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RESEARCH ARTICLE

Adverse pregnancy outcomes in women at increased risk of preterm pre-eclampsia on first-trimester combined screening

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Abstract

Objective: Uteroplacental dysfunction may not only result in pre-eclampsia (PE) but also in preterm birth (PTB), small-for-gestational-age (SGA) birth and stillbirth. The aim of this study is to evaluate the positive predictive value (PPV) of first-trimester combined PE screening for all of these placenta-mediated adverse pregnancy outcomes.

Design: Retrospective cohort study.

Setting: Tertiary referral maternity unit.

Sample: A total of 13 211 singleton pregnancies.

Methods: First-trimester combined screening for preterm PE using the Fetal Medicine Foundation (FMF) algorithm.

Main outcomes measures: Hypertensive disorders of pregnancy (HDP), PTB, SGA birth and stillbirth were combined to assess composite adverse and severe adverse pregnancy outcomes (CAPO and CAPO-S). The PPVs for CAPO and CAPO-S were calculated for women with a combined risk for preterm PE of ≥1 in 50 and ≥1 in 100.

Results: First-trimester combined screening identified 2215 women (16.8%) with a risk of ≥1 in 100 for preterm PE. The PPVs for a risk of ≥1 in 100 for CAPO and CAPO-S were 38.8% and 18.2%, respectively. The equivalent PPVs for a risk of ≥1 in 50 were 45.1% and 21.1%, respectively.

Conclusions: Women identified at high risk of preterm PE are also at increased risk of other placenta-mediated adverse pregnancy outcomes, such as PTB, SGA birth and stillbirth. Women at high risk for preterm PE after first-trimester screening may benefit from a higher surveillance care pathway, with interventions to mitigate all the adverse outcomes associated with placental dysfunction.

KEYWORDS
composite adverse outcomes of pregnancy, first trimester, pre-eclampsia, preterm birth, screening, small for gestational age, stillbirth, uteroplacental dysfunction

1 | INTRODUCTION

Pre-eclampsia (PE) is a severe clinical condition with a globally estimated prevalence of 4.6%,[1] which has remained stable over the decades.[2,3] In contrast, PE-related morbidity and mortality have continued to increase progressively, perhaps as a result of the deteriorating cardiovascular health of the population.[4,5] The latter trend is inevitably compounded by poor risk assessment for PE in early pregnancy, leading to inadequate and ineffective use of aspirin prophylaxis.[6] In 2013, the Fetal Medicine Foundation (FMF) developed an algorithm that provided a means of effective screening for

PE and preterm PE in the first trimester of pregnancy based on maternal demographic characteristics, medical/obstetric history, and biophysical and biochemical markers.[7] The FMF algorithm performed four times better than the risk classification proposed by the UK National Institute for Health and Clinical Excellence (NICE),[8] by doubling the sensitivity and halving the false-positive rate for preterm PE screening.[6]

The efficacy of the FMF screening programme was established by a multicentre, double-blind, placebo-controlled trial that showed a 62% reduction in the incidence of preterm PE in women treated with aspirin, compared with the placebo group.[9] However, it is rarely acknowledged that PE is a cluster of signs and symptoms that are a consequence of uteroplacental dysfunction rather than a distinct disease entity. The disorder of uteroplacental dysfunction is also associated with other adverse pregnancy outcomes, such as preterm birth (PTB),[10,11] small-for-gestational-age (SGA) birth,[12–14] and stillbirth.[15] In keeping with this assertion, both preterm PE and term SGA birth were reduced by 80% and 45%, respectively, with a programme of FMF screening and intervention.[12] The rate of perinatal death in SGA and PE pregnancies was also reduced by 72%, demonstrating the targeted impact of this screening programme on severe adverse fetal outcomes related to uteroplacental dysfunction.[15] More recently, it has been noted that the risk for spontaneous PTB is reduced by about 30% by low-dose aspirin prophylaxis in women with a history of previous PTB.[16] The aim of this study is to evaluate the positive predictive value of first-trimester combined screening for all of these placenta-mediated adverse pregnancy outcomes.

