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RESEARCH ARTICLE

First-trimester prediction of preterm pre-eclampsia and prophylaxis by aspirin: Effect on spontaneous and iatrogenic preterm birth

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Abstract

Objective: To report the predictive performance for preterm birth (PTB) of the Fetal Medicine Foundation (FMF) triple test and National Institute for health and Care Excellence (NICE) guidelines used to screen for pre-eclampsia and examine the impact of aspirin in the prevention of PTB.

Design: Secondary analysis of data from the SPREE study and the ASPRE trial.

Setting: Multicentre studies.

Population: In SPREE, women with singleton pregnancies had screening for preterm pre-eclampsia at 11–13 weeks of gestation by the FMF method and NICE guidelines. There were 16 451 pregnancies that resulted in delivery at ≥24 weeks of gestation and these data were used to derive the predictive performance for PTB of the two methods of screening. The results from the ASPRE trial were used to examine the effect of aspirin in the prevention of PTB in the population from SPREE.

Methods: Comparison of performance of FMF method and NICE guidelines for pre-eclampsia in the prediction of PTB and use of aspirin in prevention of PTB.

Main outcome measure: Spontaneous PTB (sPTB), iatrogenic PTB for pre-eclampsia (iPTB-PE) and iatrogenic PTB for reasons other than pre-eclampsia (iPTB-noPE).

Results: Estimated incidence rates of sPTB, iPTB-PE and iPTB-noPE were 3.4%, 0.8% and 1.6%, respectively. The corresponding detection rates were 17%, 82% and 25% for the triple test and 12%, 39% and 19% for NICE guidelines, using the same overall screen positive rate of 10.2%. The estimated proportions prevented by aspirin were 14%, 65% and 0%, respectively.

Conclusion: Prediction of sPTB and iPTB-noPE by the triple test was poor and poorer by the NICE guidelines. Neither sPTB nor iPTB-noPE was reduced substantially by aspirin.

KEYWORDS
aspirin, ASPRE trial, competing risks model, mean arterial pressure, NICE guidelines, placental growth factor, pre-eclampsia, preterm birth, SPREE study, uterine artery Doppler

1 | INTRODUCTION

Pre-eclampsia, which affects about 5% of singleton pregnancies, is a major cause of maternal and perinatal mortality and morbidity and it is associated with increased long-term cardiovascular risk for both the mother and the child.[1] Reduction in the incidence of preterm pre-eclampsia can be achieved by the prophylactic use of aspirin (150 mg per day from 12 to 36 weeks of gestation) in women identified by screening as being at high risk for the disease.[2] The traditional approach to screening, as recommended by the National Institute of Health and Care Excellence (NICE) is based on risk scoring; women are considered to be at high risk if they have one major risk factor (chronic hypertension, diabetes mellitus, chronic renal disease, autoimmune disease or history of previous pre-eclampsia)

or two of moderate risk factors (age ≥40 years, body mass index ≥35 kg/m^2, family history of pre-eclampsia, first pregnancy, inter-pregnancy interval >10 years).[3] An alternative method of screening for pre-eclampsia, proposed by the Fetal Medicine Foundation (FMF) is based on the competing risks model, which combines maternal demographic characteristics and elements from the medical history together with measurements of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and placental growth factor (PlGF) to calculate the individual patient-related risk for pre-eclampsia (triple test).[4–7]

A screening programme for pre-eclampsia (SPREE) study, compared the predictive performance of the competing risks model for preterm pre-eclampsia to that of the method recommended by the NICE guidelines.[8] In a total of 16 747 singleton pregnancies, including 142 (0.8%) who developed preterm pre-eclampsia, the detection rate (DR) of preterm pre-eclampsia, at a 10% screen positive rate, was 82% by the triple test and 41% by the NICE guidelines.[8]

There is some contradictory evidence as to whether women at high risk of developing pre-eclampsia are also at increased risk of spontaneous (s) and iatrogenic (i) preterm birth (PTB) for reasons other than pre-eclampsia and whether the incidence of these conditions is also reduced by prophylactic use of aspirin.[9–13] The objectives of this study are: first, to compare the predictive performance of the FMF triple test and NICE guidelines for sPTB and iPTB, and second, to examine the impact of prophylactic use of aspirin in the prevention of these pregnancy complications.

