Accepted: 2 August 2022 | Published Online 17 October 2022

DOI: 10.1111/1471-0528.17296

BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE

Maternal Medicine

Effect of race on the measurement of angiogenic factors for prediction and diagnosis of pre-eclampsia

Alan Wright[1] | Peter von Dadelszen[2] | Laura A. Magee[2] | Argyro Syngelaki[3] | Ranjit Akolekar[4,5] | Dave Wright[1] | Kypros H. Nicolaides[3]

[1]Institute of Health Research, University of Exeter, Exeter, UK

[2]School of Life Course and Population Sciences, Institute of Women and Children's Health, King's College London, London, UK

[3]Fetal Medicine Research Institute, King's College Hospital, London, UK

[4]Fetal Medicine Unit, Medway Maritime Hospital, Gillingham, UK

[5]Institute of Medical Sciences, Canterbury Christ Church University, Chatham, UK

Correspondence
Kypros H. Nicolaides, Fetal Medicine Research Institute, King's College Hospital, 16-20 Windsor Walk, Denmark Hill, London SE5 8BB, UK.
Email: kypros@fetalmedicine.com

Funding information
Fetal Medicine Foundation

Abstract

Objective: To examine the effect of self-declared race on serum placental growth factor (PlGF) and sFlt-1/PlGF ratio and the impact on pre-eclampsia (PE) prediction.

Design: Prospective observational study.

Setting: Two UK maternity hospitals.

Population: 29 035 women with singleton pregnancies attending a routine 35^{+0} to 36^{+6} weeks' gestation hospital visit, including 654 (2.3%) who subsequently developed PE.

Methods: The predictive performance of PlGF and sFlt-1/PlGF for PE in minority racial groups (versus white) was examined.

Main outcome measure: Delivery with PE.

Results: Compared with white women, mean PlGF was higher and sFlt-1/PlGF ratio lower in black, South Asian, East Asian and mixed race women. In white women at a PlGF concentration cut-off corresponding to a screen-positive rate (SPR) of 10%, detection rates (DRs) were 49.1% for PE at any time and 72.3% for PE within 2 weeks after screening. In black women, at the same PlGF concentration cut-off for white women, the SPR was 5.5%, and DRs 33.6% and 55.0%, respectively; the number of PE cases was too small to evaluate screening performance in other racial groups. Using a fixed cut-off in sFlt-1/PlGF ratio to identify women at risk of developing PE, similarly diagnostically disadvantaged black women. Bias was overcome by adjusting metabolite concentrations for maternal characteristics and use of the competing risks model to estimate patient-specific risks.

Conclusion: Screening for PE with fixed cut-offs in PlGF or sFlt-1/PlGF diagnostically disadvantages black women. It is essential that measured levels of PlGF be adjusted for race as well as other maternal characteristics.

KEYWORDS
angiogenic factors, competing risks model, pre-eclampsia, race

1 | INTRODUCTION

Assessment of angiogenic imbalance has now been included in the International Society for the Study of Hypertension in Pregnancy definition of pre-eclampsia (PE), and is recommended in the UK as part of the assessment of women with suspected PE.[1] The assessment uses maternal serum concentration of the proangiogenic placental growth factor (PlGF),

Linked article: This article is commented on by Philip J. Steer, pp. 88 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.17305.

which is decreased in those developing PE, and maternal serum concentration of the antiangiogenic soluble fms-like tyrosine kinase (sFlt-1), which is increased in those developing PE.[2,3]

In clinical practice, measurements of PlGF or sFLT/PlGF ratio are compared with fixed cut-offs to categorise women's risk status.[4–6] However, it is well established that black race[4] is associated with hypertensive disorders in pregnancy and that after allowing for covariates such as maternal weight and gestational age, PlGF is increased substantially in black women relative to white women.[5,6] This makes black women appear at lower risk of hypertensive disorders in pregnancy. Without appropriate adjustments for race, the use of PlGF as a marker will disadvantage black women. They are less likely to screen positive for, or be diagnosed with, PE, despite having a greater a priori risk.[7] The use of the sFLT/PlGF ratio rather than PlGF alone negates, to some degree, the extent of this problem because sFLT is increased in black women, which counters the effect on PlGF. However, it is unclear whether any bias remains.

Although the use of PlGF and sFLT/PlGF ratio to define risk groups has the advantage of simplicity in clinical implementation, it does not take account of the *prior* risk of PE and ignores the effects of maternal characteristics, such as race, and gestational age on PlGF and sFLT.[8,9] It is well known that PlGF is less discriminatory at later gestations, so the use of a single cut-off on PlGF or sFLT/PlGF alone is not as effective at later gestations.[10]

These shortcomings have been addressed by the competing risks model that derives patient-specific risks for PE by combining the prior distribution of gestational age at delivery with PE, with likelihoods obtained from multiple of the median (MoM) values of biomarkers, which are adjusted for maternal characteristics, such as self-declared maternal race, and gestational age.[7–15]

The objectives of the study are, first, to examine the effect of race on maternal serum PlGF concentration and the sFlt-1/PlGF concentration ratio in pregnancy and, secondly, to compare performance of PE screening using fixed cut-offs in PlGF concentration and the sFlt-1/PlGF concentration ratio with use of the competing risks model in different racial groups.

2 | METHODS

2.1 | Study design and participants

This was a prospective observational cohort study of women who attended a routine hospital visit at 35^{+0} to 36^{+6} weeks' gestation at King's College Hospital, London, and Medway Maritime Hospital, Gillingham, UK, between October 2016 and September 2021. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks' gestation or the fetal head circumference at 19–24 weeks' gestation.[16,17]

The visit included recording of maternal demographic characteristics and medical history, measurement of maternal weight and height, ultrasound examination for fetal anatomy and biometry, and measurement of maternal serum PlGF and sFlt-1 in pg/ml by an automated biochemical analyser (BRAHMS KRYPTOR compact PLUS; Thermo Fisher Scientific). Participants completed a questionnaire, which was then reviewed by a doctor together with the woman. When there was a language barrier, professional translation services were offered to participants. Patient characteristics included: maternal age; race (white, black, South Asian, East Asian, and mixed); method of conception, such as natural or using assisted reproductive technology (ART, defined as in vitro fertilisation or use of ovulation drugs); cigarette smoking during pregnancy; medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome; family history of PE in the woman's mother; and obstetric history that included parity (parous or nulliparous if no previous pregnancies at ≥24 weeks' gestation) and, for parous women, previous PE and interpregnancy interval. Chronic hypertension was defined as hypertension (i.e. systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) diagnosed before pregnancy or before 20 weeks' gestation.

