Accepted: 20 June 2023

DOI: 10.1111/1471-0528.17598

BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE

First trimester screening for pre-eclampsia and targeted aspirin prophylaxis: a cost-effectiveness cohort study

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Abstract

Objective: Investigate cost-effectiveness of first trimester pre-eclampsia screening using the Fetal Medicine Foundation (FMF) algorithm and targeted aspirin prophylaxis in comparison with standard care.

Design: Retrospective observational study.

Setting: London tertiary hospital.

Population: 5957 pregnancies screened for pre-eclampsia using the National Institute for Health and Care Excellence (NICE) method.

Methods: Differences in pregnancy outcomes between those who developed pre-eclampsia, term pre-eclampsia and preterm pre-eclampsia were compared by the Kruskal–Wallis and Chi-square tests. The FMF algorithm was applied retrospectively to the cohort. A decision analytic model was used to estimate costs and outcomes for pregnancies screened using NICE and those screened using the FMF algorithm. The decision point probabilities were calculated using the included cohort.

Main outcome measures: Incremental healthcare costs and QALY gained per pregnancy screened.

Results: Of 5957 pregnancies, 12.8% and 15.9% were screen-positive for development of pre-eclampsia using the NICE and FMF methods, respectively. Of those who were screen-positive by NICE recommendations, aspirin was not prescribed in 25%. Across the three groups, namely, pregnancies without pre-eclampsia, term pre-eclampsia and preterm pre-eclampsia there was a statistically significant trend in rates of emergency caesarean (respectively 21%, 43% and 71.4%; $P < 0.001$), admission to neonatal intensive care unit (NICU) (5.9%, 9.4%, 41%; $P < 0.001$) and length of stay in NICU. The FMF algorithm was associated with seven fewer cases of preterm pre-eclampsia, cost saving of £9.06 and QALY gain of 0.00006/pregnancy screened.

Conclusions: Using a conservative approach, application of the FMF algorithm achieved clinical benefit and an economic cost saving.

KEYWORDS

aspirin, cost-effectiveness, Fetal Medicine Foundation, first trimester combined screening, mean arterial blood pressure, National Institute for Health and Care Excellence, pre-eclampsia, pregnancy associated plasma protein-A, preterm pre-eclampsia

1 | INTRODUCTION

Pre-eclampsia (PE) affects 6–7% of pregnancies and carries significant risks of maternal and perinatal morbidity and mortality, particularly when occurring preterm.[1] As a result, pregnancies complicated by PE generate higher maternity costs.

Preterm PE is associated with a greater likelihood of admission to the neonatal intensive care unit (NICU) and need for caesarean delivery. These costly interventions are the primary drivers of the excess economic burden arising with PE.[2] Therefore, strategies implemented to reduce the prevalence of preterm PE would not only have considerable health benefits but also deliver cost-savings to the healthcare system.

One such proven intervention is the use of aspirin. When given at a daily dose of 150 mg prior to 16 weeks' gestation to women who are at high risk of PE as determined by a combination of maternal characteristics and biomarkers, aspirin reduces the risk of preterm PE and admission to NICU by 62% and 66%, respectively.[3,4]

Currently, in the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) recommends identifying women who would benefit from aspirin using maternal characteristics alone.[5] There are limitations to this method. First, compliance is low, with only 23% of women at high risk for PE being prescribed aspirin from the first trimester.[6] Secondly, the performance of the NICE method in the prediction of preterm PE is poor, with a detection rate (DR) of 40.8%.[6] This combination of low compliance and poor sensitivity in identifying truly high-risk pregnancies likely accounts for the more modest reductions in PE with aspirin observed in earlier studies.[7]

The Fetal Medicine Foundation (FMF) algorithm for first trimester prediction of PE combines maternal characteristics with biomarkers that include placental growth factor (PLGF) or pregnancy-associated plasma protein-A (PAPP-A).[6,8] The DR for preterm PE using the FMF algorithm has been demonstrated to be 69%. With the addition of first trimester uterine artery pulsatility index (UtA-PI) Doppler, the DR increases to 75%.[8] Increased physician compliance in aspirin prescribing and reduction in the prevalence of preterm PE and delivery of SGA infants have been reported with implementation of the FMF method.[9–11] However, concerns around the increased costs incurred by the package of care associated with the FMF method, which includes routine third trimester ultrasound, have limited its wider implementation.

