OBSTETRICS

Prediction of imminent preeclampsia at 35—37 weeks gestation

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BACKGROUND: In the weeks preceding the clinical onset of preeclampsia, the maternal serum level of the angiogenic placental growth factor is decreased and that of the antiangiogenic factor soluble fms-like tyrosine kinase-1 is increased. Women presenting at specialist clinics with signs or symptoms of hypertensive disorders have been stratified according to concentrations of placental growth factor or the ratio of concentrations of soluble fms-like tyrosine kinase-1 and placental growth factor to determine clinical management for the subsequent 1-4 weeks. An alternative approach for the prediction of preeclampsia is use of the competing risks model, a Bayes' theorem based method, to derive patient-specific risk for preeclampsia by various combinations of maternal characteristics and medical history with multiples of the median values of biomarkers.

OBJECTIVE: The purpose of this study was to compare the performance of screening for delivery with preeclampsia at ≤2 and ≤4 weeks after assessment at 35^{+0}—36^{+6} weeks gestation between the use of percentile cut-offs in placental growth factor alone or the soluble fms-like tyrosine kinase-1/placental growth factor ratio and the competing risks model.

STUDY DESIGN: This was a prospective observational study in women who attended a routine hospital visit at 35^{+0}—36^{+6} weeks gestation in 2 maternity hospitals in England. The visits included the recording of maternal demographic characteristics and medical history and the measurement of serum placental growth factor and soluble fms-like tyrosine kinase-1 and mean arterial pressure. The areas under the receiver operating characteristics curves were used to compare the predictive performance for preeclampsia with delivery at ≤2 and ≤4 weeks from assessment of screening by placental growth factor alone and the soluble fms-like tyrosine kinase-1/placental growth factor ratio with that of a previously developed competing risks model with a combination of maternal factors, placental growth factor, soluble fms-like tyrosine kinase-1, and mean arterial pressure (triple test).

RESULTS: First, the study population of 15,247 pregnancies included 326 pregnancies (2.1%) that subsequently experienced preeclampsia. Second, in the screening for delivery with preeclampsia at ≤2 and ≤4 weeks from assessment, the performance of the triple test was superior to that of placental growth factor alone or the soluble fms-like tyrosine kinase-1/placental growth factor ratio. The area under the receiver operating characteristics curves for preeclampsia at ≤2 weeks in screening by the triple test (0.975; 95% confidence interval, 0.964—0.985) was higher than that of placental growth factor alone (0.900; 95% confidence interval, 0.866—0.935; $P<.0001$) and the soluble fms-like tyrosine kinase-1/placental growth factor ratio (0.932; 95% confidence interval, 0.904—0.960; $P=.0001$). Similarly, the areas under the receiver operating characteristics curves for preeclampsia at ≤4 weeks in screening by the triple test (0.907; 95% confidence interval, 0.886—0.928) was higher than that of placental growth factor alone (0.827; 95% confidence interval, 0.800—0.854; $P<.0001$) or the soluble fms-like tyrosine kinase-1/placental growth factor ratio (0.857; 95% confidence interval, 0.830—0.883; $P<.0001$). Third, at most, screen-positive rates of 2—30% the detection rate of delivery with preeclampsia at ≤2 and ≤4 weeks that was achieved by the triple test was approximately 10% higher than that of the soluble fms-like tyrosine kinase-1/placental growth factor ratio and 20% higher than that of placental growth factor alone; the negative predictive value was similar for the 3 tests.

CONCLUSION: At 35^{+0}—36^{+6} weeks gestation, the performance of screening for imminent delivery with preeclampsia by the competing risks model is superior to that of placental growth factor alone or the soluble fms-like tyrosine kinase-1/placental growth factor ratio.

Key words: biomarker, competing risks model, mean arterial pressure, placental growth factor, preeclampsia, screening, soluble fms-like tyrosine kinase-1, third trimester

Development of preeclampsia is preceded by a decrease in the maternal serum concentration of the angiogenic placental growth factor (PlGF) and an increase in the level of antiangiogenic soluble fms-like tyrosine kinase-1 (sFLT).[1—11] In women with signs or symptoms of hypertensive disorders who are seen at specialist clinics, the use of cut-offs in the concentration of PLGF or the ratio of the concentrations of sFLT and PlGF have been used to predict the development of preeclampsia within the subsequent 1—4 weeks.[5,6,9,10] The recommended cut-offs that can be used to stratify women into a high-risk group in need of intensive surveillance or hospitalization and delivery and a low-risk group who could be reassured that imminent preeclampsia was unlikely are serum PlGF <5th percentile for gestation[6] and sFLT/PLGF ratio >38,[9] which at 36 weeks gestation represents the 90th percentile.[11] This approach has the advantage of simplicity in clinical implementation. However, it does not take into account the previous risk of the individual patient in the study population or the measurement of blood pressure at presentation, which is a prerequisite in the diagnosis of preeclampsia, and ignores the effects of maternal characteristics and gestational age on the measured serum concentrations.

An alternative approach for the prediction of preeclampsia at predefined

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AJOG at a Glance

Why was this study conducted?