We included women with singleton pregnancies delivering a non-malformed live birth or stillbirth at ≥24 weeks' gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities. Maternity care providers were blinded to the competing risks model results.

Women gave written informed consent to take part in the study, which was approved by the NHS Research Ethics Committee. There was no patient involvement in the design of the study.

2.2 | Baseline characteristics and outcome measure

Data were collected from the hospital maternity records or those of the women's general medical practitioners. Self-declared race was defined according to the broad categories of the UK Office of National Statistics (ONS), using their approach (https://www.ons.gov.uk/methodology/classificationsandstandards/measuringequality/ethnicgroupnationalidentityandreligion; accessed 8 July 2022). Women who self-described as Indian, Pakistani or Bangladeshi were classified as South Asian and those who self-classified as either Chinese or other Asian were classified as East Asian.

Gestational hypertension (GH) was defined as new-onset hypertension (i.e. systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, on at least two occasions, 4 hours apart, developing after 20 weeks' gestation in previously normotensive women).

The outcome of primary interest was delivery with PE, defined as: (i) gestational or chronic hypertension and (ii) at least one of the following: proteinuria (≥300 mg/24 h or

protein to creatinine ratio ≥30 mg/mmol or ≥2+ on dipstick testing), renal insufficiency (with serum creatinine >97 micromol/L in the absence of underlying renal disease), hepatic dysfunction (with blood concentration of transaminases more than twice the upper limit of normal, corresponding to ≥65 iu/L for our laboratory), thrombocytopoenia (platelet count <100 000/microl), neurological complications (e.g. cerebral or visual symptoms) or pulmonary oedema.[18] Also of interest was delivery with PE within 2 weeks.

2.3 | Statistical methods

Data were summarised by median and interquartile range (IQR) for continuous variables, and *n* and percentage for categorical variables. Student's *t*-test, and Chi-square or Fisher's exact tests were used for comparing outcome groups for continuous and categorical data, respectively.

To examine the effect of race on PlGF and sFLT/PlGF ratio, multivariate linear regression models were fitted with $\log_{10}$ PlGF and $\log_{10}$ sFlt-1/PlGF concentrations as dependent variables. Gestational age at measurement, race, PE status (yes or no) by race, and other maternal characteristics and medical history were included as predictors. Estimates from these models, along with 95% CIs, for race and race by PE status, were used to assess differences in marker profiles between the different racial groups, allowing for gestational age, maternal characteristics and medical history. *P*-values for the effects of race and their interactions are reported. Partial residuals from the fitted models, excluding the contribution of PE or GH, comprised the $\log_{10}$ MoM values.

The competing risks model was used to estimate the individual patient-specific risks of delivery with PE by a combination of maternal demographic characteristics and medical history and PlGF and sFlt-1 MoM values.[7] The screening performance for all PE and for PE within 2 weeks of the study visit, by racial group, was assessed by detection rates (DRs) and 95% CIs using cut-offs that give a 10% screen-positive rate (SPR) in white women. Screening performance was compared between PlGF concentration and risks calculated from history plus PlGF MoM and between sFlt-1/PlGF concentration ratio and risks calculated from history plus PlGF MoM plus sFlt-1 MoM.

No corrections were made to *P*-values or CIs for multiple comparisons.

The statistical software package R was used for data analyses.[19]

3 | RESULTS

3.1 | Study participants

In the cohort of 29 035 pregnancies, 654 (2.3%) women developed PE ('PE' group), including 128 (0.4%) who delivered with PE within 2 weeks of assessment, and 28 381 did not develop PE ('No PE' group).

Maternal and pregnancy characteristics of the cohort are summarised in Table 1. Women in the 'PE' group, compared with women in the 'No PE' group, differed significantly ($P < 0.05$) in a number of ways: higher median weight and body mass index; more often black; more often had a history of chronic hypertension or diabetes mellitus; less often smoked; more often conceived by ART and were nulliparous and, among parous women, more often had a previous pregnancy affected by PE and a longer interpregnancy interval.

TABLE 1 Maternal and pregnancy characteristics among the study population

Feature	Pre-eclampsia (*n* = 654)	No pre-eclampsia (*n* = 28 381)	*P*-value
Age, years	32.0 (27.9, 36.1)	32.5 (28.6, 35.9)	0.321
Weight, kg	86.0 (76.0, 99.8)	79.0 (71.0, 89.5)	<0.0001
Height, cm	165 (161, 169)	165 (161, 170)	0.376
Body mass index, kg/m^2	31.4 (28.1, 36.3)	28.8 (26.0, 32.6)	<0.0001
Gestational age, weeks	36.0 (35.6, 36.3)	36.0 (35.6, 36.3)	0.627
Race			
White	507 (77.5)	22 659 (79.8)	<0.0001
Black	107 (16.4)	2969 (10.5)	
South Asian	17 (2.6)	1368 (4.8)	
East Asian	9 (1.4)	587 (2.1)	
Mixed	14 (2.1)	798 (2.8)	
Medical history			
Chronic hypertension	44 (6.7)	207 (0.7)	<0.0001
Diabetes mellitus type 1	2 (0.3)	78 (0.3)	0.021
Diabetes mellitus type 2	10 (1.5)	182 (0.6)	0.021
SLE/APS	0 (0.0)	74 (0.3)	0.344
Smoker	21 (3.2)	1529 (5.4)	0.043
Family history of pre-eclampsia	63 (9.6)	1101 (3.9)	<0.0001
Method of conception			
Spontaneous	602 (92.1)	27 030 (95.2)	0.0008
In vitro fertilisation	46 (7.0)	1185 (4.2)	
Ovulation drugs	6 (0.9)	166 (0.6)	
Parity			
Nulliparous	463 (70.8)	13 304 (46.9)	<0.0001
Parous, no previous pre-eclampsia	144 (22.0)	14 470 (51.0)	
Parous, previous pre-eclampsia	47 (7.2)	607 (2.1)	
Interpregnancy interval (years)	3.6 (2.2–6.5)	2.6 (1.6–4.4)	<0.0001

Note: Results are presented as *n* (%) or median (interquartile range). No adjustments for multiple testing were made, $\alpha = 0.05$.