Our objective was to investigate the cost-effectiveness of first trimester PE screening using the FMF algorithm in comparison with current standard care recommended by NICE.

2 | METHODS

2.1 | Study design and population

This was a retrospective observational study of all pregnant women who booked for antenatal care and delivery at University College London Hospital NHS Foundation, UK, between March 2019 and December 2022. The inclusion criteria for this study were singleton pregnancies resulting in the live- or stillbirth of an infant without any serious congenital anomalies at ≥24 weeks' gestation. We excluded patients who declined first trimester combined screening testing (CST) for trisomy 21, 13 and 18, as PAPP-A results were not available for this cohort. We also excluded those who did not have a BP recorded from their booking visit and those who were lost to follow-up. Data on maternal characteristics and pregnancy outcomes were collected from the hospital maternity records. Gestational age was determined by crown–rump length (CRL) measurement performed at the first trimester scan between 11^{+2} and 14^{+1} weeks.

Standard care, using the NICE guidance, identified women at their booking midwifery or Obstetric appointment as high risk of developing PE if they had any one major factor (hypertensive disease in previous pregnancy, chronic kidney disease, autoimmune disease, diabetes mellitus or chronic hypertension) or any two moderate factors (first pregnancy at age ≥40 years, interpregnancy interval >10 years, body mass index at first visit ≥35 kg/m^2 or family history of PE). The current recommendation by NICE is that all women who screen positive by this method should be offered aspirin prophylaxis of 150 mg until 36 weeks' gestation. Subsequent pregnancy management including the need for third trimester fetal growth surveillance or for earlier induction of labour was scheduled as recommended by NICE.[12] Maternal serum PAPP-A was measured in those who consented to CST. Only those with MAP taken according to standardised protocols by midwives or healthcare assistants were included in the study.

PE was defined according to the International Society for the Study of Hypertension (2014) guidelines as having, in addition to hypertension, at least one of the following problems: renal involvement (proteinuria 300 mg/24 hours and/or creatinine 90 mmol/l or 1 mg/dl), liver impairment (transaminases >70 IU/L), neurological complications (e.g. eclampsia), thrombocytopenia (platelet count <150 000/ml), uteroplacental dysfunction (e.g. fetal growth restriction).[13] In addition, according to gestational age at diagnosis, PE was subdivided into preterm PE with onset at <37 weeks' gestation and term PE with onset beyond 37 weeks. SGA was defined as birthweight <5th percentile for gestational age.[14]

2.2 | Statistical analysis

2.2.1 | Cohort study

Numeric and categorical data were expressed as median (interquartile range) and proportions, respectively. Differences in pregnancy outcomes between those without PE, those with term PE and those with preterm PE were compared by the analysis of variance or Kruskal–Wallis tests (for numerical parametric or nonparametric data) with the Bonferroni correction for post-hoc analysis. The Chi-square test was

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performed for categorical variables and for trend when the proportions between groups demonstrated an obvious trend.

The FMF algorithm was applied retrospectively (Table S1). Pregnancies were screened based on maternal characteristics, MAP at booking and serum PAPP-A. Women with estimated risks of preterm PE of 1 in 100 or higher were considered high risk, and those with risks below 1 in 100 were considered low risk. The risk cut-off of ≥1:150 for preterm pre-eclampsia resulted in a high screen-positive rate of 24% in our cohort. Therefore, a pragmatic decision was taken to reduce the cut-off to ≥1:100 with an expected screen-positive rate of between 10% and 15%. In addition to requiring aspirin prophylaxis, all women who are screen-positive using the FMF algorithm would require third trimester fetal growth ultrasound surveillance.

