Preeclampsia

Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women With Suspected Preeclampsia
INSPIRE

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Abstract—The ratio of maternal serum sFlt-1 (soluble fms-like tyrosine kinase 1) to PlGF (placental growth factor) has been used retrospectively to rule out the occurrence of preeclampsia, a pregnancy hypertensive disorder, within 7 days in women presenting with clinical suspicion of preeclampsia. A prospective, interventional, parallel-group, randomized clinical trial evaluated the use of sFlt-1/PlGF ratio in women presenting with suspected preeclampsia. Women were assigned to reveal (sFlt-1/PlGF result known to clinicians) or nonreveal (result unknown) arms. A ratio cutoff of 38 was used to define low (≤38) and elevated risk (>38) of developing the condition in the subsequent week. The primary end point was hospitalization within 24 hours of the test. Secondary end points were development of preeclampsia and other adverse maternal-fetal outcomes. We recruited 370 women (186 reveal versus 184 nonreveal). Preeclampsia occurred in 85 women (23%). The number of admissions was not significantly different between groups (n=48 nonreveal versus n=60 reveal; *P*=0.192). The reveal trial arm admitted 100% of the cases that developed preeclampsia within 7 days, whereas the nonreveal admitted 83% (*P*=0.038). Use of the test yielded a sensitivity of 100% (95% CI, 85.8–100) and a negative predictive value of 100% (95% CI, 97.1–100) compared with a sensitivity of 83.3 (95% CI, 58.6–96.4) and negative predictive value of 97.8 (95% CI, 93.7–99.5) with clinical practice alone. Use of the sFlt-1/PlGF ratio significantly improved clinical precision without changing the admission rate.

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Preeclampsia, a heterogeneous, multisystem disorder defined by the new onset of hypertension and proteinuria or evidence of end-organ dysfunction after 20 weeks of gestation affects 2 to 5% of pregnancies worldwide.[1,2] Preeclampsia is associated with a high risk of iatrogenic preterm birth, small for gestational age (SGA) infant, placental abruption, and perinatal mortality, along with significant maternal morbidity and mortality.[3]

Although hypertension and proteinuria are hallmarks of the disease, they have poor predictive value for the development of adverse outcomes.[4] In addition, the initial clinical presentation is heterogeneous and current clinical tools applied to women who present with clinical suspicion of the disease do not allow accurate prediction of the development of preeclampsia even in the short term; this inability to effectively rule in or rule out the condition in those at risk means some cases are missed,[5] whereas many women are unnecessarily admitted for monitoring or followed up intensively.

Recently, angiogenic factors (specifically sFlt-1 [soluble fms-like tyrosine kinase 1] and/or PlGF [placental growth factor]) have been suggested as good candidate biomarkers for the prediction of preeclampsia occurring in the short term. The largest study conducted to date analyzed the performance of the sFlt-1/PlGF ratio in women who presented with suspected preeclampsia.[6] The study showed that a ratio ≤38 conferred a negative predictive value (NPV) of 99.3%

(95% CI, 97.9–99.9) for developing preeclampsia within 7 days, whereas a ratio >38 conferred a positive predictive value (PPV) of 36.7% (95% CI, 28.4–45.7) for developing preeclampsia within 4 weeks.[6]

Several authors suggested that implementation of sFlt-1/PlGF into clinical practice may be of benefit by reducing unnecessary admissions for those at low risk of developing the disease in the short term and by more targeted increase in surveillance for those at high risk.[7–10] Additionally, given its good correlation with outcomes,[11–14] it has been suggested that it could be valuable in guiding management in women with preeclampsia, such as optimization of timing of delivery or timing of corticosteroid administration. Collectively this could allow better resource allocation by reducing costs in low-risk women, and potentially improve outcomes in both low- and high-risk women.[8] However, existing studies are either observational or retrospective and meaning that economic analyses and recommendations for clinical use have limitations.[15]

To address these shortcomings, we designed this randomized clinical trial to assess whether the sFlt-1/PlGF ratio, used in combination with current clinical guidelines as used in real-life practice, could reduce the number of women admitted due to a suspicion of preeclampsia and to assess the real-world performance and clinical utility of this test in its ability to detect preeclampsia in daily clinical practice.

Methods

Additional information on the data, materials, or analytic methods that support the findings of this study are available from the corresponding author on reasonable request.

Trial Design

INSPIRE (Interventional Study Evaluating the Short-Term Prediction of Preeclampsia / Eclampsia In Pregnant Women With Suspected Preeclampsia) was a prospective interventional randomized, parallel-group, controlled trial conducted in the United Kingdom.

We used a 1:1 ratio for randomization. Participants were individually randomized to either standard clinical management or standard clinical management + sFlt-1/PlGF ratio result. The allocation was determined by the laboratory team using 1:1 randomization using a computer-based system. The allocation was not known to the clinical teams assessing the women.

