First-trimester screening for preeclampsia and small-for-gestational-age: A comparison of the Gaussian and FMF algorithms

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Abstract

Objective: To compare the predictive accuracy of the Gaussian and FMF algorithms for preeclampsia (PE) and small for gestational age fetuses (SGA). Design: Secondary analysis of a prospective cohort study. Setting: Tertiary referral hospital. Population: 2641 singleton pregnancies attending routine first-trimester scan from October 2015 to September 2017. Methods: Maternal characteristics, mean arterial blood pressure (MAP), and mean uterine artery pulsatility index (UtAPI) were recorded at the first-trimester scan. Serum placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A) were assessed between 8+0 and 13+6 weeks of gestation. Main outcome measures: The areas under the curve (AUC) for the predictive performance for early-onset (delivery <34 weeks) and preterm (delivery <37 weeks) PE, and early-onset (delivery <32 weeks) and preterm (delivery <37 weeks) SGA, were calculated with the Gaussian and FMF algorithms, and were subsequently compared. Results: Among the 2641 participants, 30 (1.14%) developed preterm PE, including 11 (0.42%) early-onset PE. Among the 2483 newborns, 44 (1.77%) were preterm SGA, including eight (0.32%) early-onset SGA. The FMF and the Gaussian algorithm showed a similar predictive performance for most outcomes and marker combinations. Conclusions: This study shows that the first-trimester Gaussian and FMF algorithms have similar performances for PE and SGA prediction. Accuracy of the FMF algorithm was similar to that reported in the original studies, adding evidence to its external validity. Funding: none Keywords: preeclampsia, screening, PlGF, early-onset preeclampsia, uterine artery Doppler, first trimester Tweetable abstract: The first-trimester Gaussian and FMF algorithms have similar predictive performances for preeclampsia and small-for-gestational-age fetuses.

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Short title: FMF and Gaussian algorithms for preeclampsia and SGA

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ABSTRACT

Objective: To compare the predictive accuracy of the Gaussian and Fetal Medicine Foundation (FMF) algorithms for preeclampsia (PE) and small for gestational age fetuses (SGA).

Design: Secondary analysis of a prospective cohort study.

Setting: Tertiary referral hospital.

Population: 2,641 singleton pregnancies attending routine first-trimester scan from October 2015 to September 2017.

Methods: Maternal characteristics, mean arterial blood pressure, and mean uterine artery pulsatility index were recorded at the first-trimester scan. Serum placental growth factor and pregnancy-associated plasma protein-A were assessed between 8+0 and 13+6 weeks of gestation.

Main outcome measures: The areas under the curve for the predictive performance for early-onset (delivery <34 weeks) and preterm (delivery <37 weeks) PE, and early-onset (delivery <32 weeks) and preterm (delivery <37 weeks) SGA, were calculated with the Gaussian and FMF algorithms, and were subsequently compared.

Results: Among the 2,641 participants, 30 (1.14%) developed preterm PE, including 11 (0.42%) early-onset PE. Among the 2483 newborns, 44 (1.77%) were preterm SGA, including eight (0.32%) early-onset SGA. The FMF and the Gaussian algorithm showed a similar predictive performance for most outcomes and marker combinations.

Conclusions: This study shows that the first-trimester Gaussian and FMF algorithms have similar performances for PE and SGA prediction. Accuracy of the FMF algorithm was similar to that reported in the original studies, adding evidence to its external validity.

Funding: none

Keywords: preeclampsia, screening, PlGF, early-onset preeclampsia, uterine artery Doppler, first trimester

Tweetable abstract: The first-trimester Gaussian and FMF algorithms have similar predictive performances for preeclampsia and small-for-gestational-age fetuses.

INTRODUCTION

Preeclampsia (PE) and small for gestational age (SGA) are the main complications of placental disease. First-trimester PE screening using algorithms that include a combination of maternal characteristics, biophysical markers (mean arterial blood pressure (MAP) and mean uterine artery pulsatility index (UtAPI)), and biochemical markers (placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A)), can accurately predict PE and SGA[1–4]. The Fetal Medicine Foundation (FMF) and Gaussian algorithms can identify 80-90% of pregnant women who will develop PE with delivery <32/<34 weeks of gestation (weeks)[1,5] and 60-70% of women who will develop PE with delivery <37 weeks[1,6], at a 10% false positive rate (FPR). These algorithms can also predict 50-60% of SGA with delivery <32 weeks and 30-40% of SGA with delivery <37 weeks[2,4].

Despite the FMF algorithm is the most used and validated worldwide, the Gaussian algorithm has some features that confer advantages in the clinical practice, reason why it is being used for routine first-trimester PE screening in most maternities across Spain since 2018. Firstly, blood sample for measurements of biochemical markers (PAPP-A and PlGF) is drawn between 8+0 weeks and 13+6 weeks as with routine aneuploidy screening (allowing the use of a two-step approach and immediate PE risk calculation at the first-trimester scan)[6]. Secondly, UtAPI assessment can be done both transabdominally and transvaginally, rendering the

algorithm more versatile to different clinical settings. Thirdly, likelihood ratios for the *a priori* risk calculation were not derived from the study population in which the algorithm was investigated, but from a larger meta-analysis that included more than 25,000,000 pregnancies[7]. This may render the Gaussian algorithm less overfitted to a given population and, therefore, more adaptable for populations with different characteristics.

The FMF algorithm has been developed and prospectively validated in large populations, showing comparable predictive performances to the original study[8–12]. By contrast, the Gaussian algorithm has been investigated only in a single cohort of participants. In the past few years, routine PE screening has been implemented in most hospitals, leaving virtually no women at a high risk for PE without aspirin treatment to prospectively assess the external validity of the Gaussian algorithm. Therefore, an indirect approach to test the performance of the Gaussian algorithm is to compare it with the most externally validated combined screening tool for PE worldwide: the FMF algorithm.

The aim of this study was to compare the predictive accuracy for PE and SGA of the Gaussian and FMF algorithms.