2 | METHODS

2.1 | Study design and participants

This is a secondary analysis of data from the previously reported SPREE study and the Aspirin for evidence-based pre-eclampsia prevention (ASPRE) trial.[2,8] In both studies, eligible women with singleton pregnancies attending for their routine hospital visit at 11^{+0}–13^{+6} weeks of gestation had first-trimester screening for preterm pre-eclampsia. Gestational age was determined from the measurement of the fetal crown–rump length.[14]

SPREE was a multicentre cohort study in 16 747 women carried out in seven National Health Service (NHS) maternity hospitals in England, between April and December 2016.[8] This study was specifically designed to examine the performance of screening by the FMF competing risks model[5] in comparison with that of the method advocated by NICE[3]; the results from screening by the competing risks model were not made available to the patients or their obstetricians. In this study, we included 16 451 pregnancies that resulted in delivery at ≥24 weeks of gestation. ASPRE was carried out between April 2014 and April 2016 in 13 maternity hospitals in England, Spain, Italy, Belgium, Greece and Israel.[2] In this study 26 941 women with singleton pregnancies had screening by the FMF competing risks model[5] and 1776 women identified as being at high risk of preterm pre-eclampsia, were randomly assigned to receive aspirin, at a dose of 150 mg per day, or placebo from 11 to 14 weeks of gestation until 36 weeks.[2]

Inclusion criteria for both studies were: age ≥ 18 years, singleton pregnancy and live fetus at the 11- to 13-week scan; exclusion criteria were: women who were unconscious or severely ill, those with learning difficulties or serious mental illness, and pregnancies with a major fetal abnormality identified at the 11- to 13-week scan. For the current study, we included women delivering a liveborn or stillborn fetus at ≥24 weeks of gestation and excluded pregnancies ending in termination, miscarriage or fetal death before 24 weeks.

In both SPREE and ASPRE, the visit at 11^{+0}–13^{+6} weeks of gestation included first, recording of maternal characteristics and medical history and measurement of maternal weight and height,[4] second, measurement of MAP by validated automated devices and standardised protocol,[15] third, measurement of the left and right UtA-PI by transabdominal colour Doppler ultrasound and calculation of the mean PI,[16] and fourth, measurement of serum concentration of PlGF (DELFIA Xpress system, Revvity or BRAHMS KRYPTOR analyser, Thermo Fisher Scientific). The measurements of MAP were carried out by healthcare assistants or sonographers who had received specific training for this purpose and measurements of UtA-PI were performed by doctors or sonographers who had obtained the Fetal Medicine Foundation Certificate of Competence in Doppler ultrasound. In both studies, quality control was applied on a monthly basis to achieve consistency of measurement of biomarkers across different hospitals throughout the duration of the study. The distribution of measurements of MAP and UtA-PI were reported to the coordinator who provided feedback and, if necessary, retraining of the personnel with large deviations from the expected values. Similarly, the laboratories were provided with diagnostics for PlGF measurements so that appropriate corrective actions could be undertaken. For both SPREE and ASPRE, quality control of screening and verification of adherence to protocol were performed by the University College London Comprehensive Clinical Trials Unit.

2.2 | Outcome measures

Outcome measures were first, sPTB at <37 and <32 weeks of gestation in the presence or absence of pre-eclampsia, second, iPTB at <37 and <32 weeks of gestation in the presence or absence of pre-eclampsia, third, iPTB at <37 and <32 weeks of gestation in the presence of pre-eclampsia, and fourth, iPTB at <37 and <32 weeks of gestation in the absence of pre-eclampsia. Pre-eclampsia was defined by the 2019 American

College of Obstetricians and Gynecologists criteria: chronic or gestational hypertension, with development of one or more of the following: new-onset proteinuria, serum creatinine >97 μmol/L in the absence of underlying renal disease, serum transaminases more than twice normal level (≥65 IU/L for our laboratory), platelet count <100 000/μL, headache or visual symptoms, or pulmonary oedema.[17] Chronic hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, at least twice, 4 h apart) was documented before pregnancy or at <20 weeks of gestation.[18] Gestational hypertension was new-onset hypertension at ≥20 weeks of gestation in a previously normotensive woman.[17]

Data on pregnancy outcome were collected from participants' hospital maternity records or those of their general medical practitioners. The maternity records of all women with chronic or gestational hypertension were examined to determine the diagnosis of pre-eclampsia and gestational hypertension.

2.3 | Statistical analysis

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

The data from SPREE were used to estimate the proportion of pregnancies delivering at <37 and <32 weeks of gestation (spontaneous delivery or iatrogenic delivery with and without pre-eclampsia) and to determine the predictive performance for these outcomes in the group of women who were screen positive by NICE guidelines and in those who were screen positive with the FMF triple test. In the study population, 1682 (10.2%) women were screen positive by NICE. The same screen positive rate of 10.2% was achieved with the FMF triple test at a risk cutoff of 1 in 80.

The data from the ASPRE trial[2] from pregnancies delivering at ≥24 weeks of gestation were then used to estimate the effect of aspirin, as a relative risk (aspirin/no aspirin), on the incidence of sPTB and iPTB (with and without pre-eclampsia) in subgroups according to gestational age at birth (<37 and <32 weeks). The effect of aspirin was quantified as reduction in each outcome.