The purpose of this study was to compare the performance of the competing risks model that combines maternal factors, placental growth factor, soluble fms-like tyrosine kinase-1and mean arterial pressure with that of placental growth factor alone or soluble fms-like tyrosine kinase-1/placental growth factor ratio in the prediction of imminent preeclampsia.

Key findings

The performance of the competing risks model with a combination of maternal factors and multiples of the median values of placental growth factor, soluble fms-like tyrosine kinase-1, and mean arterial pressure (triple test) was superior to that of placental growth factor alone or the soluble fms-like tyrosine kinase-1/placental growth factor ratio in screening for delivery with preeclampsia at ≤2 and ≤4 weeks from assessment. At most, screen-positive rates of 2−30% of the detection rate of delivery with preeclampsia at ≤2 and ≤4 weeks that was achieved by the triple test was approximately 10% higher than that of the soluble fms-like tyrosine kinase-1/placental growth factor ratio and 20% higher than that of placental growth factor alone; the negative predictive value was similar for the 3 tests.

What does this add to what is known?

The competing risks model provides effective prediction of imminent preeclampsia.

intervals from assessment is the use of the competing risks model, a Bayes' theorem−based method, to derive patient-specific risk for preeclampsia by various combinations of maternal characteristics and medical history with multiples of the median (MoM) values of biomarkers.[12−20] In a previous study of 3590 singleton pregnancies, we developed a competing risks model of screening for preeclampsia at 35−37 weeks gestation and reported that the best performance of screening was achieved by a combination of maternal factors, mean arterial pressure (MAP), PlGF, and sFLT (triple test).[17]

The objective of this prospective observational study in a population that underwent routine screening at 35^{+0} to 36^{+6} weeks gestation was to compare the performance of a strategy with the use of percentile cut-offs in PlGF or the sFLT/PlGF ratio and estimated risk cut-offs in the triple test. The justification of the study is that identification of the test with the highest predictive performance for the subsequent development of preeclampsia would be useful in the assessment and stratification of treatment (1) of the heterogeneous group of women who present to specialist clinics with signs and/or symptoms of hypertensive disorders and (2) of women who undergo routine screening in the late third trimester of pregnancy.

Methods

Study design and participants

This was a prospective observational study in women who attended a routine hospital visit at 35^{+0} to 36^{+6} weeks gestation at King's College Hospital, London, or Medway Maritime Hospital, Gillingham, UK, between October 2016 and September 2018. This visit included the recording of maternal demographic characteristics and medical history, an ultrasound examination for fetal anatomy and growth, the measuring of MAP by validated automated devices and a standardized protocol,[21] and measuring of the serum concentration of PlGF and sFLT (in picograms/per milliliters) by an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS; Thermo Fisher Scientific, Hennigsdorf, Germany). In this analyzer the interassay coefficients of variation for the low and high concentrations were 22% and 5% for PlGF, and 5% and 5% for sFLT, respectively; assays cover a measurement range from 3.6−7000 pg/mL for PlGF and from 22−90,000 pg/mL for sFLT. Gestational age was determined by the measurement of fetal crown-rump length at 11−13 weeks or the fetal head circumference at 19−24 weeks.[22,23] The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

Inclusion/exclusion criteria

The inclusion criteria for this study were singleton pregnancies examined at 35^{+0} to 36^{+6} weeks gestation that delivered a nonmalformed live birth or stillbirth. We excluded pregnancies with aneuploidies and major fetal abnormalities. Some of the patients in this study were included in our previous publication (n=9390).[19]

Outcome measures

Outcome measures were delivery with preeclampsia at ≤2 and ≤4 weeks after assessment. Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with preexisting or pregnancy-associated hypertension were examined to determine the diagnosis of preeclampsia. This was based on the finding of hypertension (systolic blood pressure, ≥140 mm Hg, or diastolic blood pressure, ≥90 mm Hg, on at least 2 occasions 4 hours apart that was experienced after 20 weeks gestation in previously normotensive women) and at least 1 of the following: proteinuria (≥300 mg/24 h or protein-to-creatinine ratio ≥30 mg/mmoL or ≥2 + on dipstick testing), renal insufficiency (serum creatinine >1.1 mg/dL or 2-fold increase in serum creatinine in the absence of underlying renal disease), liver involvement (blood concentration of transaminases >70 IU/L or 2-fold increase in the normal level), neurologic complications (eg, cerebral or visual symptoms), thrombocytopenia (platelet count <100,000/μL), or pulmonary edema.[24,25]

Statistical analysis

The competing risks model allows estimation of the individual patient-specific risks of delivery with preeclampsia before any specified gestational age by a combination of maternal demographic characteristics and medical history with biomarkers.[12,13] In this approach, which is based on a survival-time model for the gestational age at delivery with preeclampsia, it is assumed that, if the pregnancy were to continue indefinitely, all women would experience preeclampsia and whether they do so or not before a specified gestational age depends on competition between delivery before or after the development of preeclampsia. Each woman has a personalized distribution of gestational age at delivery with preeclampsia and the risk of delivery with preeclampsia before a specified gestational age, assuming that no other cause of delivery is given by the area under the probability density curve. The posterior distribution of gestational age at delivery with preeclampsia is obtained with the Bayes theorem by multiplying the previous probability density from maternal factors by the likelihood function from biomarker MoM values. The measured values of biomarkers are converted to MoMs for standardization to remove the effects of characteristics such as gestational age, weight and race, method of conception, medical conditions, elements from the obstetric history that are associated with the individual being measured, and characteristics that are associated with the instrument used for the measurement (Appendix). The risk calculator is freely available at the website of the Fetal Medicine Foundation (https://fetalmedicine.org).

