

## OBSTETRICS

# Pregnancy and perinatal outcomes stratified by soluble fms-like tyrosine kinase-1 and placental growth factor gestation-specific thresholds in women with suspected preeclampsia

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**OBJECTIVE:** To evaluate gestational age appropriate soluble fms-like tyrosine kinase-1 and placental growth factor concentrations in determining abnormal outcomes in women with suspected preeclampsia.

**STUDY DESIGN:** Retrospective single-center study of 457 singleton pregnancies from a tertiary referral center in the United Kingdom. Four subgroups were defined using gestational age-adjusted thresholds for soluble fms-like tyrosine kinase-1 (>95th centile) and placental growth factor (<fifth centile). Continuous variables were assessed for normality; non-normally distributed data were analyzed using the Kruskal–Wallis test with Bonferroni-adjusted pairwise comparisons. Log-transformed biochemical, angiogenic, and ultrasound variables were analyzed using one-way analysis of variance (df=3) with Dunnett post hoc comparisons versus controls (df=1). Categorical variables were compared using chi-square or Fisher's exact tests with post hoc comparisons where appropriate. A two-tailed *P* value <0.05 was considered statistically significant.

**RESULTS:** Amongst singleton pregnancies with available soluble fms-like tyrosine kinase-1/placental growth factor ratios, angiogenic profiling classified women into 4 groups. Group 1 (soluble fms-like tyrosine kinase-1 >95th, PlGF <fifth; n=100), Group 2 (soluble fms-like tyrosine kinase-1 >95th, placental growth factor >fifth; n=58), Group 3 (soluble fms-like tyrosine kinase-1 <95th, placental growth factor <fifth; n=31), and controls (Group 4) (soluble fms-like tyrosine kinase-1 <95th, placental growth factor >fifth; n=268). Distinct angiogenic and ultrasonographic profiles were observed between groups (one-way analysis of variance, *F* (3,453), *P*<0.001). On post hoc Dunnett's, when compared to controls, Groups 1 and 3 with low placental growth factor (<fifth centile) had a significantly lower mean first trimester pregnancy associated plasma protein-A (0.6, [95% CI 0.6–0.7] and 0.5, [0.4–7.0] vs 0.9 [0.8–1.0]; df=1, *P*<0.001) and higher second trimester combined uterine artery Doppler pulsatility index (1.47 [1.35–1.59] and 1.31 [1.13–1.51] vs 0.98 [0.93–1.02]; df=1, *P*<0.001).

Markers of maternal end-organ involvement also demonstrated strong group-level differences (one-way analysis of variance, *F*(3,453), *P*<0.001). On post hoc Dunnett's, when compared to controls, Groups 1 and 2 (sFlt-1 >95th centile) had a significantly lower mean platelet count (182.8 [168–198.8] and 176.7 [160.4–194.6] vs 212.5 [204.9–220.4]; df=1, *P*<0.01), higher mean creatinine levels (70.1 [65.2–75.4] and 70.1 [63.3–78.3] vs 59.4 [57.7–61.2]; df=1, *P*<0.01) and higher mean urine protein: creatinine ratios (93 [68.7–126.1] and 58.9 [38.9–89.0] vs 25.8 [22.2–29.9]; df=1, *P*<0.01).

The incidence of preeclampsia occurring before 37 weeks was higher in Groups 1 to 3 when compared to the controls, occurring in 78.0%, 39.7%, 31.3%, and 6.7% of pregnancies, respectively (*P*<0.001). Adverse neonatal outcomes were clustered particularly in Group 1 which had the lowest median gestational age at birth (median 33.4 [29.2–35.7] and lowest birthweight centile (0.26 [0.00–2.71]). The incidence of small for gestational age infants and need for neonatal intensive care unit admission was significantly higher across Groups 1 to 3 when each of the groups was individually compared to the controls (*P*<0.001 for all). Stillbirths occurred only in Groups 1 (5.3%, n=5) and 3 (6.9%, n=2) which had low placental growth factor levels <fifth centile.

**CONCLUSION:** Stratification of women with suspected preeclampsia using gestational age-specific thresholds for soluble fms-like tyrosine kinase-1 and placental growth factor can identify distinct maternal and fetal phenotypes with significantly different clinical outcomes. Elevated soluble fms-like tyrosine kinase-1 concentrations appear to be strongly associated with severe maternal disease, whilst low placental growth factor appears to correlate with adverse fetal and neonatal outcomes including growth restriction, stillbirth, and prolonged neonatal intensive care stay.

**Key words:** sFlt-1/PlGF, preeclampsia, phenotype, hypertension, fetal growth restriction, gestational hypertension, PAPP-A, uterine artery Dopplers

## Introduction

The antiangiogenic factor, soluble fms-like tyrosine kinase 1 (sFlt-1) and the proangiogenic factor, placental growth

factor (PlGF) have received considerable attention for their ability to predict the onset and severity of preeclampsia (PE).<sup>1</sup> Utero-placental hypoxia in pregnancies destined to develop PE is associated with a reduction in circulating maternal PlGF levels and an increase in sFlt-1. sFlt-1, when released into the circulation, antagonizes the activity of vascular endothelial growth factor and PlGF leading to endothelial dysfunction.

