Ultrasound Obstet Gynecol 2023; **61**: 682–690
Published online 5 May 2023 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.26183.

Pre-eclampsia screening in Denmark (PRESIDE): national validation study

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KEYWORDS: acetylsalicylic acid; competing-risk models; Fetal Medicine Foundation; first trimester; pre-eclampsia; screening

CONTRIBUTION

What are the novel findings of this work?
This study is an independent validation of the Fetal Medicine Foundation (FMF) first-trimester screening algorithm for pre-eclampsia, completed in a predominantly white low-risk population in Denmark. We found that the FMF algorithm was effective in the Danish population and it had higher detection rates for preterm pre-eclampsia compared with the current Danish strategy based on single major maternal risk factors.

What are the clinical implications of this work?
This study supports the superiority and applicability of screening for preterm pre-eclampsia in the first trimester using the FMF algorithm. The results provide evidence for a national implementation of this screening approach in Denmark.

ABSTRACT

Objectives *To investigate the predictive performance of the Fetal Medicine Foundation (FMF) first-trimester screening algorithm for pre-eclampsia in a Danish population and compare screening performance with that of the current Danish strategy, which is based on maternal risk factors.*

Methods *This was a prospective study of women with a singleton pregnancy attending for their first-trimester ultrasound scan and screening for aneuploidies at six Danish university hospitals between May 2019 and December 2020. Prenatal data on maternal characteristics and medical history were recorded, and measurements of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum pregnancy-associated plasma protein-A (PAPP-A) and serum placental growth factor (PlGF) were collected without performing a risk assessment for pre-eclampsia. Information on acetylsalicylic acid use was recorded. After delivery, pregnancy outcome, including gestational age at delivery and pre-eclampsia diagnosis, was recorded. Pre-eclampsia risk assessment for each woman was calculated blinded to outcome using the FMF screening algorithm following adjustment to the Danish population. Detection rates (DRs) of the FMF algorithm*

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Accepted: 13 February 2023

were calculated for a fixed screen-positive rate (SPR) of 10% and for the SPR achieved in the current Danish screening.

Results *A total of 8783 pregnant women were included, with a median age of 30.8 (interquartile range (IQR), 28.1–33.9) years. The majority were white (95%), naturally conceiving (90%), non-smokers (97%) and had no family history of pre-eclampsia (96%). The median body mass index was 23.4 (IQR, 21.2–26.6) kg/m^2. A complete risk assessment including maternal characteristics, MAP, UtA-PI, PlGF and PAPP-A was available for 8156 women (92.9%). In these women, UtA-PI was measured bilaterally with a median value of 1.58 (IQR, 1.27–1.94) and the median resting MAP of 80.5 (IQR, 76.1–85.4) mmHg in two consecutive measurements. Among these, 303 (3.7%) developed pre-eclampsia, including 55 (0.7%) cases of pre-eclampsia with delivery < 37 weeks of gestation and 16 (0.2%) cases of pre-eclampsia with delivery < 34 weeks. At a SPR of 10%, combined screening using the FMF algorithm based on maternal characteristics, MAP, UtA-PI, PlGF and PAPP-A had a DR of 77.4% (95% CI, 57.6–97.2%) for pre-eclampsia with delivery < 34 weeks, 66.8% (95% CI, 54.4–79.1%) for pre-eclampsia with delivery < 37 weeks and 44.1% (95% CI, 38.5–49.7%) for pre-eclampsia with delivery at any gestational age. The current Danish screening strategy using maternal risk factors detected 25.0% of women with pre-eclampsia with delivery < 34 weeks and 19.6% of women with pre-eclampsia with delivery < 37 weeks at a SPR of 3.4%. When applying the FMF algorithm including maternal characteristics, MAP, UtA-PI and PlGF at the fixed SPR of 3.4%, the DRs were 60.5% (95% CI, 36.9–84.1%) for PE with delivery < 34 weeks and 45.2% (95% CI, 32.0–58.5%) for PE with delivery < 37 weeks.*

Conclusion *In this large Danish multicenter study, the FMF algorithm based on maternal characteristics, MAP, UtA-PI, PlGF and PAPP-A predicted 77.4% of cases with pre-eclampsia with delivery < 34 weeks and 66.8% of cases with pre-eclampsia with delivery < 37 weeks of gestation at a SPR of 10%, suggesting that the performance of the algorithm in a Danish cohort matches that in other populations. © 2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Pre-eclampsia (PE) affects 2–8% of all pregnancies and is a major cause of maternal and fetal morbidity and mortality[1,2]. Women at risk of developing PE benefit from treatment with acetylsalicylic acid (ASA), which reduces the rate of preterm PE (with delivery before 37 weeks of gestation) by up to 65%, provided that the daily dose is ≥ 100 mg and the onset of treatment is before 16 weeks of gestation. Furthermore, ASA treatment has been reported to reduce the length of stay in neonatal intensive care by 68%[3].