Participants

Eligible participants were pregnant women (18 years old or older), between 24+0 and 37+0 weeks of gestation with a clinical suspicion of preeclampsia. This was judged according to the following: new onset elevated blood pressure[6] or worsening of preexisting hypertension or new onset proteinuria (any protein in the urine >trace on dipstick) or worsening of preexisting proteinuria or new onset headache, visual disturbance, edema or right upper quadrant pain, or any other clinical suspicion of preeclampsia.

Exclusion criteria were preexisting diagnosed preeclampsia/eclampsia or hemolysis, elevated liver enzyme levels, and low platelet counts syndrome, multiple pregnancy, inability to provide informed consent/unwillingness to participate or significant disease (ie, cancer) or disorder (ie, significant mental health problems), which in the opinion of the investigator might either put the participants at risk or influence the result of the study or the participant's ability to participate in the study.

Settings and Locations Where Data Was Collected

The study took place at the John Radcliffe Hospital (Oxford University Hospitals NHS Foundation Trust) in Oxford, United Kingdom from June 2015 to April 2017. The John Radcliffe is a tertiary referral center with a preeclampsia prevalence of 2.9%.

Standard Clinical Management of Suspected Preeclampsia

Management of suspected preeclampsia involved initial assessment of blood pressure, proteinuria (first by urine dipstick and then by urine protein:creatinine ratio if dipstick was positive), urine microscopy and culture, baseline blood tests (full blood count, urea and electrolytes, liver function tests, and clotting), as well as physical examination and cardiotocography. Blood pressure was managed according to the National Institute for Health and Care Excellence guidelines.[16] Decisions to admit were made by the attending doctor (either alone or after discussion with a senior colleague) and depended on clinical condition or concerns. Ultrasonographic assessment of the fetus was usually performed on those patients who were admitted.

Intervention

Women who presented with signs or symptoms of preeclampsia were approached to participate in the study. After informed consent, they had clinical assessment and standard clinical management blood taken as well as an additional sample for sFlt-1/PlGF. Blood samples were processed in the central laboratory, and turn-around time was 60 minutes. Once the sample was received, women were randomized by the laboratory team to either nonreveal (comparator; standard clinical management) or reveal (intervention; standard clinical management + sFlt-1/PlGF ratio result) trial arms and the clinical team informed of the allocation.

In the reveal (intervention) arm, the sFlt-1/PlGF results were available to the clinicians alongside the other requested blood samples. In the nonreveal (comparator) arm, the sFlt-1/PlGF results were not available until trial completion, and patients were managed according to standard clinical management, without knowledge of sFlt-1/PlGF ratio. The same clinical team attended women from the reveal and nonreveal trial arms.

In the reveal arm, sFlt-1/PlGF ratio was incorporated into the clinical decision framework with a ratio of ≤38 considered to confer low risk of developing preeclampsia within 7 days and a ratio >38 deemed elevated risk.[6] The clinical algorithm for the reveal group advised discharge of women with ratio ≤38 unless deemed necessary by the clinician due to concerning clinical features. For women with ratio >38, a low threshold for admission or increased surveillance was advised.

Admission was defined as any admission arising within 24 hours, driven by clinical assessment (+ sFlt-1/PlGF ratio in the reveal group only) at the time of recruitment. (S1 Appendix in the online-only Data Supplement). Importantly, the decision-making in the reveal group was not based only on the ratio but on the consideration of the ratio in conjunction with assessment of the clinical picture (ie, if the attending clinician thought admission was warranted, the patient was admitted). Although pathways for the intervention and control arms were provided to clinicians, the final management decision, based on either subjective or structured risk assessment, as well as test results, was at the clinician's discretion, reflecting a pragmatic approach to more reliably assess real-world effectiveness. Continuous training and education about the ratio and its clinical interpretation were given before and during the trial. Knowledge of the ratio was used only as an indication for admission and follow-up not for delivery, which was performed according to current clinical guidelines. Research staff recorded, but did not intervene in, clinical decisions.

sFlt-1/PlGF Test

Serum samples were sent from the clinical area to the laboratory and were centrifuged within 1 hour of sample collection. sFlt-1 and PLGF were measured using fully automated methods on the Roche e411 analyzer (Roche Diagnostics Limited, Burgess Hill, United Kingdom). Method reproducibility, assessed as interassay percent coefficient of variation, for sFlt-1 was 5.1% at 102 pg/mL and 2.8% at 1043 pg/mL and for PLGF was 3.0% at 106 pg/mL and 2.9% at 1069 pg/mL.