To account for uncertainty in estimation, we adopted a Bayesian approach. We assumed conjugate beta priors for incidence, detection rate and aspirin effect and binomial likelihoods for data on the number of cases without screening and treatment and the number of cases after screening by either the FMF triple test of NICE guidelines, and treatment with aspirin. We assumed a constant 85% compliance. Within this framework, we simulated 10 000 hypothetical populations, each consisting of 100 000 women and summarised our results by mean and 95% credibility intervals.

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

3 | RESULTS

3.1 | Study participants

In the cohort of 16 451 women who participated in SPREE,[8] there were 555 (3.37%) with sPTB at <37 weeks of gestation, 395 (2.40%) with iPTB, and 15 501 (94.22%) with delivery at ≥37 weeks of gestation.

Table 1 summarises maternal and pregnancy characteristics in the total SPREE population and in subgroups with sPTB, iPTB, iPTB with pre-eclampsia, and iPTB without pre-eclampsia. In the iPTB group versus the sPTB group the median maternal weight and body mass index were higher, and there was a higher incidence of Black women, those with chronic hypertension, and parous women with previous pre-eclampsia. Similarly, in the iPTB group with pre-eclampsia versus the iPTB group without pre-eclampsia, the median maternal weight and body mass index were higher, and there was a higher incidence of women of Black, South Asian, East Asian and mixed ethnicity, those with chronic hypertension and parous women with previous pre-eclampsia.

The indications of iPTB are summarised in Table 2. The three commonest indications for iPTB at <37 weeks were pre-eclampsia, fetal growth restriction and suspected fetal compromise and the commonest indications for iPTB at <32 weeks were pre-eclampsia, stillbirth and fetal growth restriction.

The cumulative incidence sPTB and iPTB with and without pre-eclampsia in the ASPRE data is shown in Figure 1. The incidence was reduced by aspirin only in the iPTB group with pre-eclampsia.

3.2 | Incidence of PTB in SPREE and prediction by the FMF triple test and NICE guidelines

Table 3 summarises the incidence of PTB in the SPREE population and the DR of PTB in screening for pre-eclampsia by the FMF triple test and NICE guidelines. The incidence of sPTB at <37 weeks of gestation was 3.37%. For the same overall screen positive rate of 10.2%, the DR for the FMF triple test and NICE were 16.9% and 11.5%, respectively. The incidence of iPTB at <37 weeks of gestation was 2.40%. For the same overall screen positive rate of 10.2%, the DR for the FMF triple test and NICE were 44.3% and 25.8%, respectively; the performance of screening for iPTB with pre-eclampsia was superior (DR by triple test 82.2% and by NICE 39.3%) and poorer for iPTB without pre-eclampsia (DR by triple test 24.6% and by NICE 14.3%). A similar pattern of findings was observed for spontaneous and iatrogenic PTB at <32 weeks of gestation.

TABLE 1 Maternal and pregnancy characteristics in the total SPREE[8] population and in subgroups with sPTB, iPTB, iPTB with no pre-eclampsia, and iPTB with pre-eclampsia.

Characteristics	All data ($n = 16\,451$)	sPTB ($n = 555$)	iPTB ($n = 395$)	iPTB, no PE ($n = 260$)	iPTB, with PE ($n = 135$)
Maternal age (years)	31.5 (27.4–35.1)	31.4 (27.6–35.35)	31.6 (26.2–35.7)	31.0 (25.3–35.2)	32.6 (27.25–36.45)
Maternal weight (kg)	67.0 (59.2–78.0)	66.1 (58.1–79.75)	71.0 (60.0–84.0)	67.1 (58.1–81.5)	78.0 (65.6–87.5)
Maternal height (cm)	165 (160–169)	164 (159–168)	164 (158–168)	164 (158–168)	165 (159–168)
Body mass index (kg/m^2)	24.7 (22.0–28.7)	24.8 (21.8–29.6)	26.3 (22.5–31.6)	24.6 (21.9–30.8)	28.4 (24.5–33.8)
Gestational age (weeks)	90.0 (87.0–93.0)	89.0 (87.0–93.0)	89.0 (86.0–92.0)	89.0 (86.8–92.0)	88.0 (86.0–92.0)
Ethnicity					
White	11 922 (72.5)	388 (69.9)	255 (64.6)	178 (68.5)	43 (31.9)
Black	2337 (14.2)	86 (15.5)	83 (21.0)	40 (15.4)	43 (31.9)
South Asian	1361 (8.3)	50 (9.0)	48 (12.2)	35 (13.5)	77 (57.0)
East Asian	407 (2.5)	14 (2.5)	4 (1.0)	2 (0.8)	2 (1.5)
Mixed	424 (2.6)	17 (3.1)	5 (1.3)	5 (1.9)	13 (9.6)
Medical history					
Chronic hypertension	137 (0.8)	5 (0.9)	28 (7.1)	6 (2.3)	22 (16.3)
Diabetes mellitus type 1	46 (0.3)	6 (1.1)	8 (2.0)	6 (2.3)	2 (1.5)
Diabetes mellitus type 2	71 (0.4)	8 (1.4)	12 (3.0)	9 (3.5)	3 (2.2)
SLE/APS	39 (0.2)	1 (0.2)	2 (0.5)	1 (0.4)	1 (0.7)
Smoker	1105 (6.7)	67 (12.1)	34 (8.6)	32 (12.3)	2 (1.5)
Family history of PE	535 (3.3)	16 (2.9)	15 (3.8)	10 (3.9)	5 (3.7)
Method of conception					
Spontaneous	15 765 (95.8)	523 (94.2)	371 (93.9)	244 (93.9)	127 (94.1)
In vitro fertilisation	561 (3.4)	28 (5.1)	22 (5.6)	14 (5.4)	8 (5.9)
Ovulation drugs	125 (0.8)	4 (0.7)	2 (0.5)	2 (0.8)	0 (0.0)
Parity					
Nulliparous	7587 (46.1)	255 (46.0)	177 (44.8)	105 (40.4)	72 (53.3)
Parous, no previous PE	8483 (51.6)	285 (51.4)	182 (46.1)	141 (54.2)	41 (30.4)
Parous, previous PE	381 (2.3)	15 (2.7)	36 (9.1)	14 (5.4)	22 (16.3)
Interpregnancy interval (years)	2.7 (1.5–4.7)	3.3 (1.7–6.5)	3.55 (1.9–5.9)	3.2 (1.8–5.7)	4.2 (2.2–6.3)

