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Prediction of hypertensive disorders after screening at 36 weeks' gestation: comparison of angiogenic markers with competing-risks model

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KEYWORDS: angiogenic factor; antiangiogenic factor; competing-risks model; mean arterial pressure; placental growth factor; PlGF; pre-eclampsia; sFlt-1; soluble fms-like tyrosine kinase-1; survival model; third-trimester screening

CONTRIBUTION

What are the novel findings of this work?
In singleton pregnancies at 35 + 0 to 36 + 6 weeks' gestation, prediction of delivery with pre-eclampsia (PE) or gestational hypertension (GH) within 1 week, within 2 weeks or at any time after assessment is superior with use of a competing-risks model 'triple test', combining maternal factors with multiples of the median (MoM) values of mean arterial pressure, serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1), compared with use of biomarkers alone. Additionally, the 'double test', which combines maternal factors with MoM values of PlGF and sFlt-1, is superior to the sFlt-1/PlGF ratio, and the 'single test', which combines maternal factors with MoM values of PlGF, is superior to PlGF alone for the prediction of PE within 2 weeks and at any time from assessment.

What are the clinical implications of this work?
At 35 + 0 to 36 + 6 weeks' gestation, the best prediction of PE or GH is achieved by using all available information, that is, history and blood pressure, in addition to angiogenic marker values. As it is unclear how best to manage screen-positive women at 36 weeks' gestation to reduce adverse pregnancy outcome, future work should address the effectiveness of strategies such as close monitoring, pharmacological intervention and/or timed birth at term.

ABSTRACT

Objective *To compare the performance at 35 + 0 to 36 + 6 weeks' gestation of screening for delivery with pre-eclampsia (PE) at various timepoints, using one of three approaches: placental growth factor (PlGF) concentration, soluble fms-like tyrosine kinase-1 (sFlt-1) to PlGF concentration ratio, or the competing-risks model, which combines maternal risk factors with biomarkers to estimate patient-specific risk.*

Methods *This was a prospective observational study of women attending for a routine hospital visit at 35 + 0 to 36 + 6 weeks' gestation at one of two maternity hospitals in England between 2016 and 2022. During the visit, maternal demographic characteristics and medical history were recorded and serum PlGF, serum sFlt-1 and mean arterial pressure (MAP) were measured. Detection rates (DRs) were evaluated for delivery with PE (defined as per American College of Obstetricians and Gynecologists 2019 criteria) within 1 week, within 2 weeks or at any time after screening, using the following strategies: (i) low PlGF (< 10th percentile); (ii) high sFlt-1/PlGF ratio (> 90th percentile); or (iii) the competing-risks model, in which maternal factors were combined with multiples of the median values of PlGF ('single test'), PlGF and sFlt-1 ('double test') or PlGF, sFlt-1 and MAP ('triple test'). Risk cut-offs corresponded to a screen-positive rate of 10%. DRs were compared between tests.*

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Results *Of 34 782 pregnancies, 831 (2.4%) developed PE. In screening for delivery with PE at any time from assessment, the DR at 10% screen-positive rate was 47% by low PlGF alone, 54% by the single test, 55% by high sFlt-1/PlGF ratio, 61% by the double test and 68% by the triple test. In screening for delivery with PE within 2 weeks from assessment, the respective values were 67%, 74%, 74%, 80% and 87%. In screening for delivery with PE within 1 week from assessment, the respective values were 77%, 81%, 85%, 88% and 91%. For prediction of PE at any time, the DR was significantly higher with the triple test compared to PlGF alone or the sFlt-1/PlGF ratio, with a DR difference (95% CI) of 20.1% (16.7–23.0%) and 12.4% (9.7–15.3%), respectively. Similar results were seen for prediction of PE within 2 weeks (20.6% (14.9–26.8%) and 12.9% (7.7–17.5%), respectively) and prediction of PE within 1 week (13.5% (5.4–21.6%) and 5.4% (0.0–10.8%), respectively). The double test was superior to the sFlt-1/PlGF ratio and the single test was superior to PlGF alone in the prediction of PE within 2 weeks and at any time from assessment, but not within 1 week of assessment.*

Conclusion *At 35 + 0 to 36 + 6 weeks' gestation, the performance of screening for PE by the competing-risks model triple test is superior to that of PlGF alone or the sFlt-1/PlGF ratio for the development of disease within 1 week, within 2 weeks and at any time from screening.* © *2023 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Pre-eclampsia (PE) complicates 2–5% of pregnancies. Globally, it is a leading cause of maternal and perinatal mortality and morbidity[1]. As the only cure for PE is delivery of the placenta, a key focus of research has been on the prediction and prevention of PE.

