (ie, the mean risks within each group). Quantitative assessment of calibration was achieved by the recording of measurements of calibration in-the-large and calibration slope. Calibration in-the-large is a measure of whether the risks generally are too high or too low. This is quantified by the estimated intercept from a logistic regression of incidence on the logit of risk with the slope fixed at 1. The intercept is a measure of the deviation of the observed incidence from the predicted incidence. For perfectly calibrated risks, the intercept should be zero. If there is a general tendency for underestimation so that the observed incidence is larger than that predicted, then the intercept will be positive. Conversely, for overestimation, the intercept will be negative.[39]

The calibration slope assesses the calibration across the range of risks and is the slope of the regression line of the logistic regression of incidence on the logit of risk. If the observed incidence of preeclampsia is equal to the predicted risk, then the slope should be 1.0. A slope <1 means that the observed incidence of preeclampsia is lower than the predicted risk of preeclampsia, thus suggesting an

TABLE 2
Comparisons of biomarkers between outcome groups

Multiples of the median	Unaffected (n=10,711)[a]	All preeclampsia (n=224)[a]	Preterm preeclampsia (n=73)[a]	Term preeclampsia (n=151)[a]
Mean arterial pressure	1.008 (1.007–1.010)	1.080 (1.065–1.096)[b]	1.099 (1.069–1.129)[c]	1.072 (1.053–1.090)[d]
Uterine artery pulsatility index	1.063 (1.058–1.068)	1.119 (1.070–1.167)	1.188 (1.097–1.279)[c]	1.085 (1.029–1.142)
Placental growth factor	1.100 (1.089–1.111)	0.842 (0.788–0.896)[b]	0.760 (0.662–0.858)[c]	0.882 (0.819–0.945)[d]

[a] Data are given as mean (95% confidence interval); [b] *P* value <.05 between no preeclampsia vs preeclampsia; [c] *P* value <.025 between no preeclampsia vs preterm preeclampsia; [d] *P* value <.025 between no preeclampsia vs term preeclampsia.

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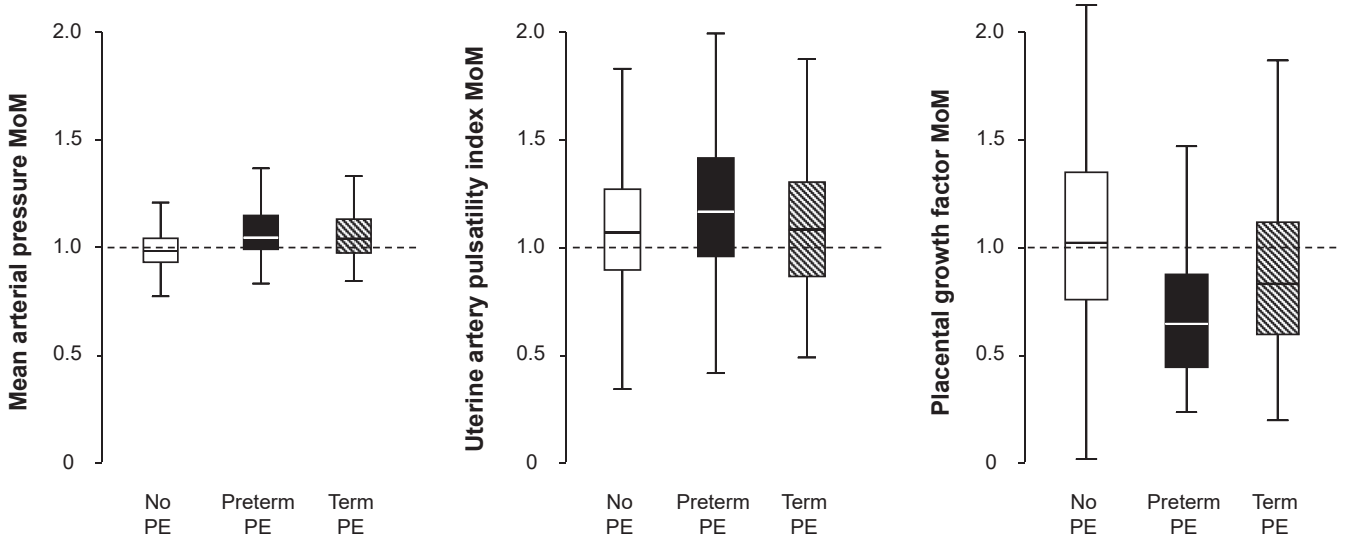
underestimation. A calibration slope >1 indicates that the observed incidence of preeclampsia is greater than the predicted risk of preeclampsia, which suggests an overestimation.[39]

The risks produced from the FMF Bayes theorem-based model are for delivery with preeclampsia before a specific gestation, assuming no other cause for delivery. Because other cause deliveries are effectively censored observations, the actual incidence of preeclampsia would be expected to be lower than predicted. For early gestations, when there are few other cause deliveries, the effects would be small. At later gestations, with many other cause deliveries, the effect of censoring may be substantial. Consequently, we applied survival analysis (Kaplan-Meier) to estimate the incidence of delivery with preeclampsia by treating the deliveries from other causes as censored observations.