As this was a retrospective and theoretical application of the FMF algorithm to a cohort that had been already screened using the NICE method, a proportion of pregnancies were high risk for the development of PE in both arms and therefore had been prescribed aspirin prophylaxis for the pregnancy that this data relates to. To adjust appropriately the effect size reported for incidence of preterm PE using the FMF algorithm, the assumption that aspirin would reduce the risk of preterm PE by 62%, as demonstrated in the ASPRE randomised controlled trial (RCT), was incorporated into analysis.[4] No difference in the rate of term PE between those taking aspirin and the placebo group was reported in the ASPRE RCT. Therefore, no effect of aspirin on term PE was considered in the model.

Statistical analysis was performed with SPSS statistical software (version 27; SPSS Inc.).

2.2.2 | Cost-effectiveness

A decision-tree model was used to estimate the incremental cost-effectiveness of replacing the NICE screening method with the FMF screening method. This model was applied to the cohort of pregnant women outlined above. An a priori decision was taken not to model for the universal use of aspirin prophylaxis as the superiority of this method over biomarker or maternal factor-based screening remains uncertain. The maternal and pregnancy characteristics of the included cohort are presented in Table 1. Model pathways for each screening outcome were defined based on initial screening test result, prescription of aspirin, rates of PE, and rates of preterm PE. The model structure is outlined in Figure S1.

All transition probabilities were calculated based on the statistical analysis of primary data described above. Aspirin prescription rates were based on observed data for the NICE screening method and based on scientific literature for the FMF screening method.[9] Aspirin patient adherence was not accounted for in the model due to the retrospective nature of the study.

Health outcomes were expressed for the mother only in terms of quality-adjusted life-years (QALYs). The prevalence

TABLE 1 Maternal, pregnancy and screening characteristics of the overall cohort.

Characteristic	Total cohort ($n = 5957$)
Maternal characteristic at booking	
Body mass index (kg/m^2), median (IQR)	23 (21–27)
Age (years), median (IQR)	33 (30–36)
Ethnicity, *n* (%)	
White	4063 (68.2)
Afro-Caribbean	569 (9.6)
South Asian	747 (12.5)
East Asian	309 (5.2)
Mixed	269 (4.5)
MAP (mmHg), median (IQR)	85.0 (79.0–90.3)
Smoker, *n* (%)	119 (2.0)
Comorbidities, *n* (%)	
Chronic hypertension	125 (2.1)
Pre-pregnancy diabetes mellitus	60 (1.0)
Systemic lupus erythematosus	20 (0.4)
Assisted conception, *n* (%)	420 (7.1)
History of pre-eclampsia, *n* (%)	111 (1.9)
Family history of pre-eclampsia, *n* (%)	235 (3.9)
PAPPA-A (MoM), median (IQR)	1.01 (0.69–1.43)
Screening characteristics	
Total screen-positive using NICE, *n* (%)	766 (12.9)
Moderate risk factor[a]	386 (6.5)
High risk factor	380 (6.4)
Total screen-positive using FMF algorithm, *n* (%)[b]	950 (15.9)
Aspirin prophylaxis in NICE screen-positive, *n* (%)	577 (75.3)
Aspirin prophylaxis in FMF screen-positive, *n* (%)	313 (33.0)
Pregnancy outcomes	
Mode of delivery, *n* (%)	
Vaginal delivery	3605 (60.5)
Elective caesarean section	989 (16.6)
Emergency caesarean section	1363 (22.9)
Gestational age at delivery (weeks), median (IQR)	38.7 (39.7–40.6)
Birthweight centile, median (IQR)	33.3 (14.4–59.2)
Pre-eclampsia (any gestation), *n* (%)	408 (6.8)
Preterm pre-eclampsia, *n* (%)	49 (0.8)
Small for gestational age <3rd centile, *n* (%)	326 (5.5)
Small for gestational age <5th centile, *n* (%)	551 (9.2)
Small for gestational age <10th centile, *n* (%)	1057 (17.7)
Stillbirth, *n* (%)	17 (0.3)
Admission to NICU, *n* (%)	385 (6.5)
LOS in NICU (days), median (IQR)	3.9 (2.1–7.7)
Admission to SCBU, *n* (%)	77 (1.3)
LOS in SCBU (days), median (IQR)	3.1 (1.1–6.5)

Note: Numerical data is presented as median (interquartile range) and categorical data as proportions.