The following steps were used to compare the predictive performance of PlGF alone, the sFLT/PlGF ratio, and the triple test for preeclampsia with delivery at ≤2 and ≤4 weeks. First, we used the competing risks model[17] to estimate the patient-specific risk for preeclampsia ≤2 weeks from assessment by a combination of maternal factors and MoM values of PlGF, sFLT, and MAP (triple test). Second, we determined the screen-positive rates for a range of risk cut-offs from 1 in 10 to 1 in 2000. Third, we identified the cut-offs in PlGF and the sFLT/PlGF ratio that corresponded to the same screen-positive rates using the triple test. Fourth, we used bootstrap to compare the area under the receiver operating characteristic curves (AUROC) of the 3 tests. We also estimated the detection rates, positive predictive values, and negative predictive values at different screen-positive rates for the 3 methods of screening.

The statistical software package R was used for data analyses.[26] The package pROC[27] was used for the receiver operating characteristic curve analysis.

Results

Study participants

The study population of 15,247 pregnancies included 326 pregnancies (2.1%) that subsequently experienced preeclampsia; delivery with preeclampsia at ≤2, 2−4, and >4 weeks from assessment occurred in 72, 150, and 104 cases, respectively. Maternal and pregnancy characteristics of the study population are summarized in Table 1. In the preeclampsia group, compared with the unaffected pregnancies, there was a higher median maternal weight, higher incidence of black racial origin, conception by in vitro fertilization, family history of preeclampsia, chronic hypertension, nulliparity, history of preeclampsia, longer interpregnancy interval, and lower incidence of smoking. In the preeclampsia group, the median values of MAP and sFLT were increased, and PlGF was decreased.

Performance of screening

Receiver operating characteristics curves for the prediction of delivery with preeclampsia at ≤2 and ≤4 weeks from assessment by the triple test, the sFLT/PlGF ratio, and PlGF alone are shown in Figure 1. The AUROC for preeclampsia at ≤2 weeks in screening by the triple test (0.975; 95% confidence interval [CI], 0.964−0.985) was higher than that of PlGF alone (0.900; 95% CI, 0.866−0.935; $P<.0001$) or the sFLT/PlGF ratio (0.932; 95% CI, 0.904−0.960; $P=.0001$); the AUROC for the sFLT/PlGF ratio was significantly higher than that for PlGF alone ($P<.0001$). Similarly, the AUROC for preeclampsia at ≤4 weeks in screening by the triple test (0.907; 95% CI, 0.886−0.928) was higher than that of PlGF alone (0.827; 95% CI, 0.800−0.854; $P<.0001$) or the sFLT/PlGF ratio (0.857; 95% CI, 0.830−0.883; $P<.0001$); the AUROC for the sFLT/PlGF ratio was significantly higher than that of PlGF alone ($P<.0001$).

Selection of a high-risk group that required intensive monitoring and/or early delivery

The detection rates, positive predictive values, and negative predictive values for preeclampsia at ≤2 and ≤4 weeks of the 3 screening tests at screen-positive rates ranged from 2−30% (Table 2). These data provide the background for decisions concerning selection of a screening strategy to achieve a desired detection rate of delivery with preeclampsia at ≤2 and ≤4 weeks from assessment. For example, if the desired detection rate of preeclampsia at ≤2 weeks was approximately 90% and the triple test was chosen for screening, the risk cut-off for selecting the high-risk group would be 1 in 100 and would be associated with a screen-positive rate of 8%, positive predictive value of 5.1%, and negative predictive value of 99.95%. To achieve the same detection rate in screening by PlGF alone or the sFLT/PlGF ratio, the screen-positive rate would need to be 3 times higher (27%) and the positive predictive value would need to be 3 times lower (1.5%); the negative predictive value would be similar (99.93%).

At 35^{+0} to 36^{+6} weeks gestation, the serum PlGF level that corresponded to the 5th percentile was 58 pg/mL. If, in screening for delivery with preeclampsia at ≤2 weeks, this cut-off was to be used for identification of the high-risk group, then the screen-positive rate would be 5% and this group would contain 60% (95% CI, 47−71%) of affected cases; if the triple test was to be used for screening at the same screen-positive rate of 5%, then the detection rate would be 85% (95% CI, 74−92%; $P=.0022$). The sFLT/PlGF ratio that