Outcomes

A Priori Defined Outcomes

Primary Outcome

The primary outcome was preeclampsia-related inpatient admission within 24 hours of the test, within 7 days, or by delivery. Preeclampsia-related inpatient admission was defined as an admission driven by

suspicion of preeclampsia defined as above, where preeclampsia has been recorded as a differential diagnosis and where ongoing blood pressure monitoring, assessment of proteinuria, and preeclampsia blood samples have been requested. Patients who were admitted without these (eg, after premature rupture of membranes or threatened preterm labor) were not deemed to have had a preeclampsia-related admission. This was defined after case report form review by experienced clinicians who were blinded to the trial arm, sFlt-1/PlGF result, and clinical outcome. If 3 independent assessors could not unanimously agree, an external arbiter (A.T. Papageorghiou) made the final decision—in 4 cases.

Secondary Outcomes

Secondary outcomes were incidence of preeclampsia within 7 days and by the time of delivery; birth weight; Special Care Baby Unit (SCBU) admission; Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at delivery; platelet count, renal, and hepatic function measured using blood tests at time of first clinical assessment (ie, study enrollment/baseline) and time of delivery.

The diagnosis of preeclampsia was made according to the following criteria: diastolic BP ≥90 mm Hg or systolic blood pressure ≥140 mm Hg together with proteinuria (urine protein/creatinine ≥30 mg/mmol) or serum creatinine >97 μmol/L, elevated liver transaminases to twice the normal concentration or platelets <100000/dL. Superimposed preeclampsia was defined as an elevation in diastolic BP of >15 mm Hg or systolic blood pressure >30 mm Hg, together with (urine protein/creatinine ≥30 mg/mmol), or serum creatinine >97 μmol/L, elevated liver transaminases to twice the normal concentration, platelets<100000/dL.

SGA was defined as birth weight <10th centile adjusted for newborn sex (Viewpoint software, GE Healthcare, United Kingdom).

Outcomes were prospectively extracted from the electronic records, and case notes from the time of birth and with outcome assessors blinded to the sFlt-1/PlGF result. In instances where preeclampsia was not reported before discharge, research staff made a 6-week phone call after delivery and searched online data portals and electronic patient records to determine if postnatal readmissions and additional relevant information existed that had not been reported previously.

Post Hoc Changes From Initial Study Protocol. The predefined definition of preeclampsia in the study was updated before the study started in line with the statement from the International Society for the Study of Hypertension in Pregnancy[2] and American College of Obstetricians and Gynecologists.[1] The new definition does not require the presence of proteinuria; therefore, patients with hypertension and no proteinuria but signs of end-organ damage were classified as preeclampsia.[1,2]

Post Hoc Analyses. In addition, we subsequently analyzed the following:
1. Time (from enrollment) to preeclampsia diagnosis.
2. Sensitivity, specificity, NPV, and PPV for the sFlt-1/PlGF ratio.

Sample Size and Statistical Analyses

We estimated that we would need to enroll 366 women (183 in each arm) to detect a 15% reduction in admission rates between trial arms with a power of 80%, a 2-sided significance level of 5% and 1:1 randomization, allowing a 5% loss to follow-up.

Analysis was undertaken on an intention-to-treat basis, and no interim analyses were performed. Characteristics of study participants were summarized using simple proportions and medians with interquartile ranges (IQR) or means with SD stratified by trial arm.

The primary outcome was reported as risk ratio and risk difference. The secondary outcomes were reported as difference in proportions between groups using the χ^2 test or differences in means or medians using t test or Wilcoxon, respectively, depending on the variables. Comparison between trial arms was performed using a difference-in-differences statistical test using ANCOVA or logistic regression for categorical variables. Significance was set at 0.05, and all the analyses were 2-sided. All statistical analysis (a priori and post hoc) was performed using STATA version 15.1 (College Station, TX).

Randomization

We used a computer-based system to randomize patients with a predetermined ratio of 1:1. The person enrolling the participant in the clinical team did not know in advance which trial arm the next patient would be allocated to.

Blinding

Women and the clinical team responsible for the enrolled women were aware of the allocated trial arm (comparator versus intervention). Women and the clinical team caring for the reveal trial arm (intervention) were aware of the sFlt-1/PlGF result. Outcome assessors and data analysts were kept blind to sFlt-1/PlGF result and trial arm. sFlt-1/PlGF results from the nonreveal trial arm were only released at the end of the study.

Role of the Funding Source

The trial was funded by Roche Diagnostics GMBH and Roche Diagnostics Ltd. The University of Oxford sponsored the study. The study protocol was designed by the investigators and reviewed by the funder. The funder had no role in data collection or data analysis or final article approval. The authors analyzed and interpreted the data and wrote the article. All authors were independent of the funders.

It was approved by the Research Ethics Committee, National Research Ethics Committee South Central–Oxford B (Research Ethics Committee number 15/SC/0126).

Results

Baseline Characteristics of Trial Population

Between June 2015 and April 2017, a total of 381 women with suspected preeclampsia presenting at the John Radcliffe Hospital, Oxford, were enrolled. Eleven women were withdrawn (Figure 1). Analysis, therefore, included 370 women with 184 in the nonreveal and 186 in the reveal groups. The baseline clinical characteristics of each group are presented in Table 1. There were no significant differences between the characteristics of nonreveal and reveal and trial arms except for body mass index, which was driven by 3 outliers in the reveal group.

