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Prediction of preterm pre-eclampsia at midpregnancy using a multivariable screening algorithm

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Abstract

Background: Competing risk models used for midpregnancy prediction of preterm pre-eclampsia have shown detection rates (DR) of 85%, at fixed false-positive rate (FPR) of 10%. The full algorithm used between 19⁺⁰ and 24⁺⁶ weeks includes maternal factors, mean arterial pressure (MAP), mean uterine artery pulsatility index (UtAPI), serum placental growth factor (PlGF) level in multiples of the median (MoM), and soluble Fms-like tyrosine kinase-1 (sFlt-1) level in MoM.

Aims: to assess performance of the Fetal Medicine Foundation (FMF) algorithm at midpregnancy to screen for preterm (<37 weeks') pre-eclampsia. The outcome measured was preterm pre-eclampsia.

Materials and Methods: Prospective study including singleton pregnancies 19-22 weeks' gestation. Maternal bloods were collected and analysed using three different immunoassay platforms. Maternal characteristics, medical history, MAP, mean UtAPI, serum PlGF MoM and serum sFlt-1 MoM were used for risk assessment. DR and FPR were calculated, and receiver operating characteristic curves produced.

Results: 512 patients were included. Incidence of preterm pre-eclampsia was 1.6%. Using predicted risk of pre-eclampsia of 1 in 60 or more and 1 in 100 or higher, as given by the FMF predictive algorithm, the combination with the best predictive performance for preterm pre-eclampsia included maternal factors, MAP, UtAPI and PlGF MoM, giving DR's 100% and 100%, respectively, and FPR's 9.3 for all platforms and 12.9-13.5, respectively. Addition

of sFlt-1 to the algorithm did not appear to improve performance. sFlt-1 MoM and PlGF MoM values obtained on the different platforms performed very similarly.

Conclusions: Second trimester combined screening for preterm pre-eclampsia by maternal history, MAP, mean UtAPI and PlGF MoM using the FMF algorithm performed very well in this patient population.

INTRODUCTION

Pre-eclampsia is a multisystem disorder affecting 3% of pregnancies in Australia ¹, responsible for maternal and perinatal morbidity and mortality ². Current evidence indicates that midpregnancy screening for pre-eclampsia may be less useful than first trimester screening, as the window of opportunity for women considered high risk for pre-eclampsia to benefit from aspirin administration will have diminished ^{3,4}. However, given that up to one third of patients in Australia commence antenatal care beyond 14 weeks' gestation ⁵, midpregnancy screening would still prove useful, avoiding unnecessary interventions in low risk women and ensuring that those at high risk are triaged to appropriate models of care.

Traditionally, pre-eclampsia risk assessment has been based on maternal demographic characteristics and medical and obstetric history, collectively referred to as maternal factors. These traditional methods, whilst inexpensive and requiring minimal resources, have poor detection rates (DR) and high false positive rates (FPR) ^{6,7}. Within the last decade, multivariable prediction algorithms have shown superior performance for the prediction of pre-eclampsia than the traditional approach of screening with maternal history alone ⁶. The Fetal Medicine Foundation (FMF) in the United Kingdom has devised a multivariable algorithm for prediction of pre-eclampsia, based on a competing risks model ⁸. The FMF algorithm calculates the individual risk of developing pre-eclampsia, similar to screening for fetal chromosomal abnormalities. This calculation takes into account maternal characteristics

(such as weight, height, ethnicity), medical history (chronic hypertension, SLE, etc), obstetric history (parity, previous pre-eclampsia), and family history (mother with pre-eclampsia) to estimate the background or *a priori* risk. This predicted risk is then adjusted according to the results of biophysical markers (uterine artery Doppler, mean arterial pressure) and biochemical markers (PIGF, sFlt-1), and the final risk is reported. This algorithm has been validated and calibrated in several different patient populations⁹⁻¹³ and is available online at www.fetalmedicine.org. When used between 19⁺⁰ and 24⁺⁶ weeks, markers required for the full algorithm include maternal factors, mean arterial pressure (MAP), mean uterine artery pulsatility index (UtAPI), serum placental growth factor (PIGF) level in multiples of the median (MoM), and soluble Fms-like tyrosine kinase-1 (sFlt1) level in MoM.