METHODS

This is a secondary analysis of a previously published data, which was used to test the Gaussian algorithm for early-onset PE prediction[3]. That study was conducted in a prospective fashion at Vall d'Hebron University Hospital (Barcelona) from October 2015 to September 2017. The local ethics committee (CEIC-VHIR PR(AMI)265/2018) approved the study protocol. A total of 3,777 unselected singleton pregnant women attending their routine first-trimester scan (from 11+0 to 13+6 weeks of gestation) were invited to participate, and 2,946 women agreed and provided their written informed consent. Of those, 305 participants (10.4%) had to be excluded due to the following reasons: missing outcome data (n=86), major fetal defects or chromosomopathies (n=13), miscarriage or fetal death <24 weeks (n=15), and insufficient remaining blood sample to measure PLGF (n=191). Before the implementation of the first-trimester combined screening for PE in 2018, no PE screening was performed at the Vall d'Hebron University Hospital; therefore, none of the remaining 2,641 participants received aspirin at any time during their pregnancy. Neonatal birthweight was not available for 158 participants; therefore, predictive accuracies for SGA were calculated with 2,483 participants. Gestational age was confirmed by fetal crown-rump length measurement during the first-trimester scan[13]. Maternal characteristics and medical and obstetric history were recorded at the first-trimester ultrasound scan via a patient questionnaire. The following maternal characteristics were recorded: age (years); height (centimetres); weight (kilograms); ethnicity (white European, South American, black, Asian, South-East Asian, and others); smoking during pregnancy (yes/no); and conception method (spontaneous/assisted reproductive technology/ovulation drugs). Medical history variables included the presence of chronic hypertension (yes/no), diabetes mellitus (Type 1/Type2/no), renal disease (yes/no), systemic lupus erythematosus (yes/no), and antiphospholipid syndrome (yes/no). Obstetric history variables included parity (nulliparous, defined as no previous deliveries before 24 weeks vs multiparous), gestational age at birth (weeks) in the last pregnancy, interval between the last delivery and the beginning of the current one (years), and personal or family history of PE (yes/no). Biochemical markers, including serum PAPP-A and PlGF, were measured at the first-trimester routine blood test for aneuploidy screening (from 8+0 to 13+6 weeks) by the fully automated Elecsys assays for PAPP-A and PlGF on an immunoassay platform (cobas e analyzers; Roche® Diagnostics, Rotkreuz, Switzerland). Biophysical markers, including MAP and UtAPI, were assessed at the first-trimester scan. Blood pressure was measured automatically using a calibrated device according to a standard procedure: a single measurement in one arm (right or left) while women were seated and after a 5-minute rest. MAP was calculated as: diastolic blood pressure + (systolic-diastolic blood pressure)/3. UtAPI was measured following the recommendations of the FMF[14]. All examiners were certified by the FMF for PE risk assessment and Doppler ultrasound assessment.

Small-for-gestational-age newborns were defined as having a birthweight below the 10th centile according to customized local charts[15]. Indication for elective delivery was based on Doppler ultrasound findings and conventional cardiotocogram interpretation, according to the current protocol[16]. Newborns were classified as early SGA if delivery occurred before 32 weeks and as preterm SGA if delivery occurred before 37 weeks.

PE was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy: systolic blood pressure of 140 mm Hg or higher and/or diastolic blood pressure of 90 mm Hg or higher, confirmed by repeated measurements over a few hours, developing after 20 weeks in previously normotensive women, accompanied by proteinuria of 300 mg or higher in 24 h, spot urine protein/creatinine ratio of 0.3 mg/mg or higher, or dipstick urinalysis of 1+ or higher when a quantitative method was not available[17]. Early-onset and preterm PE were defined as PE requiring delivery before 34 and 37 weeks, respectively.

For the Gaussian algorithm, multiples of the median (MoMs) for each marker were calculated according to the methodology described in a previous study[3]. For the FMF algorithm, MoMs were obtained using the batch calculation tool provided in the FMF website[18]. We then coded the variables required for the prediction formulas according to the description provided in the corresponding published articles[1,3]. For the Gaussian algorithm, the prenatal screening software SsdwLab 6 (SBP Soft 2007 S.L, Girona, Spain) was used to calculate early-onset PE probability scores. For the FMF algorithm, the risk calculation tool provided in the FMF website was used[19].

Besides the "a priori" risks, the 4 markers (PAPP-A, PlGF, MAP and UtAPI) can be incorporated alone or in combination of 2, 3 or 4 for risk calculation, depending on the markers available in the clinical practice. Therefore, there are 15 possible marker combinations. Nevertheless, only the 7 most clinically relevant have been investigated in this study (MAP alone, MAP + PlGF, MAP + UtAPI, MAP + PAPP-A, MAP + UtAPI + PAPP-A, MAP + UtAPI + PlGF, and MAP + UtAPI + PlGF + PAPP-A).

Statistical Analysis

The statistical software RStudio Team (version 1.2.5033 [2019], RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL:*http://www.rstudio.com/*) was used for statistical analysis. Categorical data were reported as frequency and percentage, and comparisons between groups were performed by chi-square or Fisher tests, as appropriate. Continuous variables were reported as the median and interquartile range, and the Mann-Whitney U test was used to assess differences between groups. Receiver-operating-characteristic (ROC) curves were generated and detection rates (DR) at fixed 5%, 10%, 15%, 20%, 25% and 30% false-positive rates (FPR) were calculated for both algorithms. The predictive accuracies of both algorithms were compared for a fixed FPR of 10% as well as for the resulting areas under the curve (AUC), which were compared by the Delong test[20]. The Bonferroni correction was used in all tests when multiple comparisons were assessed. Statistical significance level was set at $p<0.05$.