Abbreviations: APS, antiphospholipid syndrome; MoM, multiple of the median; SLE, systemic lupus erythematosus.

BJOG An International Journal of Obstetrics and Gynaecology

3.2 | Distributional properties of PlGF and sFlt-1

Table 2 gives means (95% CIs) for PlGF concentrations, sFlt-1/PlGF concentration ratio, PlGF MoM and sFlt-1/PlGF MoM ratio, according to both development of 'PE' and racial group. Among women screened at 35^{+0} to 36^{+6} weeks', those who subsequently developed PE (versus. those who did not) had lower PlGF concentration and low PlGF MoM (by at least half), and higher sFlt-1/PlGF concentration ratio and higher sFlt-1/PlGF MoM ratio (by approximately four-fold). In black (versus white) women, mean PlGF concentration was higher and sFlt-1/PlGF concentration ratio lower in both the 'PE' and 'No PE' groups; similar trends were observed in South Asian, East Asian, and mixed race women, but the number of PE cases was small. In contrast, after adjustment of the measured values of metabolites for maternal characteristics and their conversion to MoM, the values of PlGF and the sFlt-1/PlGF ratio were similar across racial groups.

After adjusting for the effects of gestational age, maternal characteristics and medical history and PE, there is overwhelming evidence that PlGF is increased in black women relative to white women. It is estimated that levels of PlGF are 46% higher in black women (95% CI 42–51, $P < 0.0001$), 13% higher in South Asian women (95% CI 8–18 $P < 0.0001$), and 10% higher in women of mixed race (95% CI 4–16, $P = 0.0010$) (Table 3). PlGF was 7% higher, but not significantly different, in East Asian women compared with white women (95% CI 0–14, $P = 0.0517$). There is no evidence of an interaction between race and PE ($P = 0.8617$) or race and gestational age at delivery with PE ($P = 0.7775$).

After adjusting for the effects of gestational age, maternal characteristics and medical history and PE, it is estimated that the sFlt-1/PlGF ratio is 20% lower in black women (95% CI 16–23, $P < 0.0001$), 14% lower in South Asian women (95% CI 8–20, $P < 0.0001$) and 12% lower in East Asian women (95% CI 5–20, $P = 0.0096$) (Table 3). The sFlt1/PlGF ratio was 5% lower, but not significantly different, in women of mixed race compared with white women (95% CI −3 to 13, $P = 0.2060$) (Table 3). There is no evidence of an interaction between race and PE ($P = 0.6619$) or race and gestational age at delivery with PE ($P = 0.4347$).

Figure 1 shows, for white and black women at 35^{+0} to 36^{+6} weeks' gestation, the distribution of PlGF concentration and PlGF MoMs, in the 'PE' group (dashed line) and the 'No PE group' (solid line). On average, for both white and black women, PlGF was lower in the 'PE' (versus 'No PE') groups; however, PlGF tended to be higher in black (versus white) women, regardless of development of PE. Consequently, in screening for PE at a given PlGF concentration cut-off, both the screen-positive and DRs in black women would be lower than in white women. PlGF MoMs were lower in the 'PE'

TABLE 2 Median with 95% confidence interval of PlGF concentration, PlGF MoM, sFlt-1 to PlGF concentration ratio and sFlt-1 to PlGF MoM ratio in women assessed at $35^{+0/7}$ to $36^{+6/7}$ weeks' gestation who did, or did not, develop pre-eclampsia by self-declared racial group

		Pre-eclampsia		No pre-eclampsia	
Method of screening	**Race**	***n***	**Median (95% CI)**	***n***	**Median (95% CI)**
PlGF concentration	White	507	84.0 (78.6, 89.9)	22 659	256.0 (253.2, 258.9)
	Black	107	127.1 (106.7–151.5)	2969	367.8 (356.6–379.4)
	South Asian	17	87.3 (62.8–121.3)	1368	280.4 (267.7–293.7)
	East Asian	9	93.4 (41.1–212.0)	587	270.3 (252.0–290.0)
	Mixed	14	117.6 (76.0–182.2)	798	280.3 (264.4–297.2)
PlGF MoM	White	507	0.37 (0.34–0.39)	22 659	1
	Black	107	0.37 (0.31–0.45)	2969	1
	South Asian	17	0.32 (0.23–0.46)	1368	1
	East Asian	9	0.39 (0.17–0.88)	587	1
	Mixed	14	0.44 (0.28–0.68)	798	1
sFlt-1/PlGF concentration ratio	White	507	57.82 (52.04–64.23)	22 659	8.42 (8.29–8.56)
	Black	107	41.01 (31.31–53.72)	2969	6.54 (6.27–6.82)
	South Asian	17	48.29 (29.54–78.95)	1368	8.09 (7.56–8.65)
	East Asian	9	45.39 (14.01–147.06)	587	8.51 (7.69–9.40)
	Mixed	14	33.87 (18.44–62.22)	798	8.02 (7.37–8.72)
sFlt-1/PlGF MoM ratio	White	507	6.02 (5.42–6.67)	22 659	1
	Black	107	5.57 (4.22–7.36)	2969	1
	South Asian	17	5.74 (3.40–9.67)	1368	1
	East Asian	9	4.50 (1.43–14.18)	587	1
	Mixed	14	4.42 (2.39–8.19)	798	1

Abbreviations: CI, confidence interval; MoM, multiple of the median; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