Previous studies using algorithms for the prediction of preterm and early-onset pre-eclampsia in the second trimester, defined as pre-eclampsia requiring delivery <37 weeks' and <32 weeks', respectively, have shown detection rates of around 85% and 99%, respectively, at a fixed false-positive rate of 10%¹¹. The FMF clinical algorithm has been previously validated in the Australian population for first trimester screening for pre-eclampsia⁹. The present study aims to assess the clinical validity of using this algorithm to screen for preterm pre-eclampsia between 19 and 22 weeks' gestation within a similar Australian population.

MATERIALS AND METHODS

Study population

This was a prospective observational study in singleton pregnancies. Women booking for antenatal care between 19 and 22 weeks' gestation at The Royal Women's Hospital in Melbourne, Australia, between June 2012 and January 2015 were eligible. Gestational age was confirmed by crown-rump length measured in the first trimester. Women with multiple

pregnancies, major fetal anomalies, fetal aneuploidy, fetal death or pregnancy loss prior to 24 weeks' gestation were excluded, as were women with substantial missing outcome data.

Study participants represented the general pregnant population, but were required to be able to give written informed consent in English. The study was approved by the Royal Women's Hospital Research and Ethics Committee (project approval number 11/23). Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at The University of Melbourne ¹⁴.

Baseline characteristics and confirmation of eligibility were obtained through participant interview. Pregnancy outcomes were determined and diagnosis of pre-eclampsia was confirmed or excluded by review of individual medical records by two independent adjudicators.

Pre-eclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) research definition, as *de novo* hypertension (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg) after 20 weeks' gestation, plus proteinuria, defined as ≥ 300 mg per day on 24 hour collection or a spot protein/creatinine ratio ≥ 30 mg/mmol ¹⁵. While the ISSHP guidelines have since been revised ^{16, 17}, the guidelines published in 2014 were applicable at the time this study was designed and conducted. Pre-eclampsia was classified according to gestation at delivery as 1) early-onset pre-eclampsia (< 34 weeks); 2) preterm pre-eclampsia (< 37 weeks) or 3) term pre-eclampsia (≥ 37 weeks). In women with pre-existing hypertension, worsening of hypertension, defined by a rise in systolic blood pressure of 20mmHg above baseline, and an increase in proteinuria from their baseline protein to creatinine ratio resulted in a diagnosis of pre-eclampsia.

Blood sample collection and storage

A single blood sample was collected from each participant at recruitment. A volume of 10mL of maternal blood was drawn and divided between non-heparinised, silicone coated tubes for serum samples and ethylenediaminetetraacetic acid (EDTA) tubes for plasma samples. Samples were centrifuged and transferred into plain polypropylene tubes and stored as serum or plasma at -80°C until the time of analysis. Sample analysis was undertaken by one technician blinded to clinical outcomes.

Immunoassay platforms

Single measurements for each patient were performed on each of three immunoassay platforms between April 2015 and February 2017 in the following order:

- 1) **DELFI[®] A₁press** (Perkin Elmer, Inc. Wallac Oy, Turku, Finland): PlGF only,
- 2) **cobas[®] e 411** (Roche Diagnostics, GmbH): PlGF and sFlt-1, and
- 3) **B.R.A.H.M.S KRYPTOR compact PLUS** (ThermoScientific, GmbH): PlGF and sFlt-1.

Sample analysis was performed according to manufacturer's instructions for each platform. Inter- and intra-assay CVs obtained within our laboratory fell within an acceptable range to demonstrate minimal variation between samples tested.

Maternal demographic characteristics and medical, obstetric and family history were recorded at enrolment, as were values for MAP, following two measurements taken from each arm according to a previously published technique¹⁸. A standardised colour Doppler technique was used to measure the right and left UtAPI by transabdominal ultrasound and the

average value was recorded ^{19, 20}. These ultrasound parameters were obtained at the time of the routine morphology scan.

Statistical analysis

Patient baseline characteristics were compared using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Data were assessed for normality and found to be non-parametric. After logarithmic transformation, the results for PlGF, sFlt-1 and the sFlt-1/PlGF ratio from each immunoassay platform were adjusted for maternal characteristics found to significantly influence the logarithmic results on backward stepwise linear regression analysis and expressed as multiples of the expected median (MoM).

Individual patient risk calculations for preterm pre-eclampsia, using the FMF multivariable algorithm, were undertaken retrospectively at the completion of the study by the same clinician (DR), who was blinded to patient outcomes. Maternal characteristics required for the purpose of the algorithm included maternal date of birth, height, weight, racial origin, smoking status, conception method, parity, history of maternal pre-eclampsia, history of chronic hypertension, diabetes, systemic lupus erythematosus or antiphospholipid syndrome.