RESULTS

Among the 2,641 participants, 30 (1.14%) women developed preterm PE including 11 (0.42%) early-onset PE. Women with chronic hypertension accounted for 1.1% (29 of 2,641) of the population, but accounted for 27.3% and 16.7% of early-onset and preterm PE cases, respectively. Women with a history of PE accounted for 1.3% (35 of 2,641) of the population, but accounted for 18.2% and 16.7% of early-onset and preterm PE cases, respectively. Median MAP MoM was significantly higher in early-onset (1.14 [1.10-1.37]) and preterm PE (1.14 [1.10-1.29]) patients as compared to unaffected women (1.06 [0.97-1.14]). Median UtAPI MoM was significantly higher in early-onset PE (1.32 [1.12-2.13]) and preterm PE (1.19 [1.01-1.44]) patients as compared to unaffected women (1.03 [0.84-1.26]). Median PAPP-A MoM was significantly lower in early-onset (0.73 [0.6-0.93]) and preterm PE (0.72 [0.57-1.05]) patients as compared to unaffected women (1.05 [0.75-1.5]). Median PlGF MoM was significantly lower in early-onset PE (0.69 [0.52-1.05]) and preterm PE (0.78 [0.63-0.98]) patients as compared to unaffected women (0.96 [0.76-1.19]).

Among the 2,483 newborns, 44 (1.77%) were preterm SGA, including 8 (0.32%) early-onset SGA. Women with chronic hypertension accounted for 1.2% (29 of 2,483) of the population, but accounted for 12.5% and 4.5% of early-onset and preterm SGA cases, respectively. Women with a history of PE accounted for 1.4% (34 of 2,483) of the population, but accounted for 12.5% and 4.5% of early-onset and preterm SGA cases, respectively. Median MAP MoM did not differ significantly between groups. Median UtAPI MoM was significantly higher in preterm SGA patients (1.20 [1.02-1.47]) as compared to unaffected women (1.02

[0.84-1.25]). Median PAPP-A MoM was significantly lower in preterm SGA patients (0.73 [0.55-1.10]) as compared to unaffected women (1.06 [0.73-1.51]). Median PlGF MoM was significantly lower in early-onset (0.60 [0.42-0.79]) and preterm SGA patients (0.72 [0.61-0.97]) as compared to unaffected women (0.96 [0.75-1.18]).

Characteristics of the study population are summarized in Table 1 and Table 2.

For prediction of early-onset and preterm PE, and early-onset and preterm SGA, the Gaussian and FMF algorithms showed a similar predictive performance with all marker combinations, except for early-onset PE prediction with MAP and PAPP-A (Gaussian AUC=0.833 [0.727-0.939] vs FMF AUC=0.771 [0.631-0.911]; p=0.002), MAP and PlGF (Gaussian AUC=0.905 [0.844-0.965] vs FMF AUC =0.858 [0.768-0.947]; p=0.01), and MAP alone (Gaussian AUC=0.795 [0.679-0.912] vs FMF AUC=0.758 [0.621-0.895]; p=0.02), where the FMF algorithm showed a significantly lower AUC.

For early-onset PE prediction, the Gaussian algorithm showed the greatest AUC when combining maternal history, MAP, UtAPI and PlGF (0.951 [0.919-0.983]), followed by the combination of all markers (0.945 [0.912-0.979]). The FMF algorithm showed the greatest AUC when combining all markers (0.945 [0.908-0.982]).

For preterm PE prediction, the Gaussian algorithm showed the greatest AUC when combining maternal history, MAP and PlGF (0.802 [0.722-0.881]), followed by the combination of all markers without PAPP-A (0.798 [0.704-0.893]). The FMF algorithm showed the greatest AUC when combining all markers (0.818 [0.728-0.907]).

For early-onset SGA prediction, the Gaussian algorithm showed the greatest AUC when combining maternal history, MAP and PlGF (0.840 [0.710-0.970]), followed by the combination of all markers without PAPP-A (0.811 [0.641-0.982]). The FMF algorithm showed the greatest AUC when combining all markers (0.906 [0.834-0.978]).

For preterm SGA prediction, the Gaussian algorithm showed the greatest AUC when combining maternal history, MAP, UtAPI and PlGF (0.697 [0.612-0.782]), followed by the combination of all markers (0.684 [0.598-0.769]). The FMF algorithm showed the greatest AUC when combining all markers (0.727 [0.645-0.809]).

DISCUSSION

Main findings

This study shows that the Gaussian and FMF algorithms have similar predictive accuracies for PE and SGA, except for early-onset PE, where the FMF algorithm showed a significantly lower AUC with the combinations of MAP and PAPP-A, MAP and PlGF, and MAP alone. These significant differences could be partly attributed to the different methodology required for MAP assessment in both algorithms. In this study, MAP was measured once, in only one arm and after a 5-minute rest, while the FMF algorithm was designed with an average of two MAP measurements performed at 1-minute intervals in both arms simultaneously after a 5-minute rest[21]. This different methodology for MAP measurements may have affected the accuracy of all combinations including MAP in the FMF algorithm, but especially MAP alone or those combinations including MAP with one other factor.

Strengths and limitations

One of the main strengths of the study includes the prospective enrolment of patients. Additionally, this study was performed within the context of routine clinical practice and patients were seen by their usual physicians, making the results more reliable and applicable in routine care settings. Furthermore, this is the first study assessing the performance of the FMF algorithm exclusively in a Spanish cohort and in a clinical setting where MAP was measured once and only in one arm, showing comparable results to those reported in the original study. Despite a previous study showed that prediction of PE is similar when biomarkers are measured before or after 11 weeks[6], the FMF algorithm was designed with biomarkers assessed between

11+0 and 13+6 weeks. In this study biomarkers were measured before 11+0 weeks in 1,675 (63.4%) women. Therefore, another remarkable strength of our work is that it provides evidence of the applicability of the FMF and Gaussian algorithms before and after 11 weeks for predicting PE and SGA.

The main limitation of our study is the low number of cases with early-onset SGA and early-onset PE, and the relatively low number of cases with preterm SGA and preterm PE. Additionally, indication for elective delivery of SGA fetuses based on Doppler and cardiotocogram findings may be different when using other fetal growth restriction protocols. However, Doppler and cardiotocogram classification is rather uniform in Spain, where the Gaussian algorithm is widely used. Another limitation to be noted is that the technique for MAP measurements may potentially reduce the FMF algorithm's performance and could explain its lower AUC versus the Gaussian algorithm for some marker combinations.