TABLE 3 Fitted regression models for PlGF and sFlt-1PlGF ratio

	Estimate (95% CI)	*P*-value
$\log_{10}$ (PlGF)		
Intercept	2.360930 (2.353028–2.368832)	<0.00001
Pre-eclampsia	−0.370697 (−0.401908 to −0.339485)	<0.00001
Gestational hypertension	−0.237869 (−0.262605 to −0.213133)	<0.00001
Gestational age at delivery with PE in weeks–40	0.086115 (0.066840–0.105390)	<0.00001
Black race	0.165775 (0.152201–0.179350)	<0.00001
Mixed race	0.040891 (0.015926–0.065856)	0.00133
South Asian race	0.053320 (0.033553–0.073088)	<0.00001
East Asian race	0.029193 (−0.000216 to 0.058602)	0.05171
Gestational age at measurement in weeks–36	−0.087620 (−0.096463 to −0.078777)	<0.00001
Maternal weight in kg–69	−0.001272 (−0.001810 to −0.000734)	<0.00001
(Maternal weight in kg–69)^2	−0.000013 (−0.000024 to −0.000002)	0.01594
Maternal age in years–35	−0.002788 (−0.003587 to −0.001990)	<0.00001
Maternal height in cm–164	0.002314 (0.001631–0.002997)	<0.00001
Diabetes mellitus	−0.085881 (−0.128706 to −0.043056)	0.00008
Smoker	0.089023 (0.070337–0.107709)	<0.00001
Family history of pre-eclampsia	−0.035159 (−0.056129 to −0.014189)	0.00102
Parous, no previous pre-eclampsia	0.109784 (0.101267–0.118302)	<0.00001
$\log_{10}$ (sFlt-1/PlGF)		
Intercept	1.075314 (1.063502–1.087126)	<0.00001
Pre-eclampsia	0.657328 (0.612740–0.701917)	<0.00001
Gestational hypertension	0.402446 (0.367061–0.437830)	<0.00001
Gestational age at delivery with PE in weeks–40	−0.153707 (−0.181247 to −0.126168)	<0.00001
Black race	−0.096858 (−0.116266 to −0.077451)	<0.00001
Mixed race	−0.023009 (−0.058668–0.012650)	0.20599
South Asian race	−0.066016 (−0.094252 to −0.037780)	<0.00001
East Asian race	−0.055499 (−0.097510 to −0.013488)	0.00962
Gestational age at measurement in weeks–36	0.147486 (0.134851–0.160121)	<0.00001
Maternal weight in Kg–69	−0.002697 (−0.003466 to −0.001927)	<0.00001
(Maternal weight in Kg–69)^2	0.000038 (0.000023–0.000054)	<0.00001
Maternal age in years–35	0.005748 (0.004575–0.006920)	<0.00001
Maternal height in cm–164	−0.003773 (−0.004750 to −0.002797)	<0.00001
Diabetes mellitus	0.155424 (0.094246–0.216603)	<0.00001
Smoker	−0.099303 (−0.126003 to −0.072603)	<0.00001
IVF conception	0.051123 (0.021038–0.081207)	0.00087
Family history of pre-eclampsia	0.060981 (0.030990–0.090972)	0.00007
Parous, no previous pre-eclampsia	−0.220006 (−0.232493 to −0.207520)	<0.00001
Parous, previous pre-eclampsia	−0.060468 (−0.100916 to −0.020020)	0.00339

Abbreviations: PE, pre-eclampsia; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

(versus 'No PE') groups, but there was little to no difference between black and white women.

3.3 | Screening performance

For various screening methods, Table 4 gives DRs for delivery with PE at any time or PE within 2 weeks following assessment at 35^{+0} to 36^{+6} weeks' gestation, across the racial groups, for cut-offs which define SPRs in white women of 10 and 5%. In general, use of the competing risks model incorporating maternal risk factors and either PlGF MoM alone or along with sFlt-1 MoM, was associated with higher DRs and SPRs in black (versus white) women, by comparison with screening using fixed cut-offs on PlGF concentration, PlGF MoMs, sFlt-1/PlGF concentration ratio or sFlt-1/PlGF MoM ratio. The numbers of women with PE in South Asian, East Asian, and mixed racial groups were insufficient to draw meaningful conclusions.

Figure 2 shows, for white and black women, SPRs (circles) and DRs (diamonds), for delivery with PE at any time after assessment (panels C and D) and delivery with PE within 2 weeks after assessment (panels A and B), according to PlGF concentration or sFlt-1/PlGF concentration ratio (solid lines and symbols) or competing risks model plus PlGF MoM or PlGF MoM and sFlt-1 MoM (broken lines and symbols). For black (versus white) women, screening using fixed cut-offs in

BJOG An International Journal of Obstetrics and Gynaecology

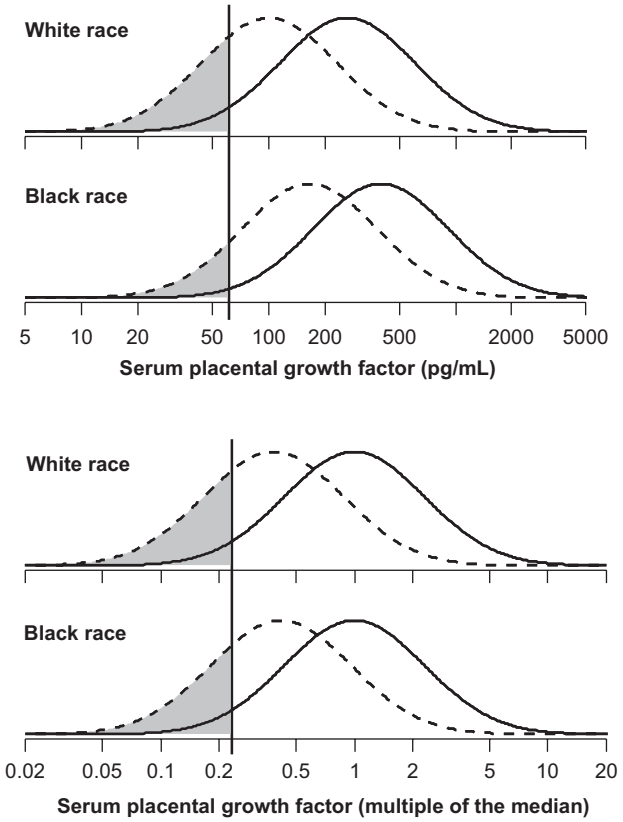

FIGURE 1 Distribution of placental growth factor (PlGF) concentration and PlGF multiple of the median in pregnancies affected by pre-eclampsia (interrupted curve) and in those unaffected by pre-eclampsia (solid curve) in white and black women. The vertical black lines represent the cut-offs corresponding to the 10th percentile for white women.