Identification of women who are at risk of PE has traditionally been based on maternal risk factors[4,5], but the performance of this screening method is modest. Screening according to the National Institute for Health and Care Excellence (NICE) guidelines provides detection rates (DRs) of 39% for PE with delivery < 37 weeks' gestation at a false-positive rate (FPR) of 10.2%. The DR of screening for PE with delivery < 37 weeks according to the American College of Obstetricians and Gynecologists (ACOG) recommendations is 90% at a FPR of 64.2%[6]. The current Danish national guidelines for offering ASA treatment are based on maternal risk factors and correspond largely to having at least one NICE major risk factor[7]. An alternative screening approach has been developed by the Fetal Medicine Foundation (FMF), which uses Bayes' theorem to combine maternal characteristics with data on mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum pregnancy-associated plasma protein-A (PAPP-A)[8–12]. The FMF combined screening is superior to the traditional approach and has a DR of preterm PE of 75% at a 10% FPR[13]. External validation studies of the FMF algorithm in American[14], Australian[15,16], European[6,17–23], Brazilian[24,25] and Asian[26,27] populations have confirmed the predictive performance, although the DRs varied, reflecting population differences in demographic characteristics.

Despite the increased focus on preventing PE, the incidence of preterm PE has remained unchanged over the last decade in Denmark[7]. Consequently, a change in strategy may be appropriate. Danish women have a positive attitude towards screening in pregnancy and more than 90% participate in first-trimester combined screening for aneuploidies (cFTS)[28]. Implementing national screening for PE in addition to the existing program requires a systematic evaluation of the screening algorithm in a Danish setting.

In this multicenter study, we aimed to investigate the predictive performance of the FMF first-trimester screening algorithm for PE in a Danish population and compare its screening performance with that of the current Danish strategy using single major maternal risk factors.

METHODS

Study design and population

The PRESIDE (Pre-eclampsia Screening in Denmark) study was a prospective, non-interventional multicenter study conducted at six Danish hospitals: Copenhagen University Hospital Rigshospitalet, Copenhagen; Copenhagen University Hospital Herlev, Herlev; Copenhagen University Hospital Hvidovre, Hvidovre; Copenhagen University Hospital North Zealand, Hillerød; Odense University Hospital, Odense; and Aarhus University Hospital, Aarhus. All hospitals serve only patients from the public healthcare system. Women with a singleton

pregnancy attending cFTS at 11 + 2 to 14 + 1 weeks of gestation between May 2019 and December 2020 were invited to participate in the study. Exclusion criteria were age < 18 years, multiple pregnancy or inability to understand Danish or English.

Measures

Maternal characteristics and information on ASA use among participants were obtained via patient questionnaires and stored in the local fetal medicine database (Astraia; Astraia GmbH, Munich, Germany).

Blood pressure was measured in accordance with international guidelines[29] using an automated blood pressure measurement station developed at the Department of Electrical and Computer Engineering at Aarhus University, Aarhus, Denmark[30]. The automated blood pressure measurement station is based on the validated dual-arm blood pressure monitor (Microlife WatchBP Office AFIB; Microlife Corp., Taipei, Taiwan). A short video guide ensured that patients complied with the guidelines for the correct blood pressure measurement technique, including correct seating (both feet flat on the floor, back supported and arms supported at heart level) in a quiet setting, no movement or talking and 5-min rest before the first measurement[29]. Measurements were performed simultaneously on both arms and repeated three times, with a 1-min interval between measurements. The measurements were transferred automatically to and stored in a REDCap® database[31,32]. MAP for each measurement was calculated and the average of the first two available MAPs was used for risk calculation in accordance with the International Federation of Gynecology and Obstetrics (FIGO) best-practice recommendations[29]. Women with systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg at inclusion were advised to see an obstetrician or their family doctor.

Measurements of right and left UtA-PI using pulsed-wave transabdominal color Doppler were made by sonographers who had obtained the FMF certificate of competence in PE screening[33]. All measurements were obtained according to a standardized protocol, adapted from Khalil *et al.*[34], and the average value was recorded. An audit on UtA-PI measurements was completed halfway through inclusion and each sonographer received individual feedback. Maternal serum concentrations of PlGF and PAPP-A were measured in a blood sample taken on the day of inclusion (11 + 2 to 14 + 1 weeks of gestation). Blood samples were stored at −80°C and analyzed in batches when all women had delivered. All biochemical analyses were performed using the BRAHMS KRYPTOR compact PLUS or KRYPTOR GOLD platform (BRAHMS GmbH, Hennigsdorf, Germany).