Interpretation

The FMF algorithm has been externally validated by several studies in various populations, showing comparable performance to that of the original study. Nevertheless, one study showed that some algorithms could underperform when applied to populations that were different to the population where they were developed[22]. In this study, we show that performance of the FMF algorithm in a Spanish population was similar to the performance obtained in the original study, further supporting the external validity of the FMF algorithm. By contrast, the predictive ability of the Gaussian algorithm has not been evaluated in other studies, aside from the original study where it was first validated. It must be noted that the Gaussian algorithm was not developed in our population, but just validated, since this algorithm was constructed using previously published data from a large meta-analysis. This might make this algorithm less likely to be overfitted to our population and therefore, less likely to underperform when applied to a different population. Since the first-trimester PE screening and aspirin prescription has been implemented in most countries across Europe, prospective external validation of the Gaussian algorithm in untreated populations seems unlikely. Therefore, a reasonable indirect approach to assess the predictive performance of the Gaussian algorithm is to compare it with the FMF algorithm, which has been extensively validated in various large populations. Although our results cannot be considered an external validation of the Gaussian algorithm, the similar accuracies of both algorithms suggest that the FMF algorithm is unlikely to outperform the Gaussian algorithm in our population where it is being routinely used in most maternities since 2018. For this reason, we believe that the Gaussian algorithm might be a reasonable alternative to the FMF algorithm for those settings where the latter cannot be applied dur to ultrasonographers performing UtAPI both transabdominally and transvaginally of for settings measuring biomarkers for the aneuploidy and PE screenings before 11 weeks.

Additionally, as seen in previous studies[23], we confirm that PAPP-A does not increase the predictive accuracy of any of the algorithms when PlGF was being used; however, when PlGF is not available, PAPP-A could increase DR by 5% with some marker combinations.

Finally, we observed that a single measurement of MAP could decrease the predictive accuracy of the FMF algorithm; therefore, the appropriate methodology should be performed when using this algorithm.

CONCLUSION

In conclusion, this study shows that the first-trimester Gaussian and FMF algorithms have similar predictive performances for PE and SGA in a Spanish population within a routine care setting. The accuracy of the FMF algorithm in our study was similar to that reported in previous studies, adding evidence to its external validity.

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DISCLOSURE OF INTEREST

This study was supported by Roche Diagnostics, who provided the reagents used for PlGF measurements. The authors report no conflict of interest. Roche Diagnostics had no influence on the study design, data collection, data analysis or interpretation of results.

CONTRIBUTION TO AUTHORSHIP

BS, MM and EC had full access to all of the data in the study and take full responsibility for the integrity of the data and accuracy of the data analysis. BS, MM and EC conceived and designed the study. BS, EB, CR, PGM, MAS, MP, CF, MTM, AP and MA contributed to literature research. BS, EB, CR, PGM, MAS, MP, CF, MTM, AP and MA contributed to data collection and confirmation. BS, EB and MM contributed to data analysis. BS, EB, MM and EC contributed to data interpretation. BS and MM were in charge of writing the manuscript draft. EC made substantial revisions to the manuscript. All authors read and approved the final manuscript.

DETAILS OF ETHICAL APPROVAL

This study was approved by the Vall d'Hebron University Hospital Ethics Committee (CEIC-VHIR PR(AMI)265/2018). Informed consent was obtained in all patients, wich was included in the patient's medical record.

FUNDING

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Table 1. Baseline characteristics of the study population based on preeclampsia outcome.

	PE <34 weeks (n=11)	**PE <37 weeks (n**
Age in years, median (IQR)	34 (32-37)	35.5 (31-38)+
BMI in kg/m2, median (IQR)	23.1 (22.5-32.1)	24.0 (22.5-27.6)
Ethnicity		
White	10 (90.9%)	25 (83.3%)
Black	0 (0.0%)	1 (3.3%)

	PE <34 weeks (n=11)	**PE <37 weeks (n**
Mixed	1 (9.1%)	2 (6.7%)
Asian	0 (0.0%)	2 (6.7%)
South-east Asian	0 (0.0%)	0 (0.0%)
Smoking during pregnancy	1 (9.1%)	3 (10.0%)
ART	1 (9.1%)	2 (6.7%)
Insemination	1 (9.1%)	1 (3.3%)
IVF	0 (0.0%)	1 (3.3%)
IVF with egg donation	0 (0.0%)	1 (3.3%)
Medical history		
Chronic Hypertension	3 (27.3%)+	5 (16.7%)+
Diabetes mellitus	0 (0.0%)	1 (3.3%)
Autoimmune disease	0 (0.0%)	3 (10.0%)
APS	0 (0.0%)	1 (3.3%)
Obstetric history		
Nulliparous	2 (18.2%)	13 (43.3%)
Previous preeclampsia	2 (18.2%)+	5 (16.7%)+
Biophysical variables		
GA at the time of first-trimester ultrasound scan in weeks, median (IQR)	12.7 (12.3-13.3)	12.7 (12.3-13.3)
MAP in mmHg, median (IQR)	96 (88.3-104.3)+	91.2 (86.7-97.3)+
MoM MAP, median (IQR)	1.14 (1.10-1.37)+	1.14 (1.10-1.29)+
Mean UtAPI, median (IQR)	2.25 (1.89-3.05)+§	1.91 (1.71-2.31)++
MoM UtAPI, median (IQR)	1.32 (1.12-2.13)+	1.19 (1.01-1.44)+
Biochemical variables		
GA for PAPP-A + PlGF measurement, median (IQR)	11.4 (9.9-12.3)	10.9 (9.9-11.7)
PAPP-A in mU/L, median (IQR)	1373 (607.3-2291)	1158 (602.3-2291)
MoM PAPP-A, median (IQR)	0.73 (0.6-0.93)+	0.72 (0.57-1.05)+
PlGF in pg/mL, median (IQR)	22.3 (19.0-29.8)+	25.0 (19.3-31.7)+
MoM PlGF, median (IQR)	0.69 (0.52-1.05)+	0.78 (0.63-0.98)+

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Categorical data are reported as frequency and percentage. Continuous data are reported as the median and interquartile range. APS, antiphospholipid syndrome; ART, assisted reproductive technique; BMI, body mass index; FGR, fetal growth restriction; GA, gestational age; IQR, interquartile range; IVF, *in vitro* fertilization; MAP, mean arterial pressure; MoM, multiples of median; PE, preeclampsia; PAAP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; UtAPI, uterine artery pulsatility index.