Screening performance for different combinations was then evaluated using receiver operating characteristic (ROC) curves. Sensitivities and specificities at risk cut-offs of 1 in 60 and 1 in 100 were evaluated to compare predictive performance using DR and FPR for preterm (<37weeks) pre-eclampsia. Data analysis was performed using Microsoft® Excel™

2016 (Redmond, Washington, USA) and IBM Statistical Package for the Social Sciences (SPSS) Version 24 (Armonk, New York, USA).

RESULTS

Descriptive Statistics

There were 600 patients recruited for the overall research study, and of these, 88 (14.6%) were excluded from analysis. Seven exclusions occurred due to diagnosis of aneuploidy or major fetal anomaly, and 81 exclusions were due to incomplete data, leaving 512 patients for inclusion in the analysis (Figure 1). There were 25 patients (4.9%) with pre-eclampsia, including 17 patients (3.3%) with term pre-eclampsia (≥ 37 weeks), 8 patients (1.6%) with preterm pre-eclampsia (< 37 weeks) and 3 patients (0.6%) with early-onset pre-eclampsia (< 34 weeks). The group who developed preterm pre-eclampsia included those who developed early-onset pre-eclampsia.

Baseline demographic and clinical characteristics of the study population are summarised in Table 1. Baseline demographic and clinical characteristics of the study population are summarised in Table 1. The majority of patients were white (75.4%), with the minority (8.6%, 8.0% and 3.5%) being East Asian, South Asian and Black, respectively. The majority of patients (45.5%) were in the healthy weight category, with 32.8% being overweight and 21.1% being obese.

ROC curves of predicted risks using the FMF algorithm for prediction of pre-eclampsia using combined values for maternal history, MAP, UtAPI MoM and PlGF MoM +/- sFlt-1 MoM are shown in Figures 2 and 3. DR and FPR using predicted risk of pre-eclampsia of 1 in 60 or more and 1 in 100 or higher before 37 weeks and areas under the curve (AUC) are summarised in Table 2.

Maternal factors alone in this patient population performed well based on AUC. The addition of PlGF MoM significantly improved the AUC compared with use of maternal factors alone, with further addition of MAP and UtAPI resulting in excellent AUC's. sFlt-1 MoM and PlGF MoM values obtained on the different platforms performed very similarly.

The best markers for prediction of preterm pre-eclampsia for the patient population in this study were UtAPI and PlGF MoM, hence combinations including these two markers demonstrated the best predictive performance (Table 2 and Supplementary Table S1). AUC was not significantly improved by the addition of sFlt-1 MoM to the algorithm.

AUC for prediction of preterm and early-onset pre-eclampsia using maternal factors, MAP, UtAPI and PlGF MoM from one of the three platforms were 0.983-0.984 (Table 2) and 0.971-0.974 (Supplementary Table S2), respectively.

As shown in Table 2 and Supplementary Table S1, the addition of PlGF MoM halved the FPR compared to maternal factors and UtAPI alone and reduced the FPR by a further 30% compared to using maternal factors, MAP and UtAPI. PPV's using the multivariable algorithm was significantly higher than that when using biomarkers alone (Supplementary Table S2).

DISCUSSION

A cut-off of 1 in 100 for preterm pre-eclampsia results in a screen positive rate of about 10%, and the fact that this cut-off has been utilised in larger studies^{4,10-13} was the reason we chose it for our study. In this study population using a screen positive as a risk of 1 in 100, for the 512 participants, 76 (14.8%) screened positive, of which 8 (1.6%) were true positives and 68 (13.2%) were false positives. We also decided to evaluate a higher risk group defined by a cut-off of 1 in 60, as this would identify approximately 5% of the population at higher risk of preterm pre-eclampsia. Using predicted risk of pre-eclampsia of 1 in 60 or more and 1 in 100 or higher, as given by the FMF predictive algorithm, the combination with the best predictive performance for preterm pre-eclampsia included maternal factors, MAP, UtAPI and PlGF MoM, giving DR of 100% and 100%, respectively, and FPR 9.3 and 12.9-13.5, respectively. Addition of sFlt-1 to the algorithm did not appear to improve performance. sFlt-1 MoM and PlGF MoM values obtained on the different platforms performed very similarly.