At 11–13 weeks' gestation, a combination of maternal characteristics and medical history, together with the measurement of mean arterial pressure (MAP), uterine artery pulsatility index and angiogenic serum placental growth factor (PlGF), can identify approximately 75% of preterm PE with delivery at < 37 weeks' gestation, at a 10% screen-positive rate (SPR)[2–4]. Importantly, treatment of the high-risk group with aspirin (150 mg/day from 12 to 36 weeks' gestation) decreases development of preterm PE by almost two-thirds[5]. However, this early pregnancy assessment identifies only about 40% of PE at term, and low-dose aspirin does not decrease the incidence of term PE[5].

At 35–36 weeks' gestation, a combination of maternal characteristics and medical history, MAP, serum PlGF and antiangiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) can identify approximately 70% of subsequent disease. PE develops most commonly at term (≥ 37 weeks' gestation), but no strategy for its prevention has been proven effective. A randomized trial is currently evaluating timed birth based on personalized risk of PE (reference: ISRCTN41632964), in light of previous work indicating the potential of this strategy to decrease the rate of term PE by about 60%[6]. The performance of clinical risk factors alone to predict PE at term is poor[6]; therefore, it appears that, at minimum, the addition of maternal serum levels of angiogenic biomarkers may be needed to improve predictive performance.

In this prospective observational study at 35 + 0 to 36 + 6 weeks' gestation, we aimed to determine the best strategy for identifying women at increased risk of PE or gestational hypertension (GH). We compared the performance of screening for PE or GH using three strategies: PlGF concentration < 5th and < 10th percentile, sFlt-1/PlGF concentration ratio > 95th and > 90th percentile, and the competing-risks model (which combines information from maternal characteristics, MAP and biomarkers), with risk cut-offs corresponding to SPRs of 5% and 10%.

METHODS

Study design and participants

This was a prospective observational study of women attending a routine hospital visit at 35 + 0 to 36 + 6 weeks' gestation at two UK maternity hospitals, King's College Hospital, London, and Medway Maritime Hospital, Gillingham, between October 2016 and September 2022. At this visit, the following were undertaken: recording of maternal demographic characteristics and medical history; ultrasound examination for fetal anatomy and growth; measurement of MAP by validated automated devices in accordance with a standardized protocol[7]; and measurement of maternal serum concentrations of PlGF and sFlt-1 in pg/mL using an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS; Thermo Fisher Scientific, Hennigsdorf, Germany). Gestational age was determined by measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks.

The participant characteristics recorded included maternal age, self-declared ethnicity (white, black, South Asian, East Asian or mixed), method of conception (natural or assisted by *in-vitro* fertilization or ovulation induction), cigarette smoking during pregnancy, medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, family history of PE (woman's mother affected) and obstetric history, including parity (parous or nulliparous, if no previous pregnancy at ≥ 24 weeks' gestation) and, for parous women, previous pregnancy with PE and interpregnancy interval.

Included were singleton pregnancies examined at 35 + 0 to 36 + 6 weeks' gestation, delivering a non-malformed liveborn or stillborn fetus at ≥ 35 weeks' gestation. Pregnancies with aneuploidy or major fetal abnormality and those with PE or GH at the time of the visit were

excluded. All participants gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee (REC reference: 02-03-033).

Outcome measures

Outcome measures were delivery with PE or GH within 1 week, within 2 weeks or at any time after assessment. PE was defined according to the 2019 American College of Obstetricians and Gynecologists criteria[8] as chronic hypertension or GH, with development of one or more of the following: new-onset proteinuria, serum creatinine $>97\,\mu$mol/L in the absence of underlying renal disease, serum transaminases more than twice the normal level (≥ 65 IU/L for our laboratory), platelet count $<100\,000/\mu$L, headache or visual symptoms or pulmonary edema. Chronic hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, at least twice, 4 h apart, documented before pregnancy or at <20 weeks' gestation[9]. GH was defined as new-onset hypertension at ≥ 20 weeks' gestation in a previously normotensive woman[8].