Because some of the subjects who were deemed to be at an increased risk, based on maternal risk factors, were prescribed aspirin (75–100 mg/day) according to the existing local protocols, which could have reduced the risk of preeclampsia, some of the participants in the screen-positive group effectively would have been converted to false-positives. Consequently, treatment of women with screen-positive maternal risk factors with aspirin would reduce the detection rate. Our approach to dealing with this was to apply multiple imputations to data on the incidence of preeclampsia that would have occurred had it not been for the effect of treatment. Markov Chain Monte Carlo was used to impute incidence data and generate 10 complete data sets for analysis.[55] Estimates of detection rate were then pooled across data. We assumed that the incidence of preeclampsia that would have occurred, had it not been for the effect of treatment, was determined

FIGURE 1
Box plots



Box plots of the multiples of the median value of mean arterial pressure (**left**), uterine artery pulsatility index (**middle**), and placental growth factor (**right**) between the outcome groups. The *clear box* indicates no PE group; the *closed box* indicates preterm PE group; the *hatched box* indicates term PE group.

MoM, multiples of the median; *PE*, preeclampsia.

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from a logistic regression model that was dependent on maternal risk factors and the center in which the incident occurred and that aspirin reduced the incidence with a prespecified probability 0.3 for all preeclampsia and 0.6 for preterm preeclampsia.[17] Although these probabilities were based on the results of the ASPRE trial in which the daily dose of aspirin was 150 mg, rather than 75 mg as recommended by professional bodies,[19] we wanted to avoid any potential criticism of bias against the method recommended by professional bodies by assuming that the effect of 75 mg was similar to that of higher doses of the drug.

The statistical software package R was used for data analyses.[56–58] The package pROC was used for the receiver-operating characteristic curve analysis, and the package survival was used for survival analysis.[56–58]

Results

Participants

In the study population of 10,935 pregnancies, there were 224 cases (2.05%) that experienced preeclampsia, including 25 (0.23%), 73 (0.67%), and 151 (1.38%) cases with delivery at <34, <37, and ≥37 weeks gestation. Baseline demographic and clinical characteristics of participants are shown in Table 1. There were 443 women (4.05%) who reported aspirin use.

Distribution of biomarkers

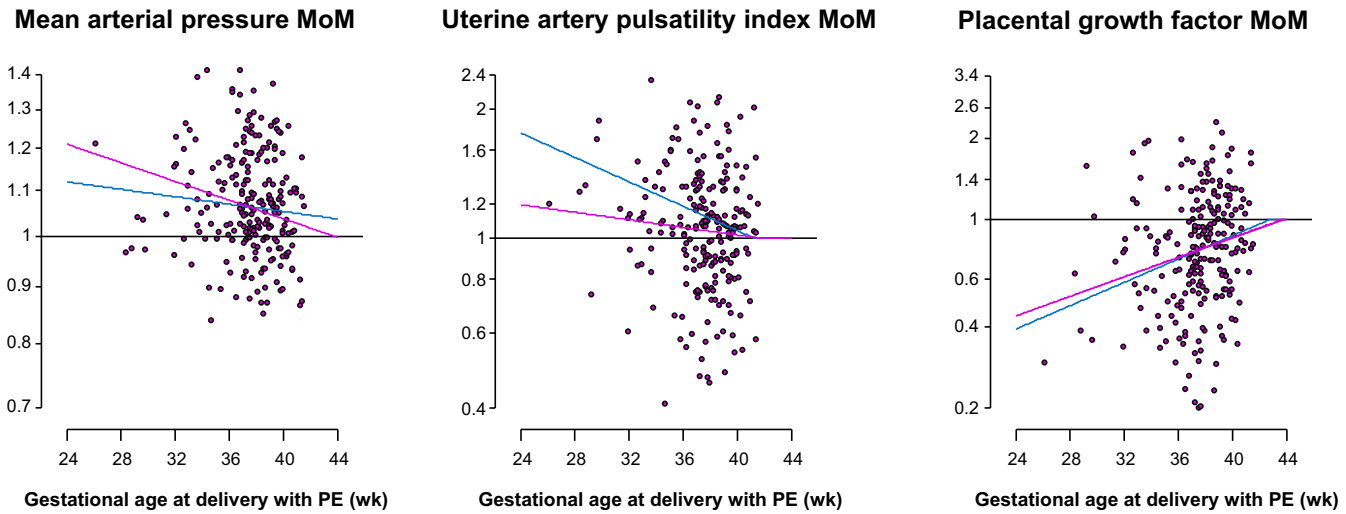
The Asian-specific biomarker MoM formulae are presented in supplemental Tables 1–3. The mean MAP MoM was significantly higher and the mean PlGF MoM was significantly lower in women with preterm and term preeclampsia than in those without. The mean UtA-PI MoM was significantly higher in women with preterm preeclampsia, but not term preeclampsia, than in those without (Table 2; Figure 1). The MoM values of the biomarkers in the preeclampsia group and the fitted regression relationships with gestational age at delivery are shown in Figure 2. All markers showed more separation at earlier than later gestations, and this observation implied that these biomarkers had better discriminatory power for the prediction of preterm preeclampsia than term preeclampsia. It is notable that the regression lines for MAP, UtA-PI, and PlGF intersect 1 MoM close to term; therefore, the screening performance of these biomarkers for term preeclampsia is limited.