Given that no single screening test for pre-eclampsia to date has demonstrated adequate performance for international health authorities to recommend use in everyday clinical practice, many researchers have combined tests in attempt to improve overall predictive value^{6, 7, 9, 11, 12, 21-24}. By using multiple parameters, pathological biochemical and biophysical abnormalities behind this multifactorial condition are more likely to be captured and hence prove beneficial in a screening setting. Combining risk factors into an algorithm to provide an individualised risk assessment has been shown to be significantly more effective than screening by maternal factors alone. Gallo in 2015¹¹ used a competing risks model in 8079 pregnancies between 19-24 weeks gestation and reported that screening by maternal factors only predicted 52%, 47% and 37% of pre-eclampsia at <32, <37 and $\geq$ 37 weeks' gestation,

respectively, for a FPR of 10%. The respective values for combined screening with maternal factors, MAP, UtAPI and PlGF MoM were 99%, 85% and 46%, with no further improvement in performance with the addition of sFlt-1. Al-Amin 2018⁷ used the same patient population as ours to compare the performance of the NICE (National Institute for Health and Clinical Excellence) and ACOG (American College of Obstetricians and Gynecologists 2013) guidelines^{25,26} for the prediction of pre-eclampsia using the multivariable FMF algorithm between 19-22 weeks' gestation including maternal history, MAP and UtAPI without the use of biochemical markers. They showed that DR using the FMF algorithm showed far superior performance over maternal factors alone, with DR for prediction of preterm pre-eclampsia 75%, 87%, 100% and 100% for NICE guidelines, ACOG recommendations, FMF algorithm with a cut-off 1 in 60 and FMF algorithm with a cut-off 1 in 100, respectively. The addition of PlGF MoM from one of the three platforms to the FMF algorithm in the present study could not further improve this DR but resulted in lower FPR's. Using a cut-off value 1 in 60, 100% cases of early-onset and preterm pre-eclampsia were detected with FPR 9.3% across all three platforms. At a cut-off of 1 in 100, 100% cases of early-onset and preterm pre-eclampsia were detected with FPR 12.9-13.5 across the three platforms.

In agreement with the study by Gallo in 2015¹¹, addition of sFlt-1 MoM did not significantly improve the predictive performance of the algorithm, which was expected given that sFlt-1 values were not significantly different in affected and unaffected pregnancies for the prediction of pre-eclampsia within our patient cohort. It would therefore be reasonable to exclude sFlt-1 MoM from the algorithm in order to minimise costs and resources and recommend that screening for preterm pre-eclampsia with the FMF algorithm, using maternal history, MAP, UtAPI and PlGF MoM gives the best predictive performance at 19-22 weeks' gestation.

Screening for preterm pre-eclampsia using the FMF multivariable algorithm significantly improved DR and lowered FPR compared with use of biomarkers alone, results which have been previously reported ²⁷. PPV using the multivariable algorithm in the present study was significantly higher than that when using biomarkers alone, with values between 22% and 24%. When using the FMF algorithm including PlGF MoM for the prediction of preterm pre-eclampsia, all 8 cases of preterm pre-eclampsia were detected, with no false negatives.

The implementation of a multivariable algorithm should prove feasible within a tertiary hospital setting. Recording of maternal factors should be routinely arranged at pregnancy booking. Measurement of MAP can easily be performed by healthcare professionals after minimal training using inexpensive blood pressure devices ¹⁸. Measurement of UtAPI requires specific training for sonographers but can be performed relatively quickly during the routine midpregnancy morphology scan ²⁰. Conversion of raw data values to MoM and pre-eclampsia risk calculation requires expertise with this technique. Regular ongoing audits for quality assurance of biomarker measurement would need to be implemented, along with auditing of pregnancy outcomes.

Adding PlGF MoM levels to this algorithm would incur costs associated with collection and analysis of blood results, commercial immunoassay machines and consumables. Whilst a formal cost-benefit analysis is required, the lower FPR observed by adding PlGF MoM to the model would reduce costs of unnecessary monitoring and could justify the cost of addition of PlGF MoM to the algorithm. The lower FPR may also reduce anxiety associated with a positive test result ²⁸.

Use of the FMF algorithm at midpregnancy to determine whether patients are at high risk or low risk for the development of preterm pre-eclampsia has multiple advantages over screening methods currently used in everyday clinical practice, which tend to detect pre-eclampsia only once symptoms arise beyond 20 weeks' gestation²⁹. Clinically, prophylactic agents shown to reduce the risk of pre-eclampsia include low-dose aspirin and calcium commenced in the first or early second trimester. Other benefits in stratifying pre-eclampsia risk in midpregnancy include triaging to appropriate models of care, enhanced surveillance for those at high risk, and reassurance for those who screen negative³⁰. From a research perspective, accurate prediction of preterm pre-eclampsia aids recruitment for future studies investigating prophylactic or therapeutic agents for pre-eclampsia, or the validation of additional predictive markers. Outcomes of such studies have the potential to improve current understanding and management of this complex disease.