Note: Data are presented as median (interquartile range) or as number (percentage).

Abbreviations: APS, antiphospholipid syndrome; iPTB, iatrogenic preterm birth; PE, pre-eclampsia; SLE, systemic lupus erythematosus; sPTB, spontaneous preterm birth.

TABLE 2 Indications for iatrogenic preterm birth at <37 and <32 weeks of gestation among the SPREE[8] cohort.

Indications for iatrogenic preterm births	Before 37 weeks ($N = 395$)	Before 32 weeks ($N = 88$)
Pre-eclampsia	135 (34.2)	32 (36.4)
Gestational hypertension	5 (1.3)	0
Gestational diabetes mellitus	4 (1.0)	0
Obstetric cholestasis	10 (2.5)	0
Maternal medical condition	27 (6.8)	2 (2.3)
Antenatal stillbirth	32 (8.1)	27 (30.7)
Fetal growth restriction	73 (18.5)	9 (10.2)
Suspected fetal compromise	41 (10.4)	3 (3.4)
Fetal defect	6 (1.5)	4 (4.5)
Placenta praevia with haemorrhage/vasa praevia	27 (6.8)	4 (4.5)
Placental abruption/Antepartum haemorrhage	29 (7.3)	7 (8.0)
Previous perinatal death	6 (1.5)	0

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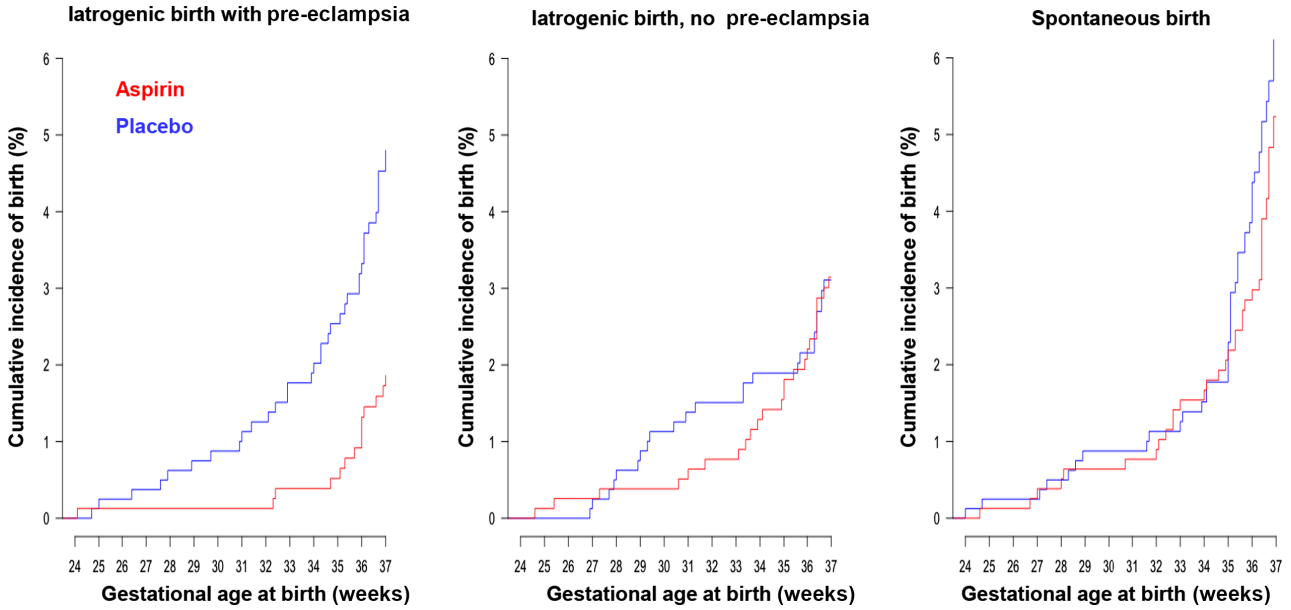