TABLE 1
Maternal and pregnancy characteristics of the study population

	No preeclampsia (n=14,921)	Preeclampsia (n=326)	*P* value
Age, y[a]	32.3 (28.3–35.8)	31.0 (27.5–35.1)	.017
Weight, kg[a]	79.0 (70.9–89.5)	86.6 (76.1–97.5)	<.0001
Height, cm[a]	165 (161–170)	165 (161–168)	.520
Gestational age at assessment, wk[a]	36.1 (35.9–36.4)	36.1 (35.9–36.4)	.627
Racial origin, n (%)			<.0001
White	11,892 (79.7)	233 (71.5)	
Black	1,622 (10.9)	65 (19.9)	
South Asian	666 (4.5)	14 (4.3)	
East Asian	313 (2.1)	3 (0.9)	
Mixed	428 (2.9)	11 (3.4)	
Medical history, n (%)			
Chronic hypertension	135 (0.9)	12 (3.7)	<.0001
Diabetes mellitus	142 (1.0)	6 (1.8)	.133
Systemic lupus erythematosus/ antiphospholipid syndrome	36 (0.2)	326 (100)	.756
Smoker, n (%)	951 (6.4)	12 (3.7)	.063
Family history of preeclampsia, n (%)	728 (4.9)	30 (9.2)	.0013
Method of conception, n (%)			.0003
Natural	14,285 (95.7)	298 (91.4)	
In vitro fertilization	551 (3.7)	26 (8.0)	
Use of ovulation drugs	85 (0.6)	2 (0.6)	
Parity, n (%)			<.0001
Nulliparous	6,895 (46.2)	226 (69.3)	
Parous no previous preeclampsia	7,776 (52.1)	81 (24.9)	
Parous previous preeclampsia	250 (1.7)	19 (5.8)	
Pregnancy interval, y[a]	2.8 (1.8–4.7)	4.2 (2.1–6.0)	.004
Gestational age at delivery, wk[a]	40.0 (39.1–40.9)	39.6 (38.4–40.4)	<.0001
Mean arterial pressure, multiples of the median[a]	1.0 (0.9–1.1)	1.1 (1.0–1.2)	<.0001
Placental growth factor, multiples of the median[a]	1.0 (0.6–1.8)	0.4 (0.2–0.7)	<.0001
Soluble fms-like tyrosine kinase-1, multiples of the median[a]	1.0 (0.7–1.4)	2.0 (1.3–3.0)	<.0001

[a] Data are given as median (interquartile range). Comparisons between outcome groups were by chi-square or Fisher exact test for categoric variables and Mann Whitney *U* test for continuous variables.

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corresponded to the 90th percentile was 52. If, in screening for delivery with preeclampsia at ≤2 weeks, this cut-off was to be used for the identification of the high-risk group, then the screen-positive rate would be 10% and this group would contain 82% (95% CI, 71–90%) of affected cases; if the triple test were to be used for screening, at the same screen-positive rate of 10%, then the detection rate would be 93% (95% CI, 85–98%; *P*=.0233).

Comment

Principal findings of this study

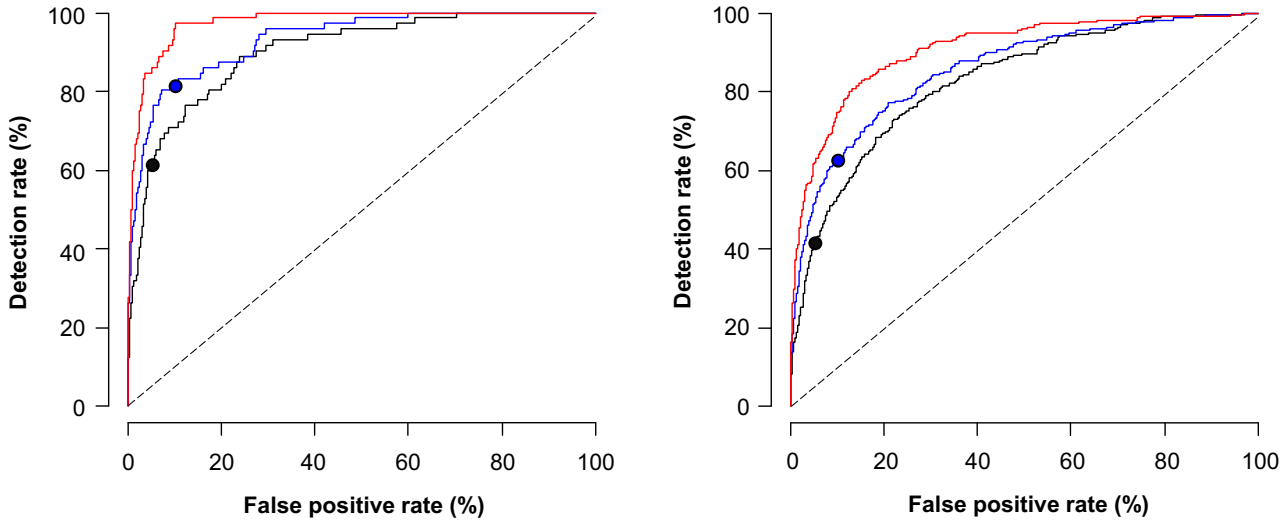
This study in singleton pregnancies that undergo routine assessment at 35^{+0} to 36^{+6} weeks gestation has demonstrated that the predictive performance for delivery with preeclampsia at ≤2 and ≤4 weeks of a competing risks model that combines maternal factors with MoM values of MAP, PlGF, and sFLT is superior to that of PlGF alone or the sFLT/PlGF ratio. For most screen-positive rates between 2 and 30%, the detection rate of delivery with preeclampsia at 2 and 4 weeks that was achieved by the triple test was approximately 10% higher than that of the sFLT/PlGF ratio and 20% higher than that of PlGF alone; the negative predictive value was similar for the 3 tests.

