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RESEARCH ARTICLE

General obstetrics

Placental growth factor testing at 19–23 weeks of gestation as a guide to subsequent care in pregnancy: A prospective observational study

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Abstract

Objective: To determine whether serum placental growth factor (PlGF) at 19–23 weeks of gestation can improve the identification of risk for adverse outcomes.

Design: Prospective observational cohort study.

Setting: Two English maternity units.

Population: Unselected singleton pregnancies attending routine ultrasound at 19–23 weeks of gestation.

Methods: Outcomes ascertained by health record review. Diagnostic test properties evaluated clinical risk factors for pre-eclampsia (according to National Institute of Care Excellence) or fetal growth restriction (according to Royal College of Obstetricians and Gynaecologists), low PlGF at 19–23 weeks of gestation (<5th percentile) or both.

Main outcome measures: Pre-eclampsia, gestational hypertension, stillbirth, birthweight below third percentile or neonatal intensive care unit (NICU) admission for ≥48 h.

Results: In 30 013 pregnancies, risk factors were present in 9941 (33.1%), low PlGF was present in 1501 (5.0%) and both ('two-stage' screening) were present in 547 (1.8%) pregnancies. Risk factors detected 41.7%–54.7% of adverse outcomes, and could not meaningfully revise the risk (all positive likelihood ratios, +LR, <5.0; all negative likelihood ratios, −LR, ≥0.2). Low PlGF detected 8.5%–17.4% of adverse outcomes, but meaningfully increased risks (other than NICU admission) associated with delivery <37 weeks of gestation (+LR = 5.03–15.55); all −LRs were ≥0.2. 'Two-stage' screening detected 4.2%–8.9% of adverse outcomes, with meaningful +LRs (6.28–18.61) at <37 weeks of gestation, except for NICU admission of ≥48 h, which had an +LR of 7.56 at <34 weeks of gestation; all −LRs were ≥0.2. No screening strategy meaningfully increased or decreased the detection of adverse outcome risk at term.

Conclusions: Clinical risk factor screening has a high screen-positive rate and a poor detection of adverse outcomes. False positives cannot be reduced by PlGF testing at 19–23 weeks of gestation; therefore, this cannot be recommended as a useful strategy on its own.

KEYWORDS
adverse pregnancy outcomes, fetal growth restrictions, placental growth factor, pre-eclampsia, risk factors

This article will have a Video Abstract presented by Laura A. Magee.

1 | INTRODUCTION

The placental disorders of pre-eclampsia (PE) and fetal growth restriction (FGR) are leading causes of maternal and fetal/newborn mortality and morbidity, worldwide. A key objective of antenatal care is to identify women and babies at increased risk for the development of these conditions, to provide preventative therapy (for PE) and enhanced maternal and fetal surveillance (for PE and FGR).

National organisations in the UK recommend that pregnancies at increased risk of PE or FGR be identified using clinical risk factors. The National Institute for Health and Care Excellent (NICE) recommends that women with one 'major' or at least two 'moderate' risk factors for PE be identified at antenatal care booking and offered low-dose aspirin.[1] In women screened using an alternative, 'competing risks' strategy, low-dose aspirin reduces the risk of preterm PE by more than 60%.[2] The Royal College of Obstetricians and Gynaecologists (RCOG) recommends that pregnancies with one 'major' or at least three 'minor' risk factors for FGR be offered enhanced ultrasonographic surveillance of fetal growth and well-being.[3] However, each of these screening strategies is known to detect less than half of pregnancies that will end in adverse placental outcomes.[4,5]

As low serum placental growth factor (PlGF) has been associated with both PE and FGR, we evaluated whether it could be measured at 19–23 weeks of gestation, in conjunction with the routine ultrasound assessment for fetal anomalies, as a 'contingency screening tool' to improve the predictive performance of clinical risk factors for the subsequent development of PE and/or FGR.[6]

2 | METHODS

2.1 | Study design and participants

The study data for this secondary analysis were derived from a prospective screening study for adverse pregnancy outcomes in women attending routine pregnancy care at 19–23 weeks of gestation at two maternity hospitals in England (King's College Hospital and Medway Maritime Hospital), from October 2011 to March 2020, inclusive. Women gave written informed consent to participate, and the study was approved by the National Health Service Research Ethics Committee (ref. 02-03-033). There was no patient involvement in the study.