PlGF concentration (solid lines and symbols) or sFlt-1/PlGF concentration ratio (broken lines and symbols), the DRs and SPRs of PE at any time after screening, and PE within 2 weeks of assessment, were lower, particular for PlGF alone. However, use of the competing risk model, incorporating maternal risk factors and either PlGF MoM or sFlt-1 MoM, resulted in higher DRs and SPRs in black (versus white) women. Panels A and C show the results of screening by PlGF concentration (solid lines and black diamonds and circles) and a combination of maternal risk factors and PlGF MoM (interrupted lines and white diamonds and circles). Panels B and D show the results of screening by the sFlt-1/PlGF concentration ratio (solid lines and black diamonds and circles) and a combination of maternal risk factors and PlGF MoM and sFlt-1 MoM (interrupted lines and white diamonds and circles).

4 | DISCUSSION

4.1 | Main findings

There are four main findings from this large prospective study of women with singleton pregnancies who were screened at 35^{+0} to 36^{+6} weeks' for PE risk, in England:

1. Compared with white women, black women have higher mean serum PlGF concentrations and lower sFlt-1/PlGF concentration ratio values, regardless of whether they go on to develop PE. A similar pattern of biomarker values was seen among South Asian, East Asian, and Mixed race women.
2. For black (versus white) women, use of fixed cut-offs in PlGF concentration, and to a lesser extent sFlt-1/PlGF concentration ratio, are associated with a lower DR for delivery with PE at any time, or within 2 weeks, after assessment. The very limited number of PE cases in other racial groups precluded firm conclusions.
3. After adjustment of measured values of metabolites for maternal characteristics and their conversion to MoMs, the values of PlGF and sFlt-1/PlGF ratio were similar across racial groups, with PlGF MoM in the PE group less than half of that in the non-PE groups, and the sFlt-1/PlGF MoM ratio in the PE group approximately four-fold higher than in the No PE group.
4. In general, use of the competing risks model incorporating maternal risk factors and either PlGF MoM alone or PlGF MoM and sFlt-1 MoM, is associated with an increase in both SPRs and DRs in black women, by comparison with screening using cut-off values in concentrations of PlGF or the sFlt-1/PlGF ratio.

4.2 | Strengths and limitations

The main strengths of the study are, first, prospective examination of a large population of women with singleton pregnancies attending for routine pregnancy care at 35–36 weeks' gestation. Secondly, we recorded maternal and pregnancy characteristics that have previously been reported to be associated with development of PE.[20] Thirdly, we prospectively measured PlGF and sFlt-1 by reliable automated analysers and their assessment as screening tools utilising both measured concentrations and MoMs.

There are two main limitations of the study. First, race was classified into the five broad categories used by the ONS and it is likely that there would be variations within each category; for example, in women classified as black, there may be differences between those who came to England from different regions in Africa (there is more genetic diversity in Africa than in Europe)[21] and those from the Caribbean (the majority of whose ancestors were from West Africa and survived the Inside Passage of the slave trade), as well as differences between those who are first-, second- or third-generation immigrants to England. As such, it is necessary that in each country and in each screening centre, the appropriate adjustments are made for maternal characteristics, including race. Also, we did not include ONS indices of multiple deprivation in our analyses; however, the competing risk model does include other social and clinical determinants of maternity outcomes (e.g. weight, smoking status) and our populations were recruited in hospitals serving largely deprived and multiracial populations.

TABLE 4 Performance of screening for pre-eclampsia at $35^{+0/6}$ to $36^{+6/7}$ weeks' gestation in different racial groups