Data on pregnancy outcome were collected from participants' hospital maternity records or those of their general medical practitioners. The maternity records of all women with chronic hypertension or GH were examined to determine the diagnosis of PE and GH.

Statistical analysis

For the screened population, biomarker cut-offs were identified for PlGF corresponding to the 5th and 10th percentiles and for the sFlt-1/PlGF ratio corresponding to the 95th and 90th percentiles. The 5th percentile was chosen for PlGF because this is used in clinical practice at late preterm gestation to assess women with suspected pre-eclampsia[10]. The 90th percentile was chosen for sFlt-1/PlGF because the cut-off of 38, used for similar purposes, represents the 90th percentile value at 36 weeks' gestation[11]. We then calculated the number and percentage of cases of PE below the 5th and 10th percentiles for PlGF and above the 90th and 95th percentiles for sFlt-1/PlGF at each timepoint of interest.

The competing-risks model was used to estimate the participant-specific risk of delivery with PE for each timepoint of interest. This method is based on a survival-time model for gestational age at delivery with PE, and uses a combination of maternal demographics, medical history and biomarkers[2]. By multiplying the prior probability density of gestational age at delivery with PE, determined from maternal factors, by the likelihood function derived from multiples of the median (MoM) values of biomarkers, a posterior distribution of gestational age at delivery with PE is obtained using Bayes' theorem[2]. The measured values of biomarkers are converted to MoMs for standardization, in order to remove the effects of characteristics pertaining to the individual, such as gestational age, weight, ethnicity, method of conception, medical conditions and obstetric history, and those associated with the instrument used for measurement.

The screening strategies were as follows: measured concentration of PlGF; ratio of the measured concentrations of sFlt-1 to PlGF; and the competing-risks model, combining maternal demographics and medical history with PlGF only ('single test'), sFlt-1 and PlGF ('double test') or MAP, PlGF and sFlt-1 ('triple test'). The following steps were used to compare the predictive performance of the strategies. First, we identified cut-offs in PlGF corresponding to the 5th and 10th percentiles and in the sFlt-1/PlGF ratio corresponding to the 95th and 90th percentiles for the screened population, and calculated the number and percentage of cases of PE below and above these cut-offs, respectively. Second, we used the competing-risks model of the single, double and triple tests to derive a risk for PE in each patient, identified the cut-offs corresponding to the 95th and 90th percentiles of risk and calculated the number and percentage of cases of PE above these cut-offs.

For prediction of PE and GH within 1 week, within 2 weeks or at any time after assessment, McNemar's test and bootstrap sampling were used to compare the performance of the triple test with that of low PlGF or high sFlt-1/PlGF ratio, the double test with that of high sFlt-1/PlGF ratio and the single test with that of low PlGF. This was undertaken for SPRs of 5% and 10%. The statistical software package R (R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis[12]. *P*-values of <0.05 were considered statistically significant.

RESULTS

Study participants

The study population of 34 782 women included 831 (2.4%) who subsequently developed PE and 997 (2.9%) who developed GH. Maternal and pregnancy characteristics of the study population are summarized in Table 1. Women who developed PE, compared with those who did not develop PE or GH, were heavier, with higher median maternal weight and body mass index, and were more likely to be black, have a history of chronic hypertension, diabetes mellitus or a family history of PE, have conceived by assisted means, and be nulliparous or, if parous, have a history of PE and a longer interpregnancy interval. In the GH group, compared with the unaffected group, women were older, heavier and more likely to have a history of diabetes mellitus or a family history of PE, have conceived by assisted means, and be nulliparous or, if parous, have a history of PE and a longer interpregnancy interval. In the PE group, and to a lesser extent in the GH group, the median MAP MoM and sFlt-1 MoM were higher and median PlGF MoM lower compared with the no PE or GH group. Figure 1 shows considerable overlap in serum PlGF concentration and sFlt-1/PlGF concentration ratio between women who developed

Table 1 Maternal and pregnancy characteristics of study population, according to development of pre-eclampsia (PE) or gestational hypertension (GH)