At the routine hospital visit at 19–23 weeks of gestation, women underwent an assessment that included the recording of maternal demographics and medical history and the measurement of serum PlGF (as described below). Gestational age was determined by the measurement of the fetal crown–rump length at 11–13 weeks of gestation.[7]

Included in the study were singleton pregnancies delivering a nonmalformed live birth or stillbirth at $\geq 24^{0/7}$ weeks of gestation. Excluded were pregnancies with aneuploidy or major fetal abnormalities.

2.2 | Risk of PE or FGR

Pregnancies were considered at increased risk of PE or FGR according to contemporaneous UK national guidance, as summarised in Table S1.

According to the 2019 NICE guidelines,[1] women are considered at high risk of PE if they have at least one high or two moderate risk factors (Table S1). The five high risk factors are: hypertensive disease in previous pregnancy; chronic hypertension; diabetes mellitus; chronic kidney disease; and autoimmune disease. The five moderate risk factors are: first pregnancy; age of >40 years; body mass index (BMI) at first visit of >35 kg/m^2; interpregnancy interval of >10 years; and family history of PE.

According to the 2014 RCOG guidance,[3] pregnancies are considered at increased risk of FGR if they have at least one major or three or more minor risk factors (Table S1). The major risk factors are: maternal age >40 years; BMI ≥ 35 kg/m^2; chronic hypertension; type 1 or 2 diabetes mellitus with vascular disease; chronic kidney disease; antiphospholipid antibody syndrome; prior small for gestational age (SGA) fetus; prior stillbirth; smoker of ≥11 cigarettes/day; cocaine use; maternal or paternal SGA; daily vigorous exercise; heavy bleeding; uterine artery pulsatility index (UtA-PI) of >95th percentile; and serum pregnancy-associated plasma protein A (PAPP-A) of <0.4 MoM (multiple of medians) in the first trimester. The minor risk factors are: maternal age of ≥35 years; a BMI of <20 or 25–34.9 kg/m^2; PE during a previous pregnancy; smoking 1–10 cigarettes/day; nulliparity; an interpregnancy interval of <6 or ≥60 months; conception by in vitro fertilisation; and low fruit intake before pregnancy.

2.3 | Serum PlGF

Placental growth factor was considered low if the level was below the fifth percentile (<108 pg/mL) for the study population, as measured by BRAHMS Kryptor compact PLUS (ThermoFisher Scientific, Waltham, MA, USA).

2.4 | Outcome measures

Adverse outcomes of interest were ascertained by health record review of electronic hospital maternity records or records held by the women's general medical practitioners.

PE and gestational hypertension (GH) were defined by the American College of Obstetricians and Gynaecologists 2013 criteria.[8] GH was defined as a systolic blood pressure (BP) ≥140 mmHg or a diastolic BP of ≥90 mmHg, measured twice, at least 4 h apart. PE was chronic or gestational hypertension with the development of at least one of the following: new-onset proteinuria; serum creatinine of >97 mmol/L (in the absence of underlying renal disease); serum transaminases more than twice the upper limit of normal (i.e. ≥65 IU/L for our laboratory); platelet count of <100 000/mL; headache or visual symptoms; or pulmonary

oedema. The maternity records of all women with pregnancy hypertension were examined to determine the diagnosis of PE or GH. The contemporaneous management of hypertension was to initiate antihypertensive therapy for a BP of 150/100 mmHg,[9] before the guidance was changed to target a BP of ≤135/85 mmHg.[1]

Birthweights below the third percentile for gestational age were based on the Fetal Medicine Foundation (FMF) fetal and neonatal weight charts.[10] Other outcomes were stillbirth (defined as the birth of a fetus at $\geq 24^{+0}$ weeks of gestation with no signs of life) and neonatal intensive care unit (NICU) admission for ≥48 h. A core outcome set was not used, as the core outcome set for obstetric studies is currently in development.

2.5 | Statistical analysis

Descriptive analysis was undertaken for baseline data, PlGF measured at 19^{+0}–23^{+6} weeks of gestation and pregnancy outcomes for the study population overall, for those with PlGF below the fifth percentile and for those deemed at risk of PE or FGR according to clinical risk factors. Continuous variables were summarised by medians and interquartile ranges, and categorical variables were presented as numbers (percentages).