Performance of screening

The performance of screening of preterm and all preeclampsia by the previous risk and the triple test with the FMF Bayes theorem-based method is given in Tables 3 and 4, respectively.

The FMF previous risk had an AUROC of 0.758 (95% confidence interval [CI], 0.749–0.766) and detection rates of 31.0% (95% CI, 20.2–41.7), 40.2 % (95% CI, 29.2–51.3), 50.8% (95% CI, 39.5–62.0), and 55.0% (95% CI, 43.9–66.2) at 5%, 10%, 15%, and 20% fixed false-positive rates, respectively, for the screening of preterm preeclampsia. The FMF triple test had an AUROC of 0.857 (95% CI, 0.851–0.864) and detection rates of 48.2% (95%

FIGURE 2
Scatterplots



Scatterplots show the fitted regression relationships between the multiples of the median value of mean arterial pressure (**left**), uterine artery pulsatility index (**middle**), and placental growth factor (**right**) with gestational age at delivery with preeclampsia. The *black line* indicates the reference based on unaffected women; the *red line* indicates the regression line from the current study; the *blue line* indicates the regression line from the Fetal Medicine Foundation study.

MoM, multiples of the median; *PE*, preeclampsia.

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TABLE 3
Performance of screening of preterm preeclampsia in screening by the Fetal Medicine Foundation Bayes theorem-based method

	Fetal Medicine Foundation previous risk				Fetal Medicine Foundation triple risk			
			Confidence interval limit, %				Confidence interval limit, %	
Variable	Risk cut-off (1 in x)[a]	Detection rate, %	Lower	Upper	Risk cut-off (1 in x)	Detection rate, %	Lower	Upper
All data								
5%	87	30.96	20.17	41.74	48	48.23	36.72	59.74
10%	111	40.23	29.17	51.29	93	64.03	53.35	74.71
15%	138	50.75	39.47	62.04	143	71.79	61.74	81.85
20%	157	55.01	43.87	66.15	193	75.80	66.25	85.36
Nulliparous								
5%	74	19.73	8.98	30.48	37	41.97	28.03	55.91
10%	98	26.76	14.45	39.07	69	53.93	40.16	67.70
15%	116	36.54	23.30	49.79	103	63.36	50.29	76.43
20%	130	46.15	32.53	59.78	140	72.43	60.39	84.47
Multiparous								
5%	150	52.70	31.86	73.53	86	65.72	46.21	85.22
10%	222	57.93	37.06	78.80	185	70.55	51.52	89.58
15%	282	74.66	56.66	92.65	285	75.08	57.45	92.71
20%	338	75.01	56.91	93.12	392	79.54	63.12	95.96

[a] "x" refers to number in the column. A screen positive test refers to women with a risk of more than "1 in x".

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CI, 36.7–59.7), 64.0% (95% CI, 53.4–74.7), 71.8% (95% CI, 61.7–83.9), and 75.8% (95% CI, 66.3–85.4) at 5%, 10%, 15%, and 20% fixed false-positive rates, respectively, for the screening of preterm preeclampsia. These figures correspond to risk cut-offs of 1 in 48, 1 in 93, 1 in 143, and 1 in 193, respectively. For all preeclampsia, the FMF previous risk and FMF triple test had AUROC values of 0.711 (95% CI, 0.703–0.720) and 0.769 (95% CI, 0.761–0.777), respectively. Performance of screening of preterm and all preeclampsia stratified by parity is shown in Tables 3 and 4, respectively.

Regarding calibration of the FMF triple test for the prediction of preterm preeclampsia, the intercept was 0.212 (95% CI, −0.028 to −0.452), and the calibration slope was 0.869 (95% CI, 0.734–1.004), which was close to 1.0 and suggests a good agreement between the predicted risks and observed incidence of preeclampsia (Figure 3).