Characteristic	*No PE or GH (n = 32 954)*	*PE (n = 831)*	*GH (n = 997)*
Maternal age (years)	32.7 (28.8–36.0)	32.5 (28.2–36.6)	33.1 (29.6–36.9)*
Maternal weight (kg)	78.8 (70.7–89.0)	86.0 (75.3–99.7)*	85.2 (75.5–98.5)*
Maternal height (cm)	165 (161–170)	165 (161–169)	166 (161–170)
Body mass index (kg/m^2)	28.7 (26.0–32.4)	31.2 (28.0–36.2)*	31.2 (27.8–35.6)*
Gestational age (weeks)	36.0 (35.6–36.3)	36.0 (35.6–36.3)	36.0 (35.6–36.3)
Race		*	
White	25 788 (78.3)	617 (74.2)	775 (77.7)
Black	3757 (11.4)	152 (18.3)	125 (12.5)
South Asian	1704 (5.2)	27 (3.2)	55 (5.5)
East Asian	708 (2.1)	14 (1.7)	14 (1.4)
Mixed	997 (3.0)	21 (2.5)	28 (2.8)
Medical history			
Chronic hypertension	277 (0.8)	55 (6.6)*	0 (0)*
Diabetes mellitus	279 (0.8)	15 (1.8)*	19 (1.9)*
SLE/APS	85 (0.3)	0 (0)	2 (0.2)
Smoker	1589 (4.8)	23 (2.8)	46 (4.6)
Family history of PE	1207 (3.7)	79 (9.5)*	80 (8.0)*
Method of conception		*	*
Spontaneous	31 289 (95.0)	755 (90.9)	925 (92.8)
In-vitro fertilization	1482 (4.5)	70 (8.4)	63 (6.3)
Ovulation drugs	183 (0.6)	6 (0.7)	9 (0.9)
Parity		*	*
Nulliparous	15 468 (46.9)	589 (70.9)	592 (59.4)
Parous, no previous PE	16 815 (51.0)	185 (22.3)	322 (32.3)
Parous, previous PE	671 (2.0)	57 (6.9)	83 (8.3)
Interpregnancy interval (years)	2.6 (1.6–4.4)	3.5 (2.1–6.4)*	2.9 (1.8–5.1)*
Biomarker level at screening			
MAP MoM	1.00 (0.95–1.05)	1.11 (1.05–1.17)*	1.10 (1.04–1.16)*
PlGF MoM	1.00 (0.56–1.81)	0.36 (0.22–0.60)*	0.54 (0.32–0.97)*
sFlt-1 MoM	1.00 (0.70–1.38)	2.16 (1.39–3.24)*	1.45 (0.97–2.21)*

Data are given as median (interquartile range) or *n* (%). *$P < 0.05$ *vs* no PE or GH group. APS, antiphospholipid syndrome; MAP, mean arterial pressure; MoM, multiples of the median; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; SLE, systemic lupus erythematosus.