Diagnostic test properties were determined for the following approaches: (i) clinical risk factor screening with one or more PE or FGR clinical risk factors; (ii) low PlGF at 19–23 weeks of gestation (for comparison); and (iii) a two-stage approach, first with clinical risk factor screening and then, for screen-positive individuals, with PlGF testing. Detection rates for each adverse outcome were calculated, overall and according to gestational age at birth, as <32, <34, <37 and ≥37 weeks of gestation. The way in which testing could inform care was interpreted as the ability to provide meaningful reassurance, taken as a negative likelihood ratio (–LR) of <0.20, or meaningful concern, taken as a positive LR (+LR) of ≥5.0, for adverse pregnancy outcomes.[11] No correction was made for multiple testing.

3 | RESULTS

Our cohort comprised 30 013 unselected pregnancies at 19–23 weeks of gestation. Table 1 shows that, on average, pregnant women were in their early 30s, with a BMI near the threshold of normal and overweight. The population was ethnically diverse, with 21% from non-white ethnicities. A small proportion were smokers. Few pregnancies were complicated by chronic medical conditions. Few women had a family history of PE. Just over half of pregnant women were parous, among whom 2.1% had experienced prior PE and 6.7% had delivered a baby with a birthweight below the tenth percentile. Prior pregnancies occurred 2–3 years previously. Few women conceived by assisted means. Only 4.2% of the women were taking low-dose aspirin.

Placental growth factor was low, as defined above, in 1501 (5.0%) pregnancies (Table 1). One-third of pregnancies had one or more clinical risk factors for PE or FGR; 10.5% had a risk factor PE (usually two or more moderate risk factors) and 29.3% had a risk factor for FGR (usually a major risk factor). Women with low PlGF or women with one or more clinical risk factors for PE or FGR appeared to differ from the population overall, with respect to many characteristics associated with the risk of placental disease, including maternal age, BMI, ethnicity, medical and family history, parity, previous obstetric complications, assisted conception and aspirin therapy.

On average, pregnancies ended at almost 40 weeks of gestation, with 5.8% preterm deliveries and 21.9% labour inductions. The mode of birth was usually vaginal. PE developed in 2.9%, GH developed in 2.8%, stillbirth occurred in 0.2%, birthweights below the third percentile occurred in 4.7% and NICU admission for ≥48 h occurred in 8.5% of pregnancies. Of the 69 stillbirths, 36 (52.2%) were associated with PE and/or with birthweights below the tenth percentile. Women with low PlGF or with one or more clinical risk factors for PE or FGR appeared to have more complicated pregnancies, including more interventions, PE, GH, stillbirth, birthweight below the third percentile and prolonged NICU admission.

Table 2 shows that a primary screening strategy using clinical risk factors for PE or FGR had a screen-positive rate of 33%, but an associated detection rate of no better than approximately 50% for any of the adverse outcomes evaluated, with detection rates of approximately 60% for preterm disease. Importantly, for none of the adverse outcomes at any gestational age could clinical risk factors raise the level of concern or reassure women and their healthcare providers.

Table 3 shows that a primary screening strategy using PlGF at 19–23 weeks of gestation had a screen-positive rate of 5% (as defined). The associated detection rate was no better than 17% for any of the adverse outcomes of interest, although it varied and was much higher for delivery with adverse outcomes at <34 weeks of gestation. However, low PlGF could meaningfully identify women at increased risk of adverse outcomes, with +LR values of at least 5.0 for delivery with PE at <37 weeks of gestation, GH at <34 weeks of gestation, stillbirth at <37 weeks of gestation and birthweight below the third percentile at <37 weeks of gestation.

Table 4 shows the results of a two-stage screening approach, first by screening with clinical risk factors, and then for the 9941 pregnancies with one or more relevant risk factors, screening by PlGF at 19–23 weeks of gestation, and considering only those with PlGF below the fifth percentile to be screen-positive. For the 547 (1.8%) pregnancies that were screen-positive, detection rates were <10% for all adverse outcomes examined, at any gestational age. Although screen-positive pregnancies were at a meaningfully increased risk of preterm adverse outcomes, no women with clinical risk factors could be reassured that adverse outcomes were unlikely to develop.

TABLE 1 Baseline characteristics, details of screening and pregnancy outcomes for the study population of 30 013 unselected pregnancies at 19–23 weeks of gestation.