+ Significant difference as compared to unaffected women; ++ Significant difference as compared to early-onset preeclampsia; SS Significant difference as compared to women with preterm preeclampsia. **Table 2. Baseline characteristics of the study population based on small-for-gestational-age outcome.**

	SGA <32 weeks (n=8)	**SGA <37 weeks**
Age in years, median (IQR)	31.5 (29-33)	32 (28.5-37)
BMI in kg/m2, median (IQR)	23.1 (21.9-24.5)	23.1 (20.2-26.4)
Ethnicity		
White	159 (94.6%)	189 (93.6%)
Black	4 (2.4%)	6 (3.0%)
Mixed	5 (3.0%)	5 (2.5%)
Asian	0 (0.0%)	1 (0.5%)
South-east Asian	0 (0.0%)	1 (0.5%)

	SGA <32 weeks (n=8)	SGA <37 weeks
Smoking during pregnancy	0 (0.0%)	15 (34.1%)+
ART		
Insemination	2 (1.2%)	3 (1.5%)
IVF	6 (3.6%)	7 (3.5%)
IVF with egg donation	0 (0.0%)	1 (2.3%) (% del to
Medical history		
Chronic Hypertension	1 (12.5%)+	2 (4.5%)
Diabetes mellitus	0 (0.0%)	2 (4.5%)
Autoimmune disease	1 (12.5%)	2 (4.5%)
APS	0 (0.0%)+	3 (6.8%)
Obstetric history		
Nulliparous	5 (62.5%)	20 (45.5%)
Previous preeclampsia	1 (12.5%)+	2 (4.5%)
Biophysical variables		
GA at the time of first trimester ultrasound scan in weeks, median (IQR)	12.4 (12.1-12.6)	12.4 (11.9-12.9)
MAP in mmHg, median (IQR)	90.8 (85.2-96)	86.7 (80-91.1)
MoM MAP, median (IQR)	1.14 (1.04-1.17)	1.07 (0.96-1.17)
Mean UtAPI, median (IQR)	1.88 (1.74-2.67)	1.94 (1.72-2.45)+
MoM UtAPI, median (IQR)	1.12 (1.01-1.60)	1.20 (1.02-1.47)+
Biochemical variables		
GA for PAPP-A + PlGF measurement median (IQR)	11.4 (10.4-12.3)	10.7 (10-11.8)
PAPP-A in mU/L, median (IQR)	1801 (932.2-2456)	964.25 (631.0-1794
MoM PAPP-A, median (IQR)	0.74 (0.6-0.89)	0.73 (0.55-1.1)+
PlGF in pg/mL, median (IQR)	20.0 (18.1-26.1)+	28.2 (19.5-38.4)
MoM PlGF, median (IQR)	0.60 (0.42-0.79)+	0.72 (0.61-0.97)+

Categorical data are reported as frequency and percentage. Continuous data are reported as the median and interquartile range. APS, antiphospholipid syndrome; ART, assisted reproductive technique; BMI, body mass index; FGR, fetal growth restriction; GA, gestational age; IQR, interquartile range; IVF, *in vitro* fertilization; MAP, mean arterial pressure; MoM, multiples of median; PAAP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; SGA, small for gestational age; UtAPI, uterine artery pulsatility index.

+ Significant difference as compared to unaffected women; ++ Significant difference as compared to early-onset small for gestational age; SS Significant difference compared to preterm small for gestational age.

Table 3. Detection rate and area under the curve for prediction of early-onset preeclampsia by the Gaussian and the Fetal Medicine Foundation algorithms.

PE<34 weeks (n=11)	**PE<34 weeks (n=11)**	**PE<34 weeks (n=11)**	**PE<34 weeks (n=11)**	**PE<34 weeks (n=11)**	**PE<34 weeks (n=11)**	**PE<34 weeks (n=11)**	**PE<34 weeks (n=11)**	**PE<34 weeks (n=11)**	**PE<34 weeks (n=11)**	**PE<34 weeks (n=11)**	**PE<34 weeks (n=11)**	**PE< weeks (n=**
Gaussian algorithm	**Gaussian algorithm**	**Gaussian algorithm**	**Gaussian algorithm**	**Gaussian algorithm**	**Gaussian algorithm**	**Gaussian algorithm**	**FMF algorithm**	**FMF algorithm**	**FMF algorithm**	**FMF algorithm**	**FMF algorithm**	**FMI algorith**