Primary Outcome

Admissions

There was no difference in preeclampsia-related admissions within 24 hours of the test between trial arms. Sixty patients were admitted in the intervention group (reveal) and 48 in the comparator group (nonreveal; risk ratio, 1.24 [0.89–1.70]; Table 2). Similarly, there was no difference in preeclampsia related admissions within 7 days (risk ratio, 1.06 [0.81–1.39]) or by delivery (risk ratio, 0.93 [0.82–1.06]). No differences were seen in admissions for any nonpreeclampsia-related reason (risk ratio, 1.22 [0.93–1.62]; Table S2).

Secondary Outcomes

Preeclampsia Within 7 Days of the Test

The overall preeclampsia rate for the entire trial population was 23% (n=85/370). There was no significant difference in the incidence of preeclampsia between the trial arms (P=0.291). Significantly more women who developed preeclampsia within 7 days were admitted in the reveal trial arm than the nonreveal trial arm (P=0.038; Table 3). In the reveal arm, 100% (n=24/24) of women who developed preeclampsia within 7 days were admitted (PPV, 40.0% [95% CI, 27.6–53.5]; sensitivity, 100% [95% CI, 85.8–100]; specificity, 77.8% [95% CI, 70.6–83.9]). This is in contrast with the nonreveal trial arm where 83% (n=15/18) were admitted (PPV, 31.3% [5% CI, 18.7–46.3], sensitivity; 83.3% [95% CI, 58.6–96.4], specificity 80.1% [95% CI, 73.2–85.9]).
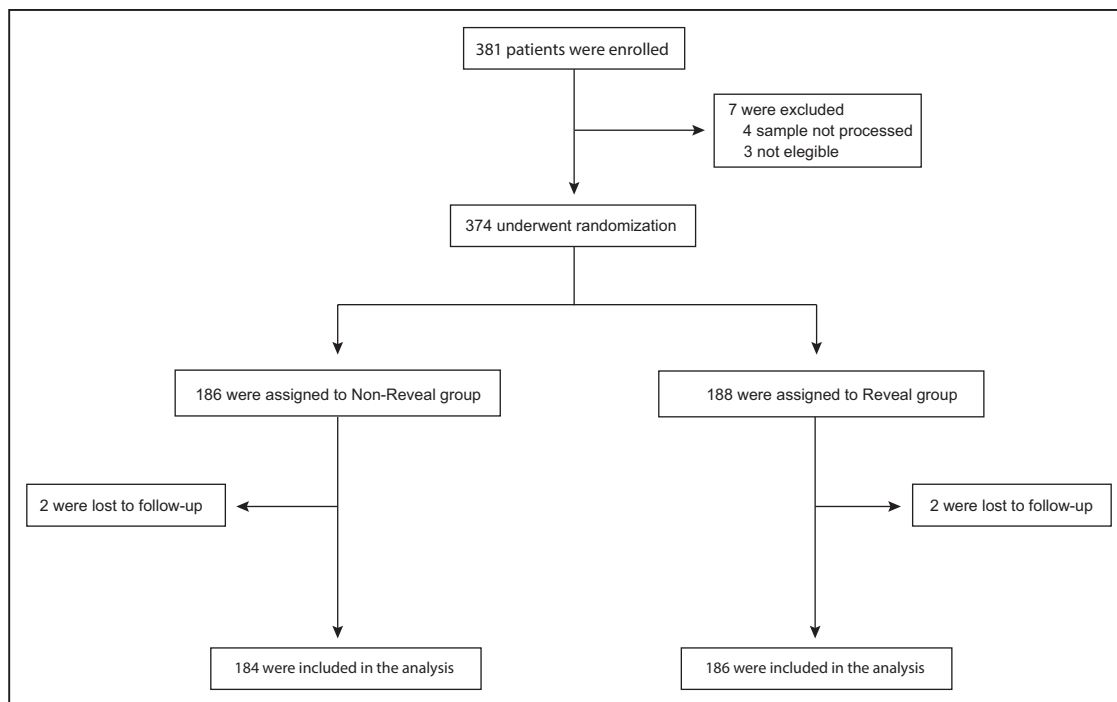
Figure 1. Recruitment, randomization, and follow-up.

Three patients who were discharged home in the nonreveal arm developed preeclampsia within 7 days (Table 3). A full breakdown of outcomes trial arms and between admitted and nonadmitted is presented in Tables S3A and S3B, respectively.

Birthweight
In both trial arms, babies of women that were admitted were smaller than those that were not admitted (Table 4). In the nonreveal arm, the median birthweight in admitted women was 3070g (IQR, 2408–3455 g), whereas it was 3305 g (IQR, 2820–3753 g) in nonadmitted women (difference, 240 g; $P=0.007$). In the reveal trial arm, this difference was significantly more pronounced, with a difference of 620 g and respective birthweight of 2818 g (IQR, 2363–3203 g) and 3433 g (IQR, 3045–3780 g; $P=0.000$; Table 4).