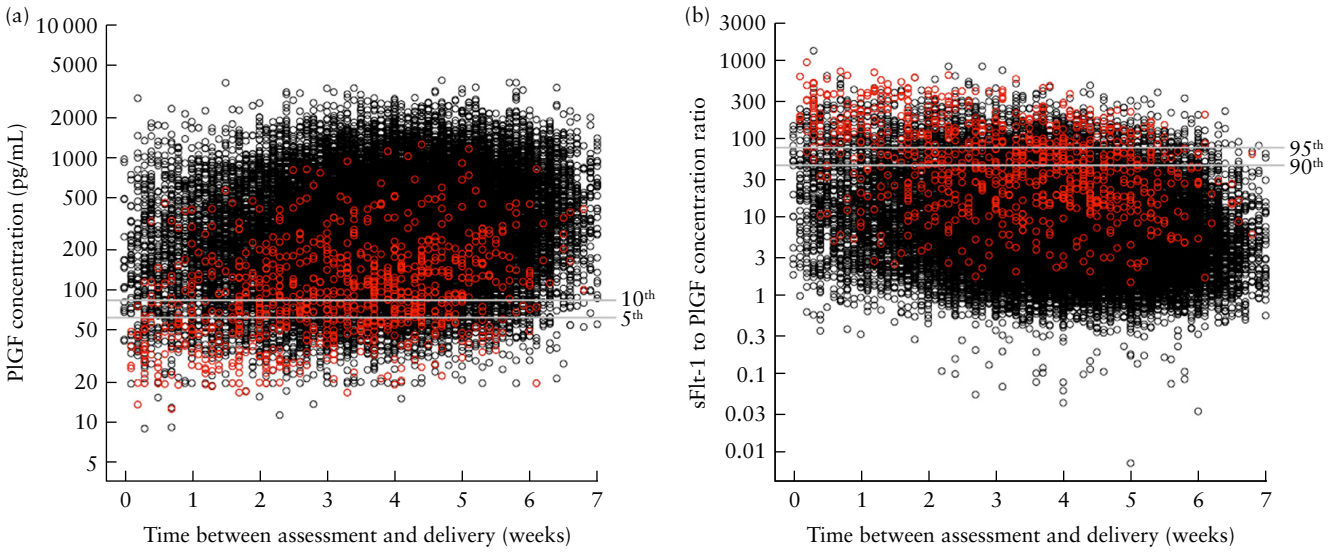

Figure 1 Relationship of serum placental growth factor (PlGF) concentration (a) and soluble fms-like tyrosine kinase-1 (sFlt-1) to PlGF concentration ratio (b) with interval between assessment and delivery, in women who developed pre-eclampsia (red), compared with those who did not (black). Horizontal gray lines in (a) represent 10th and 5th percentiles, and in (b), 90th and 95th percentiles.

PE and those who did not, regardless of when birth occurred.

McNemar's test demonstrated that the performance of the triple test was superior to that of low PlGF or high sFlt-1/PlGF ratio in the prediction of PE or GH within 1 week, within 2 weeks or at any time from assessment, at a SPR of 5% and 10% (Table 2). At 10% SPR, the performance of the double test was superior to that of high sFlt-1/PlGF ratio in the prediction of PE within 2 weeks or at any time from assessment, but not within 1 week from assessment; in the case of GH, screening by the double test was superior to that by high sFlt-1/PlGF ratio only for delivery at any time from screening, but not within 1 or 2 weeks from assessment. At 10% SPR, the performance of the single test was superior to that of low PlGF in the prediction of PE and GH within 2 weeks or at any time from assessment, but not within 1 week from assessment.

Performance of screening

The detection rates (DRs) for delivery with PE or GH within 1 week, within 2 weeks or at any time after assessment are given in Table 3. The DRs for PE were lowest for PlGF alone and highest for the triple test, for all timepoints of interest and for SPRs of 10% and 5%. For prediction of PE within 1 week, DRs ranged from 77.0% to 90.5% at a SPR of 10%, and from 64.9% to 87.8% at a SPR of 5%; for prediction of PE within 2 weeks, the respective DR values were 66.5–87.1% and 53.6–76.8%; and for prediction of PE at any time after assessment, DR values were 47.4–67.5% and 31.9–49.6%, respectively. The performance of screening for GH was poorer than that for PE by all approaches, at each timepoint and for 10% and 5% SPRs; however, as for PE, the best results were obtained using the triple test.

Table 2 Results of McNemar's test for comparison of performance of competing-risks models to that of low placental growth factor (PlGF) or high soluble fms-like tyrosine kinase-1 (sFlt-1) to PlGF ratio in the prediction of pre-eclampsia and gestational hypertension at various timepoints, at screen-positive rates of 5% and 10%