It is this widespread endothelial dysfunction that produces the maternal manifestations of PE including hypertension and proteinuria.<sup>2,3</sup>

Use of the sFlt-1/PlGF ratio is currently supported by many national and international bodies to aid in the diagnosis of women with clinical manifestations of PE.<sup>4,5</sup> Using a single cut-off, the sFlt-1/PlGF ratio has a high negative predictive value (NPV) for

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## AJOG at a glance

**Why was this study conducted?**

Preeclampsia is a heterogeneous disorder linked to maternal, fetal, and neonatal complications. Whilst the soluble fms-like tyrosine kinase-1/placental growth factor ratio (sFlt-1/PlGF) is increasingly recognized to predict adverse outcomes, the individual significance of gestational-age specific sFlt-1 and PlGF concentrations is less well understood. This study was conducted to investigate whether gestational age-specific thresholds of sFlt-1 and PlGF can identify distinct preeclampsia phenotypes, which may support individualized patient care strategies.

**Key findings**

Stratification of women with suspected preeclampsia according to gestational-age specific thresholds for sFlt-1 and PlGF does identify distinct maternal and fetal phenotypes. High sFlt-1 concentrations are associated with more severe maternal disease, whilst low PlGF reflects impaired placental angiogenesis and is associated with a greater incidence of fetal growth restriction and increased perinatal morbidity and mortality rates.

**What does this add to what is known?**

Evaluating the individual contributions of sFlt-1 and PlGF positions angiogenic profiling as both a diagnostic and prognostic tool. This provides insight beyond the ratio and may enable phenotype-specific personalized surveillance in preeclampsia.

ruling out PE within 7 days, and adverse maternal outcomes or delivery for PE within 14 days.<sup>1</sup> Whilst clinical guidelines currently recommend that the sFlt-1/PlGF ratio should not be used to make decisions on timing of birth,<sup>4</sup> there is growing recognition of the added utility of biomarkers in the prediction of poor maternal and perinatal outcomes.<sup>6–9</sup>

There are limitations in the use of a single ratio cut-off, as the clinician cannot disentangle the relative contributions of the individual angiogenic parameters within the ratio. PE is a heterogeneous condition with varying degrees of contribution from the dysfunctional maternal endothelium and the placenta.<sup>10</sup> This may be reflected clinically by either a more severe maternal or feto-placental phenotype, defined as reproducible patterns of maternal or fetal clinical features associated with differing angiogenic biomarker profiles. Given its antiangiogenic properties and role in the etiology of endothelial dysfunction, we proposed that a raised sFlt-1 may be associated with a more severe maternal preeclamptic phenotype, characterized by hypertension and abnormal maternal hematologic and biochemical parameters. In contrast,

low circulating levels of the proangiogenic PlGF may be associated with a more severe fetal phenotype related to profound placental insufficiency, defined as impaired placental function, commonly manifesting as fetal growth restriction (FGR).<sup>11</sup> There remains a paucity of data on how sFlt-1 and PlGF can help towards phenotyping PE when interpreted against gestational age-specific thresholds, and whether such an approach can meaningfully improve the stratification and care of women with PE.

The primary objective of this study was to assess how gestational age-specific angiogenic marker thresholds, defined by sFlt-1 concentrations above or below the 95th centile and PlGF concentrations above or below the fifth centile for gestational age,<sup>12</sup> correlated with maternal and/or perinatal adverse outcomes in women with suspected PE. We proposed that these findings may allow for better targeted surveillance and management of PE, anticipating that women with high circulating levels of the anti-angiogenic sFlt-1 would have more severe “maternal” disease, driven by hypertensive diseases of pregnancy and women with very low levels of the proangiogenic PlGF would demonstrate

greater rates of fetal and neonatal complications including FGR.

**Materials and methods****Study population, design, and setting**

This was a retrospective single-center observational cohort study at University College London Hospital (UCLH), United Kingdom (UK) between November 2021 and May 2024. The inclusion criteria were singleton pregnancies that had at least one sFlt-1/PlGF ratio performed in women attending the maternal day assessment unit at UCLH for suspected PE and were between 20 and 34+6 weeks gestation (Figure). Women with suspected PE are managed according to a standardized protocol at UCLH agreed by senior Maternal Fetal Medicine clinicians. The use of sFlt-1/PlGF has been implemented as part of routine clinical service at UCLH since 2021. Data was accessed utilizing the Epic electronic health database. Pregnancies with fetal aneuploidies or major congenital anomalies diagnosed in the antenatal or neonatal period and pregnancies ending in miscarriage at <24 weeks were excluded.