FIGURE 1 Cumulative incidence spontaneous and iatrogenic preterm birth (sPTB and iPTB, respectively) with and without pre-eclampsia in the ASPRE. The incidence was reduced by aspirin only in the iPTB group with pre-eclampsia.

4 | PREVENTION OF PTB BY PROPHYLACTIC USE OF ASPIRIN

Table 4 reports the effect of prophylactic use of aspirin, derived from the ASPRE trial,[2] on the incidence of PTB in women identified as being at high risk for preterm pre-eclampsia by the FMF triple test and NICE guidelines in 10 000 modelled populations of 100 000 pregnancies. In these calculations it was assumed that first, in both the FMF triple test and NICE guidelines screen positive women the compliance to aspirin would be 85% (this was the case in the ASPRE trial[2]), and second, the effectiveness of aspirin in the two screen positive groups would be the same. The flow chart in Figure 2 gives an overview of this process. We performed 10 000 simulations and Table 4 presents means and 95% credibility intervals (95% CI) from these simulations.

As shown in Table 4, the expected number of cases of iPTB at <37 weeks of gestation was 2400 (95% CI 2158–2663) and screening by the FMF triple test detected 44.3% (1063) of these cases (see Table 3). Prophylactic use of aspirin would prevent 38% (95% CI 8–59%) of these cases. Assuming constant 85% compliance, screening by the FMF triple test and treatment with aspirin would result in a reduction of 335 cases, to 2065 (95% CI 1772–2418). Comparatively, screening and treatment by NICE guidelines would result in a reduction of 193 cases, to 2207 (95% CI 1949–2494). The average absolute difference in risk was 0.135% (95% CI 0.020–0.261%).

Therefore, in a trial comparing screening by the FMF triple test versus NICE guidelines, in a population of 2*100 000, and treatment of the screen positive group with aspirin, it is estimated that the difference in incidence of iPTB between the two groups would be 0.135 (95% CI 0.022–0.261%).

5 | DISCUSSION

5.1 | Main findings

There are three main findings from this study of women with singleton pregnancies who had assessment of risk for pre-eclampsia by the FMF triple test and NICE guidelines at 11^{+0}–13^{+6} weeks of gestation in NHS hospitals in the UK.

First, the overall incidence of PTB at <37 weeks of gestation was about 6%. In about 60% of these cases the PTB was spontaneous and in 40% it was iatrogenic; in one-third of iPTB there was associated pre-eclampsia and in two-thirds there was no pre-eclampsia.

Second, the FMF triple test predicted 17%, 44%, 82% and 25%, of sPTB, iPTB, iPTB with pre-eclampsia and iPTB without pre-eclampsia, respectively, at a screen positive rate of 10.2%. The respective values achieved by screening with the NICE guidelines were 12%, 26%, 39% and 14%. A similar pattern of findings was observed for sPTB and iPTB at <32 weeks of gestation. Therefore, first-trimester prediction of sPTB and iPTB in the absence of pre-eclampsia by the FMF triple test, and more so by NICE guidelines, is poor; in contrast, in the case of iPTB in association with pre-eclampsia there was a high prediction by the FMF triple test, but poor prediction by the NICE guidelines.

Third, the ASPRE trial demonstrated that prophylactic use of aspirin (150 mg per day from 11–14 weeks to 36 weeks of gestation) in women identified by the FMF triple test as being at high-risk of pre-eclampsia reduces the incidence of preterm pre-eclampsia, with delivery at <37 weeks of gestation, by 62% and the incidence of early pre-eclampsia, with delivery at <32 weeks, by 90%.[2] However, the aspirin-related reduction in iPTB at <37 and <32 weeks was only 33% and

TABLE 3 Incidence of each pregnancy complication in a population of 16 451 singleton pregnancies examined in SPREE[8] and detection rate with 95% confidence interval, in screening for preterm pre-eclampsia by the FMF triple test and NICE guidelines.