2 | METHODS

The data for this study was collected from March 2018 to May 2022 at St George's University Hospitals NHS Foundation Trust, where the first-trimester combined screening programme for PE, based on the FMF multifactorial algorithm, has been introduced. The algorithm combines maternal factors, mean arterial pressure (MAP) and uterine artery pulsatility index (UtA-PI), measured using a standardised protocol,[17,18] and pregnancy-associated plasma protein-A (PAPP-A) to assess the probability of developing preterm PE. A previous study in this cohort demonstrated that using either placental growth factor (PlGF) or PAPP-A in routine first-trimester combined screening did not make a significant clinical difference to the detection of preterm PE.[19] Women with a probability of ≥1 in 50 were classified as high risk and offered 150 mg prophylactic aspirin as well as serial ultrasound growth scans at 28 and 36 weeks of gestation, and induction of labour from 40 weeks of gestation.[12] Women with a risk of <1 in 50 were managed with routine antenatal care. For all women who attended the unit in this period, maternal demographic, obstetric and medical history data were obtained at the routine ultrasound conducted at 11–13 weeks of gestation and a blood sample was collected for the measurement of maternal PAPP-A. Gestational age was established by measuring crown–rump length and UtA-PI and MAP were measured in the same visit. A total of 15 442 women were assessed in the first trimester for preterm PE risk in the study period. From this cohort, 2231 women (14%) had no outcome records and were excluded from the study: 1591 women (71%) had transferred care and 640 women (29%) were lost to follow-up.

2.1 | Outcome measures

Hypertensive disorders of pregnancy (HDP) was defined by the presence of high blood pressure (BP), i.e. systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, in repeated measurements after 20 weeks of gestation, according to International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines,[20] with or without the development of PE. PTB was defined according to the World Health Organization (WHO) definition as a live birth occurring before 37 completed weeks of pregnancy.[21] SGA was defined as a birthweight on the tenth centile or below according to the international standards developed by Intergrowth-21.[22] Composite of adverse pregnancy outcomes (CAPO) was defined as the presence of any of the interrelated outcomes associated with placental dysfunction, namely HDP, PTB, SGA birth at or below the tenth centile and stillbirth. Severe composite of adverse perinatal outcomes (CAPO-S) was defined as the presence of preterm HDP, PTB at <34 weeks of gestation, SGA infants at or below the fifth centile and stillbirth at <37 weeks of gestation. The outcome data were retrospectively collected from the ultrasound database and maternity birth registry, which undergo systematic clinical governance evaluation. The present study was deemed not to require ethics approval or signed patient consent, in accordance with the Health Research Authority decision tool.

2.2 | Statistical analysis

Descriptive data were represented by median and interquartile range for continuous variables and by number and percentage for categorical variables. In the first-trimester screening programme implemented at St George's, women are considered at high risk when the probability of developing PE according to the FMF algorithm is higher than 1 in 50, with an expected screen-positive rate of approximately 10%.[23] In the present study, another group with a risk cut-off of 1 in 100 was considered. The descriptive statistical metrics of the screening test were computed for each adverse pregnancy outcome and for the CAPO and CAPO-S groups. Receiver operating characteristic (ROC) curve analysis was used to compare the performance of the screening test in detecting each of the adverse outcomes as well as CAPO and CAPO-S with a confidence interval of 95%. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 28.0.1.0; IBM, Armonk, NY, USA).

BJOG An International Journal of Obstetrics and Gynaecology

3 | RESULTS

Data were collected on 13 211 singleton pregnancies between March 2018 and May 2022. The average maternal age was 32 years with a body mass index (BMI) of 24.3 kg/m^2 and a majority of white women (64.5%) (Table 1). The first-trimester combined screening test identified 993 women (7.5%) with a risk of ≥1 in 50 and 2215 women (16.8%) with a risk of ≥1 in 100 for preterm PE.

The ROC analysis showed good prediction for preterm HDP (area under the ROC curve, AUC = 0.88) and overall HDP (AUC = 0.78) (Figures S2 and S3; Tables 2 and 3). The prediction for composite adverse pregnancy outcome (CAPO; AUC = 0.66) and severe composite adverse pregnancy outcome (CAPO-S; AUC = 0.65) was classified as moderate. These AUC values translated to a sensitivity for preterm HDP, stillbirth and CAPO-S of 75%, 39% and 32%, respectively, in women with a risk of ≥1 in 100 for preterm PE on first-trimester FMF combined screening (Table 4).

The positive predictive values of combined first-trimester screening for adverse pregnancy outcomes are presented in Figures 1 and S1, Tables 2 and 3 and supplementary Tables S1-S4. In women with a risk of ≥1 in 100 and a risk of ≥1 in 50, the risks of developing CAPO were 38.8% and 45.1%, respectively, and the risks of developing CAPO-S were 18.2% and 21.1%, respectively.