		10% screen-positive rate in white women								5% screen-positive rate in white women							
		All PE				PE within 2 weeks				All PE				PE within 2 weeks			
Method of screening	Race	*n*	Total	DR (95% CI)	SPR	*n*	Total	DR (95% CI)	SPR	*n*	Total	DR (95% CI)	SPR	*n*	Total	DR (95% CI)	SPR
PlGF concentration	White	249	507	49.1 (44.7–53.6)	10.0	73	101	72.3 (62.5–80.7)	10.0	167	507	32.9 (28.9–37.2)	5.0	60	101	59.4 (49.2–69.1)	5.0
	Black	36	107	33.6 (24.8–43.4)	5.5	11	20	55.0 (31.5–76.9)	5.5	22	107	20.6 (13.4–29.5)	2.6	10	20	50.0 (27.2–72.8)	2.6
	South Asian	6	17	35.3 (14.2–61.7)	8.5	1	4	25.0 (0.6–80.6)	8.5	4	17	23.5 (6.8–49.9)	4.8	1	4	25.0 (0.6–80.6)	4.8
	East Asian	4	9	44.4 (13.7–78.8)	9.9	2	2	100 (15.8–100)	9.9	4	9	44.4 (13.7–78.8)	5.5	2	2	100 (15.8–100)	5.5
	Mixed	6	14	42.9 (17.7–71.1)	7.6	0	1	0 (0–97.5)	7.6	5	14	35.7 (12.8–64.9)	3.4	0	1	0 (0–97.5)	3.4
PlGF MoM	White	218	507	43.0 (38.6–47.4)	10.0	66	101	65.3 (55.2–74.5)	10.0	133	507	26.2 (22.5–30.3)	5.0	51	101	50.5 (40.4–60.6)	5.0
	Black	52	107	48.6 (38.8–58.5)	12.0	13	20	65 (40.8–84.6)	12.0	36	107	33.6 (24.8–43.4)	6.9	10	20	50.0 (27.2–72.8)	6.9
	South Asian	7	17	41.2 (18.4–67.1)	12.9	1	4	25.0 (0.6–80.6)	12.9	6	17	35.3 (14.2–61.7)	8.3	1	4	25.0 (0.6–80.6)	8.3
	East Asian	4	9	44.4 (13.7–78.8)	13.8	2	2	100 (15.8–100)	13.8	4	9	44.4 (13.7–78.8)	8.1	2	2	100 (15.8–100)	8.1
	Mixed	7	14	50.0 (23.0–77.0)	8.7	0	1	0 (0–97.5)	8.7	4	14	28.6 (8.4–58.1)	3.7	0	1	0 (0–97.5)	3.7
History[a] + PlGF MoM	White	285	507	56.2 (51.8–60.6)	10.0	81	101	80.2 (71.1–87.5)	10.0	202	507	39.8 (35.6–44.3)	5.0	68	101	67.3 (57.3–76.3)	5.0
	Black	81	107	75.7 (66.5–83.5)	26.1	17	20	85.0 (62.1–96.8)	26.1	68	107	63.6 (53.7–72.6)	16.4	17	20	85.0 (62.1–96.8)	16.4
	South Asian	12	17	70.6 (44.0–89.7)	16.4	3	4	75.0 (19.4–99.4)	16.4	9	17	52.9 (27.8–77)	9.8	3	4	75.0 (19.4–99.4)	9.8
	East Asian	5	9	55.6 (21.2–86.3)	10.9	2	2	100 (15.8–100)	10.9	4	9	44.4 (13.7–78.8)	6.4	2	2	100 (15.8–100)	6.4
	Mixed	5	14	35.7 (12.8–64.9)	10.8	0	1	0 (0–97.5)	10.8	4	14	28.6 (8.4–58.1)	5.2	0	1	0 (0–97.5)	5.2
sFlt-1/PlGF concentration ratio	White	292	507	57.6 (53.2–61.9)	10.0	83	101	82.2 (73.3–89.1)	10.0	204	507	40.2 (35.9–44.7)	5.0	72	101	71.3 (61.4–79.9)	5.0
	Black	54	107	50.5 (40.6–60.3)	7.0	16	20	80.0 (56.3–94.3)	7.0	38	107	35.5 (26.5–45.4)	3.9	12	20	60.0 (36.1–80.9)	3.9
	South Asian	7	17	41.2 (18.4–67.1)	9.2	1	4	25.0 (0.6–80.6)	9.2	5	17	29.4 (10.3–56)	5.3	1	4	25.0 (0.6–80.6)	5.3
	East Asian	4	9	44.4 (13.7–78.8)	10.6	2	2	100 (15.8–100)	10.6	4	9	44.4 (13.7–78.8)	6.2	2	2	100 (15.8–100)	6.2
	Mixed	6	14	42.9 (17.7–71.1)	8.4	1	1	100 (2.5–100)	8.4	5	14	35.7 (12.8–64.9)	3.6	1	1	100 (2.5–100)	3.6
sFlt-1/PlGF MoM ratio	White	267	507	52.7 (48.2–57.1)	10.0	79	101	78.2 (68.9–85.8)	10.0	185	507	36.5 (32.3–40.8)	5.0	65	101	64.4 (54.2–73.6)	5.0
	Black	58	107	54.2 (44.3–63.9)	10.3	16	20	80.0 (56.3–94.3)	10.3	43	107	40.2 (30.8–50.1)	5.9	12	20	60.0 (36.1–80.9)	5.9
	South Asian	9	17	52.9 (27.8–77.0)	11.8	1	4	25.0 (0.6–80.6)	11.8	7	17	41.2 (18.4–67.1)	6.4	1	4	25.0 (0.6–80.6)	6.4
	East Asian	4	9	44.4 (13.7–78.8)	12.1	2	2	100 (15.8–100)	12.1	4	9	44.4 (13.7–78.8)	7.6	2	2	100 (15.8–100)	7.6
	Mixed	8	14	57.1 (28.9–82.3)	9.0	1	1	100 (2.5–100)	9.0	4	14	28.6 (8.4–58.1)	3.6	1	1	100 (2.5–100)	3.6
History[a] + PlGF MoM + sFlt-1 MoM	White	330	507	65.1 (60.8–69.2)	10.0	88	101	87.1 (79.0–93.0)	10.0	235	507	46.4 (41.9–50.8)	5.0	77	101	76.2 (66.7–84.1)	5.0
	Black	74	107	69.2 (59.5–77.7)	18.1	17	20	85 (62.1–96.8)	18.1	61	107	57.0 (47.1–66.5)	9.4	17	20	85.0 (62.1–96.8)	9.4
	South Asian	11	17	64.7 (38.3–85.8)	13.6	3	4	75.0 (19.4–99.4)	13.6	7	17	41.2 (18.4–67.1)	7.4	1	4	25.0 (0.6–80.6)	7.4
	East Asian	4	9	44.4 (13.7–78.8)	10.4	2	2	100 (15.8–100)	10.4	4	9	44.4 (13.7–78.8)	4.5	2	2	100 (15.8–100)	4.5
	Mixed	8	14	57.1 (28.9–82.3)	9.5	1	1	100 (2.5–100)	9.5	3	14	21.4 (4.7–50.8)	3.7	0	1	0 (0–97.5)	3.7

Note: The cut-offs for the different methods of screening are fixed to achieve screen-positive rates of 10 and 5% for white women. Results are presented as % (95% CI).

Abbreviations: PE, pre-eclampsia; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

[a]The competing risks model used history – maternal demographic characteristics and medical history – and a combination of PlGF and sFlt-1 MoM values to estimate an individual woman's patient-specific risks of delivery with PE.[8]