		FMF triple test[a]		NICE guidelines[3]	
Outcome measure	**Incidence *n*/16451 (%)**	***x***	**Detection rate *x*/*n* (%)**	***x***	**Detection rate *x*/*n* (%)**
Delivery <37 weeks					
Spontaneous	555 (3.37)	94	16.9 (13.9–20.3)	64	11.5 (9.0–14.5)
Pre-eclampsia	142 (0.86)	116	81.7 (74.3–87.7)	58	40.8 (32.7–49.4)
Iatrogenic	395 (2.40)	175	44.3 (39.3–49.4)	102	25.8 (21.6–30.4)
With pre-eclampsia	135 (0.82)	111	82.2 (74.7–88.3)	53	39.3 (31.0–48.0)
Without pre-eclampsia	260 (1.58)	64	24.6 (19.5–30.3)	49	18.9 (14.3–24.1)
Delivery <32 weeks					
Spontaneous	84 (0.51)	13	15.5 (8.5–25.0)	9	10.7 (5.0–19.4)
Pre-eclampsia	33 (0.20)	30	90.9 (75.7–98.1)	17	51.5 (33.5–69.2)
Iatrogenic	88 (0.53)	46	52.3 (41.4–63.0)	27	30.7 (21.3–41.4)
With pre-eclampsia	32 (0.19)	29	90.6 (75.0–98.0)	16	50.0 (31.9–68.1)
Without pre-eclampsia	56 (0.34)	17	30.4 (18.8–44.1)	11	19.6 (10.2–32.4)

Abbreviations: FMF, Fetal Medicine Foundation; NICE, National Institute of Health and Care Excellence.

[a]FMF triple test, combination of maternal characteristics and elements of medical history with multiple of the median values of mean arterial pressure, uterine artery pulsatility index and placental growth factor.

63%, respectively, because the majority of cases of iPTB occur in the absence of pre-eclampsia and in such cases the impact of aspirin is small or nil. Similarly, aspirin does not prevent sPTB.

5.2 | Strengths and limitations

The main strength of the study is that the data were derived from two major multicentre studies.[2,8] In both SPREE and ASPRE there was prospective examination of a large number of pregnant women in several maternity units covering a wide spectrum of demographic and racial characteristics; the results are therefore likely to be generalisable across the UK and other countries. Consistency in data collection was maintained throughout the study period by ensuring adequate training for all investigators based on standardised protocols, external validation and quality assurance of biomarker measurements and regular monitoring by an independent clinical trial unit.

The SPREE study was powered to detect differences in predictive performance for preterm pre-eclampsia of the FMF model versus NICE guidelines and the ASPRE trial was powered for a global test of the effect of aspirin on preterm pre-eclampsia in a high-risk population. The statistical power for comparisons in detecting and preventing PTB, especially sPTB and iPTB in the absence of pre-eclampsia, is inevitably poor. Consequently, there was some uncertainty on the estimation of the effect of different methods of screening and aspirin prophylaxis in the reduction of risk of PTB. Nevertheless, there was a very clear trend that both the prediction and prevention of sPTB and iPTB in the absence of pre-eclampsia was poor and therefore, the outcome measure in comparison of different models of screening for preterm pre-eclampsia should be preterm pre-eclampsia.

5.3 | Results of previous studies

There is controversial evidence as to whether methods of screening for pre-eclampsia are also useful in the prediction of sPTB or iPTB in the absence of pre-eclampsia. A large cohort study of 33 629 women with singleton pregnancies demonstrated that although increased UtA-PI >95th centile at 22–24 weeks of gestation was more frequent among pregnancies resulting in sPTB at <33 weeks of gestation, compared with pregnancies delivering at ≥33 weeks, its inclusion did not result in a significant improvement in the prediction of sPTB provided by maternal characteristics and previous obstetric history.[9] Another cohort study of 34 025 singleton pregnancies, investigating the value of various biomarkers of placental perfusion and function at 11–13 weeks of gestation, including UtA-PI and maternal serum pregnancy-associated plasma protein-A (PAPP-A), free β-human chorionic gonadotrophin, PlGF, placental protein 13, ADAM12, inhibin-A and activin-A, in the prediction of sPTB at <34 weeks, reported that first, in the sPTB group, compared with unaffected pregnancies there were no significant differences in any of these biomarkers, except for PAPP-A which was reduced; and second, inclusion of these biomarkers did not improve the prediction of sPTB provided by maternal risk factors.[10] A smaller study of 11 437 women undergoing first-trimester screening for preterm pre-eclampsia by a combination of maternal risk factors, MAP, UtA-PI and PAPP-A, reported that in those with estimated risk of ≥1 in 50, compared with those with a risk <1 in 50, the odds ratio for iPTB was 6.0 (95% CI 4.29–8.43) and

TABLE 4 Effect of prophylactic use of aspirin, derived from the ASPRE trial,[2] on the incidence of preterm birth in women identified as being at high-risk for preterm pre-eclampsia by the FMF triple test and NICE guidelines in a population of 100 000 pregnancies with the characteristics of women in SPREE.[8]