TABLE 1 Maternal demographics and pregnancy characteristics of the study cohort (n = 13 211).

Characteristics	Median (IQR) or number (%)
Maternal age (years)	32.0 (35.0–29.0)
Weight (kg)	66.0 (75.9–58.9)
Height (cm)	164.0 (169.0–160.0)
BMI (kg/m^2)	24.3 (28.0–21.8)
Ethnicity	
White	8514 (64.5%)
Asian	2580 (19.5%)
Black	1534 (11.6%)
Mixed	583 (4.4%)
Parity	
Nulliparous	6484 (49.1%)
Multiparous	6727 (50.9%)
Alcohol use	505 (3.8%)
Current smoker	521 (3.9%)
Conception by ART	519 (3.9%)
Diabetes	142 (1.1%)
Chronic hypertension	111 (0.8%)
Previous FGR	493 (3.7%)
Previous PE	337 (2.6%)

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; FGR, fetal growth restriction; IQR, interquartile range; PE, pre-eclampsia; SGA, small for gestational age.

TABLE 2 PPV, 100-NPV, OR and AUC values from ROC analysis for individual adverse pregnancy outcomes and CAPO in women classified as being at high risk for preterm pre-eclampsia after first-trimester combined screening.

		Risk of ≥1 in 50			Risk of ≥1 in 100		
	AUC (95% CI)	PPV (95% CI)	100-NPV (95% CI)	OR (95% CI)	PPV (95% CI)	100-NPV (95% CI)	OR (95% CI)
HDP	0.78 (0.77–0.79)	24.2% (22.0%–26.5%)	3.5% (3.3%–3.7%)	8.8 (7.4–10.4)	16.7% (15.6%–17.8%)	2.7% (2.5%–3.0%)	7.1 (6.1–8.4)
PTB < 37 weeks of gestation	0.63 (0.62–0.64)	12.3% (10.5%–14.3%)	4.4% (4.2%–4.5%)	3.1 (2.5–3.8)	9.3% (8.4%–10.4%)	4.1% (4.9%–4.3%)	2.4 (2.0–2.9)
SGA < 10th centile	0.63 (0.62–0.63)	25.6% (23.1–28.2%)	12.7% (12.5%–12.9%)	2.4 (2.0–2.7)	23.4% (21.9%–24.9%)	11.7% (11.4%–12.1%)	2.3 (2.1–2.6)
Stillbirth	0.66 (0.66–0.67)	1.8% (1.2%–2.7%)	0.4% (0.3%–0.5%)	4.6 (2.7–7.9)	1.2% (0.9%–1.6%)	0.4% (0.3%–0.4%)	3.2 (1.9–5.2)
CAPO	0.66 (0.65–0.67)	45.1% (42.2%–48.0%)	18.4% (18.1%–18.6%)	3.7 (3.2–4.2)	38.8% (37.2%–40.6%)	16.7% (16.3%–17.1%)	3.2 (2.9–3.5)

Abbreviations: AUC, area under the curve; CAPO, composite of adverse pregnancy outcomes; CI, confidence interval; HDP, hypertensive disorders of pregnancy; NPV, negative predictive values; OR, odds ratio; PPV, positive predictive values; PTB, preterm birth; ROC, receiver operating characteristic; SGA, small for gestational age.

TABLE 3 PPV, 100-NPV, OR and AUC values from ROC analysis for individual severe adverse pregnancy outcomes and CAPO-S in women classified as being at high risk for preterm pre-eclampsia after first-trimester combined screening.