**Main outcome measures**

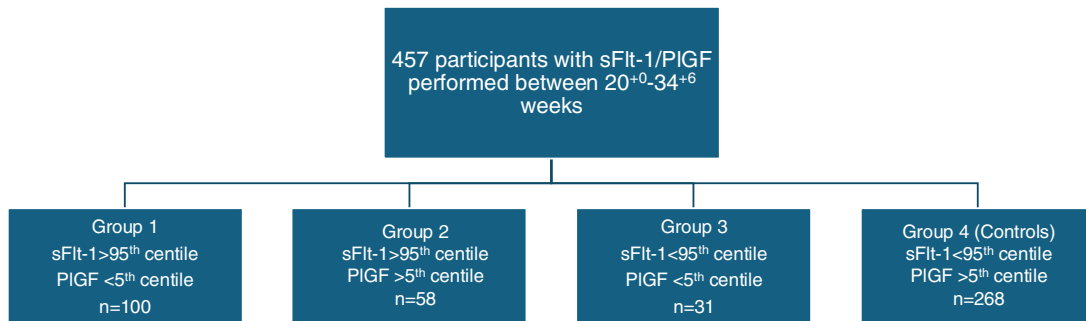
Measurements were performed for sFlt-1 and PlGF on the Roche Elecsys system (Roche Diagnostics, Mannheim, Germany). Four distinct groups were created for analysis, defined by the gestational age-appropriate marker cut-offs for anti-angiogenic sFlt-1 and proangiogenic PlGF.<sup>12</sup>

- F095 Group 1: sFlt-1 >95th percentile, PlGF <fifth percentile
- F095 Group 2: sFlt-1 >95th percentile, PlGF >fifth percentile
- F095 Group 3: sFlt-1 <95th percentile, PlGF <fifth percentile
- F095 Controls: sFlt-1 <95th percentile, PlGF >fifth percentile

As this is a retrospective study of “real-world” clinical data, clinicians were not blinded to sFlt-1 and PlGF levels. If an individual had more than one sFlt-1 and PlGF result available, the highest sFlt-1 result and the lowest PlGF

## FIGURE

## Selection of study cohort and stratification into groups



PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

results were utilized. In accordance with national guidance on PlGF-based testing, a ratio  $\geq 85$  was considered supportive of a diagnosis of PE in the presence of hypertension, and repeat sampling was generally not performed in these cases.<sup>4</sup> Conversely, women with an initial ratio  $< 85$  who later developed concerning clinical features underwent repeat testing as clinically indicated. As this was a retrospective real-world study, sampling intervals were not prospectively defined and varied according to clinical need.

PE was defined according to the International Society for the Study of

Hypertension in Pregnancy definition of 2021, as gestational hypertension  $\geq 140/90$  mmHg in pregnancy with one or more of the following new-onset conditions following 20 weeks of gestation (see Box 1); proteinuria, other maternal end-organ disease, or uteroplacental dysfunction (including angiogenic imbalance, referring to an excess of antiangiogenic sFlt-1 relative to pro-angiogenic PlGF).<sup>13</sup> PE was subdivided into preterm with onset  $< 37$  weeks or with onset  $< 34$  weeks' gestation. Severe hypertension was defined in accordance with the Maternal and Fetal Adverse Events grading, as the presence of

systolic blood pressure  $> 160$  mmHg and/or diastolic blood pressure  $> 110$  mmHg.<sup>14</sup> Small for gestational age (SGA) was defined as birthweight centile and characterized as  $< 10^{\text{th}}$ ,  $< 5^{\text{th}}$  and  $< 3^{\text{rd}}$  percentiles without adjustment for maternal characteristics.<sup>15</sup>

### Ethical approval

Ethical approval for this study was granted by the Data Trust Committee of University College London Hospitals under the Data Access Process for Research (DAP-R), IRAS ID: 299,136 on the 23rd of September 2024.

### Statistical analysis

Normality of continuous variables was assessed using the Shapiro–Wilk test. For continuous variables not normally distributed, comparisons between Groups 1 and 3 and the controls were made using the Kruskal–Wallis test with Bonferroni adjusted pairwise comparisons applied when the overall test was statistically significant. Numerical data were reported as median and interquartile range.

Biochemical, haematologic, angiogenic, and ultrasound-derived variables were log transformed to approximate normality. These were then analyzed using one-way analysis of variance (ANOVA), with Dunnett's post hoc tests performed to compare each of groups 1 to 3 with the controls. For log-transformed variables, results are

### Box 1

#### International Society for the Study of Hypertension in Pregnancy (ISSHP) definition of preeclampsia (2021)

Preeclampsia is gestational hypertension accompanied by one or more of the following new-onset conditions at or after 20 wks' gestation.

1. Proteinuria ( $\geq 300$  g in 24-hour collection or protein:creatinine ratio  $\geq 30$  mg/mmol or albumin:creatinine ratio (ACR)  $\geq 8$  mg/mmol or  $\geq 2+$  by urinary dipstick if confirmatory testing is not available).
2. Other maternal organ dysfunction, including
  - F095 Acute kidney injury (AKI); creatinine  $\geq 90$   $\mu\text{mol/L}$ .
  - F095 Liver involvement; elevated transaminases (ALT/AST  $> 40$  IU/mL) with or without right upper quadrant or epigastric abdominal pain.
  - F095 Neurological complications (eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata).
  - F095 Pulmonary edema
  - F095 Hematologic complications (platelet count  $< 150,000/\mu\text{L}$ , disseminated intravascular coagulation, hemolysis)
3. Uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler, intrauterine fetal death, placental abruption, and angiogenic imbalance).

presented as the geometric means (95% confidence interval (CI)) after back transformation.