			After screening and treatment				
			FMF triple test		NICE guidelines		
Outcome measure	Expected cases	Relative risk (aspirin/no aspirin) % (95% CI)	Cases	Risk (%)	Cases	Risk (%)	Risk difference (%)
Delivery <37 weeks							
Spontaneous	3370 (3082–3681)	86 (57–100)	3295 (2985–3621)	3.295 (2.985–3.621)	3318 (3022–3636)	3.318 (3.022–3.636)	0.017 (−0.003 to 0.088)
Pre-eclampsia	860 (719–1018)	38 (19–69)	489 (351–706)	0.489 (0.351–0.706)	676 (544–838)	0.676 (0.544–0.838)	0.182 (0.080–0.284)
Iatrogenic	2400 (2158–2663)	63 (41–92)	2065 (1772–2418)	2.065 (1.772–2.418)	2207 (1949–2494)	2.207 (1.949–2.494)	0.135 (0.022–0.261)
With pre-eclampsia	817 (680–978)	35 (17–64)	445 (318–646)	0.445 (0.318–0.646)	641 (513–801)	0.641 (0.513–0.801)	0.190 (0.092–0.293)
Without pre-eclampsia	1577 (1379–1795)	103 (57–100)	1548 (1332–1776)	1.548 (1.332–1.776)	1555 (1347–1779)	1.555 (1.347–1.779)	0.0 (−0.008 to 0.050)
Delivery <32 weeks							
Spontaneous	507 (398–635)	69 (22–100)	486 (378–614)	0.486 (0.378–0.614)	492 (386–620)	0.492 (0.386–0.620)	0.003 (−0.012 to 0.038)
Pre-eclampsia	199 (134–280)	10 (0–45)	59 (29–128)	0.059 (0.029–0.128)	120 (73–187)	0.120 (0.073–0.187)	0.058 (0.018–0.107)
Iatrogenic	532 (421–661)	33 (12–70)	374 (276–507)	0.374 (0.276–0.507)	440 (339–560)	0.440 (0.339–0.560)	0.064 (0.009–0.129)
With pre-eclampsia	193 (129–274)	10 (0–46)	57 (28–125)	0.057 (0.028–0.125)	119 (71–186)	0.119 (0.071–0.186)	0.058 (0.019–0.109)
Without pre-eclampsia	338 (251–443)	51 (16–100)	296 (212–407)	0.296 (0.212–0.407)	311 (227–416)	0.311 (0.227–0.416)	0.011 (−0.011 to 0.053)

Note: Assuming that first, in both the FMF triple test and NICE guidelines screen positive women the compliance to aspirin is 85%, and second, the effectiveness of aspirin in the two screen positive groups is the same.

Abbreviations: FMF, Fetal Medicine Foundation; NICE, National Institute of Health and Care Excellence.

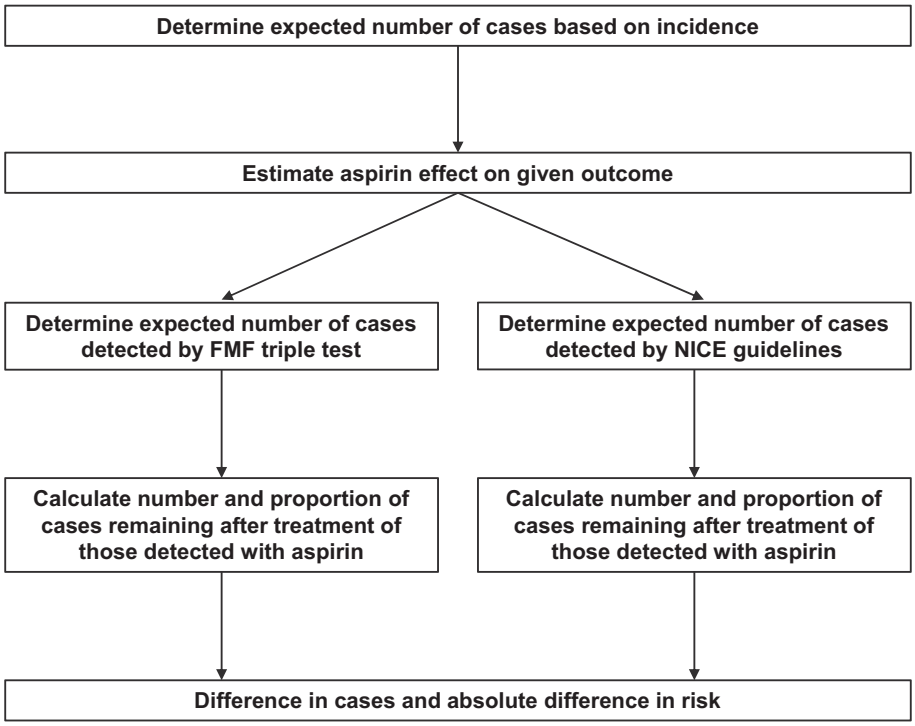

FIGURE 2 Flow chart explaining the study design.