Abbreviations: FMF, Fetal Medicine Foundation; LOS, length of stay; NICE, National Institute for Health and Care Excellence; NICU, neonatal intensive care unit; SCBU, special care baby unit.

[a]Screen-positive based on presence of two or more moderate risk factors.

[b]Using a cut-off of ≥1:100.

of health events of interest was based on primary data, and health utility values were based on available secondary data. All relevant inputs for the calculation of QALYs are outlined in Table 2. Both outcomes and costs account for different probabilities of delivery modes and neonatal outcomes depending on PE status.

Costs were estimated from the provider perspective and included the costs of the PE screening, third trimester ultrasound for fetal growth surveillance, aspirin prophylaxis, delivery costs, the postpartum stay of the mother and the baby, the costs of stillbirth[15] and admission of a preterm neonate to NICU. Again, relevant probabilities were based on primary data, and unit costs were based on the NHS England 2022/23 National Tariff Workbook and the British National Formulary. Unit cost inputs are provided in Table S2.

Incremental cost-effectiveness ratios were estimated to represent the additional cost per QALY gained from adopting the FMF screening algorithm. To assess model sensitivity to uncertainty in key parameters, a univariate sensitivity analysis was conducted where each input parameter was varied in isolation based on its upper and lower 95% confidence limits. A probabilistic sensitivity analysis was also conducted, where variation in parameters was simultaneously modelled based on assumed distributions 1000 times (i.e. Monte Carlo simulations). Parameters varied in the sensitivity analysis consisted of healthcare costs, health-state utility values and all transition probabilities (i.e. effectively the number of PE cases under each intervention). Beta distributions were assumed for probabilities and utility values, and gamma distributions were assumed for costs. Details are provided in Table S3. All costs are reported in 2022 British pounds. All cost-effectiveness analysis was conducted in R using the 'rdecision' package.

TABLE 2 Health outcome input values.

Parameter	Value	Reference
Outcome probabilities		
Stillbirth		
Term PE stillbirth probability	0.002	[15]
Preterm PE stillbirth probability	0.016	[15]
No preeclampsia stillbirth probability	0.004	[15]
Delivery parameters		
Postpartum haemorrhage probability, no aspirin	0.078	[28]
Vaginal delivery probability, no PE	61.70%	Primary data, 2019–2022
Vaginal delivery probability, term PE	46.10%	Primary data, 2019–2022
Vaginal delivery probability, preterm PE	20.40%	Primary data, 2019–2022
Emergency caesarean probability, no PE	21.20%	Primary data, 2019–2022
Emergency caesarean probability, term PE	43.00%	Primary data, 2019–2022
Emergency caesarean probability, preterm PE	71.40%	Primary data, 2019–2022
Elective caesarean probability, no PE	17.10%	Primary data, 2019–2022
Elective caesarean probability, term PE	10.90%	Primary data, 2019–2022
Elective caesarean probability, preterm PE	8.20%	Primary data, 2019–2022
Neonatal admission		
NICU admission, no PE	5.90%	Primary data, 2019–2022
NICU admission, term PE	9.40%	Primary data, 2019–2022
NICU admission, preterm PE	41.00%	Primary data, 2019–2022
LOS in NICU, no PE (days)	4	Primary data, 2019–2022
LOS in NICU, term PE (days)	3	Primary data, 2019–2022
LOS in NICU, preterm PE (days)	13	Primary data, 2019–2022
SCBU admission, no PE	1.40%	Primary data, 2019–2022
SCBU admission, term PE	2.60%	Primary data, 2019–2022
SCBU admission, preterm PE	12.00%	Primary data, 2019–2022
LOS in SCBU, no PE	13	Primary data, 2019–2022
LOS in SCBU, term PE	3	Primary data, 2019–2022
LOS in SCBU, preterm PE	3	Primary data, 2019–2022
Aspirin		
Aspirin (150mg) effectiveness	62%	[4]
Aspirin prescription rate (NICE algorithm)	75%	Primary data, 2019–2022
Aspirin prescription rate (FMF algorithm)	99%	[9]
Health state utility values		
Utility, mother's age (25–34 years)	0.911	[37]