Categorical variables were compared between groups with the chi-squared or Fisher's exact test as appropriate. Where the overall test reached significance, post hoc pairwise comparisons between Groups 1 and 3 and the controls were undertaken to identify specific differences.

A 2 tailed *P*-value of  $<0.05$  was considered as clinically significant for all analyses.

Data were anonymized and managed via Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) before analysis using SPSS version 29 (IBM, Armonk, NY, USA).

Where more than one sFlt-1 and PlGF measurement was available, to reflect real world practice, the highest sFlt-1 and lowest PlGF values were used to reflect the peak angiogenic derangement during the pregnancy upon which clinical decision making is often based. To assess the robustness of these findings, a sensitivity analysis was performed using the first available angiogenic measurements.

## Results

Overall, data from 458 singleton pregnancies were included in the analysis. For one patient, a PlGF was available but an sFlt-1 level was not. Therefore, the total number of pregnancies within the 4 groups was 457. Figure shows the number of participants in each group. In the overall cohort, 348/457 (76.15%) had a single sFlt-1/PlGF measurement, whilst 109 of 457 (23.85%) had repeat testing. For the sensitivity analysis, women with more than one sample were then re-grouped according to their first sFlt-1/PlGF sample result.

## Population characteristics

Table 1 outlines maternal baseline demographics stratified by group. Maternal body mass index (BMI), ethnicity, smoking status, previous and/or family history of PE, presence of comorbidities and mean arterial pressure at booking were similar between controls and Groups 1 to 3.

## Ultrasound and maternal biomarkers

Table 2 summarizes the ultrasound and maternal variables stratified by group. These variables were included as they form part of routine screening protocols within our institution and reflect baseline placental and maternal vascular risk. Low first-trimester pregnancy associated plasma protein-A (PAPP-A) and elevated uterine artery Doppler PI (UtAD PI) are recognized markers of impaired placentation and have been associated with FGR and stillbirth, while booking mean arterial pressure reflects the baseline maternal cardiovascular and hypertensive risk profile.<sup>16,17</sup>

Across all variables examined, distinct patterns were observed between the 4 angiogenic profiles. Groups 1 and 3 included women with PlGF levels  $<$ fifth centile, and when compared to the controls, both groups had a significantly lower mean PAPP-A result. There was also a statistically significant trend towards higher mean and combined UtAD PI in Groups 1 and 3 compared to controls.

As with the ultrasound and angiogenic variables, markers of maternal end-organ involvement demonstrated strong group-level differences. Groups 1 and 2, both with sFlt-1 levels  $>$ 95th centile, had significantly lower platelets when compared to controls and higher creatinine and urine protein:creatinine ratio. In contrast, no differences were observed in any of the hematological and biochemical variables between Group 3 (with sFlt-1 levels  $<$ 95th centile) and the controls. Although a significant trend was observed for alanine transferase levels, this only reached statistical significance for Group 1 (sFlt-1  $>$ 95th centile and PlGF  $<$ fifth centile) when compared with controls.

In summary, Groups 1 and 2 with elevated sFlt-1, demonstrated clinical features consistent with a maternal disease phenotype characterized by lower platelet counts, renal dysfunction, proteinuria and hepatic involvement. Groups 1 and 3 with low PlGF levels  $<$ fifth centile appeared to be associated with markers of placental insufficiency

including low PAPP-A and abnormal uterine artery Dopplers.<sup>16,17</sup>

## Maternal and perinatal outcomes

Table 3 shows the maternal and perinatal outcomes, stratified by group. Iatrogenic clinician-initiated maternal outcomes include admission to hospital with hypertension, the initiation of antihypertensives, use of magnesium sulphate, and the emergency Cesarean section rate. Overall, Group 1 had the heaviest burden of maternal and perinatal morbidity with Groups 2 and 3 demonstrating a more moderate risk category when compared to the controls. Severe hypertension and antenatal admission for management of hypertension were common in Groups 1 and 2 with the greatest sFlt-1 levels, whereas Group 3 did not differ significantly from the controls.

Median gestational age at birth was significantly earlier in Groups 1 to 3 when compared to controls. There were 16 spontaneous preterm live births (3.75%) and 127 iatrogenic preterm births (29.74%) in the entire cohort. The median interval between the last sFlt-1/PlGF sample and preterm birth was 8.5 days [IQR 2.5–38.5] for spontaneous preterm labor, and 13 days [IQR 3.5–28.5] for iatrogenic preterm birth. The median gestational age for iatrogenic preterm births was 34.0 weeks [IQR 31.25–35.7] and 94.49% were Cesarean deliveries ( $n=120$ ). Similar to gestational age, birthweight centile was lower across all 3 groups, when compared to controls particularly in Group 1 and Group 3. Stillbirth occurred only in Groups 1 ( $n=5$ , 5.3%) and 3 ( $n=2$ , 6.9%) with no events in Group 2 and controls. The median interval between biomarker sampling and intrauterine fetal death was 16 days (IQR 14–29 days). The median gestational age of stillbirth was 27.0 weeks (IQR 26.14–28.93 weeks), consistent with late second- to early third-trimester fetal demise. The incidence of SGA and need for neonatal intensive care unit (NICU) admission were substantially higher across Groups 1 to 3 when each of the groups was individually