that for sPTB was 2.0 (95% CI 1.46–2.86).[11] Another study of 9298 singleton pregnancies reported that first-trimester biomarkers of placental function can be used to screen for sPTB; inclusion of PlGF and PAPP-A improved the DR of sPTB at <37 weeks of gestation provided by maternal risk factors from 17% to 25%, at FPR of 10%.[12]

A Swedish register-based cohort study investigated the association between low-dose aspirin use and PTB among 22 127 women with a previous PTB and concluded that low-dose aspirin use was associated with a reduced risk for sPTB (relative risk [RR] 0.70; 95% CI 0.57–0.86) but had no significant effect on iPTB (RR 1.09; 95% CI 0.91–1.30).[13] A double-blind, placebo-controlled trial of low-dose aspirin (81 mg daily) versus placebo from 6 to 13 weeks of gestation until 36 weeks in 11 976 nulliparous women with singleton pregnancies found that aspirin was associated with an 11% reduction in the risk of PTB at <37 weeks of gestation (RR 0.89, 95% CI 0.81–0.98) but the study did not provide data as to whether the PTB was spontaneous or iatrogenic and whether there was any association with pre-eclampsia.[26] In our study, we demonstrated the poor or no impact of aspirin in sPTB and iPTB in the absence of pre-eclampsia and the high impact on the prevention of iPTB associated with pre-eclampsia.

5.4 | Interpretation of results and implications for clinical practice

The FMF triple test provides effective first-trimester prediction of preterm pre-eclampsia and treatment of the high-risk group with aspirin substantially reduces the incidence of the disease.[2,6,20] The model, which was originally described in 2012, was subsequently validated in many studies in the UK and other countries that reported high predictive performance for preterm pre-eclampsia and good agreement between estimated risk and observed incidence of the disease.[21-27] In the absence of serum PlGF, serum PAPP-A can be used, but the performance of the latter is poor by comparison with PlGF.[28] Additionally, the studies reported that in screening for pre-eclampsia it is a necessity to establish a programme for continuous quality assurance of biomarker measurements, as is the case in screening for fetal trisomies in the UK.

On the basis of the extensive existing evidence in favour of replacing the current poor performing method of screening for preterm pre-eclampsia based on NICE guidelines with the considerably more effective method of the FMF triple test, the International Society for the Study of Hypertension in Pregnancy, the International Federation of Gynecology & Obstetrics and the International Society of Ultrasound in Obstetrics and Gynaecology now recommend early screening for pre-eclampsia with the FMF algorithm.[29-31]

In contrast, this approach has not been endorsed by the UK National Screening Committee, which acknowledged that there may be enough evidence to support screening for preterm pre-eclampsia but recommended that more work should be done to evaluate the harms and benefits of a screening programme.[32] The National Institute for Health Research has funded a trial to compare the FMF triple test versus NICE guidelines in selecting women to be treated with aspirin; the primary outcome of the study is

the difference in the incidence of iPTB (FMF versus NICE). Two problems with the proposed trial are as follows. First, to assess the evidence of harm resulting from rare but very serious adverse events, a sample size far beyond the scope of the proposed trial is needed. Second, the existing evidence from two landmark studies (SPREE and ASPRE) shows that the difference in incidence of iPTB is likely to be very small, so the proposed trial is very unlikely to reach a positive outcome for efficacy. A large-scale well-designed NHS in-service evaluation should be conducted to determine the harms from a screening programme and determine how the benefits found in SPREE and ASPRE can be achieved within an NHS screening programme.

6 | CONCLUSIONS

There are three main conclusions of the study. First, the FMF triple test, compared with NICE guidelines, predicts twice as many cases of preterm pre-eclampsia. Second, both the FMF triple test and NICE guidelines provide poor prediction of sPTB and iPTB in the absence of pre-eclampsia. Third, prophylactic use of aspirin in women at high-risk of preterm pre-eclampsia is effective in reducing the incidence of preterm pre-eclampsia, but it has no substantial effect on the incidence of sPTB or iPTB in the absence of pre-eclampsia.

AUTHOR CONTRIBUTIONS

KN, AS, AW and DW conceptualised and designed the study. KN wrote the first draft of the paper. LCP and MYT were responsible for the SPREE study and DLR and LCP were responsible for the ASPRE trial. All authors revised and contributed to the intellectual content of the manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS APPROVAL STATEMENT

Approval for SPREE was obtained from the London-Surrey Borders Research Ethics Committee; the study is registered with the ISRCTN registry, number 83611527. Approval for ASPRE was obtained from the relevant research ethics committee and competent authority in each country in which the trial was conducted; the study is registered with the ISRCTN registry, number 13633058.

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