Based on the previously published FMF study, the detection rates of the triple test for preterm preeclampsia were 50.0% (95% CI, 6.8–93.2), 68.8% (95% CI, 62.7–75.5), and 72.8% (95% CI, 65.8–79.1), respectively, at fixed false-positive rate of 10%, for East Asian, White, and Afro-Caribbean women.[29] The corresponding detection rates at fixed false-positive rate of 20% were 75.0% (95% CI, 19.4–99.4), 83.2% (95% CI, 78.0–87.6), and 83.7% (95% CI, 77.5–88.7). The detection rates in the validation dataset were comparable with the detection rates for East Asian women in previously published data from the FMF study.

The frequencies of women who are at high risk according to the ACOG and NICE recommendations were 20.7% (n=2261) and 5.6% (n=614), respectively. Screening with the use of the ACOG recommendations had a detection rate of 54.6% (95% CI, 43.5–65.9) at 20.4% false-positive rate for the screening of preterm preeclampsia (Table 5). NICE recommendation had a detection rate of 26.3% (95% CI, 16.3–36.3) at 5.5% false-positive rate (Table 6). The detection rate according to the FMF triple test is superior to that derived from the ACOG and NICE recommendations for both preterm and all preeclampsia (Tables 5 and 6).

The predictive performance of the FMF previous risk, FMF triple test, ACOG recommendations, and NICE recommendations for the detection of preterm preeclampsia is given in Figure 4. The FMF triple test achieved the highest detection rate. Similar findings were observed for the detection of all preeclampsia (Figure 4).

Comment

Principal findings of the study

With regard to the screening of preterm preeclampsia in an Asian population, the study has demonstrated that (1) all biomarkers show more separation

TABLE 4
Performance of screening of all preeclampsia in screening by the Fetal Medicine Foundation Bayes theorem-based method

	Fetal Medicine Foundation previous risk				Fetal Medicine Foundation triple test			
			Confidence interval limit, %				Confidence interval limit, %	
Variable	Risk cut-off (1 in x)[a]	Detection rate, %	Lower	Upper	Risk cut-off (1 in x)	Detection rate, %	Lower	Upper
All data								
5%	87	25.17	19.46	30.88	47	34.90	28.55	41.25
10%	116	33.17	26.92	39.41	93	49.43	42.90	55.97
15%	137	44.89	38.37	51.41	140	59.90	53.54	66.27
20%	157	51.94	45.43	58.45	190	65.57	59.39	71.75
Nulliparous								
5%	77	19.13	13.04	25.22	40	31.14	23.96	38.31
10%	102	25.10	18.37	31.84	70	44.17	36.55	51.80
15%	116	33.97	26.53	41.41	104	54.85	47.16	62.55
20%	130	43.45	35.84	51.06	140	63.00	55.63	70.38
Multiparous								
5%	141	36.30	24.27	48.33	92	42.86	30.44	55.28
10%	222	39.66	27.60	51.73	171	52.47	39.71	65.23
15%	286	52.19	39.84	64.53	279	58.14	45.94	70.35
20%	335	59.98	47.90	72.06	400	64.26	52.43	76.08

[a] "x" refers to number in the column. A screen positive test refers to women with a risk of more than "1 in x".
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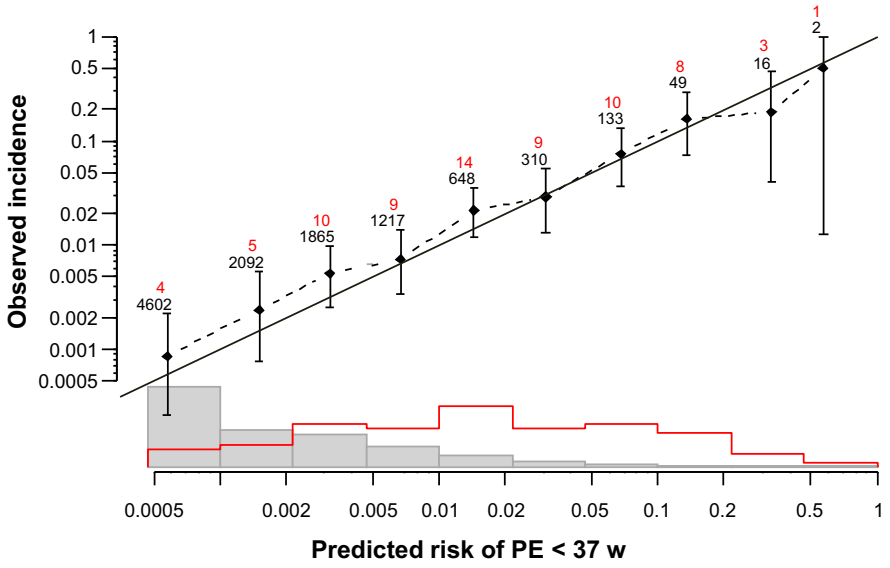
between affected and unaffected pregnancy at earlier rather than later gestations, which implies that the performance of screening based on these biomarkers is related inversely to the gestational age at delivery because of preeclampsia; (2) the regression lines for all biomarkers against gestational age at delivery with preeclampsia intersect 1 MoM close to term; therefore, these biomarkers perform poorly in screening for term preeclampsia; (3) the FMF Bayes theorem-based method achieves detection rates of 64.0% and 75.8% at 10% and 20% false-positive rates, respectively, which are comparable with that of previously published data from the FMF study; (4) there is good agreement between the predicted risks and observed incidence of preeclampsia; and (5) the FMF triple test achieves the highest detection rate for the detection of preterm preeclampsia in comparison with ACOG and NICE recommendations.