TABLE 1

Maternal baseline demographics stratified by group, defined by gestational age appropriate angiogenic marker cut-offs. All data presented as either n (%) or median (IQR)

| Variable                     | Controls n=267   | Group 1 sFlt-1>95 <sup>th</sup> ,<br>PlGF <5 <sup>th</sup><br>n=100 | Group 2 sFlt-1 >95 <sup>th</sup> ,<br>PlGF >5 <sup>th</sup><br>n=58 | Group 3 sFlt-1 <95 <sup>th</sup> ,<br>PlGF <5 <sup>th</sup><br>n=31 | P value |
|------------------------------|------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|---------|
| Age, median (IQR)            | 34 (33–38.5)     | 38 (35.0–39.8) <sup>a</sup>                                         | 33 (31.5–44) <sup>a</sup>                                           | 36.5 (32–38.8)                                                      | 0.004   |
| BMI, median (IQR)            | 27.0 (22.6–31.3) | 28.5 (23.8–30.5)                                                    | 27.3 (25.8–28.9)                                                    | 26.3 (22.8–30.8)                                                    | 0.580   |
| Ethnicity, n (%)             |                  |                                                                     |                                                                     |                                                                     | 0.486   |
| White                        | 151 (56.3)       | 52 (51.5)                                                           | 30 (51.7)                                                           | 18 (58.1)                                                           |         |
| Black                        | 52 (19.4)        | 19 (18.8)                                                           | 13 (22.4)                                                           | 8 (25.8)                                                            |         |
| South Asian                  | 39 (14.6)        | 19 (18.8)                                                           | 9 (15.5)                                                            | 2 (6.5)                                                             |         |
| East Asian                   | 10 (3.7)         | 5 (5)                                                               | 3 (5.2)                                                             | 1 (3.2)                                                             |         |
| Mixed                        | 16 (6.0)         | 6 (5.9)                                                             | 3 (5.2)                                                             | 2 (6.5)                                                             |         |
| IVF, n (%)                   | 33 (12.3)        | 29 (29) <sup>b</sup>                                                | 16 (27.6) <sup>c</sup>                                              | 6 (19.4)                                                            | <0.001  |
| Smoking, n (%)               | 15 (5.6)         | 4 (4.0)                                                             | 3 (5.2)                                                             | 2 (3.2)                                                             | 0.648   |
| Previous PE, n (%)           | 35 (13.1)        | 11 (10.9)                                                           | 8 (13.8)                                                            | 10 (32.3)                                                           | 0.918   |
| Sister/mother with PE, n (%) | 23 (8.6)         | 4 (4.0)                                                             | 5 (8.6)                                                             | 3 (10.0)                                                            | 0.442   |
| Chronic hypertension, n (%)  | 47 (17.5)        | 11 (10.9)                                                           | 10 (17.2)                                                           | 8 (25.8)                                                            | 0.407   |
| SLE/APLS, n (%)              | 9 (3.4)          | 5 (5.0)                                                             | 1 (1.7)                                                             | 2 (6.5)                                                             | 0.982   |
| Pre-existing diabetes, n (%) | 10 (3.7)         | 2 (2.0)                                                             | 5 (8.6)                                                             | 1 (3.2)                                                             | 0.399   |
| Aspirin prophylaxis, n (%)   | 132 (49.3)       | 58 (57.4)                                                           | 38 (66.7) <sup>a</sup>                                              | 19 (61.3)                                                           | 0.012   |
| MAP at booking, median (IQR) | 90.8 (83.8–97.7) | 91.3 (84.7–96.3)                                                    | 95.2 (86.8–101.3)                                                   | 91.3 (84.7–99.0)                                                    | 0.284   |

APLS, antiphospholipid syndrome; BMI, body mass index; FGR, fetal growth restriction; IVF, in vitro fertilization; PTB, preterm birth; SLE, systemic lupus erythematosus.

<sup>a</sup> P=0.05; <sup>b</sup> P=0.001; <sup>c</sup> P=0.01.

compared to the controls ( $P<0.001$  for all). NICU admission rates were 81.4%, 41.5%, 48.1% for Groups 1, 2, and 3, respectively, vs 18.1% of controls ( $P<0.001$ ).

In summary, women with elevated sFlt-1 (Groups 1 and 2) experienced higher rates of severe hypertension, hospital admission and need for anti-hypertensive treatment, suggestive of a high-risk maternal phenotype of PE. Low PlGF (Groups 1 and 3) identified a high-risk fetal phenotype with greater rates of SGA infants, NICU admission, and all observed stillbirths.

### Sensitivity analysis

A sensitivity analysis using the first available sFlt-1 and PlGF measurement was performed for completion. The groups were reorganized as per the first sample results (see [Supplemental Tables 1–3](#)). The results yielded were

consistent with the primary analysis. No material differences in effect direction or statistical significance were observed (see [Supplemental Tables 1–3](#)).

## Discussion

### Principal findings

In this retrospective cohort study, stratification of women using gestational age-specific thresholds for sFlt-1 and PlGF appeared to identify clinical distinct patterns of disease. Elevated sFlt-1 concentration were associated with markers of maternal end-organ dysfunction, whereas low PlGF levels, reflecting impaired placental angiogenesis, were associated with features of placental insufficiency such as FGR and increased neonatal morbidity. Women with normal angiogenic profiles experienced the most favorable maternal and perinatal outcomes.