Irrespective of whether assessment of risk in the late third trimester is carried out in the general population or in women with signs and/or symptoms of hypertensive disorders, the objective of the identification of a high-risk group that is in need of intensive monitoring and/or delivery and a low-risk group that may not require hospitalization and intensive monitoring is the same. Ideally, the high-risk group should be small and contain most cases that would experience sufficiently severe preeclampsia to necessitate delivery within the subsequent 2 weeks. We found that, for any desired detection rate, the proportion of the population stratified into the high-risk group is substantially lower when screening is carried out by the triple test than PlGF alone or the sFLT/PlGF ratio.

Comparison with previous studies

Previous studies have demonstrated that useful biomarkers for preeclampsia in the first and second trimesters of pregnancy are PlGF, MAP, and the uterine artery pulsatility index,[13-15] in the early third trimester are PlGF, sFLT, MAP, and the uterine artery pulsatility index,[16] and in the late third trimester are PlGF, sFLT, and MAP.[17-19] Studies that have

FIGURE 1
Receiver operating characteristic curves



Receiver operating characteristic curves for the prediction of preeclampsia at ≤2 and ≤4 weeks from assessment (left and right) by placental growth factor (*black*), soluble fms-like tyrosine kinase-1/placental growth factor ratio (*blue*), and by a combination of maternal factors with multiples of the median values of placental growth factor, soluble fms-like tyrosine kinase-1, and mean arterial pressure (*red*). The *black circle* represents the performance of placental growth factor <5th percentile; the *blue circle* represents the performance of the soluble fms-like tyrosine kinase-1 to placental growth factor ratio >90th percentile.

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investigated serum PlGF and sFLT at 19–25, 30–34, and 35–37 weeks gestation have demonstrated that, in pregnancies that experience preeclampsia, serum PlGF is decreased and sFLT is increased, but the separation in MoM values from normal was greater when the interval between sampling and the development of preeclampsia was closer.[28,29]

A previous study in a heterogeneous group of women with signs and/or symptoms of hypertensive disorders at 24–37 weeks gestation examined the predictive performance of the sFLT/PLGF ratio >38.[9] The detection rate and false positive rate of preeclampsia at ≤1 week of assessment were 80% and 22%, respectively; the values for preeclampsia at ≤4 weeks were 66% and 17%. Another study in women with signs and/or symptoms of hypertensive disorders examined the predictive performance of serum PlGF <5th percentile for gestation.[6] The detection rate and false positive rate of preeclampsia at ≤2 weeks of assessment in pregnancies at <35 weeks gestation were 96% and 45%, respectively; the values in those pregnancies at 35^{+0} to 36^{+6} weeks were 70% and 36%. The authors of these studies suggested that their results are highly predictive of imminent preeclampsia and that high sFLT/PlGF ratio or low PlGF could be used to stratify women into a high-risk group that is in need of intensive surveillance or hospitalization and delivery and a low-risk group that could be reassured that imminent preeclampsia was unlikely.[6,9]

Our approach to the prediction of preeclampsia takes into account maternal characteristics, medical history, and blood pressure in addition to PlGF and sFLT to estimate the individual patient-specific risk for delivery with preeclampsia at any prespecified interval from assessment. The subsequent intensity of monitoring and decisions concerning delivery could then be individualized. In this study, we compared the performance of screening for imminent preeclampsia by different strategies and demonstrated the superiority of the competing risks approach to those of PlGF alone or the sFLT/PlGF ratio. The objective of assessment of pregnancies for imminent preeclampsia should be to identify most of such cases if we want to avoid false reassurance and mismanagement of high-risk pregnancies by stratifying them into a low-risk group. A policy that aims for a high detection rate inevitably would be associated with a high screen-positive rate, which as demonstrated by our study could be minimized through the competing risks approach rather than the use of PlGF alone or the sFLT/PlGF ratio.