		Risk of ≥1 in 50			Risk of ≥1 in 100		
	AUC (95% CI)	PPV (95% CI)	100-NPV (95% CI)	OR (95% CI)	PPV (95% CI)	100-NPV (95% CI)	OR (95% CI)
HDP < 37 weeks	0.89 (0.88–0.89)	5.4% (4.6%–6.4%)	0.3% (0.2%–0.4%)	20.6 (13.4–31.8)	3.0% (2.6%–3.4%)	0.2% (0.1%–0.3%)	15.3 (9.4–24.9)
PTB < 34 weeks	0.63 (0.62–0.64)	3.3% (2.4%–4.5%)	1.3% (1.2%–1.4%)	2.6 (1.8–3.8)	2.9% (2.4%–3.5%)	1.2% (1.1%–1.3)	2.5 (1.9–3.4)
SGA < 5th	0.64 (0.63–0.65)	17.5% (15.4%–19.8%)	7.4% (7.2%–7.5%)	2.7 (2.2–3.2)	15.2% (14.0%–16.5%)	6.7% (6.4%–7.0%)	2.5 (2.2–2.9)
Stillbirth < 37 weeks	0.66 (0.65–0.67)	1.5% (1.0%–2.3%)	0.3% (0.3%–0.4%)	4.9 (2.7–9.0)	0.9% (0.7%–1.3%)	0.3% (0.2%–0.4%)	3.3 (1.9–5.7)
CAPO-S	0.65 (0.64–0.65)	21.1% (18.9%–23.6%)	8.5% (8.2%–8.7%)	2.9 (2.4–3.4)	18.1% (16.8%–19.5%)	7.7% (7.5%–8.0%)	3.2 (2.9–3.5)

Abbreviations: AUC, area under the curve; CAPO, composite of adverse pregnancy outcomes; CI, confidence interval; HDP, hypertensive disorders of pregnancy; NPV, negative predictive values; OR, odds ratio; PPV, positive predictive values; PTB, preterm birth; ROC, receiver operating characteristic; SGA, small for gestational age.

4 | DISCUSSION

Women assessed at high risk of preterm PE are also at increased risk of other placenta-mediated adverse pregnancy outcomes, such as PTB, SGA birth and stillbirth. Specifically, almost half of the women with a risk of ≥1 in 50 for preterm PE will develop at least one of these adverse pregnancy outcomes. Women identified as being at high risk for preterm PE by first-trimester combined screening may benefit from a modified care pathway, with increased surveillance and specific interventions to mitigate the adverse outcomes associated with uteroplacental dysfunction as well as low-dose aspirin prophylaxis.

4.1 | Comparison of study findings with existing literature

At a risk of ≥1 in 100, the combined first-trimester screening test detected the majority of preterm (75%) and term (55%) HDP in the study cohort. This finding is consistent with previous studies, which demonstrated that the sensitivity of the FMF algorithm was 75% for preterm PE and 41% for term PE.[24] Similarly, the observed sensitivities for SGA births below the tenth and fifth centiles were 29% and 31%, respectively. These detection rates are comparable with those reported by the FMF for SGA births below the tenth centile (26%) and SGA births below the fifth centile (32%).[25] In a study of 80 000 pregnancies, Mastrodima et al. developed a specific first-trimester prediction model for stillbirth with a 40% detection rate,[26] similar to the finding of a 39% sensitivity in the current study using a PE screening model. These findings confirm that the FMF algorithm was implemented effectively and performed as expected in this cohort.

Most previous studies have not reported the positive predictive values (PPVs) for composite adverse pregnancy outcomes, except for one.[27] Boutin et al. undertook combined first-trimester PE screening using the FMF algorithm in a smaller study of 4575 women and showed a PPV of 30% for CAPO and 8.1% for CAPO-S at a screen-positive rate of 16%. Boutin et al. included only nulliparous women in their study and the vast majority (95%) of their population were white. Furthermore, the authors excluded all women who had ingested aspirin at any time in the pregnancy, irrespective of the reason for administration, to minimise treatment paradox. These restrictions limit the prevalence of adverse pregnancy outcomes in the former study and would have led to an underestimate of the PPV for CAPO. In the current study, the PPVs for CAPO and CAPO-S were considerably higher, 39% and 18%, respectively, at a similar screen-positive rate of 17%. A similar study from Rolnik et al.[28] reported significantly improved pregnancy outcomes in a cohort screened using the FMF algorithm compared with those receiving usual care. In particular, women with an estimated combined risk of preterm PE of ≥1 in 100 in the first trimester showed higher rates of adverse outcomes compared with the non-screened population, and the opposite trend was noted in women classified as being at low risk. These findings demonstrate

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TABLE 4 Number and sensitivity for adverse pregnancy outcomes in the study cohort of 13 211 women screened with the FMF combined algorithm with different risk stratification.