The strengths of this study included: 1) two independent adjudicators checking patient outcomes; 2) use of fully automated platforms to optimise accuracy of results; 3) one technician for blood sample analysis, blinded to outcomes throughout testing and 4) conversion of biomarker levels to MoM. Limitations included: 1) small sample size, particularly for preterm (8 patients) and early-onset (3 patients) pre-eclampsia. Another potential limitation was the increasing proportion of previously thawed samples when using the second (Cobas) and third (Kryptor) analysers, however, in a previous paper published by our group (submitted for publication), there did not appear to be any marked difference in results obtained for samples that had undergone up to five freeze-thaw cycles.

Screening at midpregnancy for the development of preterm pre-eclampsia using the multivariable FMF algorithm, incorporating maternal factors, MAP, UtAPI and PlGF MoM,

appears to be effective within an Australian population, with superior performance compared with screening using PIGF or the sFlt-1/PIGF ratio alone. Whilst the addition of PIGF reduced the false-positive rate and different platforms performed equally well, the use of sFlt-1 was not useful. Future studies comparing patients who are screened with this algorithm with those undergoing usual care are required to determine the extent to which combined screening may optimise clinical outcomes.

TABLE AND FIGURE LEGENDS

Table 1. Characteristics of the study population for midpregnancy prediction of pre-eclampsia

Table 2. Detection rates (DR) and False-positive rates (FPR) for preterm pre-eclampsia using different combinations of biophysical and biochemical markers with maternal factors. MAP = mean arterial pressure. UtAPI = mean uterine artery pulsatility index. AUC = area under the receiver operating characteristics curve.

Figure 1. Consort Observational Study Diagram

Figure 2. ROC curves using the FMF algorithm for prediction of pre-eclampsia using combined values for maternal history, MAP, UtAPI MoM and PlGF MoM for Delfia, Cobas and Kryptor platforms.

Figure 3. ROC curves using the FMF algorithm for prediction of pre-eclampsia using combined values for maternal history, MAP, UtAPI MoM, PlGF MoM and sFlt-1 MoM for Cobas and Kryptor platforms.

Supplementary Table S1. Detection rates (DR) and False-positive rates (FPR) for preterm pre-eclampsia using different combinations of biophysical and biochemical markers with maternal factors.

Supplementary Table S2. Prediction of preterm pre-eclampsia using the FMF algorithm, combining values for maternal history, MAP, UAPI MoM, PlGF MoM +/- sFlt-1 MoM values.

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Maternal Characteristics	Unaffected (n=487)	PE < 34 weeks (n=3)	PE < 37 weeks (n=8)	PE ≥ 37 weeks (n=17)
Maternal age in years	35.4 (31.2-38.3)	35.7 (33.3-36.9)	33.8 (30.0-36.0)	33.1 (29.5-35.4)
Maternal weight in kg	68.2 (62.0-78.0) *	96.0 (84.0-97.0)	85.5 (70.5-97.0) *	76.0 (64.0-93.0)
Maternal height in cm	164.8 (160.0-169.0)	164.0 (160.0-167.3)	163.3 (157.8-169.3)	164 (163-167)
BMI	25.2 (23.0-28.4) *	33.7 (30.3-36.6) *	32.1 (27.3-34.8) *	28.7 (23.8-34.6)
GA in weeks	20.3 (20.0-20.9)	20.7 (20.4-21.0)	20.3 (20.1-21.0)	20.6 (20.1-21.3)
GA at delivery	39.3 (38.1-40.4)	30.1 (29.2-31.1)	35.9 (31.1-36.3)	38.14 (37.7-39.1)
Racial origin, n (%)				
Caucasian	366 (75.2)	2 (66.6)	5.0 (62.5)	15.0 (88.2)
Afro-Caribbean	17.0 (3.5)	0.0	1.0 (12.5)	0.0
South Asian	40.0 (8.2)	0.0	1.0 (12.5)	0.0
East Asian	41.0 (8.4)	1 (33.3)	1.0 (12.5)	2.0 (11.8)
Mixed	23.0 (4.7)	0.0	0.0	0.0
Medical History, n (%)				
Chronic hypertension	17 (3.5)	1 (33.3)	3 (37.5) *	0.0
Diabetes Mellitus, n (%)				
Type 1	14 (2.9)	1(33.3)	1 (12.5)	3 (17.6) *
Type 2	8 (1.6)	0.0	1 (12.5)	0.0
Gestational Diabetes	22 (4.5)	0.0	2 (25.0)	0.0
SLE	2 (0.4)	0.0	0.0	0.0
APS	3 (0.6)	0.0	0.0	1 (5.9)
Cigarette smokers, n (%)	33 (6.8)	0.0	1 (12.5)	2 (11.8)
Family history of PE, n (%)	33 (6.8)	0.0	0.0	1 (5.9)
Parity, n (%)				
Nulliparous	206 (42.3)	1 (33.3)	1 (12.5)	11 (64.7)
Parous with no previous PE	248 (50.9)	2 (66.6)	4 (50.0)	4 (23.5)
Parous with previous PE	33 (6.8)	0.0	3 (37.5) *	2 (11.8)
Infant Characteristics				
Birthweight (g)*	3351.0 (3028.0-3690.0)	1193.0 (1088.0-1244.0)*	2114.0 (1244.0-3161.5)*	3420.0 (3192.0-3680.0)