Implications for clinical practice and research

In the heterogeneous group of women with some signs and/or symptoms of hypertensive disorders who attend specialist clinics, the use of cut-offs in measured biomarkers or their ratio to define clinical management has the advantage of simplicity. Such simplicity would be truly advantageous only if there was no overlap in the distributions of biomarkers between women who would experience preeclampsia from those that would not experience imminent preeclampsia; in such case, the test

TABLE 2

Detection rate, positive predictive value, and negative predictive value at the same screen-positive rate in screening for delivery with preeclampsia at ≤2 and ≤4 weeks from assessment by the triple test, the soluble fms-like tyrosine kinase-1/placental growth factor ratio, and placental growth factor alone

Cut-off	Screen-positive rate	History+mean arterial pressure+placental growth factor+soluble fms-like tyrosine kinase-1			Soluble fms-like tyrosine kinase-1/ placental growth factor ratio			Placental growth factor alone		
		Detection rate (95% confidence interval)	Positive predictive value (95% confidence interval)	Negative predictive value (95% confidence interval)	Detection rate (95% confidence interval)	Positive predictive value (95% confidence interval)	Negative predictive value (95% confidence interval)	Detection rate (95% confidence interval)	Positive predictive value (95% confidence interval)	Negative predictive value (95% confidence interval)
Screening for delivery with preeclampsia at ≤2 weeks from assessment										
10	2	62 (50–74)	17.9 (13.3–23.2)	99.82 (99.74–99.88)	47 (35–59)	13.5 (9.5–18.3)	99.75 (99.65–99.82)	32 (21–44)	9.2 (5.9–13.4)	99.67 (99.57–99.76)
20	3	76 (65–86)	11.5 (8.7–14.7)	99.88 (99.82–99.93)	60 (47–71)	9.0 (6.6–11.9)	99.80 (99.72–99.87)	43 (31–55)	6.5 (4.4–9.1)	99.72 (99.62–99.80)
40	5	85 (74–92)	7.9 (6.1–10.1)	99.92 (99.86–99.96)	71 (59–81)	6.6 (5.0–8.6)	99.85 (99.78–99.91)	60 (47–71)	5.6 (4.1–7.5)	99.80 (99.71–99.87)
50	6	86 (76–93)	7.0 (5.4–8.9)	99.93 (99.87–99.97)	76 (65–86)	6.2 (4.7–8.0)	99.88 (99.81–99.93)	61 (49–72)	5.0 (3.7–6.7)	99.81 (99.72–99.87)
100	8	90 (81–96)	5.1 (4.0–6.5)	99.95 (99.90–99.98)	81 (70–89)	4.5 (3.5–5.8)	99.90 (99.83–99.95)	69 (57–80)	3.9 (2.9–5.1)	99.84 (99.76–99.90)
150	10	93 (85–98)	4.3 (3.3–5.4)	99.96 (99.91–99.99)	82 (71–90)	3.8 (2.9–4.8)	99.90 (99.84–99.95)	71 (59–81)	3.3 (2.4–4.3)	99.85 (99.77–99.90)
200	12	97 (90–100)	3.8 (3.0–4.8)	99.99 (99.95–100)	83 (73–91)	3.3 (2.5–4.2)	99.91 (99.84–99.95)	72 (60–82)	2.8 (2.1–3.7)	99.85 (99.77–99.91)
250	13	97 (90–100)	3.5 (2.7–4.4)	99.98 (99.95–100)	83 (73–91)	3.0 (2.3–3.8)	99.91 (99.84–99.95)	76 (65–86)	2.7 (2.1–3.5)	99.87 (99.79–99.93)
500	18	97 (90–100)	2.6 (2.0–3.2)	99.98 (99.94–100)	86 (76–93)	2.3 (1.8–2.9)	99.92 (99.85–99.96)	81 (70–89)	2.1 (1.6–2.8)	99.89 (99.81–99.94)
1000	23	99 (93–100)	2.0 (1.6–2.5)	99.99 (99.95–100)	88 (78–94)	1.8 (1.4–2.3)	99.92 (99.85–99.96)	86 (76–93)	1.7 (1.3–2.2)	99.91 (99.84–99.96)
1500	27	99 (93–100)	1.7 (1.3–2.2)	99.99 (99.95–100)	89 (79–95)	1.5 (1.2–2.0)	99.93 (99.86–99.97)	89 (79–95)	1.5 (1.2–2.0)	99.93 (99.86–99.97)
2000	30	100 (95–100)	1.6 (1.2–2.0)	100 (99.97–100)	96 (88–99)	1.5 (1.2–1.9)	99.97 (99.92–99.99)	92 (83–97)	1.4 (1.1–1.8)	99.94 (99.88–99.98)

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(continued)

TABLE 2

Detection rate, positive predictive value, and negative predictive value at the same screen-positive rate in screening for delivery with preeclampsia at ≤2 and ≤4 weeks from assessment by the triple test, the soluble fms-like tyrosine kinase-1/placental growth factor ratio, and placental growth factor alone

(continued)