Maternal characteristics	Cohort overall (*N* = 30 013)	PlGF <5th percentile (*n* = 1501, 5.0%)	Clinical risk factors for PE/FGR (*n* = 9941, 33.1%)[a]
Maternal age (years)	32.1 (28.3–35.6)	31.7 (27.6–35.1)	34.6 (28.9–38.1)
Body mass index (kg/m^2)	24.6 (22.0–28.5)	26.2 (23.0–31.6)	26.3 (22.7–31.0)
Ethnic origin			
White	23 715 (79.0)	1296 (86.3)	7623 (76.7)
Black	3328 (11.1)	103 (6.9)	1301 (13.1)
South Asian	1497 (5.0)	50 (3.3)	539 (5.4)
East Asian	584 (1.9)	17 (1.1)	178 (1.8)
Mixed	889 (3.0)	35 (2.3)	300 (3.0)
Smoker	1956 (6.5)	38 (2.5)	1956 (19.7)
Medical history			
Chronic hypertension	296 (1.0)	25 (1.7)	296 (3.0)
Systemic lupus/APAS	67 (0.2)	2 (0.1)	67 (0.7)
Diabetes mellitus (type 1 or 2)	241 (0.8)	26 (1.7)	241 (2.4)
Family history: mother had PE	1109 (3.7)	73 (4.9)	807 (8.1)
Obstetric history: parity			
Nulliparous	14 129 (47.1)	772 (51.4)	4171 (42.0)
Parous, no previous PE	15 264 (50.9)	687 (45.8)	5150 (51.8)
Parous, no prior SGA (<10th percentile)	13 873 (46.2)	629 (41.9)	3759 (37.8)
Parous, prior PE	620 (2.1)	42 (2.8)	620 (6.2)
Parous, prior SGA (<10th percentile)	2011 (6.7)	100 (6.7)	2011 (20.2)
This pregnancy			
Interpregnancy interval (years)	2.7 (1.6–4.6)	2.6 (1.6–4.2)	3.3 (1.8–6.1)
Method of conception			
Spontaneous	28 558 (95.2)	1438 (95.8)	8901 (89.5)
Ovulation drugs	196 (0.7)	9 (0.6)	56 (0.6)
In vitro fertilisation	1259 (4.2)	54 (3.6)	984 (9.9)
On low-dose aspirin	1264 (4.2)	76 (5.1)	940 (9.5)
Gestational age at screening (weeks)	21.6 (21.1–22.0)	21.3 (21.0–21.7)	21.6 (21.1–22.0)
Clinical risk factors for PE or FGR	9941 (33.1)	547 (36.4)	9941 (100)
PE risk factor (any)	3151 (10.5)	237 (15.8)	3151 (31.7)
PE risk factor (major)	1147 (3.8)	88 (5.9)	1147 (11.5)
PE risk factor (≥2 moderate)	2146 (7.2)	165 (11.0)	2146 (21.6)
FGR risk factor (any)	8801 (29.3)	446 (29.7)	8801 (88.5)
FGR risk factor (major)	6632 (22.1)	340 (22.7)	6632 (66.7)
FGR risk factor (≥3 minor)	3294 (11.0)	166 (11.1)	3294 (33.1)
UtArt-PI >95th centile at 20–24 weeks	207/3294 (6.3)	31/166 (18.7)	207/3294 (6.3)
Gestational age at birth (weeks)	39.9 (39.0–40.7)	39.6 (38.1–40.6)	39.4 (38.4–40.4)
Preterm birth <37 weeks	1730 (5.8)	215 (14.3)	860 (8.7)
Induction of labour	6564 (21.9)	377 (25.1)	2277 (22.9)
Vaginal delivery	21 296 (71.0)	968 (64.5)	6415 (64.5)
Caesarean delivery	8717 (29.0)	533 (35.5)	3526 (35.5)
Pre-eclampsia	861 (2.9)	139 (9.3)	442 (4.4)
Gestational hypertension	838 (2.8)	82 (5.5)	401 (4.0)
Stillbirth	69 (0.2)	12 (0.8)	34 (0.3)
Birthweight <3rd percentile	1398 (4.7)	234 (15.6)	765 (7.7)
NICU admission for ≥48 h	2544 (8.5)	217 (14.5)	1060 (10.7)

Note: data are expressed as *N* pregnancies (%) or median value (IQR).

Abbreviations: APAS, antiphospholipid antibody syndrome; FGR, fetal growth restriction; IQR, interquartile range; NICU, neonatal intensive care unit; PI, pulsatility index; PlGF, placental growth factor; UtArt, uterine artery.

[a]For the clinical risk factors for PE and FGR, see Table S1.