Continuous variables were maternal age (years), height (cm), weight (kg), BMI (kg/m^2), gestational age (GA) at the time of the scan (days), GA at delivery (days) and birth weight (g). Categorical variables were maternal family history of PE, smoking during pregnancy, previous PE, chronic hypertension, diabetes Type 1, diabetes Type 2, systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), ethnicity (white, south Asian, mixed, east Asian or black), parity (nulliparous or parous) and conception (natural, via *in-vitro* fertilization or using ovulation drugs). The biophysical and biochemical markers considered in this study were MAP (mmHg), mean UtA-PI, PAPP-A concentration (IU/L) and PlGF concentration (ng/L) at inclusion. The measured values of MAP, UtA-PI, PlGF and PAPP-A were converted into multiples of the median (MoM) and the PE risk assessment for each woman was calculated blinded to outcome using the FMF screening algorithm. Data on ASA use among participants were verified in maternal records. Subjects were included for further analysis if they had complete information regarding the four risk markers used in the FMF algorithm, i.e. MAP, UtA-PI, PlGF and PAPP-A, in addition to maternal characteristics. For women who did not have all markers available, the measurements either were unsuccessful or were not completed. Most of the missing measurements were due to study blood samples that had not been taken, as we did not exclude women without a full set of samples from the study. A minor proportion of the missing markers were UtA-PI measurements that were unsuccessful due to poor ultrasound view and blood pressure measurements that were not performed because of dizziness of study participants.

Outcomes

Pregnancy outcomes, including GA at delivery and PE diagnosis, were collected from birth registries. For women with a diagnosis of PE or preterm birth and for a random sample of 15% without PE, the diagnosis was validated by going through maternal records.

Women with PE were categorized consistent with the FIGO initiative on PE[29], according to GA at delivery in the following groups: PE with delivery < 34 weeks of gestation (PE < 34 weeks, early-onset PE), PE with delivery < 37 weeks (PE < 37 weeks, preterm PE) and PE with delivery ≥ 37 weeks (PE ≥ 37 weeks, term PE). PE was defined according to the International Society for the Study of Hypertension in Pregnancy guidelines (ISSHP; 2018)[35] as follows: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg at least twice 4 h apart after 20 weeks of gestation and one or more of the following: proteinuria (dipstick analysis ≥ 1+ or 30 mg/dL, urinary protein ≥ 300 mg/24 h or spot urine protein/creatinine ratio ≥ 30 mg/mmol), renal insufficiency (plasma creatinine concentration ≥ 0.09 mmol/L or oliguria), liver disease (raised plasma transaminases > 40 IU/L and/or severe right upper-quadrant or epigastric pain), neurological problems (convulsions (eclampsia)), hyper-reflexia with clonus, severe headaches with hyper-reflexia, scotoma, hematological disturbances (thrombocytopenia, disseminated intravascular coagulation, hemolysis) or fetal growth restriction (ultrasound-estimated fetal weight < 10th percentile). In this study, for women with chronic hypertension, PE was defined as new signs and/or symptoms associated with PE

after 20 weeks of gestation. GA at birth was calculated using the estimated due date based on measurements of crown–rump length at cFTS.

None of the women with complete marker data was excluded from the analysis due to missing outcome or pregnancy termination, because the aim was a clinically applicable conservative intention-to-treat analysis of screening performance and because the anticipated missing data would be about 1%, corresponding to fewer than one woman developing preterm PE.

Statistical analysis

Sample size calculation was based on an estimated 80% DR of PE < 37 weeks' gestation for the FMF screening. The hypothesis was a significant difference in DRs between the FMF screening and the current Danish screening program with an estimated DR of 30% for PE < 37 weeks[7,9,36]. The results indicated that a sample of at least 8300 pregnant women, of which 250 would develop PE at any gestation, 58 would develop PE < 37 weeks and 25 would develop PE < 34 weeks, was required to obtain a power of 80% ($1-\beta=0.80$) and a risk of Type-I error of 5% ($\alpha=0.05$).

A statistical analysis plan was written to document the planned analyses and finalized before accessing the data. MoM values of MAP, UtA-PI, PlGF and PAPP-A were calculated according to the FMF default models[36] with adjustments applied based on standard quality control measures. Risks were calculated according to the FMF competing-risks model. MoM values, with center-specific adjustments, and risks were calculated blinded to outcome reflecting what would happen in standard practice[10,13].