Cut-off	Screen-positive rate	History+mean arterial pressure+placental growth factor+soluble fms-like tyrosine kinase-1			Soluble fms-like tyrosine kinase-1/ placental growth factor ratio			Placental growth factor alone		
		Detection rate (95% confidence interval)	Positive predictive value (95% confidence interval)	Negative predictive value (95% confidence interval)	Detection rate (95% confidence interval)	Positive predictive value (95% confidence interval)	Negative predictive value (95% confidence interval)	Detection rate (95% confidence interval)	Positive predictive value (95% confidence interval)	Negative predictive value (95% confidence interval)
Screening for delivery with preeclampsia at ≤4 weeks from assessment										
10	2	37 (31–44)	32.9 (27.2–39.1)	99.07 (98.91–99.22)	27 (21–33)	23.8 (18.7–29.6)	98.92 (98.74–99.08)	19 (14–25)	16.7 (12.3–21.9)	98.80 (98.61–98.97)
20	3	49 (42–56)	22.7 (19.0–26.7)	99.23 (99.08–99.37)	39 (33–46)	18.1 (14.8–21.9)	99.09 (98.92–99.23)	27 (22–34)	12.8 (9.9–16.1)	98.91 (98.73–99.07)
40	5	57 (50–64)	16.5 (14.0–19.4)	99.34 (99.20–99.47)	48 (41–55)	13.9 (11.6–16.6)	99.21 (99.05–99.34)	39 (33–46)	11.3 (9.2–13.8)	99.07 (98.90–99.22)
50	6	62 (55–68)	15.4 (13.1–18.0)	99.41 (99.27–99.53)	52 (45–59)	13.0 (10.8–15.4)	99.25 (99.1–99.39)	42 (35–49)	10.6 (8.6–12.8)	99.10 (98.93–99.25)
100	8	67 (61–73)	11.7 (10.0–13.6)	99.48 (99.34–99.59)	58 (51–65)	10.1 (8.5–11.9)	99.33 (99.19–99.46)	49 (42–56)	8.5 (7.1–10.2)	99.19 (99.03–99.33)
150	10	72 (66–78)	10.2 (8.8–11.8)	99.55 (99.42–99.65)	62 (55–68)	8.8 (7.4–10.3)	99.38 (99.23–99.5)	52 (45–59)	7.4 (6.2–8.8)	99.23 (99.06–99.37)
200	12	76 (70–82)	9.2 (8.0–10.7)	99.61 (99.48–99.70)	63 (56–69)	7.6 (6.4–8.9)	99.38 (99.23–99.51)	55 (48–62)	6.7 (5.6–7.9)	99.25 (99.09–99.39)
250	13	79 (73–84)	8.7 (7.5–10.0)	99.64 (99.53–99.74)	66 (59–72)	7.2 (6.2–8.5)	99.43 (99.28–99.55)	58 (51–64)	6.4 (5.3–7.5)	99.29 (99.13–99.43)
500	18	83 (78–88)	6.8 (5.9–7.8)	99.70 (99.59–99.79)	72 (65–77)	5.8 (5.0–6.8)	99.5 (99.36–99.61)	65 (59–72)	5.3 (4.5–6.3)	99.39 (99.23–99.51)
1000	23	87 (82–91)	5.4 (4.7–6.2)	99.75 (99.64–99.83)	77 (71–83)	4.8 (4.1–5.6)	99.57 (99.44–99.68)	73 (67–79)	4.5 (3.9–5.3)	99.49 (99.34–99.61)
1500	27	89 (84–93)	4.8 (4.1–5.5)	99.77 (99.67–99.85)	79 (73–84)	4.2 (3.6–4.9)	99.58 (99.44–99.69)	76 (70–82)	4.1 (3.5–4.7)	99.52 (99.38–99.64)

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would be diagnostic, but in reality, this is not so for the proposed biomarkers. However, such an approach for stratification of pregnancy care is limited because (1) it does not take into account the previous risk of the individual patient based on maternal characteristics and medical history, (2) it does not adjust the measured biomarkers for those maternal and pregnancy characteristics that are known to affect these measurements, (3) it ignores the level of deviation from normal blood pressure, which is an integral part of the condition under investigation, and (4) it does not quantify the patient-specific risk and lacks the necessary flexibility of allowing healthcare professionals to select the desired proportion of cases with imminent preeclampsia that can be allocated to the high-risk group. Use of the competing risks approach overcomes these limitations and can form the basis of future research that would quantify and incorporate into the model symptoms such as headache and epigastric pain and proteinuria, creatinine, liver enzymes, and platelets.

Routine screening for preeclampsia with the use of the competing risks approach at 11−13 weeks gestation predicts approximately 90% of those who experience early preeclampsia with delivery at <32 weeks gestation, 75% of preterm-preeclampsia, and only approximately 40−45% of term preeclampsia, at 10% screen-positive rate; prophylactic use of aspirin (150 mg/d from 11−14 to 36 weeks gestation) in the screen-positive group reduces the incidence of early preeclampsia by approximately 90% and preterm preeclampsia by 60%, with no significant effect on the incidence of term preeclampsia.[12-14,30-33] However, >70% of cases of preeclampsia occur at term[34]; the predictive performance of screening for term preeclampsia at 20 and 32 weeks gestation is poor.[15,16] However, as shown in this study, screening by the triple test at 35−37 weeks gestation can predict a high proportion of cases of preeclampsia with delivery at ≤2 and ≤4 weeks from assessment, at acceptably low screen-positive rates.[17-19] The best management of the screen-positive group with the objective of the reduction of maternal and perinatal mortality and morbidity rates remains to be determined. This study provides the necessary data for the development of policies to achieve the prenatal prediction of imminent preeclampsia and for future research for the potential benefit of such strategies as close monitoring, pharmacologic intervention, or early delivery.