### Results in the context of what is known

Previous studies have shown that severe maternal PE, including hemolysis, elevated liver enzymes and low platelets (HELLP syndrome) is associated with significant derangements in both sFlt-1 and sFlt-1/PlGF ratios.<sup>6,8</sup> Hastie *et al* reported that women with HELLP had an approximately 2- and 10- fold increase in sFlt-1 levels and sFlt1/PlGF ratio, respectively, when compared to women without severe features.<sup>8</sup> Our findings align with this, demonstrating that elevated sFlt-1 levels correspond to a maternal-dominant phenotype characterized by end-organ dysfunction even when PlGF is not profoundly reduced.

There is also strong evidence supporting the use of PlGF, independent of the ratio, to predict adverse perinatal outcomes. In women with suspected preterm PE, measurement of PlGF

TABLE 2

Maternal biochemical and ultrasound variables stratified by group defined by gestational age appropriate angiogenic marker cut-offs

| Variable                                        | Controls n=267      | Group 1 sFit-1>95 <sup>th</sup> , PIGF <5 <sup>th</sup><br>n=100 | Group 2 sFit-1 >95 <sup>th</sup> , PIGF >5 <sup>th</sup><br>n=58 | Group 3 sFit-1 <95 <sup>th</sup> , PIGF <5 <sup>th</sup><br>n=32 | F statistic | P value |
|-------------------------------------------------|---------------------|------------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------------|-------------|---------|
| Ultrasound, angiogenic and placental biomarkers |                     |                                                                  |                                                                  |                                                                  |             |         |
| PAPPA MoM, mean (95% CI)                        | 0.9 (0.8–1.0)       | 0.6 (0.6–0.7) <sup>a</sup>                                       | 1.0 (0.9–1.2)                                                    | 0.5 (0.4–7) <sup>b</sup>                                         | 6.9         | <0.001  |
| Mean UtAD PI, mean (95% CI)                     | 0.98 (0.93–1.02)    | 1.47 (1.35–1.59) <sup>b</sup>                                    | 1.01 (0.89–1.14)                                                 | 1.31 (1.13–1.51) <sup>b</sup>                                    | 10.2        | <0.001  |
| Combined UtAD PI, mean (95% CI)                 | 1.95 (1.87–2.04)    | 2.94 (2.70–3.20) <sup>b</sup>                                    | 2.02 (1.79–2.29)                                                 | 2.62 (2.26–3.03) <sup>b</sup>                                    | 10.2        | <0.001  |
| Highest sFit-1/PIGF, mean (95% CI)              | 6 (5.6–7.4)         | 203 (172.7–240.7) <sup>b</sup>                                   | 44.24 (34.6–56.5) <sup>b</sup>                                   | 53.7 (38–75.9) <sup>b</sup>                                      | 126.1       | <0.001  |
| Highest sFit-1 (pg/ml), mean (95% CI)           | 2189 (1037–2352)    | 9202 (8383–10101) <sup>b</sup>                                   | 8786 (7717–10002) <sup>b</sup>                                   | 3157 (2611–3815) <sup>a</sup>                                    | 218.8       | <0.001  |
| Lowest PIGF (pg/ml), mean (95% CI)              | 343 (312–377)       | 41.4 (36.4–47.12) <sup>b</sup>                                   | 189.9 (161.9–222.8) <sup>b</sup>                                 | 58.3 (47.82–71.06) <sup>b</sup>                                  | 236.6       | <0.001  |
| Maternal hematologic and biochemical variables  |                     |                                                                  |                                                                  |                                                                  |             |         |
| Lowest platelet count, mean (95% CI)            | 212.5 (204.9–220.4) | 182.8 (168–198.8) <sup>a</sup>                                   | 176.7 (160.4–194.6) <sup>a</sup>                                 | 210.7 (186.3–238.2)                                              | 5.7         | 0.01    |
| Highest ALT (IU/ml), mean (95% CI)              | 22.9 (20.9–25.2)    | 40.1 (34.2–47.0) <sup>b</sup>                                    | 32.0 (24.9–41.1)                                                 | 23.7 (20.1–27.9)                                                 | 6.1         | 0.01    |
| Highest Cr (umol/L), mean (95% CI)              | 59.4 (57.7–61.2)    | 70.1 (65.2–75.4) <sup>b</sup>                                    | 70.1 (63.3–78.3) <sup>a</sup>                                    | 51.4 (41.5–63.7)                                                 | 9.1         | <0.001  |
| Highest PCR (mg/mmol), mean (95% CI)            | 25.8 (22.2–29.9)    | 93 (68.7–126.1) <sup>b</sup>                                     | 58.9 (38.9–89.0) <sup>a</sup>                                    | 44.3 (27.8–70.8)                                                 | 15.0        | <0.001  |

The results of the ANOVA were back transformed into geometric means and 95% confidence intervals. The comparisons between the controls and groups 1 – 3 are included with statistical significance identified through.<sup>c</sup>

ALT, alanine transferase; Cr, creatinine; MoM, multiples of median; PAPPA, pregnancy-associated plasma protein-A; PCR, protein: creatinine ratio; UtAD PI, uterine artery Doppler pulsatility index.