	PE<34 weeks (n=11)	PE<34 weeks (n=11)	PE<34 weeks (n=11)	PE<34 weeks (n=11)	PE<34 weeks (n=11)	PE<34 weeks (n=11)	PE<34 weeks (n=11)	PE<34 weeks (n=11)	PE<34 weeks (n=11)	PE<34 weeks (n=11)	PE<34 weeks (n=11)	PE<34 weeks (n=11)	PE< weel (n=
A priory risk +	**AUC (95% CI)**	**DR at 5% FPR (95% CI)**	**DR at 10% FPR (95% CI)**	**DR at 15% FPR (95% CI)**	**DR at 20% FPR (95% CI)**	**DR at 25% FPR (95% CI)**	**DR at 30% FPR (95% CI)**	**AUC (95% CI)**	**DR at 5% FPR (95% CI)**	**DR at 10% FPR (95% CI)**	**DR at 15% FPR (95% CI)**	**DR at 20% FPR (95% CI)**	**DR at 25% FPR (95% CI)**
MAP	0.795 (0.679-0.912)	36.4 (9.09-63.6)	45.5 (18.2-72.7)	54.6 (27.3-81.8)	54.6 (27.3-81.8)	72.7 (45.5-100.0)	72.7 (45.5-100.0)	0.758 (0.621-0.895)	27.3 (0.0-54.6)	27.3 (0.0-54.6)	27.3 (9.09-63.6)	54.6 (27.3-90.9)	72.7 (45.5 100.0
MAP + PlGF	0.905 (0.844-0.965)	36.4 (9.09-63.6)	63.6 (36.4-90.9)	81.8 (54.6-100.0)	81.8 (54.6-100.0)	81.8 (54.6-100.0)	90.9 (72.7-100.0)	0.858 (0.768-0.947)	45.5 (18.2-72.7)	45.5 (18.2-72.7)	63.6 (36.4-90.9)	72.7 (45.5-100.0)	81.8 (54.6 100.0
MAP + UtAPI	0.908 (0.840-0.975)	63.6 (36.4-90.9)	63.6 (36.4-90.9)	63.6 (36.4-90.9)	72.7 (45.5-100.0)	90.9 (72.7-100.0)	100.0 (100.0-100.0)	0.868 (0.775-0.961)	45.5 (18.2-72.7)	54.6 (27.3-81.8)	63.6 (36.4-90.9)	72.7 (45.5-100.0)	81.8 (54.6 100.0
MAP + PAPP-A	0.833 (0.727-0.939)	36.4 (9.09-63.6)	54.6 (27.3-81.8)	54.6 (27.3-81.8)	72.7 (45.5-95.6)	72.7 (45.5-95.6)	72.7 (45.5-95.6)	0.771 (0.631-0.911)	27.3 (0.0-54.6)	27.3 (0.0-54.6)	54.6 (27.3-81.8)	63.6 (36.4-90.9)	72.7 (45.5 95.6)
MAP + UtAPI + PAPP-A	0.910 (0.844-0.977)	63.6 (36.4-90.9)	63.6 (36.4-90.9)	72.7 (45.5-100.0)	72.7 (45.5-100.0)	81.8 (54.6-100.0)	100.0 (100.0-100.0)	0.870 (0.768-0.972)	45.5 (18.2-72.3)	54.6 (27.3-81.8)	72.7 (45.5-90.9)	81.8 (54.6-100.0)	81.8 (54.6 100.0
MAP + UtAPI + PlGF	0.951 (0.919-0.983)	54.6 (27.3-81.8)	81.8 (54.5-100.0)	90.9 (72.7-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	0.923 (0.864-0.982)	63.6 (36.4-90.9)	72.7 (45.5-100.0)	72.7 (45.5-100.0)	90.9 (72.7-100.0)	90.9 (72.7 100.0
MAP + UtAPI + PlGF + PAPP-A	0.945 (0.912-0.979)	54.6 (27.3-81.8)	81.8 (54.6-100.0)	90.9 (72.7-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	0.945 (0.908-0.982)	54.6 (27.3-81.8)	90.9 (54.6-100.0)	90.9 (72.7-100.0)	90.9 (72.7-100.0)	100 (100 100)

AUC, area under the curve; CI, confidence interval; DR, detection rate; FPR, false positive rate; MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PE, preeclampsia; PlGF, placental growth factor; UtAPI, mean uterine artery pulsatility index. Comparisons between AUC were performed by two-tailed p values.

Table 4. Detection rate and area under the curve for prediction of preterm preeclampsia by the Gaussian and the Fetal Medicine Foundation algorithms.

	PE<37+PE weeks (n=30)	PE<37+PE weeks (n=30)	PE<37+PE weeks (n=30)	PE<37+PE weeks (n=30)	PE<37+PE weeks (n=30)	PE<37+PE weeks (n=30)	PE<37+PE weeks (n=30)	PE<37+PE weeks (n=30)	PE<37+PE weeks (n=30)	PE<37+PE weeks (n=30)	PE<37+PE weeks (n=30)	PE<37+PE weeks (n=30)	PE< weel (n=
A priory risk +	**Gaussian algorithm AUC (95% CI)**	**Gaussian algorithm DR at 5% FPR (95% CI)**	**Gaussian algorithm DR at 10% FPR (95% CI)**	**Gaussian algorithm DR at 15% FPR (95% CI)**	**Gaussian algorithm DR at 20% FPR (95% CI)**	**Gaussian algorithm DR at 25% FPR (95% CI)**	**Gaussian algorithm DR at 30% FPR (95% CI)**	**FMF algorithm AUC (95% CI)**	**FMF algorithm DR at 5% FPR (95% CI)**	**FMF algorithm DR at 10% FPR (95% CI)**	**FMF algorithm DR at 15% FPR (95% CI)**	**FMF algorithm DR at 20% FPR (95% CI)**	**FMF algorithm DR at 25% FPR (95% CI)**
MAP	0.737 (0.648-0.827)	0.2667 (13.3-43.3)	36.7 (20.0-53.3)	50.0 (33.3-66.7)	53.3 (33.3-70.0)	56.7 (40.0-73.3)	63.3 (46.7-80.0)	0.727 (0.637-0.817)	26.7 (10.0-43.3)	26.7 (13.3-46.7)	36.7 (20.0-53.3)	50.0 (33.3-70.0)	60.0 (43.3-76.7)
MAP + PlGF	0.802 (0.722-0.881)	26.7 (13.3-43.3)	46.7 (30.0-63.3)	60.0 (43.3-76.6)	66.7 (50.0-82.2)	73.3 (53.3-86.7)	76.7 (60.0-90.0)	0.790 (0.712-0.868)	36.7 (20.0-53.3)	40.0 (23.3-60.0)	53.3 (33.3-70.0)	60.0 (43.3-76.7)	66.7 (50.0-83.3)
MAP + UtAPI	0.782 (0.692-0.872)	36.7 (20.0-53.3)	40.0 (23.3-56.7)	46.7 (30.0-63.3)	56.7 (36.7-76.7)	76.7 (60.0-90.0)	80.0 (63.3-93.3)	0.786 (0.701-0.871)	30.0 (13.3-50.0)	43.3 (26.7-63.3)	46.7 (30.0-63.3)	63.3 (46.7-80.0)	70.0 (53.3-86.7)
MAP + PAPP-A	0.773 (0.687-0.859)	33.3 (20.0-50.0)	43.3 (26.7-63.3)	53.3 (33.3-70.0)	63.3 (46.7-80.0)	63.3 (46.7-80.0)	63.3 (46.7-80.0)	0.747 (0.658-0.836)	23.3 (10.0-40.0)	36.7 (20.0-53.3)	50.0 (33.3-66.7)	53.3 (36.7-70.0)	60.0 (40.0-76.7)
MAP + UtAPI + PAPP-A	0.797 (0.708-0.886)	36.7 (20.0-53.3)	43.3 (26.7-60.0)	53.3 (36.7-73.3)	70.0 (53.3-83.4)	76.7 (56.7-90.0)	83.3 (70.0-96.7)	0.800 (0.714-0.887)	36.7 (16.7-53.3)	50.0 (33.3-66.7)	56.7 (40.0-73.3)	70.0 (50.0-86.7)	76.7 (60.0-90.0)
MAP + UtAPI + PlGF	0.798 (0.704-0.893)	36.7 (20.0-56.7)	46.7 (30.0-66.7)	56.7 (40.0-73.3)	80.0 (63.3-93.3)	80.0 (63.3-93.3)	80.0 (63.3-93.3)	0.818 (0.739-0.897)	36.7 (20.0-53.3)	50.0 (30.0-66.7)	56.7 (40.0-73.3)	66.7 (50.0-83.3)	80.0 (63.3-93.3)
MAP + UtAPI + PlGF + PAPP-A	0.782 (0.683-0.882)	33.3 (16.7-50.0)	46.7 (30.0-66.7)	63.3 (46.7-80.0)	76.7 (60.0-90.0)	76.7 (60.0-90.0)	76.7 (60.0-90.0)	0.818 (0.728-0.907)	36.7 (20.0-56.7)	63.4 (43.3-80.0)	70.0 (53.3-86.7)	73.3 (53.3-86.7)	76.7 (60.0-90.0)