TABLE 2 Primary screening by NICE and RCOG guidelines of the total population of 30 013 pregnancies, from which 9941 (33.1%) women were screen-positive.

Outcomes	Event rate (%)	DR (%)	+LR (95% CI)	−LR (95% CI)
PE	861 (2.9)	442/861 (51.3)	1.58 (1.47–1.68)	0.72 (0.67–0.77)
<32 weeks	30 (0.10)	12/30 (40.0)	1.21 (0.78–1.87)	0.90 (0.67–1.20)
<34 weeks	66 (0.22)	35/66 (53.0)	1.60 (1.28–2.01)	0.70 (0.54–0.91)
<37 weeks	180 (0.60)	104/180 (57.8)	1.75 (1.54–1.99)	0.63 (0.53–0.75)
≥37 weeks	681 (2.3)	338/681 (49.6)	1.52 (1.40–1.64)	0.75 (0.69–0.81)
GH	838 (2.8)	401/838 (47.9)	1.46 (1.36–1.57)	0.77 (0.73–0.83)
<32 weeks	10 (0.03)	6/10 (60.0)	1.81 (1.09–3.01)	0.60 (0.28–1.28)
<34 weeks	15 (0.05)	10/15 (66.7)	2.01 (1.41–2.88)	0.50 (0.24–1.02)
<37 weeks	66 (0.2)	41/66 (62.1)	1.88 (1.56–2.27)	0.57 (0.42–0.77)
≥37 weeks	772 (2.6)	360/772 (46.6)	1.42 (1.32–1.54)	0.79 (0.74–0.85)
Stillbirth	69 (0.02/1000)	34/69 (49.3)	1.49 (1.17–1.89)	0.76 (0.60–0.96)
<32 weeks	27 (0.9/1000)	12/27 (44.4)	1.34 (0.88–2.05)	0.83 (0.59–1.16)
<34 weeks	34 (1.1/1000)	15/34 (44.1)	1.33 (0.91–1.95)	0.84 (0.62–1.13)
<37 weeks	44 (1.5/1000)	21/44 (47.7)	1.44 (1.06–1.97)	0.78 (0.59–1.04)
≥37 weeks	25 (0.8/1000)	13/25 (52.0)	1.57 (1.08–2.29)	0.72 (0.48–1.08)
SGA < 3rd percentile	1398 (4.7)	765/1398 (54.7)	1.71 (1.62–1.79)	0.67 (0.63–0.71)
<32 weeks	76 (0.3)	44/76 (57.9)	1.75 (1.44–2.12)	0.63 (0.48–0.82)
<34 weeks	128 (0.4)	78/128 (60.9)	1.85 (1.61–2.12)	0.58 (0.47–0.72)
<37 weeks	331 (1.1)	198/331 (59.8)	1.82 (1.67–1.99)	0.60 (0.52–0.68)
≥37 weeks	1067 (3.6)	567/1067 (53.1)	1.64 (1.55–1.74)	0.69 (0.65–0.74)
NICU stay ≥ 48 h	2544 (8.5)	1060/2544 (41.7)	1.29 (1.23–1.35)	0.86 (0.83–0.89)
<32 weeks	199 (0.7)	112/199 (56.3)	1.71 (1.51–1.93)	0.65 (0.56–0.76)
<34 weeks	360 (1.2)	207/360 (57.5)	1.75 (1.60–1.92)	0.63 (0.56–0.71)
<37 weeks	899 (3.0)	472/899 (52.5)	1.61 (1.51–1.72)	0.70 (0.66–0.75)
≥37 weeks	1645 (5.5)	588/1645 (35.7)	1.08 (1.01–1.16)	0.96 (0.92–0.99)

Abbreviations: DR, detection rate; GH, gestational hypertension; LR, likelihood ratio; NICU, neonatal intensive care unit; PE, pre-eclampsia; SGA, small for gestational age.

4 | DISCUSSION

4.1 | Main findings

In this cohort of more than 30 000 unselected singleton pregnancies at 19–23 weeks of gestation, clinical risk factor screening had a high screen-positive rate (of 33%). Although this was primarily because of risk factors for FGR, there was substantial overlap in risk factors with PE, such that two-thirds of women with risk factors for FGR were also identified as being at high risk of PE.

Clinical risk factors for PE or FGR identified only about half of those destined to develop an adverse outcome of PE, GH, stillbirth, birthweight below the third percentile or NICU admission for ≥48 h. Importantly, among those who were screen-positive, the risk of adverse outcome was not meaningfully increased compared with those without any clinical risk factors.