<sup>a</sup> P=0.01; <sup>b</sup> P=0.001; <sup>c</sup> P=0.05.

TABLE 3

**Maternal and neonatal outcomes stratified by group defined by gestational age appropriate angiogenic marker cut-offs**

| Variable                           | Controls n=267     | Group 1 sFlt-1>95 <sup>th</sup> ,<br>PIGF <5 <sup>th</sup><br>n=100 | Group 2 sFlt-1 >95 <sup>th</sup> ,<br>PIGF >5 <sup>th</sup><br>n=58 | Group 3 sFlt-1 <95 <sup>th</sup> ,<br>PIGF <5 <sup>th</sup><br>n=32 | P value |
|------------------------------------|--------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|---------|
| <b>Maternal outcomes</b>           |                    |                                                                     |                                                                     |                                                                     |         |
| Preeclampsia <37 wks, n (%)        | 18 (6.7)           | 78 (78.0) <sup>a</sup>                                              | 23 (39.7) <sup>a</sup>                                              | 10 (31.3) <sup>a</sup>                                              | <0.001  |
| Preeclampsia <34 wks, n (%)        | 10 (3.7)           | 64 (64.0) <sup>a</sup>                                              | 7 (12.1) <sup>b</sup>                                               | 7 (21.9) <sup>a</sup>                                               | <0.001  |
| PIH, n (%)                         | 37 (13.9)          | 4 (4.0) <sup>b</sup>                                                | 8 (13.8)                                                            | 1 (3.1)                                                             | 0.130   |
| Severe hypertension, n (%)         | 29 (10.9)          | 48 (48.0) <sup>a</sup>                                              | 13 (22.4) <sup>c</sup>                                              | 6 (18.8)                                                            | <0.001  |
| Admission with hypertension, n (%) | 42 (37.2)          | 66 (66.7) <sup>a</sup>                                              | 25 (43.1) <sup>a</sup>                                              | 9 (28.1)                                                            | <0.001  |
| ≥ 2 antihypertensives, n (%)       | 39 (34.5)          | 52 (52.0) <sup>a</sup>                                              | 16 (27.6) <sup>c</sup>                                              | 9 (28.1) <sup>c</sup>                                               | 0.011   |
| Magnesium sulphate, n (%)          | 1 (0.9)            | 22 (22.0) <sup>a</sup>                                              | 6 (10.3) <sup>a</sup>                                               | 2 (6.3) <sup>b</sup>                                                | <0.001  |
| Placental abruption, n (%)         | 4 (1.5)            | 2 (2.0)                                                             | 1 (1.7)                                                             | 2 (6.3)                                                             | 0.780   |
| GDM, n (%)                         | 53 (19.8)          | 22 (22.0)                                                           | 17 (29.3)                                                           | 8 (25.0)                                                            | 0.161   |
| Emergency CS, n (%)                | 85 (31.8)          | 74 (73.0) <sup>a</sup>                                              | 27 (46.6) <sup>c</sup>                                              | 19 (59.4) <sup>b</sup>                                              | <0.001  |
| <b>Perinatal outcomes</b>          |                    |                                                                     |                                                                     |                                                                     |         |
| Gestation at birth, median (IQR)   | 38.4 (37.4–39.5)   | 33.4 (29.2–35.7) <sup>a</sup>                                       | 36.6 (35.7–37.9) <sup>a</sup>                                       | 36.8 (33–38) <sup>a</sup>                                           | <0.001  |
| Birthweight centile, median (IQR)  | 24.05 (7.94–54.37) | 0.26 (0.00–2.71) <sup>a</sup>                                       | 9.49 (0.83–36.7)                                                    | 1.15 (0.01–21.22) <sup>a</sup>                                      | <0.001  |
| Stillbirth, n (%)                  | 0                  | 5 (5.3) <sup>a</sup>                                                | 0                                                                   | 2 (6.9) <sup>a</sup>                                                | 0.048   |
| SGA <10 <sup>th</sup> , n (%)      | 73 (27.2)          | 94 (94.0) <sup>a</sup>                                              | 29 (50) <sup>a</sup>                                                | 20 (62.5) <sup>a</sup>                                              | <0.001  |
| SGA <fifth, n (%)                  | 45 (16.8)          | 86 (86) <sup>a</sup>                                                | 25 (43.1) <sup>a</sup>                                              | 20 (62.5) <sup>a</sup>                                              | <0.001  |
| SGA <third, n (%)                  | 33 (12.3)          | 79 (78.2) <sup>a</sup>                                              | 22 (37.9) <sup>a</sup>                                              | 19 (59.4) <sup>a</sup>                                              | <0.001  |
| NICU admission, n (%)              | 47 (18.1)          | 70 (81.4) <sup>a</sup>                                              | 22 (41.5) <sup>a</sup>                                              | 13 (48.1) <sup>a</sup>                                              | <0.001  |

CS, caesarean section; GDM, gestational diabetes; NICU, neonatal intensive care unit; PIH, pregnancy-induced hypertension; SGA, small for gestational age.