Strengths and limitations

The strengths of this study are (1) the examination of a large population of pregnant women seeking routine care in a gestational age range, which is being used increasingly for assessment of fetal growth and wellbeing,[34] (2) the recording of data on maternal characteristics and medical history to define the previous risk, (3) the use of automated machines to provide accurate measurement within 40 minutes of sampling of maternal serum concentration of PlGF and sFLT, (4) the expression of the values of the biomarkers as MoMs after adjustment for maternal factors and reagents used that affect the measurements, (5) the use of Bayes theorem to combine the previous risk from maternal factors with MoM values of biomarkers to estimate patient-specific risks and the performance of the prediction of delivery with preeclampsia at different stages after assessment, and (6) the direct comparison of performance for the prediction of delivery with preeclampsia by the competing risks approach to that of PlGF alone or the sFLT-1/PlGF ratio.

A limitation of the study relates the predictive performance of screening in an unselected population rather than in those with signs and/or symptoms of hypertensive disorders who attend specialist clinics. These populations would differ inevitably in terms of incidence and screening performance. However, the improved performance seen in the general population would be expected to be translated to those who attend specialist clinics. It could also be argued that, in the setting of specialist clinics, the value of MAP as a predictive biomarker would be limited because those attending these clinics generally have high blood pressure. However, differences in levels of MAP between patients would be informative and would improve screening performance. In any case, in the 2 studies that advocate the use of PlGF or the sFLT/PlGF ratio for stratification of care, new onset hypertension or worsening preexisting hypertension was present in only 79% and 41% of patients, respectively.[6,9] Another potential factor that could affect performance of screening in women who attend specialist clinics, compared with those who undergo routine assessment, is that, in the former, a higher proportion would undergo iatrogenic delivery at term before they actually experience preeclampsia. However, such a policy would not affect the incidence of preeclampsia within 2 weeks of assessment at 35^{+0} to 36^{+6} weeks gestation.

Conclusions

In third-trimester screening for preeclampsia, serum sFLT and PlGF are powerful biomarkers of delivery with preeclampsia within the subsequent 2−4 weeks. Low PlGF and high sFLT-1/PlGF ratio as methods of screening for preeclampsia, both in the general population and in the high-risk pregnancies, are attractive because of their simplicity. However, PlGF ≥5th percentile or sFLT/PlGF ≤90th percentile do not rule out the development of preeclampsia during the subsequent 2 or 4 weeks and respective values <5th or >90th percentile have only a modest performance in the identification of women who will experience preeclampsia within these time frames. The performance of a model that combines maternal characteristics, medical history, and blood pressure with PlGF and sFLT is superior to that of PlGF alone or the sFLT/PlGF ratio. The competing risks model provides a personalized risk for delivery with preeclampsia that could lead to personalized stratification of the intensity of monitoring and timing of delivery. ■

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APPENDIX
Formulas for the calculation of multiples of the median values at 35–37 weeks gestation

Term	Estimate
Mean arterial pressure	
Intercept	1.871000000
Gestational age, d minus 77	0.000389500
Weight, kg minus 69	0.001067000
Weight, kg minus 69-2	−0.000006979
Height, cm minus 164	−0.000294100
Racial origin	
Black	−0.010640000
South Asian	−0.006367000
East Asian	−0.007574000
Mixed	−0.004967000
Medical history of chronic hypertension	0.029890000
Parous with no history of preeclampsia	−0.007914000
Parous with history of preeclampsia	0.008956000
Serum placental growth factor	
Intercept: Cobas e411 analyzer[a]	4.0816010
Intercept: BRAHMS kryptor analyzer[b]	3.9960000
Gestational age, d minus 77	−0.0095120
Weight, kg minus 69	−0.0009272
Weight, kg minus 69-2	−0.0000237
Maternal age, y minus 35	−0.0035600
Racial origin	
Black	0.1661000
South Asian	0.0467400
East Asian	0.0491600
Smoker	0.0779000
Medical history of diabetes mellitus type 1	−0.1405000
Medical history of diabetes mellitus type 2	−0.0814300
Parous with no history of preeclampsia	0.1234000
Serum soluble fms-like tyrosine kinase-1	
Intercept: Cobas e411 analyzer[a]	1.94599700
Intercept: BRAHMS kryptor analyzer[b]	1.89200000
Gestational age, d minus 77	0.00883000
Weight, kg minus 69	−0.00409700
Weight, kg minus 69-2	0.00002945
Maternal age, y minus 35	0.00284600

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APPENDIX

Formulas for the calculation of multiples of the median values at 35–37 weeks gestation *(continued)*

Term	Estimate
Racial origin	
Black	0.06691000
East Asian	−0.02495000
Conception by in vitro fertilization	0.05252000
Medical history of systemic lupus erythematosus	0.06754000
Medical history of diabetes mellitus type 1	0.18460000
Medical history of diabetes mellitus type 2	0.04972000
Parous with no history of preeclampsia	−0.11130000

Note: These are default parameters and their suitability should be checked before use.

[a] Roche Diagnostics, Penzberg, Germany; [b] Thermo Fisher Scientific, Hennigsdorf, Germany

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