Small for Gestational Age
The percentage of SGA infants in nonreveal trial arm was 22.9% (n=11/48) in the admitted and 14.7% (n=20/136) in the non admitted women ($P=0.19$). In contrast, there was a significant difference in the reveal trial arm, with the rate of SGA being 26.7% (16/60) in the admitted women and 11.9% (15/126) in the nonadmitted women ($P=0.012$; Table 4).

SCBU Admission
SCBU attendance showed a similar pattern to SGA. (Table 2A). In the nonreveal trial arm, there was a similar rate of SCBU attendance between admitted (16.7%) and non admitted women (14.7%; $P=0.745$). This is in contrast with the reveal trial arm where there was a significant difference among infants of admitted and nonadmitted women. Infants of admitted women had a higher rate of SCBU attendance than infants from nonadmitted women (26.7% versus 14.3% respectively, $P=0.041$; Table 4).

APGAR Score at First Minute
There was no difference between admitted (9 [IQR, 8–10]) and nonadmitted (9 [IQR, 8–10]) women in the nonreveal trial arm ($P=0.938$), but there was a significant difference in the reveal trial arm (9 [IQR, 8–9]) in infants of admitted and (9 [IQR, 8–10]) nonadmitted women ($P=0.000$; Table 4).

Maternal Blood Tests
In the nonreveal group, there was no difference between admitted versus nonadmitted patients for platelets, creatinine, ALT (alanine aminotransferase), and uric acid at time of delivery. In contrast, in the reveal group, there were significantly higher levels of creatinine, uric acid, and significantly lower levels of platelets between admitted and nonadmitted women (Table 4).

The same pattern was seen when analyzing maternal blood samples at presentation alone or change per day, with no difference between admitted and nonadmitted in nonreveal trial arm and a significant difference in the reveal trial arm (data not shown).

Trial Arm Comparison
Trial arm comparison revealed significant differences in the segregation of at-risk patients (admitted versus nonadmitted). This showed that use of the ratio was significantly more effective at discriminating and directing admission of patients at risk of preeclampsia within 7 days, lower birth weight, lower APGAR scores, SGA babies, and worse maternal biochemical profiles, as well as time of delivery compared with standard clinical management (Table 4).

Post Hoc Analyses
Time to Preeclampsia Diagnosis in Both Trial Arms
To assess if knowledge of the ratio would allow us to make the diagnosis of preeclampsia earlier, we assessed the time to preeclampsia diagnosis in both trial arms (Figure 2 and Table S4). The median time to diagnosis in nonreveal was 9.5 days (IQR, 0–32) compared with 7 days (IQR, 0–29)

Table 1. Baseline Characteristics of Trial Participants

Patient Characteristics	Nonreveal Arm (n=184)	Reveal Arm (n=186)	Statistical Significance; P Value
GA at recruitment, week, median (IQR)	34.4 (31.4–35.7)	34.3 (31.3–36.0)	0.903
Maternal age at recruitment, y, median (IQR)	31.1 (26.7–34.7)	30.9 (27.4–35.8)	0.473
BMI, median (IQR)	26.7 (23.1–31.7)	28.3 (24.3–32.4)	0.045
Parity n (%)			0.351
Nulliparous	94 (51.1%)	86 (46.2%)	
Multiparous	90 (48.9%)	100 (53.8%)	
Smoking status n (%)			0.398
Current smoker	16 (8.7%)	17 (9.1%)	
Never smoker	118 (64.1%)	107 (57.5%)	
Previous smoker	50 (27.12%)	62 (33.3%)	
Ethnicity n (%)			0.794
White	166 (90.2%)	166 (89.2%)	
Other	15 (8.2%)	18 (9.7%)	
Not recorded	3 (1.6%)	2 (1.1%)	
Highest systolic BP at presentation, median (IQR)	132 (120–146)	131 (120–148)	0.826
Highest diastolic BP at presentation, median (IQR)	80 (71–92)	84 (70–93)	0.900

$P \leq 0.05$ was considered statistically significant. BMI was calculated as the weight (kilograms) divided by the square of the height (meters); ethnic group was reported by the participants. BMI indicates body mass index; BP, blood pressure; GA, gestational age; and IQR, interquartile range.

in the reveal arm (P=0.6387). The Kaplan-Meier analysis consistently showed a trend towards earlier diagnosis in the reveal arm (Figure 2). Preeclampsia severity and additional maternal adverse outcomes are presented in Tables S5A and S5B.