Comparisons with results of previous studies

A few first-trimester prediction algorithms that use multiple biomarkers have been developed in Asian populations.[59–64] However, these models have been developed from single centers with moderate population size, thus implying the high probability of model overfitting. The FMF first-trimester prediction model has been evaluated previously in a case-control study of 30 preeclampsia cases and 3300 unaffected cases that demonstrate that the performance of screening in a South Chinese population is lower than that obtained from the original study.[65] The lower detection rate can be attributed to 2 possible reasons: (1) the blood pressure was not measured according to the FMF protocol, and it was measured only once in any arm with an automated device that is not validated for use in pregnancy and (2) the UtA-PI has been shown to be measured distal to the internal cervical os, which leads to a 15% reduction in the pulsatility index value and a 7% reduction in the detection rate.[66]

In the current study, we have provided training for all research procedures according to the FMF criteria to all investigators before commencement of the study to ensure standardization of biomarker acquisition. Our study population constitutes 94% of East Asian women; therefore, the screening performance of the FMF Bayes theorem-based method is most representative for East Asian women. We have demonstrated that the screening performance of the FMF triple test for preterm preeclampsia in East Asian women is comparable with that of previously published data from the FMF.[29] However, the performance of screening for preterm preeclampsia in East Asian women is inferior to that of White and Afro-Caribbean women.[29] We have attempted to understand these differences in

FIGURE 3
Calibration plot



Calibration plot for screening with the Fetal Medicine Foundation Bayes theorem-based model for prediction of preterm preeclampsia (PE) with the use of the combination of maternal factors, mean arterial pressure, uterine artery pulsatility index, and placental growth factor. The *diagonal black line* is the line of perfect agreement; the *vertical interrupted line* is the overall mean risk, and the *horizontal interrupted line* is the overall incidence. The histograms show the distribution of risks in pregnancies with preterm preeclampsia *(red)* and those without preterm preeclampsia (*gray*).

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screening performance by comparing our biomarker distributions to that of previously published data from the FMF study.[29] The regression line of MAP MoM in our study is steeper than that of the FMF.[29] In contrast, the regression line of UtA-PI MoM of the FMF study is steeper than that obtained in our study (Figure 2). As for PlGF MoM, the regression lines from both studies are almost identical, which implies that PlGF performs equally well in both populations (Figure 2). The lower performance of screening in East Asian women can be explained partly by the under-performing UtA-PI, which is not compensated by the better-performing MAP, because the latter is not a specific marker for impaired placentation. The lower performance of screening in Asian women can further be explained by the fact that there is a lower frequency of preterm preeclampsia and a lower frequency of risk factors in Asian women. Specifically, the rates of preterm, term, and all preeclampsia in our study are 0.67%, 1.38%, and 2.05%, respectively. Differences in anthropometric measurements, sociodemographic factors, living standard, education level, accessibility to healthcare, and climate might contribute to the geographic differences in preeclampsia rates.[67-69] Compared with the European population from which the first-trimester Bayes theorem-based model has been developed, our population has lower median body mass index (21.5 vs 24.5 kg/m^2), lower frequencies of chronic hypertension (0.5% vs 1.6%), diabetes mellitus (0.3% vs 0.9%), family history of preeclampsia (1.6% vs 4.2%), and history of preeclampsia (0.7% vs 3.6%).[29] However, a higher frequency of systemic lupus erythematosus or antiphospholipid syndrome has been observed in our study population compared with the European population (0.4% vs 0.15%).