Receiver-operating-characteristics (ROC) curves were constructed based on the FMF algorithm using maternal characteristics alone and in combination with the MoM values of MAP, UtA-PI, PlGF and PAPP-A. DRs of the FMF algorithm were calculated for a fixed screen-positive rate (SPR) of 10%. All DRs were calculated for maternal characteristics alone and for the different combinations of markers.

A proportion of women in the study, expected to be 3.5%[7], were prescribed ASA based on the current Danish guidelines. In the screen-positive group of women, some will develop PE and others will not. Furthermore, some of these women take ASA that is known to prevent preterm PE. By converting outcomes that would, without ASA, be true positives into false positives, treatment with ASA biases the assessment of screening performance. To reduce this bias, 10 datasets were generated in which none of the women was treated with ASA. These without-ASA datasets were produced by generating PE outcomes for some women who received ASA in the original dataset and delivered without PE. This process of imputation was implemented using Markov chain Monte Carlo methods using a model in which the incidence of PE that would have occurred, had it not been for the effect of treatment, was determined from a logistic regression model dependent on the logit transformation of risk using all four markers (MAP, UtA-PI, PlGF and PAPP-A)[37]. Estimates from the 10 without-ASA datasets were pooled using Rubin's Rules[38]. The WinBUGS software[39] was used for multiple imputation of preterm PE cases that were prevented by treatment with ASA. The R software[40] was used for other analyses. The pROC[41] package was used for the ROC-curve analysis. The MICE package[42] was used for pooling estimates from multiple imputations.

RESULTS

A total of 8783 women with a singleton pregnancy were included in the PRESIDE study. The median age of the study population was 30.8 years, 8335 (94.9%) were white and 4653 (53.0%) were nulliparous. Twenty-eight (0.3%) cases had APS/SLE, 10 (0.1%) had pregestational diabetes mellitus and 43 (0.5%) had chronic hypertension. The use of ASA at inclusion was found in 3.1%. Baseline characteristics of the study population are given in Table 1.

Table 1 Maternal and pregnancy characteristics of study population

Characteristic	*Total cohort* (n = *8783*)	*Cohort with four risk markers* (n = *8156*)*
Age (years)	30.8 (28.1–33.9)	30.8 (28.1–34.0)
Weight (kg)	66.0 (60.0–75.9)	66.0 (60.0–75.0)
Height (cm)	168 (164–173)	168 (164–173)
Body mass index (kg/m^2)	23.4 (21.2–26.6)	23.4 (21.2–26.5)
GA at scan (days)	89.0 (87.0–92.0)	89.0 (87.0–92.0)
Ethnicity†		
White	8335 (94.9)	7748 (95.0)
South Asian	168 (1.9)	155 (1.9)
Mixed	126 (1.4)	117 (1.4)
East Asian	86 (1.0)	76 (0.9)
Black	68 (0.8)	60 (0.7)
Medical history		
Chronic hypertension	43 (0.5)	37 (0.5)
DM Type 1	7 (0.1)	6 (0.1)
DM Type 2	3 (0.0)	2 (0.0)
SLE/APS	28 (0.3)	26 (0.3)
Smoker	270 (3.1)	246 (3.0)
Family history of PE	313 (3.6)	289 (3.5)
Method of conception		
Natural	7934 (90.3)	7367 (90.3)
In-vitro fertilization	580 (6.6)	543 (6.7)
Ovulation drugs	269 (3.1)	246 (3.0)
Parity		
Nulliparous	4653 (53.0)	4296 (52.7)
Parous, no PE	3897 (44.4)	3638 (44.6)
Parous, PE	233 (2.7)	222 (2.7)
GA at delivery (days)	281 (274–287)	281 (274–287)
Birth weight (g)	3558 (3232–3880)	3560 (3235–3880)
Acetylsalicylic acid use	276 (3.1)	254 (3.1)

Data are given as median (interquartile range) or *n* (%). *Women with complete information regarding four risk markers included in Fetal Medicine Foundation first-trimester screening algorithm for pre-eclampsia (PE), i.e. mean arterial pressure, uterine artery pulsatility index, serum pregnancy-associated plasma protein-A and serum placental growth factor. †Ethnicity reported by participants. APS, antiphospholipid syndrome; DM, diabetes mellitus; GA, gestational age; SLE, systemic lupus erythematosus.

A complete risk assessment, including maternal characteristics, MAP, UtA-PI, PlGF and PAPP-A, was available for 8156 (92.9%) women. Delivery outcome was available for 8028/8156 (98.4%) cases, of which 12 (0.1%) pregnancies were terminated before 21 + 6 weeks of gestation, 19 (0.2%) had a miscarriage, three (0.04%) resulted in intrauterine death ≥ 22 + 0 weeks, 19 (0.2%) delivered at home or at a private clinic and 69 (0.9%) were lost to follow-up (moved out of Denmark ($n = 34$) or records were not accessible ($n = 35$)).