As an alternative primary screening strategy, PlGF testing at 19–23 weeks of gestation had low detection rates (under 20%) for adverse outcomes, but pregnancies with low PlGF were indeed at a meaningfully higher risk of complications at preterm, but not term, gestational age.

Two-stage screening, first with clinical risk factors and then, if present, with PlGF testing at 19–23 weeks of gestation, could not address the high screen-positive rate associated with clinical risk factor screening in early pregnancy, as the large number of women who screened positive with clinical risk factors could not be reassured if their PlGF levels were then normal at 19–23 weeks of gestation.

4.2 | Interpretation

Currently, UK national guidelines recommend clinical risk factor screening to identify PE and FGR risk, in which risk factors are treated independently. Similar to our findings, others have identified that this approach is associated with a low detection rate for preterm (approx. 40%) or term (approx. 35%) PE,[12] or preterm (55%) or term (47%) SGA (birthweight below tenth percentile).[13] However, PE and FGR risk factors have been evaluated separately, despite their substantial

TABLE 3 Primary screening by serum PlGF below the fifth percentile of the total population of 30 013 pregnancies, from which 1501 (5.0%) women were screen-positive.[a]

Outcomes	Event rate (%)	DR (%)	+LR (95% CI)	−LR (95% CI)
PE	861 (2.9)	139/861 (16.1)	3.46 (2.94, 4.06)	0.88 (0.85–0.91)
<32 weeks	30 (0.10)	23/30 (76.7)	15.55 (12.69–19.06)	0.25 (0.13–0.47)
<34 weeks	66 (0.22)	41/66 (62.1)	12.74 (10.49–15.48)	0.40 (0.29–0.54)
<37 weeks	180 (0.60)	67/180 (37.2)	8.12 (6.67–9.88)	0.66 (0.59–0.74)
≥37 weeks	681 (2.3)	72/681 (10.6)	2.17 (1.73–2.72)	0.94 (0.92–0.96)
GH	838 (2.8)	82/838 (9.8)	2.01 (1.63–2.49)	0.95 (0.93–0.97)
<32 weeks	10 (0.03)	5/10 (50.0)	10.0 (5.38–19.0)	0.53 (0.28–0.98)
<34 weeks	15 (0.05)	7/15 (46.7)	9.37 (5.44–16.0)	0.56 (0.35–0.90)
<37 weeks	66 (0.2)	15/66 (22.7)	4.58 (2.93–7.17)	0.81 (0.71–0.93)
≥37 weeks	772 (2.6)	67/772 (8.7)	1.77 (1.40–2.24)	0.96 (0.94–0.98)
Stillbirth	69 (0.02/1000)	12/69 (17.4)	3.50 (2.09–5.86)	0.87 (0.78–0.97)
<32 weeks	27 (0.9/1000)	9/27 (33.3)	6.70 (3.92–11.0)	0.70 (0.54–0.92)
<34 weeks	34 (1.1/1000)	10/34 (29.4)	5.91 (3.50–9.98)	0.74 (0.60–0.92)
<37 weeks	44 (1.5/1000)	11/44 (25.0)	5.03 (3.01–8.41)	0.79 (0.67–0.94)
≥37 weeks	25 (0.8/1000)	1/25 (4.0)	0.80 (0.12–5.46)	1.01 (0.93–1.09)
SGA < 3rd percentile	1398 (4.7)	234/1398 (16.7)	3.78 (3.32–4.30)	0.87 (0.85–0.89)
<32 weeks	76 (0.3)	48/76 (63.2)	13.0 (11.0–16.0)	0.39 (0.29–0.52)
<34 weeks	128 (0.4)	69/128 (53.9)	11.0 (9.51–13.0)	0.48 (0.40–0.58)
<37 weeks	331 (1.1)	122/331 (36.9)	7.93 (6.83–9.22)	0.66 (0.61–0.72)
≥37 weeks	1067 (3.6)	112/1067 (10.5)	2.19 (1.82–2.63)	0.94 (0.92–0.96)
NICU stay for ≥48 h	2544 (8.5)	217/2544 (8.5)	1.82 (1.59–2.09)	0.96 (0.95–0.97)
<32 weeks	199 (0.7)	46 (23.1)	4.74 (3.66–6.13)	0.81 (0.75–0.87)
<34 weeks	360 (1.2)	80 (22.2)	4.64 (3.80–5.66)	0.82 (0.77–0.86)
<37 weeks	899 (3.0)	141 (15.7)	3.36 (2.86–3.94)	0.88 (0.86–0.91)
≥37 weeks	1645 (5.5)	76 (4.6)	0.92 (0.73–1.15)	1.00 (0.99–1.02)

Abbreviations: DR, detection rate; GH, gestational hypertension; LR, likelihood ratio; NICU, neonatal intensive care unit; PE, pre-eclampsia; PlGF, placental growth factor; SGA, small for gestational age.