PE = pre-eclampsia; GA = gestational age; BMI = body mass index; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome. Values reported in median (interquartile range) unless otherwise stated.

* p<0.05 when compared to the unaffected group

Table 1. Characteristics of the study population for midpregnancy prediction of pre-eclampsia.

Data entered into FMF algorithm	AUC	Cut-Off 1/50		Cut-Off 1/100		FPR 5%	FPR 10%
		DR (%)	FPR (%)	DR (%)	FPR (%)	DR (%)	DR (%)
Maternal factors	0.847	75.0	14.3	87.5	29.4	75.0	75.0
Maternal factors with:							
UtAPI + DELFIA® Xpress PIGF MoM	0.987	100	10.1	100	18.3	100	100
UtAPI + cobas® e 411 PIGF MoM	0.988	100	10.3	100	18.1	100	100
UtAPI + KRYPTOR PIGF MoM	0.988	100	9.9	100	18.3	100	100
UtAPI + cobas® e 411 sFlt-1 MoM	0.974	100	15.7	100	24.8	87.5	87.5
UtAPI + KRYPTOR sFlt-1 MoM	0.974	100	15.7	100	24.0	87.5	87.5
UtAPI + cobas® e 411 PIGF MoM + cobas® e 411 sFlt-1 MoM	0.988	100	9.9	100	17.5	100	100
UtAPI + KRYPTOR PIGF MoM + KRYPTOR sFlt-1 MoM	0.988	100	10.1	100	17.7	100	100
MAP + UtAPI + DELFIA® Xpress PIGF MoM	0.984	100	8.1	100	13.5	87.5	100
MAP + UtAPI + cobas® e 411 PIGF MoM	0.984	100	7.9	100	13.3	87.5	100
MAP + UtAPI + KRYPTOR PIGF MoM	0.983	100	7.9	100	12.9	87.5	100
MAP + UtAPI + cobas® e 411 sFlt-1 MoM	0.972	87.5	10.9	100	17.5	87.5	87.5
MAP + UtAPI + KRYPTOR sFlt-1 MoM	0.974	87.5	10.9	100	17.7	87.5	87.5
MAP + UtAPI + cobas® e 411 PIGF MoM + cobas® e 411 sFlt-1 MoM	0.985	100	8.1	100	12.7	87.5	100
MAP + UtAPI + KRYPTOR PIGF MoM + KRYPTOR sFlt-1 MoM	0.983	100	7.7	100	12.9	87.5	100

Table 2. Detection rates (DR) and False-positive rates (FPR) for preterm pre-eclampsia using different combinations of biophysical and biochemical markers with maternal factors. MAP = mean arterial pressure. UtAPI = mean uterine artery pulsatility index. AUC = area under the receiver operating characteristics curve.

Figure 1. Patients who developed preeclampsia from those included for analysis.

Figure 2. ROC curves using the FMF algorithm for prediction of pre-eclampsia using combined values for maternal history, MAP, UtAPI MoM and PIGF MoM for Delfia, Cobas and Kryptor platforms.

Figure 3. ROC curves using the FMF algorithm for prediction of pre-eclampsia using combined values for maternal history, MAP, UtAPI MoM, PIGF MoM and sFlt-1 MoM for Cobas and Kryptor platforms.

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