We have demonstrated that the performance of screening by the FMF previous risk and the FMF triple test are superior to those derived from the ACOG and the NICE recommendations. This finding is consistent with previous studies that involved mixed-European and British populations.[29,40] The approach to screening by the ACOG and NICE recommendations is different to that of the FMF method because it treats each of the maternal risk factors as a separate test with additive detection and false-positive rates. The FMF method uses a multivariable logistic model to generate the previous risk based on maternal factors.[26] Each maternal factor contributes a different relative importance to the risk algorithm that allows estimation of the patient-specific risk of preeclampsia that requires delivery before a specified gestation.[26] The previous risk can then be adjusted according to the results of the biophysical and biochemical tests.[26]

One important observation derived from this study is that the performance of the current ACOG recommendations is greater than that of the previous version published in 2013.[23,40] According to the ACOG 2013 recommendation, low-dose aspirin should be given to women with a history of early onset preeclampsia that required preterm delivery at <34 weeks gestation or recurrent preeclampsia.[20] This method of screening achieves only a detection rate of 5% (95% CI, 2−14) at 0.2% false-positive rate for preterm preeclampsia.[23] In 2018, ACOG expanded the list of risk factors to identify the women who are at high risk and in need of aspirin prophylaxis. This has contributed to the improvement in the screening performance.[22]

Implications of clinical practice

Clinical implementation is defined as the ability to accomplish any type of strategy to provide practical effects or be used officially.[70] In the context of screening, the key question is whether the developed prediction model is ready to be implemented in routine clinical practice. Ideally, the model should be validated externally in new patients in a new setting by other researchers. This step is particularly necessary in settings in which the populations are significantly

TABLE 5
Comparison of performance of screening of preeclampsia by the Fetal Medicine Foundation Bayes theorem-based method and the American College of Obstetricians and Gynecologists recommendations

Variable	Detection rate, %	Confidence interval limit, %		False-positive rate, %[a]
		Lower	Upper	
Preterm preeclampsia				
American College of Obstetricians and Gynecologists	54.64	43.48	65.90	20.43
Fetal Medicine Foundation previous risk	57.52	46.71	68.32	20.43
Fetal Medicine Foundation triple test	75.80	66.25	85.36	20.43
All preeclampsia				
American College of Obstetricians and Gynecologists	44.16	37.65	50.67	20.17
Fetal Medicine Foundation previous risk	52.38	47.12	57.63	20.17
Fetal Medicine Foundation triple test	66.00	59.84	72.16	20.17

[a] Fixed according to American College of Obstetricians and Gynecologists recommendation.

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different from the populations from which the prediction model has been developed.[71-73]

Our study, which includes >10,000 subjects, has validated the FMF Bayes theorem-based method for the first-trimester screening of preterm preeclampsia in the largest Asian population. Recording maternal characteristics and obstetrics, medical, and drug history, measurement of blood pressure, and hospital attendance at $11-13^{+6}$ weeks gestation for an ultrasound scan are an integral part of routine antenatal care. Measurement of UtA-PI can be carried out by the same sonographers and the same ultrasound machines that are used for the routine scan at $11-13^{+6}$ weeks gestation. However, this requires training, and the measurement adds approximately 2−3 minutes to the current 20−30 minutes used for the scan. Serum PlGF can be measured in the same blood sample and by the same automated platforms that are used currently for measurement of serum pregnancy that is associated plasma protein-A, as part of routine clinical practice in screening for fetal trisomies; however, there is an additional cost for the reagents. The calculator for the estimation of patient-specific risk of preterm preeclampsia is available on existing medical record software for the risk calculation of fetal trisomies. All components of the preeclampsia screening program are achievable, because similar components have been successfully demonstrated through the

TABLE 6
Comparison of performance of screening of preeclampsia by the Fetal Medicine Foundation Bayes theorem-based method and National Institute for Health and Care Excellence recommendations

Variable	Detection rate, %	Confidence interval limit, %		False-positive rate. %[a]
		Lower	Upper	
Preterm preeclampsia				
National Institute for Health and Care Excellence	26.31	16.34	36.28	5.46
Fetal Medicine Foundation previous risk	33.21	23.63	42.79	5.46
Fetal Medicine Foundation triple test	48.49	39.88	57.09	5.46
All preeclampsia				
National Institute for Health and Care Excellence	20.45	15.08	25.83	5.29
Fetal Medicine Foundation previous risk	25.60	19.86	31.34	5.29
Fetal Medicine Foundation triple test	36.59	30.27	42.90	5.29

[a] Fixed according to National Institute for Health and Care Excellence recommendation.