BJOG An International Journal of Obstetrics and Gynaecology

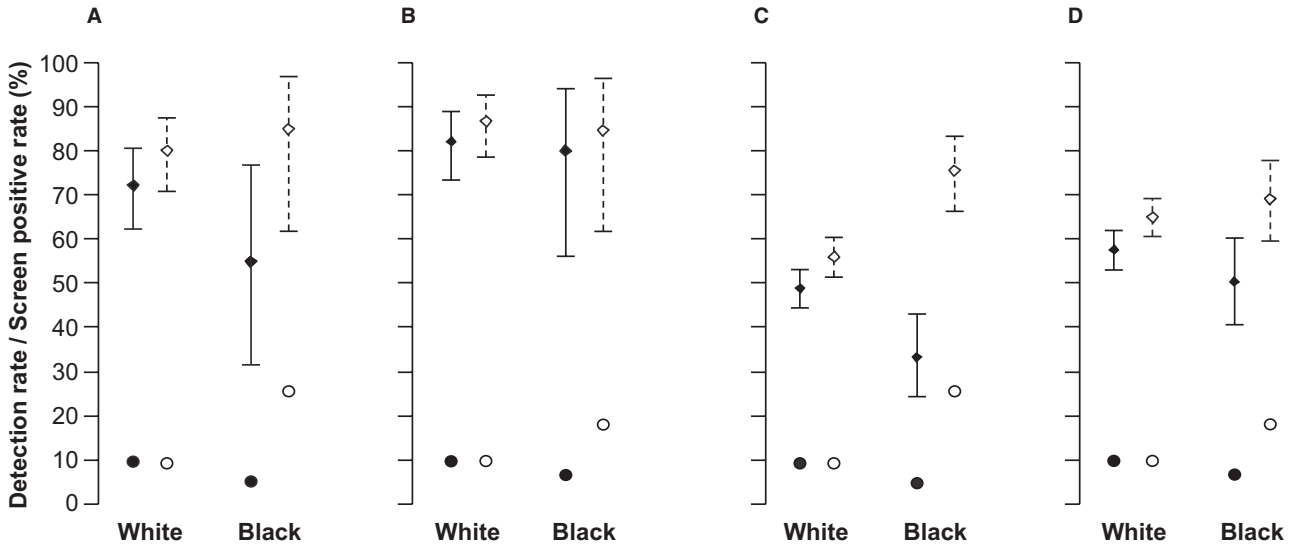

FIGURE 2 Detection rates (diamonds) with 95% confidence intervals and screen-positive rates (circles) of delivery with pre-eclampsia within 2 weeks (panels A and B) and at any time after assessment (panels C and D) in white and black women. Panels A and C show the results of screening by placental growth factor (PlGF) concentration (solid lines and black diamonds and circles) and a combination of maternal risk factors and PlGF multiple of the median (MoM) (interrupted lines and white diamonds and circles). Panels B and D show the results of screening by the sFlt-1/PlGF concentration ratio (solid lines and black diamonds and circles) and a combination of maternal risk factors and PlGF MoM and sFlt-1 MoM (interrupted lines and white diamonds and circles).

4.3 | Interpretation of results and implications for clinical practice

As in this study, low PlGF or high sFlt-1/PlGF ratio has been associated with PE in both white and non-white women.[22,23] Our study showed that in black and South Asian (versus white) women, serum PlGF is 47 and 13% higher, respectively, and the sFlt-1/PlGF ratio 20 and 14% lower. This is consistent with the published literature. Across gestations in many thousands of women in each trimester, serum PlGF and sFlt-1 concentrations were higher in black, South Asian, East Asian, and mixed race women, compared with white women.[8,9] The effect of race on serum concentrations was consistent across trimesters. There are few other published studies of PlGF and sFlt-1/PlGF values in minority ethnic group women and these have often involved small sample sizes. In a cohort of 398 normotensive black women in Ghana, sub-Saharan Africa, gestational age-corrected PlGF MoM values were higher compared with European standards (median PlGF MoM 1.25, IQR 0.95–1.80).[24] Those authors proposed that possible explanations for higher levels of angiogenic markers in non-white racial group women include higher placental production, similar production with lower affinity for antigen-presenting sites or reduced clearance.[24] A notable exception to raised PlGF among black women was seen in a small study in which PlGF concentrations across trimesters was not different in 63 black women; however, the comparison group was 54 'non-Black' women who included women of European and Asian family origin.[25] Further adequately powered evaluations of angiogenic factors in pregnancy in black women from a variety of African regions, and other racial groups (e.g. South-East Asia, Polynesia) are required to inform interpretation of these findings beyond this cohort.

Women in racial and ethnic minority groups, particularly black women, more often have a hypertensive disorder of pregnancy, including PE, and more often suffer associated maternal and fetal complications.[25–27] Based on systematic review and a large prospective and contemporary cohort study, black (versus white) women have a two-fold higher risk of PE across gestational ages, and South Asian (versus white) women have a 1.5-fold higher risk of preterm PE.[28]What underlies the association has not been established. Possibilities include factors at the individual level, such as pre-existing conditions (e.g. obesity) or genetic mutations (e.g. sickle cell disease).[27] However, possibilities also include social and health system determinants, and the role that racism plays through these determinants to increase risk factors for PE and associated adverse outcomes.[26]

Our work has demonstrated that there is a biological underpinning to inclusion of race in predictive models for PE, and this has implications for using fixed cut-offs for evaluation of women with suspected PE. Applying a fixed cut-off to all members of a multiracial society disadvantages both black and South Asian women. They are less likely to screen positive for, or be diagnosed with, PE, despite having a greater a priori risk of PE;[20] As such, it is essential that measured levels of PlGF and sFlt-1 be adjusted for maternal characteristics, including race.

Adjustments of metabolite levels for race are widely accepted in other screening strategies and have been carried out for several decades in screening for fetal trisomies. For example, in trisomy 21 pregnancies, first-trimester serum pregnancy associated plasma protein-A (PAPP-A) is, on average, half the value of euploid pregnancies; however, serum PAPP-A is about 60% higher in black than white women.

Consequently, failure to adjust levels of PAPP-A for race would underestimate the true risk of trisomy 21 in black women.[29] As shown in this study, in screening for PE with the competing risks model, in a multiracial society with a fixed risk cut-off, both the DR and SPR in black women are higher than in white women, reflecting the higher incidence of PE in this group of women. While an alternative strategy would be to fix the SPR and define different risk cut-offs for women of different racial groups, this is inappropriate, as such a practice would mask the increased risk for PE in certain racial groups.

5 | CONCLUSIONS

Ignoring race when evaluating angiogenic balance in singleton pregnancies will diagnostically disadvantage those black and, possibly, other non-white women who have higher incidences of PE and GH.

AUTHOR CONTRIBUTIONS

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

FUNDING INFORMATION

This study was supported by grants from the Fetal Medicine Foundation (UK Charity No: 1037116). Reagents and equipment for the measurement of serum placental growth factor and sFlt-1 were provided free of charge by Thermo Fisher Scientific, Hennigsdorf, Germany. These bodies had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the article for publication.

CONFLICT OF INTERESTS

None declared. Completed disclosure of interest forms are available to view online as supporting information.