In the final study population of 8156 pregnancies, 303 (3.7%) developed PE, including 16 (0.2%) with PE < 34 weeks' gestation, 55 (0.7%) with PE < 37 weeks and 248 (3.0%) women with PE ≥ 37 weeks. Median MAP was 80.5 (interquartile range (IQR), 76.1–85.4) mmHg and median MAP MoM was 0.99 (IQR, 0.95–1.05). Median UtA-PI was 1.58 (IQR, 1.27–1.94) and median UtA-PI MoM was 1.01 (IQR, 0.82–1.24). Median PAPP-A MoM and median PlGF MoM were 1.05 (IQR, 0.74–1.44) and 1.03 (IQR, 0.78–1.33), respectively.

DRs for different combinations of risk markers are summarized in Table 2. Combined screening based on maternal characteristics, MAP, UtA-PI, PlGF and PAPP-A detected 77.4% (95% CI, 57.6–97.2%) of cases with PE < 34 weeks, 66.8% (95% CI, 54.4–79.1%) of cases with PE < 37 weeks and 44.1% (95% CI, 38.5–49.7%) of cases with any PE at a 10% SPR. The results presented in Table 2 were obtained from multiple imputations with adjustment for ASA. The mean number of cases imputed was 1.8, 4.0 and 8.4 for PE < 34 weeks, PE < 37 weeks and PE with delivery at any GA, respectively. The results obtained without imputation were very similar, reflecting the low uptake of ASA (Table S1). Our analysis suggested that PlGF was superior to PAPP-A in the model including maternal characteristics, MAP and UtA-PI, as the addition of PlGF increased the DR for PE < 37 weeks from 53.4% (95% CI, 40.2–66.6%) to 68.5% (95% CI, 56.2–80.7%), whereas the addition of PAPP-A increased the DR to 55.1% (95% CI, 42.0–68.2%) at a 10% SPR. This finding was not tested statistically, as this study was not powered to compare DRs between the multiple marker combinations shown in Table 2.

For prediction of PE < 34 weeks, the model including maternal characteristics, MAP, UtA-PI, PlGF and PAPP-A showed an area under the ROC curve (AUC) of 0.93 (95% CI, 0.87–0.98). For prediction of PE < 37 weeks, the same model had an AUC of 0.89 (95% CI, 0.85–0.93). Figure 1 shows ROC curves and corresponding AUCs for PE < 34 weeks, PE < 37 weeks and any PE for the model including all markers. Figure 2 shows calibration plots for the predictive performance of the FMF screening algorithm.

The observed incidence of PE < 37 weeks was consistent with the one predicted by the FMF algorithm, as the calibration plot for preterm PE had a slope of 0.90 (95% CI, 0.74–1.05) (target value, 1) and an intercept of 0.39 (95% CI, 0.11–0.67) (target value, 0).

A total of 3.4% (278/8156) had at least one major risk factor corresponding to the current Danish screening (previous PE, diabetes mellitus, SLE, APS, chronic hypertension, chronic kidney disease and egg donation). The DRs for the current Danish screening after adjustment for ASA treatment were 25.0% (95% CI, 2.7–47.4%) for PE < 34 weeks and 19.6% (95% CI, 9.0–30.3%) for PE < 37 weeks in the PRESIDE cohort. When applying the FMF algorithm including maternal characteristics, MAP, UtA-PI and PlGF at the fixed SPR of 3.4%, the DRs were 60.5% (95% CI, 36.9–84.1%) for PE < 34 weeks

Table 2 Detection rates (DR) of pre-eclampsia (PE) with delivery < 34 weeks, < 37 weeks and at any gestational age (GA) for different combinations of risk markers, with imputation to adjust for acetylsalicylic acid treatment