Adverse pregnancy outcomes	Number of adverse outcomes in women with risk of ≥1 in 50	Sensitivity of risk of ≥1 in 50 (95% CI)	Number of adverse outcomes in women with risk of ≥1 in 100	Sensitivity of risk of ≥1 in 100 (95% CI)
HDP ($n = 669$)	240	35.9% (32.2%–39.6%)	369	55.2% (51.3%–59.0%)
HDP < 37 weeks of gestation ($n = 88$)	54	61.4% (50.4%–71.6%)	66	75.0% (64.6%–83.6%)
PTB ($n = 658$)	122	18.5% (15.6%–21.7%)	207	31.5% (27.9%–35.2%)
PTB < 34 weeks of gestation ($n = 193$)	33	17.1% (12.1%–23.2%)	64	33.2% (26.6%–40.3%)
SGA < 10th centile ($n = 1810$)	254	14.0% (12.5%–15.7%)	518	28.6% (26.5%–30.8%)
SGA < 5th centile ($n = 1074$)	174	16.2% (14.6%–18.5%)	337	31.4% (28.6%–34.3%)
Stillbirth ($n = 67$)	18	26.9% (16.8%–39.1%)	26	38.8% (27.1%–51.5%)
Stillbirth < 37 weeks of gestation ($n = 53$)	15	28.3% (16.8%–42.4%)	21	39.6% (26.5%–54.0%)
CAPO ($n = 2695$)	448	16.6% (15.2%–18.1%)	860	31.9% (30.2%–33.7%)
CAPO-S ($n = 1252$)	210	16.8% (14.7%–19.0%)	402	32.1% (29.5%–34.8%)

Note: The number and sensitivity for these outcomes in women screened using the FMF first-trimester combined algorithm with a risk of ≥1 in 50 and ≥1 in 100 are shown.
Abbreviations: AUC, area under the curve; CAPO, composite of adverse pregnancy outcomes; CI, confidence interval; HDP, hypertensive disorders of pregnancy; NPV, negative predictive values; OR, odds ratio; PPV, positive predictive values; PTB, preterm birth; ROC, receiver operating characteristic; SGA, small for gestational age.

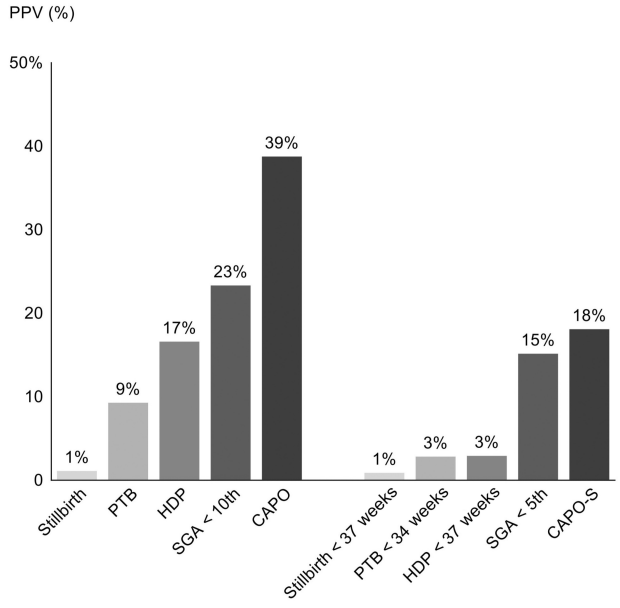

FIGURE 1 Positive predictive values (PPVs) for individual adverse pregnancy outcomes and a composite of adverse pregnancy outcomes (CAPO and CAPO-S) in women with a risk of ≥1 in 100 ($n = 2215$) for preterm pre-eclampsia after first-trimester combined screening. CAPO, composite of adverse pregnancy outcomes; CAPO-S, composite of severe adverse pregnancy outcomes; HDP, hypertensive disorders of pregnancy; PTB, preterm birth; SGA, small for gestational age.

clinically significant PPVs for serious adverse pregnancy outcomes when FMF first-trimester combined screening for preterm pre-eclampsia is used in an unselected population.

4.2 | Interpretation and biological plausibility of the study findings

The findings of this study confirm that pregnancies considered at high risk of developing PE also have an increased risk of being complicated by PTB, SGA birth and stillbirth, which are secondary to uteroplacental dysfunction. SGA birth may also occur secondary to congenital viral infection, chromosomal abnormalities or small maternal stature, whereas stillbirth can be caused by severe fetal abnormality or aneuploidy. However, the majority of fetal growth restriction leading to avoidable stillbirths are considered to be a consequence of uteroplacental dysfunction.[29,30] Iatrogenic PTB may be undertaken for PE or fetal growth restriction, whereas spontaneous PTB is typically related to infection, uterine overdistention or cervical weakness. Although less well acknowledged, uteroplacental malperfusion has also been proposed as one of the possible biological mechanisms resulting in spontaneous PTB.[31–33] Indeed, consistent with this assertion, a recent meta-analysis demonstrated that among women with a previous preterm birth, low-dose aspirin use was associated with a reduced risk for spontaneous preterm birth in a subsequent pregnancy.[16] The findings of this study indicate that a substantial proportion of PTB, SGA birth and stillbirth occur in women assessed to be at high risk of preterm PE. This is consistent with a common placenta-mediated aetiology for these adverse pregnancy outcomes.