AUC, area under the curve; CI, confidence interval; DR, detection rate; FPR, false positive rate; MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PE, preeclampsia; PlGF, placental growth factor; UtAPI, mean uterine artery pulsatility index. Comparisons between AUC were performed by two-tailed p values.

Table 5. Detection rate and area under the curve for prediction of early-onset small-for-gestational-age by the Gaussian and the Fetal Medicine Foundation algorithms.

	SGA <32+0 weeks (n=8)	SGA <32+0 weeks (n=8)	SGA <32+0 weeks (n=8)	SGA <32+0 weeks (n=8)	SGA <32+0 weeks (n=8)	SGA <32+0 weeks (n=8)	SGA <32+0 weeks (n=8)	SGA <32+0 weeks (n=8)	SGA <32+0 weeks (n=8)	SGA <32+0 weeks (n=8)	SGA <32+0 weeks (n=8)	SGA <32+0 weeks (n=8)	SGA <32 weeks (n=
A priory risk +	**Gaussian algorithm AUC (95% CI)**	**Gaussian algorithm DR at 5% FPR (95% CI)**	**Gaussian algorithm DR at 10% FPR (95% CI)**	**Gaussian algorithm DR at 15% FPR (95% CI)**	**Gaussian algorithm DR at 20% FPR (95% CI)**	**Gaussian algorithm DR at 25% FPR (95% CI)**	**Gaussian algorithm DR at 30% FPR (95% CI)**	**FMF algorithm AUC (95% CI)**	**FMF algorithm DR at 5% FPR (95% CI)**	**FMF algorithm DR at 10% FPR (95% CI)**	**FMF algorithm DR at 15% FPR (95% CI)**	**FMF algorithm DR at 20% FPR (95% CI)**	**FMF algorithm DR at 25% FPR (95% CI)**
MAP	0.700 (0.546-0.854)	12.5 (0.0-37.5)	12.5 (0.0-37.5)	37.5 (0.0-75.0)	37.5 (12.5-75.0)	62.5 (25.0-87.8)	62.5 (25.0-87.8)	0.722 (0.604-0.841)	12.5 (0.0-37.5)	12.5 (0.0-37.5)	12.5 (0.0-37.5)	37.5 (12.5-75.0)	62.5 (25.0 87.8)
MAP + PlGF	0.840 (0.710-0.970)	25.0 (0.0-62.5)	37.5 (12.5-75.0)	75.0 (37.5-100.0)	75.0 (37.5-100.0)	87.5 (62.5-100)	87.5 (62.5-100)	0.865 (0.784-0.945)	37.5 (0.0-75.0)	37.5 (12.5-75.0)	50.0 (12.5-87.5)	87.5 (50.0-100.0)	87.5 (62.5 100)
MAP + UtAPI	0.740 (0.564-0.916)	25.0 (0.0-62.5)	37.5 (12.5-75.0)	37.5 (12.5-75.0)	50.0 (12.5-87.5)	62.5 (25.0-87.8)	62.5 (25.0-100)	0.777 (0.655-0.898)	25.0 (0.0-62.5)	25.0 (0.0-62.5)	37.5 (12.5-75.0)	50.0 (12.5-87.5)	62.5 (25.0 87.8)
MAP + PAPP-A	0.743 (0.581-0.905)	12.5 (0.0-37.5)	37.5 (1.6-75.0)	37.5 (12.5-75.0)	62.5 (25.0-87.8)	62.5 (25.0-100)	62.5 (25.0-100)	0.746 (0.619-0.873)	12.5 (0.0-37.5)	12.5 (0.0-37.5)	37.5 (12.2-75.0)	50.0 (12.5-87.5)	62.5 (25.0 87.8)
MAP + UtAPI + PAPP-A	0.757 (0.589-0.925)	25.0 (0.0-62.5)	37.5 (0.0-75.0)	50.0 (12.5-87.5)	50.0 (12.5-87.5)	50.0 (12.5-87.5)	75.0 (49.7-100.0)	0.795 (0.663-0.926)	25.0 (0.0-62.5)	37.5 (0.0-75.5)	50.0 (12.5-87.5)	62.5 (25.0-87.5)	62.5 (25.0 87.5)
MAP + UtAPI + PlGF	0.811 (0.641-0.982)	37.5 (12.5-75.0)	62.5 (25.5-87.5)	75.0 (50.0-100.0)	75.0 (50.0-100.0)	75.0 (50.0-100.0)	75.0 (50.0-100.0)	0.875 (0.774-0.976)	62.5 (25.0-87.5)	62.5 (25.0-87.5)	62.5 (25.0-87.5)	75.0 (37.5-100.0)	75.0 (37.5 100.0
MAP + UtAPI + PlGF + PAPP-A	0.806 (0.635-0.978)	37.5 (12.5-75.0)	62.5 (25.5-87.5)	75.0 (37.5-100.0)	75.0 (37.5-100.0)	75.0 (37.5-100.0)	75.0 (37.5-100.0)	0.906 (0.834-0.978)	50.0 (12.5-87.5)	75.0 (37.5-100.0)	75.0 (50.0-100.0)	75.0 (50.0-100.0)	87.5 (62.5 100.0