	DR at 10% SPR (95% CI) (%)		
Marker combination	*PE < 34 weeks (n = 16)*	*PE < 37 weeks (n = 55)*	*PE at any GA (n = 303)*
MF*	36.3 (12.4–60.2)	39.1 (26.1–52.2)	30.0 (24.8–35.3)
MF + MAP	53.3 (29.5–77.0)	53.4 (40.3–66.5)	38.2 (32.6–43.8)
MF + PlGF	60.5 (36.9–84.1)	59.1 (46.4–71.9)	39.5 (34.0–45.1)
MF + PAPP-A	31.2 (7.6–54.7)	37.3 (24.3–50.3)	28.6 (23.4–33.8)
MF + UtA-PI	42.5 (18.1–66.8)	40.7 (27.6–53.8)	29.5 (24.3–34.7)
MF + MAP + PlGF	60.5 (36.9–84.1)	63.4 (50.9–75.9)	43.6 (37.9–49.2)
MF + MAP + PAPP-A	48.1 (23.7–72.5)	49.6 (36.3–63.0)	39.4 (33.8–45.0)
MF + MAP + UtA-PI	66.1 (43.4–88.8)	53.4 (40.2–66.6)	36.9 (31.3–42.4)
MF + PlGF + PAPP-A	54.8 (30.6–79.0)	57.6 (44.8–70.4)	38.9 (33.3–44.4)
MF + UtA-PI + PlGF	60.5 (36.9–84.1)	57.6 (44.6–70.6)	37.1 (31.7–42.5)
MF + UtA-PI + PAPP-A	43.0 (18.8–67.3)	39.3 (26.0–52.6)	28.6 (23.6–33.7)
MF + MAP + PlGF + PAPP-A	66.1 (43.4–88.8)	63.2 (50.7–75.8)	43.6 (38.0–49.2)
MF + MAP + UtA-PI + PlGF	77.4 (57.6–97.2)	68.5 (56.2–80.7)	43.5 (37.9–49.1)
MF + MAP + UtA-PI + PAPP-A	66.1 (43.4–88.8)	55.1 (42.0–68.2)	38.3 (32.8–43.8)
MF + UtA-PI + PlGF + PAPP-A	60.5 (36.9–84.1)	59.5 (46.7–72.3)	39.0 (33.6–44.5)
MF + MAP + UtA-PI + PlGF + PAPP-A	77.4 (57.6–97.2)	66.8 (54.4–79.1)	44.1 (38.5–49.7)

*Maternal factors (MF): family history of PE, smoking during pregnancy, previous PE, chronic hypertension, diabetes Type 1 or 2, systemic lupus erythematosus, antiphospholipid syndrome, ethnicity, parity (nulliparous or parous), mode of conception. MAP, mean arterial blood pressure; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; SPR, screen-positive rate; UtA-PI, uterine artery pulsatility index.

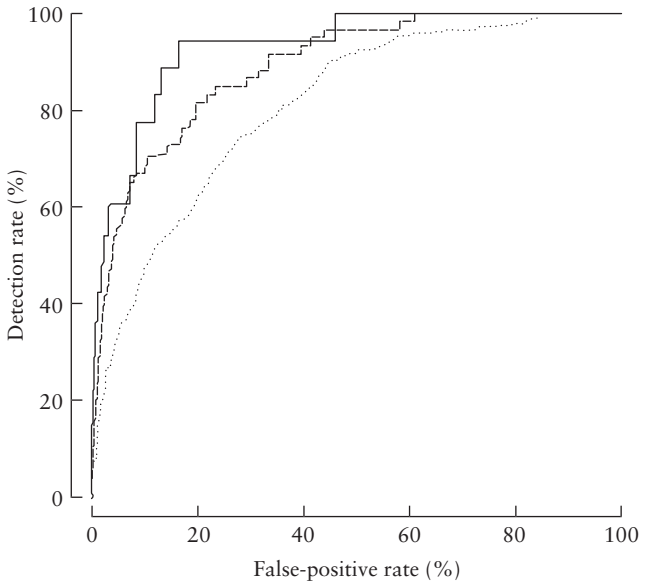

Figure 1 Receiver-operating-characteristics (ROC) curves for prediction of pre-eclampsia with delivery < 34 weeks (area under ROC curve (AUC), 0.93 (95% CI, 0.87–0.98)) (——), < 37 weeks (AUC, 0.89 (95% CI, 0.85–0.93)) (----) and at any gestational age (AUC, 0.81 (95% CI, 0.79–0.83)) (·····), using Fetal Medicine Foundation algorithm, including maternal factors, mean arterial blood pressure, uterine artery pulsatility index, placental growth factor and pregnancy-associated plasma protein-A.

and 45.2% (95% CI, 32.0–58.5%) for PE < 37 weeks. Thus, the increase in DR achieved by the FMF algorithm compared with the current Danish screening at a SPR of 3.4% was 35.5 (95% CI, 7.5–63.4) percentage points for PE < 34 weeks and 25.6 (95% CI, 11.7–39.5) percentage points for PE < 37 weeks.