	Pre-eclampsia		*Gestational hypertension*	
Comparison of outcome measure	*Difference in DR (%)*	P	*Difference in DR (%)*	P
5% screen-positive rate				
Delivery within 1 week				
Triple test *vs* PlGF concentration	23.0 (13.5 to 33.8)	< 0.001	36.4 (18.2 to 51.5)	< 0.001
Triple test *vs* sFlt-1/PlGF ratio	8.1 (2.7 to 14.9)	< 0.001	24.2 (9.1 to 36.4)	< 0.001
Double test *vs* sFlt-1/PlGF ratio	1.4 (−5.4 to 9.5)	0.548	0 (−12.1 to 9.1)	0.936
Single test *vs* PlGF concentration	4.1 (−5.4 to 13.5)	0.366	9.1 (0 to 21.2)	< 0.001
Delivery within 2 weeks				
Triple test *vs* PlGF concentration	23.2 (16.5 to 29.9)	< 0.001	28.3 (19.1 to 36.7)	< 0.001
Triple test *vs* sFlt-1/PlGF ratio	10.3 (5.2 to 15.5)	< 0.001	20.0 (10.8 to 26.7)	< 0.001
Double test *vs* sFlt-1/PlGF ratio	3.1 (−2.6 to 7.2)	0.268	1.7 (−4.2 to 7.5)	0.524
Single test *vs* PlGF concentration	6.7 (1.0 to 13.4)	0.022	7.5 (1.7 to 14.2)	0.008
Delivery at any time after screening				
Triple test *vs* PlGF concentration	17.7 (14.2 to 20.8)	< 0.001	11.9 (9.2 to 14.9)	< 0.001
Triple test *vs* sFlt-1/PlGF ratio	10.2 (7.3 to 13.2)	< 0.001	9.6 (7.2 to 11.9)	< 0.001
Double test *vs* sFlt-1/PlGF ratio	3.7 (1.2 to 6.3)	0.002	0.4 (−1.5 to 2.2)	0.648
Single test *vs* PlGF concentration	6.6 (3.5 to 9.1)	< 0.001	1.5 (−0.5 to 3.5)	0.122
10% screen-positive rate				
Delivery within 1 week				
Triple test *vs* PlGF concentration	13.5 (5.4 to 21.6)	< 0.001	15.2 (3.0 to 27.3)	< 0.001
Triple test *vs* sFlt-1/PlGF ratio	5.4 (0 to 10.8)	0.014	15.2 (6.1 to 27.3)	< 0.001
Double test *vs* sFlt-1/PlGF ratio	2.7 (−2.7 to 8.1)	0.216	6.1 (−6.1 to 18.2)	0.216
Single test *vs* PlGF concentration	4.1 (−4.1 to 12.2)	0.250	6.1 (−6.1 to 15.2)	0.330
Delivery within 2 weeks				
Triple test *vs* PlGF concentration	20.6 (14.9 to 26.8)	< 0.001	27.5 (18.3 to 36.7)	< 0.001
Triple test *vs* sFlt-1/PlGF ratio	12.9 (7.7 to 17.5)	< 0.001	20.8 (13.3 to 30.8)	< 0.001
Double test *vs* sFlt-1/PlGF ratio	5.7 (1.0 to 9.3)	0.010	5.8 (−0.8 to 11.7)	0.070
Single test *vs* PlGF concentration	7.7 (2.6 to 13.4)	0.002	7.5 (0.8 to 14.2)	0.024
Delivery at any time after screening				
Triple test *vs* PlGF concentration	20.1 (16.7 to 23.0)	< 0.001	17.3 (14.4 to 20.3)	< 0.001
Triple test *vs* sFlt-1/PlGF ratio	12.4 (9.7 to 15.3)	< 0.001	15.1 (12.3 to 17.8)	< 0.001
Double test *vs* sFlt-1/PlGF ratio	5.8 (3.4 to 8.2)	< 0.001	5.6 (3.4 to 7.6)	< 0.001
Single test *vs* PlGF concentration	6.9 (3.6 to 9.9)	< 0.001	3.5 (1.3 to 5.9)	< 0.001

Values in parentheses are 95% CI. Triple test refers to a combination of maternal characteristics and medical history, with multiples of the median (MoM) values of mean arterial pressure, PlGF and sFlt-1. Double test refers to a combination of maternal characteristics and medical history, with MoM values of PlGF and sFlt-1. Single test refers to a combination of maternal characteristics and medical history, with MoM values of PlGF. DR, detection rate.

Table 3 Detection rate, at the same screen-positive rate, for delivery with pre-eclampsia or gestational hypertension at various timepoints after screening