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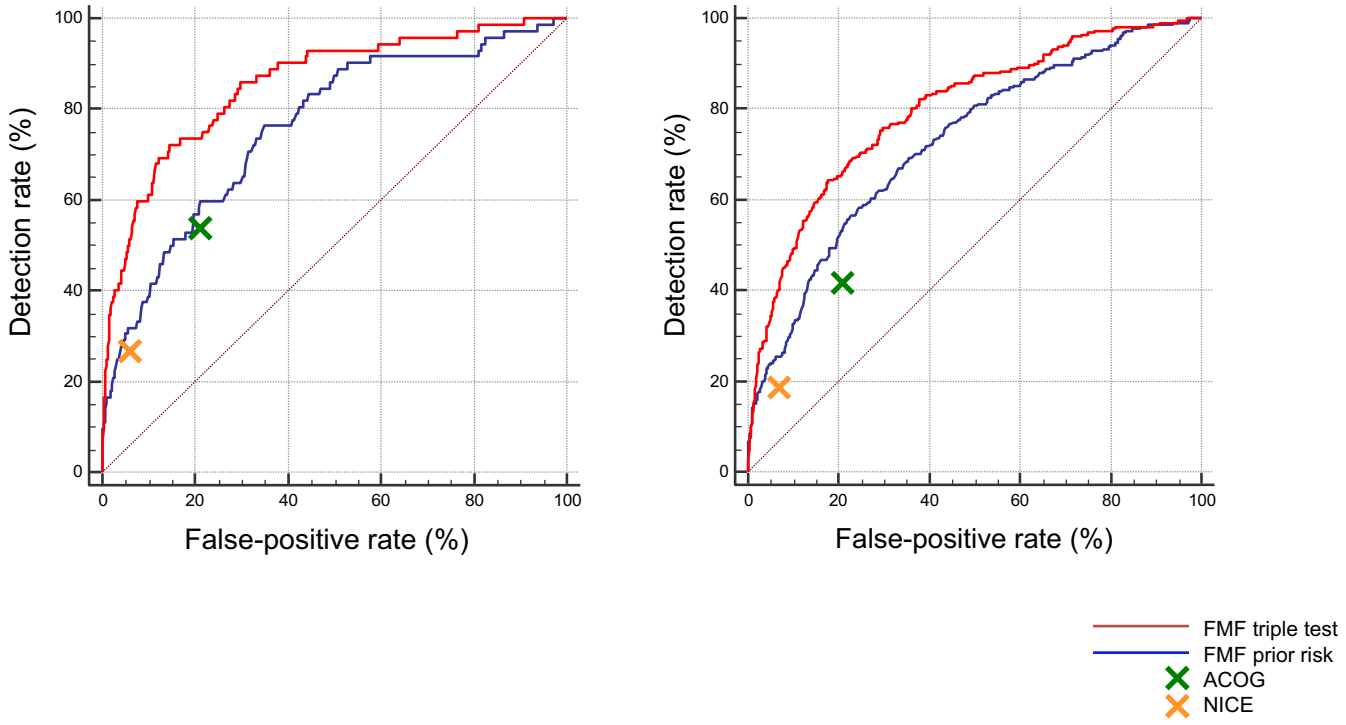
FIGURE 4
Receiver operating characteristics plots



Receiver operating characteristics plots of screening for preterm preeclampsia (**left**) and all preeclampsia (**right**) by the Fetal Medicine Foundation previous risk (*blue*), the Fetal Medicine Foundation triple test (*red*), the American College of Obstetricians and Gynecologists (*green cross*), and National Institute for Health and Care Excellence (*orange cross*) recommendations.

ACOG, the American College of Obstetricians and Gynecologists; *FMF*, Fetal Medicine Foundation; *NICE*, the National Institute for Health and Care Excellence.

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implementation of screening for fetal trisomies.[74] The current study has also shown successful implementation of the screening program through the utilization of the existing infrastructure of early prenatal care. By expanding the first-trimester screening program to include the identification of women at high risk for experiencing preterm preeclampsia and the use of aspirin prophylaxis at the appropriate dose has the potential substantially to reduce the risk of this adverse outcome.[14,17,18,75–86]

Strengths and limitations

Our study is the largest study to date for the evaluation of the first-trimester prediction of preeclampsia in an Asian population. We acquired biomarker values in a standardized approach. We converted the measured biomarkers into MoMs according to Asian-specific formulae, and the prediction model was applied appropriately. Limitations relate to the lower incidence of preeclampsia and the lower rate of maternal risk factors of preeclampsia in the studied population; the latter could be attributed to under reporting. However, the numbers that were observed in this study are consistent with previous studies performed in Asia.[50,59–64,87–89]

Conclusions

In conclusion, this study, which includes a large number of subjects, has demonstrated that the FMF Bayes theorem-based model is effective in the prediction of preterm preeclampsia in an Asian population. This approach uses existing infrastructure technologies and has the potential to be implemented easily as part of routine prenatal care. We have also shown that the FMF triple test is, by far, superior to the ACOG and NICE recommendations for the detection of preeclampsia. ■

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Supplemental Reference

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SUPPLEMENTAL TABLE 1

Formula for calculation of mean arterial pressure multiples of the median values at 11−13+6 weeks gestation