DISCUSSION

Main findings and clinical implications

In this Danish multicenter study, we evaluated the predictive performance of the FMF first-trimester PE screening algorithm in 8156 pregnant women. We found that the FMF screening algorithm based on maternal characteristics, MAP, UtA-PI, PlGF and PAPP-A detected 77.4% of cases with PE < 34 weeks' gestation, 66.8% of cases with PE < 37 weeks and 44.1% of cases with any PE at a 10% SPR. These DRs are substantially higher compared to those found using the current Danish strategy based on single major risk factors.

Our findings have at least four implications. First, this study is an independent validation of the FMF first-trimester screening algorithm for preterm PE completed in a predominantly white, low-risk population. Our findings are comparable to the results reported in the FMF study[13] and are in line with prior validation

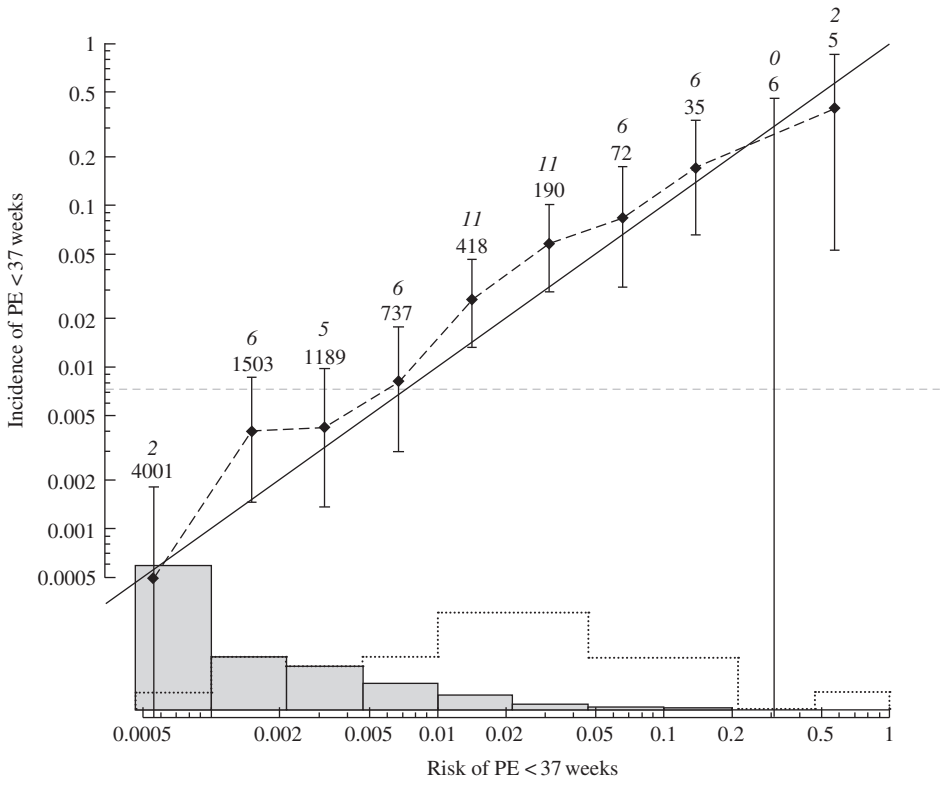

Figure 2 Calibration plot for performance of Fetal Medicine Foundation algorithm in predicting pre-eclampsia (PE) with delivery < 37 weeks (slope, 0.8953 (95% CI, 0.7441–1.0465); intercept, 0.3895 (95% CI, 0.1097–0.6692)). Diamonds show observed incidence within each risk group and error bars are 95% CI. Numbers above error bars show total number of cases and number of cases with PE < 37 weeks (italic). Histograms show distribution of pregnancies without PE (□) and those with PE < 37 weeks (·····). Diagonal line indicates perfect calibration, in which predicted and observed probabilities are equal.

studies conducted in Asian[26,27] and Brazilian[24,25] populations. Previous validation studies have shown that performance of FMF screening depends on the ethnic composition of the population and DRs for preterm PE range from 64%[26] to 91%[43] at a SPR of 10%. In the study of Tan *et al.*[36], using data from three previously reported prospective non-intervention screening studies, participants were categorized according to ethnicity, and the DR for PE < 37 weeks among white women was 69%, which is in accordance with our findings. Knowledge about ethnic differences is particularly important, since the original FMF studies were performed in mixed European populations[13,23,44].

Second, we found that the FMF screening algorithm had overall higher DRs for preterm PE compared with the current Danish strategy using single major risk factors[7]. The current Danish strategy yielded DRs of 25.0% for PE < 34 weeks and 19.6% for PE < 37 weeks at a SPR of 3.4%, compared with respective values of 60.5% and 45.2% yielded by the FMF algorithm including maternal characteristics, MAP, UtA-PI and PlGF at the same SPR. National implementation of PE screening in Denmark based on our results would translate into an increased detection of preterm PE and a higher proportion of pregnant women being offered prophylactic treatment with ASA. Treatment with ASA has previously been shown to effectively reduce preterm PE in high-risk pregnancies and is well-tolerated in pregnancy.