	Pre-eclampsia			*Gestational hypertension*		
Method of screening	*Within 1 week* (n = 74)	*Within 2 weeks* (n = 194)	*At any time after screening* (n = 831)	*Within 1 week* (n = 33)	*Within 2 weeks* (n = 120)	*At any time after screening* (n = 997)
5% screen-positive rate						
PlGF < 5th percentile	48 (64.9 (52.9–75.6))	104 (53.6 (46.3–60.8))	265 (31.9 (28.7–35.2))	9 (27.3 (13.3–45.5))	29 (24.2 (16.8–32.8))	158 (15.8 (13.6–18.3))
Single test (MF + PlGF)	51 (68.9 (57.1–79.2))	117 (60.3 (53.1–67.2))	320 (38.5 (35.2–41.9))	12 (36.4 (20.4–54.9))	38 (31.7 (23.5–40.8))	173 (17.4 (15.1–19.8))
sFlt-1/PlGF > 95th percentile	59 (79.7 (68.8–88.2))	129 (66.5 (59.4–73.1))	327 (39.4 (36.0–42.8))	13 (39.4 (22.9–57.9))	39 (32.5 (24.2–41.7))	181 (18.2 (15.8–20.7))
Double test (MF + PlGF + sFlt-1)	60 (81.1 (70.3–89.3))	135 (69.6 (62.6–76.0))	358 (43.1 (39.7–46.5))	13 (39.4 (22.9–57.9))	41 (34.2 (25.8–43.4))	185 (18.6 (16.2–21.1))
Triple test (MF + PlGF + sFlt-1 + MAP)	65 (87.8 (78.2–94.3))	149 (76.8 (70.2–82.5))	412 (49.6 (46.1–53.0))	21 (63.6 (45.1–79.6))	63 (52.5 (43.2–61.7))	277 (27.8 (25.0–30.7))
10% screen-positive rate						
PlGF < 10th percentile	57 (77.0 (65.8–86.0))	129 (66.5 (59.4–73.1))	394 (47.4 (44.0–50.9))	19 (57.6 (39.2–74.5))	51 (42.5 (33.5–51.9))	272 (27.3 (24.5–30.2))
Single test (MF + PlGF)	60 (81.1 (70.3–89.3))	144 (74.2 (67.5–80.2))	451 (54.3 (50.8–57.7))	21 (63.6 (45.1–79.6))	60 (50.0 (40.7–59.3))	307 (30.8 (27.9–33.8))
sFlt-1/PlGF > 90th percentile	63 (85.1 (75.0–92.3))	144 (74.2 (67.5–80.2))	458 (55.1 (51.7–58.5))	19 (57.6 (39.2–74.5))	59 (49.2 (39.9–58.4))	293 (29.4 (26.6–32.3))
Double test (MF + PlGF + sFlt-1)	65 (87.8 (78.2–94.3))	155 (79.9 (73.6–85.3))	506 (60.9 (57.5–64.2))	21 (63.6 (45.1–79.6))	66 (55.0 (45.7–64.1))	349 (35.0 (32.0–38.1))
Triple test (MF + PlGF + sFlt-1 + MAP)	67 (90.5 (81.5–96.1))	169 (87.1 (81.6–91.5))	561 (67.5 (64.2–70.7))	24 (72.7 (54.5–86.7))	84 (70.0 (61.0–78.0))	444 (44.5 (41.4–47.7))

Data are given as *n* (% (95% CI)). MAP, mean arterial pressure; MF, maternal factors; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

DISCUSSION

Principal findings

This prospective study in women with a singleton pregnancy undergoing routine assessment at 35 + 0 to 36 + 6 weeks' gestation demonstrated that prediction of delivery with PE within 1 week, within 2 weeks or at any time after assessment is superior with use of a competing-risks model triple test, combining maternal factors with MoM values of MAP, PlGF and sFlt-1, compared with use of biomarkers alone. Additionally, the double test was superior to the sFlt-1/PlGF ratio and the single test was superior to PlGF alone for the prediction of PE within 2 weeks and at any time from assessment, at a SPR of 10%. The performance of screening for GH was poorer than that for PE by all three approaches, but, as in the case of PE, the best results were obtained using the triple test.

Comparison with previous studies

Our data provide evidence that, at 35 + 0 to 36 + 6 weeks' gestation, the best prediction of PE or GH is achieved by using all available information; that is, history and blood pressure, in addition to angiogenic marker values. Even in under-resourced settings in which prenatal care registration occurs well after the first trimester, almost all women have a prenatal visit by 36 weeks' gestation, and all prenatal care guidelines advise measurement of blood pressure at each visit.

We have expanded our previous work[13] on PE prediction at 35 + 0 to 36 + 6 weeks' gestation, extending our much smaller sample size of 15 247 pregnancies (2014–2018), and presenting an updated and more comprehensive picture of PE and GH prediction in clinical practice. In our previous study, the estimated risks of delivery with PE were harmonized to compare the associated DRs, whereas in this study, we compared DRs using cut-offs that could be applied in clinical practice. We have also extended our findings by: (i) assessing the prediction of PE at a SPR of 5% (in addition to 10%), and within 1 week and at any time after assessment (compared with 2 or 4 weeks); (ii) presenting not only the screening performance of PlGF concentration, sFlt-1/PlGF ratio and the competing-risks model triple test (maternal history, MAP and angiogenic markers), but also that of the single and double tests, referring, respectively, to PlGF alone and both PlGF and sFlt-1, adjusted for maternal history; and (iii) evaluating the prediction of GH in a similar fashion.