<sup>a</sup>  $P=0.001$ ; <sup>b</sup>  $P=0.01$ ; <sup>c</sup>  $P=0.05$ .

outperforms the use of ultrasound estimated fetal weight or abdominal circumference to identify SGA infants <third centile.<sup>18</sup> Additionally, low PIGF appears to identify histologically-confirmed placental-mediated FGR with a high sensitivity and NPV.<sup>11</sup> Consistent with these studies, women in our cohort with a PIGF concentration <fifth centile demonstrated evidence of placental insufficiency with lower first trimester PAPP-A levels, higher uterine artery Doppler indices, lower birthweight centiles, and a higher rate of neonatal unit admission. Notably, all stillbirths in our study occurred in pregnancies with low PIGF concentrations, reinforcing this known association between severe placental angiogenic failure and fetal demise.<sup>19</sup>

### Clinical and research implications

Current guidelines appropriately support the use of sFlt-1/PIGF ratio rule-in and rule-out thresholds of 85 and 38, respectively, to help guide immediate clinical decision making.<sup>4</sup> However, this study supports the hypothesis that examining the sFlt-1 and PIGF individually, and not just as a ratio, may provide additional clinically-relevant information in distinguishing maternal-dominant and fetal-dominant PE profiles.

If validated prospectively, this approach would support adopting more individualized surveillance and management strategies when PE is suspected. Women with a maternal-dominant PE phenotype characterized by sFlt-1 above 95th centile may benefit

from intensified monitoring and control of blood pressure and serum markers of end-organ dysfunction. Conversely, women with a fetal-dominant phenotype characterized by PIGF below fifth centile may derive greater benefit from close fetal surveillance with serial growth ultrasounds and Doppler monitoring.

Future research could focus upon the development of prognostic models combining sFlt-1, PIGF, and clinical variables to predict severe maternal, fetal, and neonatal outcomes. Similarly, prospective multicenter studies are warranted to validate these findings and prospectively analyze whether angiogenic marker-based phenotyping can predict adverse maternal and fetal outcomes of PE.

## Strengths and limitations

This study includes a relatively large cohort of patients from a tertiary referral center in the UK with robust maternal and perinatal outcome data. Outcomes were captured from a comprehensive electronic medical record system, and each clinical record was individually examined by one of the co-authors to ensure data accuracy for laboratory, obstetric and neonatal variables and outcomes. By examining the independent contributions of sFlt-1 and PlGF, our study provides novel insights beyond existing retrospective data.

There are understandable limitations to the dataset, due to the retrospective single center design of the study. Testing was almost universally performed when there was clinical suspicion of PE or FGR and therefore the results are subject to selection bias and a lack of clinician blinding. Our cohort includes high-risk women attending or referred to a tertiary level hospital. We acknowledge that women cared for in this setting are more likely to have severe disease or significant co-morbidities compared with those managed in other settings. However, the aim of this work is to explore whether gestational age-specific sFlt-1 and PlGF levels can identify clinically distinct phenotypes of PE, as opposed to evaluating their use as a screening tool in unselected populations. Therefore, our authors would expect similar results in lower-risk populations whereby women present with suspected PE. Prospective multicenter studies are essential to externally validate these findings and confirm that distinct maternal and fetal phenotypes

of PE correlate with different biomarker profiles. Therefore, current discussion of angiogenic-based “phenotypes” only reflects observational associations and should not guide clinical decision-making.

We acknowledge that using the most abnormal angiogenic values may also bias classification towards more severe disease. Because preeclampsia is typically a progressive condition antenatally, it would be most common for the highest ratio value to feature at a more advanced gestational age, and in clinical practice this may then form the basis for definitive prognostication and pregnancy management. However, a sensitivity analysis using the first measurement demonstrated that our findings were robust to this alternative approach and was more in alignment with real-world clinical practice. Whilst outcomes such as stillbirth are hugely clinically significant, the numbers in this study were small, and we accept that this may limit the statistical power of this study to detect true subgroup differences for rare events.

## Conclusion

The findings of this study demonstrate that by utilizing gestational-age specific thresholds for sFlt-1 and PlGF, distinct clinical phenotypes with differing clinical outcomes are observed. Low PlGF concentrations below the fifth centile appear to correlate with a predominantly fetal phenotype, with greater rates of FGR, neonatal admission and stillbirth, reflecting impaired placental angiogenesis. Elevated sFlt-1 concentrations >95th centile, are predominantly associated with adverse maternal

outcomes including severe hypertension and end-organ dysfunction. This highlights the potential clinical merit of angiogenic marker-based phenotyping, beyond the use of sFlt-1/PlGF alone to either “rule-in” or “rule out” PE, to individualize patient surveillance. Larger, multicenter prospective studies are however required to externally validate these findings and determine if incorporating gestational-age specific angiogenic profiling into routine clinical practice can improve maternal and perinatal outcomes in PE. ■

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## Glossary

FGR: fetal growth restriction  
HELLP: hemolysis, elevated liver enzymes, low platelets  
NICU: neonatal intensive care unit  
PE: preeclampsia  
PlGF: placental growth factor  
sFlt-1: soluble FMS-like tyrosine kinase-1  
SGA: small for gestational age  
UtAD PI: uterine artery Doppler pulsatility index

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