Variable	Estimate	95% Confidence interval	Standard error	*P* value
Intercept	1.93418100	1.92949985−1.93886288	0.00239	<.00001
Gestational age in days−77	−0.00075353	−0.00095119 to −0.00055587	0.00010	<.00001
Weight in kg−69	0.00177577	0.00165423−0.00189731	0.00006	<.00001
Weight in Kg-69^2	−0.00000487	−0.00001013−0.00000039	0.00000	.03487
Height in cm−164	−0.00063626	−0.00078043 to −0.00049208	0.00007	<.00001
South Asian racial origin	−0.00780220	−0.01625093−0.00064654	0.00431	.03515
Chronic hypertension	0.06610905	0.05600273−0.07621537	0.00516	<.00001
Chronic hypertension (weight in kg−69)	−0.00082027	−0.00151479 to −0.00012574	0.00035	.01031
Family history of preeclampsia: mother	0.00515976	−0.00073261−0.01105212	0.00301	.04305
Smoking	−0.00606381	−0.00963745 to −0.00249017	0.00182	.00044
In vitro fertilization	0.00820490	0.00501916−0.01139064	0.00163	<.00001
Parous				
No previous preeclampsia	−0.00458774	−0.00609738 to −0.00307809	0.00077	<.00001
Previous preeclampsia	0.01801119	0.00938525−0.02663712	0.00440	.00002

Effects are shown relative to the reference group (East Asian racial origin, nulliparous, spontaneous conception, no family history of preeclampsia, no smoking, and no chronic hypertension). Weight and height have been centered according to the Fetal Medicine Foundation approach so that the constant is the estimated mean gestational age at delivery for the reference group with a weight of 69 kg and height of 164 cm.[1]

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SUPPLEMENTAL TABLE 2
Formula for calculation of uterine artery pulsatility index multiples of the median values at 11−13+6 weeks gestation

Variable	Estimate	95% Confidence interval	Standard error	*P* value
Intercept	0.29144795	0.27622450−0.30667140	0.00777	<.00001
Gestational age in days−77	−0.00518189	−0.00578710 to −0.00457668	0.00031	<.00001
Weight in kg−69	−0.00072825	−0.00097374 to −0.00048276	0.00013	<.00001
Systemic lupus erythematosus/antiphospholipid syndrome	−0.04956090	−0.08500215 to −0.01411965	0.01808	.00306
In vitro fertilization	−0.07718998	−0.08696615 to −0.06741381	0.00499	<.00001
Ovulation induction	0.02222935	0.00399922−0.04045949	0.00930	.00842
Parous: no previous preeclampsia	−0.01228126	−0.01687859 to −0.00768394	0.00235	<.00001

Effects are shown in relative to the reference group (East Asian racial origin, nulliparous, spontaneous conception, no family history of preeclampsia, no smoking, and no chronic hypertension). Weight has been centered according to the Fetal Medicine Foundation approach so that the constant is the estimated mean gestational age at delivery for the reference group with a weight of 69 kg.[1]

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SUPPLEMENTAL TABLE 3
Formula for calculation of placental growth factor multiples of the median values at 11−13+6 weeks gestation

Variable	Estimate	95% Confidence interval	Standard error	*P* value
Intercept: Cobas[a]	1.50772860	1.45079017− 1.56466704	0.02905	<.00001
Intercept: DELFIA or AutoDELFIA[b]	1.33411781	1.27126438− 1.39697125	0.03207	<.00001
Intercept: KRYPTOR[c]	1.36882513	1.30829765− 1.42935262	0.03088	<.00001
Gestational age in days−77	0.01031970	0.00605577− 0.01458363	0.00218	<.00001
Gestational age, d 77^2	0.00033988	0.00014893− 0.00053083	0.00010	.00024
Weight in kg−69	−0.00173563	−0.00215847 to 0.00131279	0.00022	<.00001
Maternal age in years−35	0.00164530	0.00074452− 0.00254607	0.00046	.00017
South Asian racial origin	0.11138258	0.06449021− 0.15827496	0.02392	<.00001
Smoking	0.07318602	0.05443189− 0.09194014	0.00957	<.00001
Parous: no previous preeclampsia	0.02521199	0.01714983− 0.03327415	0.00411	<.00001

Effects are shown in relative to the reference group (East Asian racial origin, nulliparous, spontaneous conception, no family history of preeclampsia, no smoking and no chronic hypertension). Age and weight have been centered according to the Fetal Medicine Foundation approach so that the constant is the estimated mean gestational age at delivery for the reference group with an age of 35 years and a weight of 69 kg.[1]

[a] Cobas e411 system (Roche Diagnostics, Mannheim, Germany); [b] AutoDELFIA or DELFIA Xpress system (PlGF 1-2-3 kits; PerkinElmer Inc, Waltham, MA); [c] ThermoFisher Scientific, Hennigsdorf, Germany.

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