[a]Results shaded in grey represent positive LR results (≥5.0) that meaningfully describe an increased risk for the adverse outcome evaluated.

overlap, as well as the overlap in PE and FGR clinical presentations and the evolution of disease during antenatal surveillance. Our findings confirm that one-third of pregnancies are screen-positive for PE and/or FGR risk factors, but despite this very high screen-positive rate, the detection rates for adverse outcomes are poor.

Alternatives to clinical risk factor screening are needed. Our findings do not suggest that taking a two-stage screening approach, by adding PlGF testing at 19–23 weeks of gestation for women who are screen-positive with clinical risk factors, could improve the screening performance of clinical risk factors. Similarly, our findings do not support the implementation of routine PlGF screening at 19–23 weeks of gestation, based on the poor detection rates for placental disorders. These results are consistent with a systematic review that demonstrated that PlGF testing alone (16 studies) is inferior to PlGF-based models (six studies) for the prediction of PE.[14]

Superior approaches are available for the detection of women at risk of delivery with PE or FGR at preterm or term gestational ages. The FMF 'competing risks' model uses the multivariable modelling of clinical, ultrasonographic and laboratory assessment of uteroplacental perfusion and function to identify those who may benefit from low-dose aspirin, to decrease the risk of preterm PE, or enhanced surveillance and timed birth, to optimise outcomes related to PE and/or FGR. The FMF model for PE detects approximately 75% of women who will develop preterm PE (when screened at 11–13 weeks of gestation) or term PE (when screened at 35–36 weeks of gestation) for screen-positive rates of 10%.[12] At 19–23 weeks of gestation, at a screen-positive rate defined by the RCOG guideline (22.5% in the relevant publication), the detection rates for SGA below the tenth percentile at <32, <37 and ≥37 weeks of gestation were 81%, 72% and 56%, respectively, using the FMF model, compared with 45%, 44% and 36%, respectively, following the RCOG guidelines.[15] The model has been updated to provide an effective personalised continuous stratification of pregnancy care pertinent to SGA, defining the appropriate timing of a subsequent

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TABLE 4 Two-stage screening for adverse outcomes.[a]