Our findings are consistent with those of others, who have found that PlGF or sFlt-1/PlGF results are highly predictive of imminent PE, and could be used to stratify women into a high-risk group in need of intensive surveillance or hospitalization and delivery, and a low-risk group that could be reassured that imminent PE is unlikely and continue to undergo 'watchful waiting'[10,14–16]. Moreover, our findings that the DRs were highest for development of PE or GH within 1 week and lowest for development of disease at any time after

screening are consistent with those of previous studies. When investigating serum PlGF and sFlt-1 levels at 19–25, 30–34 and 35–37 weeks' gestation, previous work has shown that, not only is serum PlGF decreased and sFlt-1 increased in pregnancies destined to develop PE, but the deviation in MoM values from normal was greater when the interval between sampling and development of PE was shorter[17–19].

While our data reflect biomarker measurement in women presenting for a routine hospital visit, our findings may inform 'time-of-disease' assessment for women with GH or other signs or symptoms of PE. There is no clear separation in PlGF or sFlt-1/PlGF values between women who develop PE or GH imminently (within the next week) and those who do not. The same is true for women who develop PE or GH within 2 weeks or thereafter.

Implications for clinical practice and research

At 35 + 0 to 36 + 6 weeks' gestation, the most accurate risk assessment for prediction of PE or GH is afforded by the competing-risks model triple test. It is unclear how best to manage screen-positive women in order to reduce maternal and perinatal death and morbidity. Future work should address the effectiveness of potential management strategies, including close monitoring, pharmacological intervention and/or early delivery. A randomized trial is currently evaluating timed birth based on personalized risk of PE (reference: ISRCTN41632964).

While use of biomarkers alone to identify women most likely to develop PE or GH is attractive for its simplicity, this approach would be advantageous only if there was no overlap in the distributions of biomarkers between women who develop PE or GH and those who do not. However, as shown in Figure 1, there is considerable overlap between these populations with regards to biomarker levels. In the case of the competing-risks model, a personalized risk for development of subsequent PE is provided for any chosen interval from the time of assessment. Future work should address, for time-of-disease assessment, whether multivariable modeling could address the risk of delivery with PE or GH, by incorporating angiogenic marker levels as well as maternal symptoms (such as headache and epigastric pain), maternal signs (such as platelet count or serum creatinine) and/or fetal signs (such as fetal growth restriction). Such a multivariable approach has been successful in predicting the risk of maternal complications in PE[20].

Strengths and limitations

Strengths of this study include our large population of more than 30 000 pregnant women attending for routine care at a gestational age at which prediction of the greatest number of women with PE is possible. Clinicians caring for women in the cohort were not aware of their PE risk status or biomarker values. The competing-risks model incorporated data that were already known prior to angiogenic marker assessment, namely maternal characteristics and medical history, to define the prior risk of PE or GH. We used automated machines to provide accurate measurement, within 40 min of sampling, of maternal serum concentration of PlGF and sFlt-1. Also, biomarker values were expressed as MoMs after adjustment for maternal factors (such as ethnicity[21]) and reagents used that affect the measurements. We used Bayes' theorem to combine the prior risk from maternal factors with MoM values of biomarkers to estimate patient-specific risk and the performance of predicting delivery with PE at different timepoints after assessment.

As a limitation, we acknowledge that ours was a screening study of asymptomatic women with a singleton pregnancy, and not a study of women with multiple pregnancy or presenting at the same gestational age with either GH or suspected PE, imminent or otherwise. These populations would inevitably differ in terms of incidence and screening performance, but the performance of the competing-risks model triple test, including MAP, which is treated as a continuous variable, observed in the screening population would be expected to translate to a symptomatic population with potential PE or GH.

Conclusions

Timing-of-birth strategies at term should be based on the most accurate assessment of the risk of developing PE or GH. While PlGF concentration and sFlt-1/PlGF ratio are powerful biomarkers of subsequent delivery with PE or GH, and attractive because of their simplicity for clinical implementation, their performance is inferior to that achieved by incorporating information that is already available, namely maternal characteristics, medical history and blood pressure, along with PlGF and sFlt-1.

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