Third, this study contributes to the growing evidence concerning the optimal combination of biomarkers in the FMF screening algorithm[13,37,45–49]. Several studies have listed DRs for the different combinations of risk markers and the ideal model will probably not be the cheapest. We found that PlGF was superior to PAPP-A in detecting preterm PE. Specifically, in the model including maternal characteristics, MAP and UtA-PI, the addition of PlGF increased the DR of PE < 37 weeks by 15.1 percentage points, whereas the addition of PAPP-A increased the DR by only 1.7 percentage points. This finding is consistent with previous reports[13,37,48]. A recent study on 25 226 women, including 194 (0.8%) women who developed preterm PE, found that the addition of PAPP-A to the model including a combination of maternal characteristics, MAP and UtA-PI did not significantly improve the DR of preterm PE[37], whilst the addition of PlGF increased the DR by approximately seven percentage points. PAPP-A is routinely measured as part of the cFTS[50,51], which has been used as an argument for using this biomarker in screening for preterm PE instead of PlGF.

Fourth, this study supports the applicability of screening for preterm PE in the setting of a public healthcare system in which cFTS is already widely used. Denmark was the first country to implement nationwide cFTS screening[52] in 2004, the current uptake is > 90% and the expansion of the existing infrastructure to include PE screening seems straightforward. PE screening may obtain an even higher acceptance rate than the cFTS, and screening for PE is also relevant in countries with a lower cFTS uptake. The proportion of pregnant women reporting treatment with ASA in this study (3.1%) was at the level expected according to current Danish guidelines (3.5%)[7]. We expect good compliance with ASA treatment among women who are screen-positive according to the FMF algorithm, because these women will be advised that the treatment is targeted at those at high risk of PE. Since screening would be offered nationwide, implementation must be approved by the Danish Health Authority. In the case of successful implementation, Denmark would be one of the first countries to offer nationwide screening for preterm PE.

Strengths and limitations

The strength of this study is the large sample size, the multicenter setup with FMF-certified sonographers and involvement of multiple central laboratories. This setup mimics the Danish healthcare system and strengthens the reproducibility of our findings. MAP measurements were conducted in a standardized setup, ensuring compliance with the guidelines for a correct blood pressure measurement technique and consistency across hospitals. Audit of UtA-PI was carried out during the inclusion period to maintain high quality of the data. The study was conducted in a low-risk population and accounted for ASA intake as specified in the statistical analysis plan.

Our findings should be interpreted within the context of their limitations. This study was based on a large sample of pregnant women recruited at six Danish maternity hospitals, all of which are university hospitals, located close to the largest Danish cities. Participants are therefore likely to be healthier and have a higher educational level compared with the national background population. Furthermore, women who were not able to understand Danish or English were not eligible for inclusion. Thus, our results may not be completely generalizable to the Danish population. cFTS quality is comparable between different regions of Denmark[28]. We therefore find it unlikely that PE screening performance would decrease if this screening is implemented nationwide. The small number of preterm PE cases is a limitation of this study and, despite the relatively large total sample size, the low frequency of the condition causes the CIs to be wide.

Conclusion

In this Danish multicenter study of 8156 singleton pregnancies, a total of 3.7% developed PE and 0.7% had PE < 37 weeks of gestation. At a SPR of 10%, the FMF algorithm, including maternal characteristics, MAP, UtA-PI, PlGF and PAPP-A, predicted 66.8% of cases developing PE < 37 weeks and 77.4% of cases developing PE < 34 weeks, suggesting that the performance of the algorithm in a Danish cohort matches that in other populations.

ACKNOWLEDGMENTS

We thank the staff at the fetal medicine departments of the participating hospitals and the following individuals who helped with recruitment and day-to-day running of the PRESIDE project: Cathrine Vedel, Emma Julie Bendix and all sonographers at the six participating hospitals.

We thank the financial supporters of the PRESIDE study: Dr Sofus Carl Emil and wife Olga Doris Friis' Grant; The A.P. Møller Foundation; The Jascha Foundation; The Copenhagen University Hospital Rigshospitalet, Copenhagen and Odense University Hospital, Odense, Denmark joint Research Fund; The Research Fund of Copenhagen University Hospital Rigshospitalet, Copenhagen Denmark; and The Research Fund of the Capital Region of Denmark.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Detection rates of pre-eclampsia by different combinations of risk markers without imputation (without adjustment for acetylsalicylic acid treatment)