Sensitivity Specificity, NPV, PPV in Both Trial Arms
In the nonreveal arm, the sensitivity in predicting the development of preeclampsia within 7 days was 83.3% (95% CI, 58.6–96.4) for a specificity of 80.1% (95% CI, 73.2–85.9); this was in contrast to the reveal arm, which resulted in a sensitivity of 100% (95% CI, 85.8–100) for a specificity of 77.8% (95% CI, 70.6–83.9). The sFlt-1/PlGF ratio alone gave a better sensitivity than the nonreveal arm at 95.8% (95% CI, 78.9–99.9). This increased sensitivity was achieved without significant loss of specificity (Figure 3).

The PPV for the development of preeclampsia within 7 days in the nonreveal arm was 31.3% (95% CI, 18.7–46.3) compared with 40% (95% CI, 27.6–53.5) in the reveal arm. The PPV for the ratio alone was 41.1% (95% CI, 28.1–55.0). The NPV for nonreveal was 97.8% (95% CI, 93.7–99.5) reflecting the 3 patients sent home in this arm. The NPV for the

reveal arm was 100% (95% CI, 97.1–100) and for the ratio alone was 99.2% (95% CI, 95.8–100; Figure 3).

Discussion
At present, the identification of those patients with suspected preeclampsia who warrant admission can be challenging, leading to either unnecessary admissions or missed diagnoses. This is mostly because of inappropriate allocation to high-risk and low-risk groups with standard clinical tools. In this pragmatic trial, women presenting with suspected preeclampsia were randomized to management by sFlt-1/PlGF ratio test in conjunction with standard clinical care versus standard clinical care alone to assess the value of this test on clinical management and admission decisions. There was no difference in the overall number of admissions between the 2 arms. However, using the sFlt-1/PlGF ratio permitted a more accurate admission of high-risk patients and discharge of low-risk patients without changing the overall admission rate. This is supported by the admission of 100% of preeclampsia patients. In addition, the admitted women were more likely to have elevated creatinine and urate and lower platelets, whereas their newborns had lower birth weight and

Table 2. Primary Outcome

Admissions for Suspected PE	Trial Arm		Statistics	
	Nonreveal (n=184)	Reveal (n=186)	Risk Ratio (95% CI)	Risk Difference (95% CI)
Within 24 h of the test, n (%)	48 (48/184=26.1%)	60 (60/186=32.3%)	1.24 (0.89 to 1.70)	0.06 (−0.03 to 0.15)
Within 7 days of the test, n (%)	65 (65/184=35%)	70 (70/186=37.6%)	1.06 (0.1 to 1.39)	0.02 (−0.07 to 0.12)
Until delivery, n (%)	134 (134/184=72.8%)	126 (126/186=67%)	0.93 (0.82 to 1.06)	−0.05 (−0.14 to 0.04)

Admissions for suspected PE within 24 h of the test, 1 wk and until delivery. Admissions were calculated as cumulative admissions divided by the total number of patients. PE indicates preeclampsia.

Table 3. Proportion of Preeclampsia Patients Admitted for Nonreveal and Reveal Trial Arms

Admission Status	PE Within 7 Days			PE Until Delivery		
	Nonreveal; n=18	Reveal; n=24	Statistics	Nonreveal; n=38	Reveal; n=47	Statistics
Admitted	15	24	…	20	31	…
Nonadmitted	3	0	…	18	16	…
Admitted proportion	(15/18) 83%	(24/24) 100%	P=0.038	(20/38) 52.6%	(31/47) 65.9%	P=0.242

PE indicates preeclampsia.

APGAR scores higher SCBU admission rates: all indicators of a higher risk group.

We hypothesized that use of the sFlt-1/PlGF ratio would reduce overall hospitalization—a proxy for a clinical concern that the patient would develop preeclampsia or preeclampsia-related problems; however, this was not found. Nevertheless, use of the test increased the proportion of high-risk patients admitted, without influencing the admission rate. The clearest example is in the correct identification of women with preeclampsia in the reveal arm where use of the ratio in combination with standard clinical management identified 100% of the patients, whereas standard clinical management (nonreveal), by the same clinical team, identified 83%. This translated to 3 patients being sent home who subsequently developed preeclampsia, and, therefore, remained at risk of adverse maternal and infant outcomes.[17,18]

In addition to preeclampsia, the use of the test allowed us to identify women at higher risk of other adverse outcomes,