AUC, area under the curve; CI, confidence interval; DR, detection rate; FPR, false positive rate; MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; SGA, small for gestational age; UtAPI, mean uterine artery pulsatility index. Comparisons between AUC were performed by two-tailed p values.

Table 6. Detection rate and area under the curve for prediction of preterm small-for-gestational-age by the Gaussian and the Fetal Medicine Foundation algorithms.

	SGA <37+0 weeks (n=44)	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37 weel (n=**
A priory risk +	**Gaussian algorithm AUC (95% CI)**	**Gaussian algorithm DR at 5% FPR (95% CI)**	**Gaussian algorithm DR at 10% FPR (95% CI)**	**Gaussian algorithm DR at 15% FPR (95% CI)**	**Gaussian algorithm DR at 20% FPR (95% CI)**	**Gaussian algorithm DR at 25% FPR (95% CI)**	**Gaussian algorithm DR at 30% FPR (95% CI)**	**FMF algorithm AUC (95% CI)**	**FMF algorithm DR at 5% FPR (95% CI)**	**FMF algorithm DR at 10% FPR (95% CI)**	**FMF algorithm DR at 15% FPR (95% CI)**	**FMF algorithm DR at 20% FPR (95% CI)**	**FMF algorithm DR at 25% FPR (95% CI)**
MAP	0.546 (0.459-0.632)	9.1 (0.7-18.2)	18.2 (6.8-29.6)	22.7 (11.4-36.4)	22.7 (11.4-36.4)	29.6 (15.9-43.2)	36.4 (22.7-50.0)	0.563 (0.477-0.649)	9.1 (2.3-18.2)	13.6 (4.5-25.0)	18.2 (9.1-29.6)	27.3 (15.9-40.9)	34.1 (20.5 47.7)
MAP + PlGF	0.630 (0.540-0.719)	9.1 (2.3-20.5)	20.5 (9.1-31.9)	38.2 (22.7-52.3)	43.2 (29.6-56.8)	45.5 (31.8-61.4)	52.3 (38.6-65.9)	0.651 (0.562-0.739)	13.6 (4.5-25.0)	22.7 (11.4-36.4)	36.4 (22.7-52.3)	43.2 (29.6-59.1)	50.0 (36.4 65.9)
MAP + UtAPI	0.653 (0.57-0.737)	15.9 (6.8-27.3)	25.0 (13.6-36.7)	29.6 (18.2-45.5)	36.4 (22.7-52.3)	52.3 (36.4-65.9)	54.6 (40.9-70.5)	0.634 (0.547-0.722)	13.6 (4.5-25.0)	20.5 (9.1-34.1)	27.3 (15.9-43.2)	38.7 (25.0-54.6)	45.5 (31.8 59.2)
MAP + PAPP-A	0.592 (0.505-0.678)	7.9 (2.3-18.2)	22.7 (11.4-34.1)	25.0 (13.6-38.6)	34.1 (22.5-50.0)	38.6 (25.0-52.3)	40.9 (27.3-56.8)	0.591 (0.504-0.677)	6.8 (0.0-15.9)	11.4 (4.5-22.7)	27.3 (13.6-40.9)	34.1 (20.5-47.7)	36.4 (22.7 50.0)
MAP + UtAPI + PAPP-A	0.670 (0.587-0.752)	15.9 (6.8-27.3)	20.5 (9.1-34.1)	29.5 (15.9-43.2)	43.2 (29.6-61.4)	52.3 (36.4-65.9)	61.4 (47.7-75.0)	0.661 (0.575-0.746)	13.6 (4.3-25.0)	25.0 (11.4-38.6)	34.1 (20.5-47.7)	40.9 (25.0-56.8)	47.7 (34.1 63.4)
MAP + UtAPI + PlGF	0.697 (0.612-0.782)	20.5 (9.1-34.0)	29.5 (15.9-43.2)	45.5 (31.8-59.1)	54.6 (38.6-68.2)	59.1 (43.2-72.7)	63.6 (47.7-77.3)	0.689 (0.601-0.776)	18.2 (6.8-31.8)	34.1 (20.5-50.0)	45.5 (31.8-59.2)	47.8 (34.1-63.6)	56.8 (40.9 70.5)

	SGA <37+0 weeks (n=44)	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37+0 weeks (n=44)**	**SGA <37 weeks (n=**
MAP + UtAPI + PlGF + PAPP-A	0.684 (0.598-0.769)	18.2 (6.8-29.6)	29.5 (15.9-43.2)	43.2 (27.3-59.1)	52.3 (36.4-65.9)	54.6 (38.6-70.5)	61.4 (47.7-75.0)	0.727 (0.645-0.809)	22.7 (11.4-38.6)	40.9 (25.0-56.8)	47.7 (34.1-63.6)	52.3 (36.4-65.9)	63.6 (49.9 79.5)

AUC, area under the curve; CI, confidence interval; DR, detection rate; FPR, false positive rate; MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; SGA, small for gestational age; UtAPI, mean uterine artery pulsatility index. Comparisons between AUC were performed by two-tailed p values.