Outcomes	Event rate (%)	DR (%)	+LR (95% CI)	–LR (95% CI)
PE	861 (2.9)	70/861 (8.1)	4.97 (3.90–6.33)	0.93 (0.92–0.95)
<32 weeks	30 (0.1)	10/30 (33.3)	18.61 (11.14–31.09)	0.68 (0.53–0.87)
<34 weeks	66 (0.2)	18/66 (27.3)	15.44 (10.32–23.10)	0.74 (0.64–0.86)
<37 weeks	180 (0.6)	30/180 (16.7)	9.62 (6.86–13.48)	0.85 (0.79–0.91)
≥37 weeks	681 (2.3)	40/681 (5.9)	3.40 (2.49–4.65)	0.96 (0.94–0.98)
GH	838 (2.8)	40/838 (4.8)	2.75 (2.01–3.76)	0.97 (0.95–0.98)
<32 weeks	10 (0.03)	3/10 (30.0)	16.55 (6.40–42.80)	0.71 (0.48–1.07)
<34 weeks	15 (0.05)	4/15 (26.7)	14.73 (6.34–34.24)	0.75 (0.55–1.01)
<37 weeks	66 (0.2)	8/66 (12.1)	6.73 (3.50–12.96)	0.89 (0.82–0.98)
≥37 weeks	772 (2.6)	32/772 (4.1)	2.35 (1.66–3.34)	0.98 (0.96–0.99)
Stillbirth	69 (0.02)	6/69 (8.7)	4.81 (2.23–10.39)	0.93 (0.86–1.00)
<32 weeks	27 (0.09)	4/27 (14.8)	8.18 (3.30–20.29)	0.87 (0.74–1.02)
<34 weeks	34 (0.11)	4/34 (11.8)	6.50 (2.58–16.37)	0.90 (0.79–1.02)
<37 weeks	44 (0.15)	5/44 (11.4)	6.28 (2.74–14.40)	0.90 (0.81–1.00)
≥37 weeks	25 (0.08)	1/25 (4.0)	2.20 (0.32–15.02)	0.98 (0.90–1.06)
SGA < 3rd percentile	1398 (4.7)	125/1398 (8.9)	6.06 (5.00–7.35)	0.92 (0.91–0.94)
<32 weeks	76 (0.3)	29/76 (38.2)	22.05 (16.36–29.73)	0.63 (0.53–0.75)
<34 weeks	128 (0.4)	39/128 (30.5)	17.92 (13.61–23.61)	0.71 (0.63–0.79)
<37 weeks	331 (1.1)	62/331 (18.7)	11.46 (9.01–14.59)	0.83 (0.78–0.87)
≥37 weeks	1067 (3.6)	63/1067 (5.9)	3.53 (2.74–4.56)	0.96 (0.94–0.97)
NICU stay for ≥48 h	2544 (8.5)	106/2544 (4.2)	2.6 (2.11–3.20)	0.97 (0.97–0.98)
<32 weeks	199 (0.7)	29/199 (14.6)	8.39 (5.93–11.87)	0.87 (0.82–0.92)
<34 weeks	360 (1.2)	46/360 (12.8)	7.56 (5.70–10.04)	0.89 (0.85–0.92)
<37 weeks	899 (3.0)	72/899 (8.0)	4.91 (3.87–6.23)	0.94 (0.92–0.95)
≥37 weeks	1645 (5.5)	34/1645 (2.1)	1.14 (0.81–1.61)	1.00 (0.99–1.00)

Abbreviations: DR, detection rate; GH, gestational hypertension; LR, likelihood ratio; NICU, neonatal intensive care unit; PE, pre-eclampsia; SGA, small for gestational age.
[a]In the first stage, all 30 013 pregnancies were screened by the RCOG and NICE guidelines. In the second stage, the 9941 (33.1%) pregnancies that were screen-positive in the first stage were screened by serum PlGF, with 547 (1.8%) considered screen-positive based on PlGF below the fifth percentile. Results shaded in grey represent positive LR results (≥5.0) that meaningfully describe an increased risk for the adverse outcome evaluated.

ultrasonographic examination of fetal growth and well-being at 24–36 weeks of gestation, depending on the individual characteristics and the biophysical marker levels at the mid-gestation assessment.[16]

4.3 | Strengths and limitations

Strengths of our study include the very large sample size recruited prospectively in an unselected fashion from a diverse clinical population, using comprehensive and standardised data collection. We evaluated the collective risk of PE or FGR (given the clinical overlap in risk factors and clinical presentations), the use of PlGF as a marker of placental dysfunction and a spectrum of relevant outcomes. All hypertensive pregnancies were reviewed to distinguish between chronic hypertension, GH and PE, using a broad definition.[8] We evaluated the detection rates and diagnostic test properties, which are prevalence independent, and evaluated whether the screening strategy meaningfully increases or decreases the detection of risk for adverse outcomes.

Limitations include the enrolment of only singleton pregnancies, so our results may not apply to multiple pregnancies. At first we evaluated serum concentrations of PlGF alone, not MoM using maternal characteristics, and then included MoM, as this is how PlGF is most commonly assessed in clinical practice.

5 | CONCLUSION

Clinical risk factor screening for PE and FGR results in a high screen-positive rate but a poor detection rate of adverse outcomes, and the high false-positive rate cannot be reduced by PlGF testing at 19–23 weeks of gestation. Importantly, clinical risk factor screening and/or the results of PlGF testing at 19–23 weeks of gestation should not be used to guide the timing of birth at term. Future research should address the optimal follow-up of women

who screen positive in the first trimester by the FMF algorithm and, specifically, whether repeat testing of PlGF has a role to play.

AUTHOR CONTRIBUTIONS

All authors conceptualised and designed the study. LAM wrote the first draft of the article. AS and RA were involved in sample collection. All authors revised and contributed to the intellectual content of the article.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest. KN led the development of The FMF competing-risks models and AS and RA were part of the development team.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the NHS Research Ethics Committee (ref. 02-03-033, 11 March 2003).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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