4.3 | Strengths and limitations

This study includes data collected over a 5-year period from a large population of women in a public healthcare setting, where first-trimester screening for preterm PE is performed by clinical staff providing routine clinical care rather than specialists or research staff. The main limitation of the study is that the use of aspirin in high-risk pregnancy specifically reduces the overall incidence of preterm PE.[9] As a consequence, screening leading to aspirin prophylaxis in women at high risk might have led to an underestimation of the PPV for CAPO and CAPO-S. Furthermore, the screening

algorithm used was validated for detecting women at high risk of preterm PE. Further development of this algorithm to include other placenta-mediated adverse outcomes of pregnancy is warranted, as this is likely to perform better in detecting PTB, SGA birth and stillbirth.

4.4 | Clinical and research implications

In many clinical settings, women at risk for adverse pregnancy outcomes are identified using a checklist-based system, which has been demonstrated to be less effective than the first-trimester FMF screening algorithm. The UK National Screening Committee (NSC) has reviewed the evidence from the FMF screening programme and found that that there may be sufficient evidence to support screening for pre-term PE.[34] The data from this cohort demonstrate that it is possible to implement effective combined first-trimester screening in a routine healthcare setting and that screen-positive women are at high risk of adverse pregnancy outcomes other than preterm PE alone. The FMF algorithm produces a numerical risk assessment that may be used to allocate women to personalised care pathways. Based on the draft NSC recommendations, this care pathway should only include low-dose aspirin prophylaxis to women considered at high risk of preterm PE. The findings of this study suggest that this group of women may also benefit from serial fetal growth and well-being assessments, the avoidance of prolonged pregnancy, to minimise the risk of stillbirth, and possibly be considered for interventions to avoid PTB.[6,9,25,35]

Despite the increased prevalence of PTB, SGA birth and stillbirth in women at high risk of preterm PE, most of these adverse pregnancy outcomes occurred in women considered at low risk for preterm PE. The area under the curves in the ROC analysis show that the sensitivity and specificity of the test for CAPO and CAPO-S are unlikely to fulfil the WHO criteria for screening.[36] To date, researchers have attempted to develop screening algorithms for PE, SGA and stillbirth whilst considering them to be distinct diseases. Given that the majority of these adverse pregnancy outcomes have a common aetiology, the development of prediction algorithms might be improved by using CAPO and/or CAPO-S as the outcomes of interest, rather than PE alone. Furthermore, screening tests for PE, SGA birth and stillbirth are significantly influenced by intervention biases – namely elective or spontaneous birth will prevent PE or stillbirth from occurring in the following weeks (also called treatment paradox). In order to mitigate these problems, future research should adopt a competing risk approach to overcome intervention bias in addition to targeting composite adverse pregnancy outcomes as reflective of underlying uteroplacental dysfunction.

5 | CONCLUSION

The FMF algorithm provides a validated screening test to identify women at high risk for developing preterm PE, who are most likely to benefit from low-dose aspirin prophylaxis in pregnancy. The same cohort of women are also at high risk of developing other adverse pregnancy outcomes related to uteroplacental dysfunction. This group of women should be considered for increased fetal growth and well-being surveillance as well as for interventions to mitigate the risks of preterm birth and stillbirth.

AUTHOR CONTRIBUTIONS

Conceptualisation: BT. Methodology: BT and AF. Data collection and processing: MM, LN, AM and MM. Statistical analysis: MM and LN. Data interpretation: MM, LN and BT. First draft of article: MM and LN. Review and editing of article: BT, AF, MM and AM.

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FUNDING INFORMATIONS

None.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS APPROVAL

This retrospective study of routinely collected clinical data were collated from a current continuous audit and was deemed not to require ethics approval or signed patient consent, in accordance with the Health Research Authority decision tool.

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SUPPORTING INFORMATION

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

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