ETHICS APPROVAL

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

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Peter von Dadelszen https://orcid.org/0000-0003-4136-3070
Laura A. Magee https://orcid.org/0000-0002-1355-610X
Argyro Syngelaki https://orcid.org/0000-0001-5856-6072
Ranjit Akolekar https://orcid.org/0000-0001-7265-5442
Kypros H. Nicolaides https://orcid.org/0000-0003-3515-7684

REFERENCES

1. NICE Guidance. PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1–2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio). Diagnostics guidance [DG23] Published: 11 May 2016.
2. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350:672–83.
3. Akolekar R, Zaragoza E, Poon LC, Pepes S, Nicolaides KH. Maternal serum placental growth factor at 11 + 0 to 13 + 6 weeks of gestation in the prediction of pre-eclampsia. Ultrasound Obstet Gynecol. 2008;32:732–9.
4. Verlohren S, Herraiz I, Lapaire O, Schlembach D, Moertl M, Zeisler H, et al. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. Am J Obstet Gynecol. 2012;206:58.e1–8.
5. Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. Circulation. 2013;128:2121–31.
6. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected pre-eclampsia. N Engl J Med. 2016;374:13–22.
7. Wright D, Wright A, Nicolaides KH. The competing risk approach for prediction of preeclampsia. Am J Obstet Gynecol. 2020;223:12–23.e7.
8. Tsiakkas A, Duvdevani N, Wright A, Wright D, Nicolaides KH. Serum placental growth factor in the three trimesters of pregnancy: effects of maternal characteristics and medical history. Ultrasound Obstet Gynecol. 2015;45:591–8.
9. Tsiakkas A, Duvdevani N, Wright A, Wright D, Nicolaides KH. Serum soluble fms-like tyrosine kinase-1 in the three trimesters of pregnancy: effects of maternal characteristics and medical history. Ultrasound Obstet Gynecol. 2015;45:584–90.
10. Dragan I, Wright D, Fiolna M, Leipold G, Nicolaides KH. Development of pre-eclampsia within 4 weeks of sFlt-1/PlGF ratio > 38: comparison of performance at 31-34 vs 35-37 weeks' gestation. Ultrasound Obstet Gynecol. 2017;49:209–12.
11. Lim S, Li W, Kemper J, Nguyen A, Mol BW, Reddy M. Biomarkers and the prediction of adverse outcomes in preeclampsia: a systematic review and meta-analysis. Obstet Gynecol. 2021;137:72–81.
12. Wright D, Dragan I, Syngelaki A, Akolekar R, Nicolaides KH. Proposed clinical management of pregnancies after combined screening for pre-eclampsia at 30-34 weeks' gestation. Ultrasound Obstet Gynecol. 2017;49:194–200.
13. Panaitescu AM, Wright D, Militelo A, Akolekar R, Nicolaides KH. Proposed clinical management of pregnancies after combined screening for preeclampsia at 35-37 weeks' gestation. Ultrasound Obstet Gynecol. 2017;50:383–7.
14. Lai J, Garcia-Tizon Larroca S, Peeva G, Poon LC, Wright D, Nicolaides KH. Competing risks model in screening for preeclampsia by serum placental growth factor and soluble fms-like tyrosine kinase-1 at 30-33 weeks' gestation. Fetal Diagn Ther. 2014;35:240–8.
15. Ciobanu A, Wright A, Panaitescu A, Syngelaki A, Wright D, Nicolaides KH. Prediction of imminent preeclampsia at 35-37 weeks gestation. Am J Obstet Gynecol. 2019;220:e1–584.e11.
16. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. Br J Obstet Gynaecol. 1975;82:702–10.
17. Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. Ultrasound Obstet Gynecol. 1994;4:34–48.
18. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Gestational hypertension and preeclampsia. ACOG practice bulletin no. 202. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2019;133:e1–25.
19. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020. https://www.R-project.org/

20. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. Am J Obstet Gynecol. 2015;213(62):e1–10.
21. Campbell MC, Tishkoff SA. African genetic diversity: implications for human demographic history, modern human origins, and complex disease mapping. Annu Rev Genomics Hum Genet. 2008;9:403–33.
22. Heimberger S, Mueller A, Ratnaparkhi R, Perdigao JL, Rana S. Angiogenic factor abnormalities and risk of peripartum complications and prematurity among urban predominantly obese parturients with chronic hypertension. Pregnancy Hypertens. 2020;20:124–30.
23. Zhu J, Zhang J, Ng MJ, Chern B, Yeo GS, Tan KH. Angiogenic factors during pregnancy in Asian women with elevated blood pressure in early pregnancy and the risk of preeclampsia: a longitudinal cohort study. BMJ Open. 2019;9:e032237.
24. Browne JL, Klipstein-Grobusch K, Koster MP, Ramamoorthy D, Antwi E, Belmouden I, et al. Pregnancy associated plasma protein-a and placental growth factor in a sub-Saharan African population: a nested cross-sectional study. PLoS One. 2016;11:e0159592.
25. Webster LM, Gill C, Seed PT, Bramham K, Wiesender C, Nelson-Piercy C, et al. Chronic hypertension in pregnancy: impact of ethnicity and superimposed preeclampsia on placental, endothelial, and renal biomarkers. Am J Physiol Regul Integr Comp Physiol. 2018;315:R36–47.
26. Johnson JD, Louis JM. Does race or ethnicity play a role in the origin, pathophysiology, and outcomes of preeclampsia? An expert review of the literature. Am J Obstet Gynecol. 2022;226(2S):S876–85.
27. Zhang M, Wan P, Ng K, Singh K, Cheng TH, Velickovic I, et al. Preeclampsia among African American pregnant women: an update on prevalence, complications, etiology, and biomarkers. Obstet Gynecol Surv. 2020;75:111–20.
28. Arechvo A, Voicu D, Gil MM, Syngelaki A, Akolekar R, Nicolaides KH. Maternal race and preeclampsia: cohort study and systematic review with meta-analysis. BJOG. 2022; DOI: 10.1111/1471-0528.17240
29. Kagan KO, Wright D, Spencer K, Molina FS, Nicolaides KH. First-trimester screening for trisomy 21 by free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-a: impact of maternal and pregnancy characteristics. Ultrasound Obstet Gynecol. 2008;31:493–502.

SUPPORTING INFORMATION

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

How to cite this article: Wright A, von Dadelszen P, Magee LA, Syngelaki A, Akolekar R, Wright D, et al. Effect of race on the measurement of angiogenic factors for prediction and diagnosis of pre-eclampsia. BJOG. 2023;130(1):78–87. https://doi.org/10.1111/1471-0528.17296