Table 4. Secondary Outcomes of Reveal and Nonreveal Trial Arms

Outcomes	Nonreveal Trial Arm				Reveal Trial Arm				P Value (*-† vs ‡-§)
	Total; n=184	Admitted*; n=48	Nonadmitted†; n=136	P Value; Admitted vs Nonadmitted (*-†)	Total; n=186	Admitted‡; n=60	Nonadmitted§; n=126	P Value; Admitted vs Nonadmitted (‡-§)	
PE within 7 d	18/184 (9.7%)	15/48 (34.8%)	3/136 (2.2%)	0.000	24/186 (12.9%)	24/60 (40%)	0/126 (0%)	0.000	0.000
Total PE	38/184 (20.6%)	20/48 (41.6%)	18/136 (13.2%)	0.000	47/186 (25.2%)	31/60 (51.6%)	16/126 (12.6%)	0.000	0.000
Birthweight, median (IQR)	3268 (2723–3700)	3070 (2408–3455)	3305 (2820–3753)	0.008	3235 (2780–3685)	2818 (2363–3203)	3433 (3045 3780)	0.000	0.000
APGAR first minute, median (IQR)	9 (8–10)	9 (8–10)[1]	9 (8–10)	0.938	0 (8–10)	9 (8–9)[2]	9 (8–10)[3]	0.000	0.001
SCBU admissions, n (%)	28/184 (15.2%)	8/48 (16.7%)	20/136 (14.7%)	0.745	34/186 (18.3%)	16/60 (26.7%)	18/126 (14.3%)	0.041	0.081
SGA, n (%)	31/184 (16.8%)	11/48 (22.9%)	20/136 (14.7%)	0.191	31/186 (16.7%)	16/60 (26.7%)	15/126 (11.9%)	0.012	0.007
Maternal Cr, median (IQR; at delivery)	58 (49–68)	57 (49–66)[4]	58 (49–70)[5]	0.689	58.5 (51–67)	62 (54–72)[6]	57 (48–63)[7]	0.002	0.030
Maternal urates median (IQR; at delivery)	349.5 (303–409)	374 (311.5–433)[8]	345 (294.5–401.5)[9]	0.209	348 (277–426)	393 (316–453)[10]	315 (265–393)[11]	0.002	0.003
Maternal Alt, median (IQR; at delivery)	14.5 (10–27)	16 (11–29)[12]	14 (10–24)[13]	0.525	15 (11–27)	17 (12–33)[14]	14.5 (10.5–23.5)[15]	0.153	0.998
Maternal Plt, median (IQR; at delivery)	219.5 (174–274)	224 (200–273)[16]	214 (173–277)[17]	0.422	220 (192–263)	204 (171–259)[18]	233 (199–269)[19]	0.030	0.360
GA at delivery weeks, median (IQR)	38.1 (37.1–39.3)	37.6 (36.3–38.7)	38.5 (37.4–39.4)	0.000	38.4 (37.3–39.6)	37.2 (36.1–38.2)	39.0 (37.9–39.9)	0.000	0.000

Proportion test, Wilcoxon, and Student t test were performed. Difference between trial arms was calculated using a difference-in-differences statistical test using ANCOVA or logistic regression for categorical variables. $P \leq 0.5$ was considered significant.[1–3] Missing data for 1;2 and 1 patients respectively.[4,7,8,11,12,15,16,19] Missing data for 1 patient.[4–15] Sample deemed not necessary by clinical team for 4;39;1;38;8;53;1;48;4;43;1 and 41 patients, respectively.[17–19] Sample deemed not necessary by clinical team for 13;1 and 14 patients, respectively. Alt indicates alanine aminotransferase; APGAR, Appearance, Pulse, Grimace, Activity, and Respiration; Cr, Creatinine; GA, gestational age; IQR, interquartile range; PE, preeclampsia; Plt, platelets; SCBU, special care baby unit; and SGA, small for gestational age.

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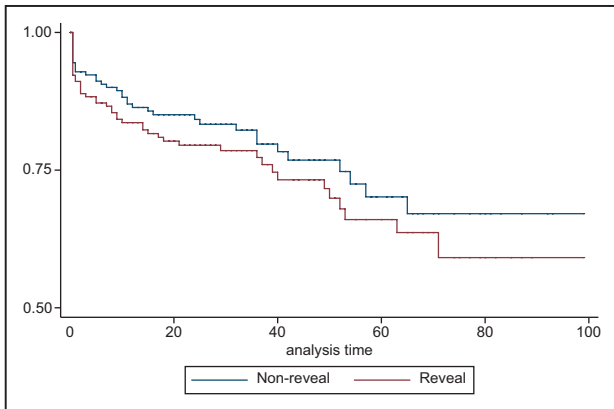
Figure 2. Kaplan-Meier survival estimate for time to preeclampsia development, by trial arm.

including lower birthweight infants, SGA infants, increased SCBU admissions, and lower APGAR scores. This suggests that use of the ratio with clinical practice might have broader clinical utility not only for predicting preeclampsia but also for related adverse outcomes, as has been suggested by observational studies.[11–13] Alongside these impacts, use of the ratio also allowed safe discharge of patients at extremely low risk of preeclampsia. In this study, 126 patients with an initial suspicion of preeclampsia had a ratio ≤38 and were not admitted; of these, none developed preeclampsia within 7 days. In effect, use of the test allowed admission of the right patients.

Post hoc analysis showed a nonsignificant trend towards a more rapid diagnosis of preeclampsia in the reveal arm. This may be of clinical value in that it suggests that the diagnosis is made more quickly with knowledge of the ratio. This may be either because of increased surveillance or admission of high-risk patients and may ultimately have an impact on infant outcomes. Larger independent studies are warranted to confirm or refute this hypothesis.

When comparing the nonreveal trial arm with reveal for admission of women who developed preeclampsia within 7 days, we saw an increase in sensitivity from 83.3% to 100% with similar specificity (80.1% versus 77.8%). The PPV of the reveal arm was 40.0% compared with 31% for the nonreveal arm. The

NPV for the reveal arm was 100% compared with 97.8% for the nonreveal arm (reflecting the 3 patients sent home). When comparing the sensitivity of the ratio alone (95.8% [95% CI, 78.9–99.9]) it outperformed standard practice (nonreveal) but was not as sensitive as the ratio in combination with clinical practice (reveal). Its specificity was comparable (79.5% [95% CI, 72.4–85.5]) with both standard practice and use of the ratio together with standard practice. Its NPV was reassuringly similar (99.2% [95.8–100]) to that reported in previous observational studies.[6] These data suggest use of the ratio together with standard clinical practice provides better performance than either the ratio alone or standard clinical practice alone.

The limitations of this study include the fact that it was confined to a single center, which might limit the generalizability of the findings; it is possible that admission rates differ in other units, although the ability of sFlt-1/PlGF to distinguish women more likely to develop preeclampsia should not be affected by this. The unit is a tertiary referral center; test performance, which included clinical assessment, may differ in a less experienced unit where we hypothesize that use of the ratio would be even more beneficial. It has not escaped our attention that the PPV of the test alone outperformed standard clinical practice. This might be beneficial in resource-poor environments where there is poorer recognition of the disease.[19]

This is the first randomized clinical trial assessing the use of angiogenic biomarkers sFlt-1 and PlGF in women with suspected preeclampsia. It provides real-world evidence for the implementation of sFlt-1/PlGF ratio in clinical practice. We observed no change in admission rates, but the results of this study clearly show that the sFlt-1/PlGF ratio in combination with standard clinical practice both identifies and leads to correct admission of women with increased risks of preeclampsia and worse biochemical profiles, infants with low birth weight, SGA, low APGAR scores, and increased SCBU admission. This ability lends itself to now asking whether the test could be used to mitigate some of these outcomes, including influencing the timing of birth. Larger studies will be needed to elucidate this.

In summary, use of the sFlt-1/PlGF ratio improved clinical precision without affecting admission rates.

Non-reveal (SCM only)	PE in 7 days			Reveal (SCM+ratio)	PE in 7 days			Reveal (ratio only)	PE in 7 days		
admission	Yes	No		admission	Yes	No		ratio	Yes	No	
Yes	15	33	48	Yes	24	36	60	>38 "admission - Yes"	23	33	56
No	3	133	136	No	0	126	126	<38 "admission - No"	1	129	130
	18	166	184		24	162	186		24	162	186

	Non-reveal SCM only	Reveal SCM+ratio	Reveal Ratio only
Sensitivity:	83.3% (58.6-96.4)	100% (85.8-100)	95.8 (78.9 – 99.9)
Specificity:	80.1 (73.2-85.9)	77.8% (70.6-83.9)	79.6 (72.6 – 85.5)
PPV:	31.3% (18.7-46.3)	40.0% (27.6-53.5)	41.1 (28.1 – 55.0)
NPV:	97.8% (93.7-99.5)	100% (97.1-100)	99.2 (95.8 – 100)

Figure 3. Post hoc analysis. Negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity of standard clinical management (SCM) with and without sFlt-1 (soluble fms-like tyrosine kinase 1)/PlGF (placental growth factor) ratio for the prediction of preeclampsia (PE) diagnosis within 7 d.

Perspectives

The management of suspected is clinically complex, principally because of the poor clinical tools currently available. The measurement of angiogenic factors (sFlt-1 and PlGF) has shown significant promise in improving this situation. Here, we present the first clinical trial on the use of sFlt-1/PlGF ratio in patients with suspected preeclampsia and showed that use of the ratio in conjunction with standard clinical practice significantly improves clinical precision without changing admission rates.

Sources of Funding

Disclosures

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Novelty and Significance

What Is New?
- This is the first clinical trial to use sFlt-1 (soluble fms-like tyrosine kinase 1)/PlGF (placental growth factor) test in triage of women with preeclampsia.

What Is Relevant?
- Use of the test allowed the correct triage and hospitalization of patients without changing admission rates.
- Use of the test in conjunction with clinical practice performed better than clinical practice alone.

- There was a trend towards reduction of time to diagnosis of preeclampsia when using the test.

Summary

The first clinical trial on the use of sFlt-1/PlGF ratio in patients with suspected preeclampsia showed that use of the ratio in conjunction with standard clinical practice significantly improves clinical precision without changing admission rates.