3 | RESULTS

3.1 | Population characteristics

The study population that met the inclusion criteria comprised 5957 pregnancies who attended the hospital for assessment between 11^{+2} and 14^{+1} weeks' gestation.

PE at any gestation developed in 408 (6.8%) pregnancies and preterm PE in 49 (0.8%) pregnancies. There was a statistically significant trend in the rates of emergency caesarean section ($P<0.001$), proportion of admission to NICU ($P<0.001$) between pregnancies without PE, pregnancies complicated by term PE and those complicated by preterm PE. Among the cohort of women without PE in our study cohort, 21% delivered by emergency caesarean. Among those with term and preterm PE, this proportion was 43% and 71.4%, respectively (Table 2).

Similarly, preterm PE was more likely to result in NICU admission. Rates of admission to NICU were 5.9%, 9.4% and 41% with uncomplicated pregnancies, term PE and preterm PE, respectively (Table 2).

TABLE 2 (Continued)

Parameter	Value	Reference
Vaginal delivery	−0.41 for 7 days	[37]
Caesarean delivery	−0.58 for 21 days	[37]
Postpartum haemorrhage	−0.25 for 10 days	[38]
Preeclampsia	−0.03	[40]
Stillbirth	−0.08	[39]
Neonatal care admission	−0.008 per day	[41]

Abbreviations: LOS, length of stay; NICU, neonatal intensive care unit; PE, preeclampsia.

The length of stay in NICU for pregnancies complicated by preterm PE was significantly longer than for pregnancies without PE and those with term PE ($P < 0.001$). With preterm PE, the duration of neonatal admission was, on average, 10 days longer than with term PE or uncomplicated pregnancies (Table 2).

Finally, the probability of stillbirth was 0.3% and 4.0% in those without PE and in those with preterm PE, respectively. Among women with term PE in our cohort, there were no stillbirths (Table 2).

3.2 | Comparison of NICE and FMF screening algorithms

Of the total cohort, 766 (12.8%) pregnancies were considered high risk for PE based on the NICE screening method; 577 (75.3%) were appropriately prescribed aspirin prophylaxis. Among the 24.7% who were screen-positive and not prescribed aspirin, 75% had at least one major risk factor as described by the NICE recommendations (Table 1).

Using a risk cut-off of ≥1:100, 950 (15.9%) pregnancies were considered high-risk based on the FMF algorithm; 391 (6.5%) of these pregnancies were also screen-positive by NICE criteria. This resulted in a third of the women screening positive using the FMF algorithm receiving aspirin prophylaxis. In comparison with the NICE method, the FMF screening algorithm identified 87 additional pregnancies complicated by PE that may have benefitted from first trimester aspirin prophylaxis (Table 1).

3.3 | Cost effectiveness

In the base case deterministic analysis, the FMF algorithm is associated with an overall cost saving of £9.06 per pregnancy screened and a QALY gain of 0.00006 when compared with standard care using the NICE screening method. Therefore, the FMF algorithm is dominant in the base case analysis. With a cohort of 5957 pregnant women, the use of the FMF algorithm resulted in seven fewer estimated cases of preterm PE (41) versus 48 pre-term PE cases with the NICE algorithm. Across a cohort of 5957 women the expected cost-saving would be approximately £54,000. Overall, the number of QALYs over a 1-year time horizon was similar across the two interventions, reflecting the fact that serious adverse events such as stillbirth are relatively rare.

Figure 1 illustrates the results of the univariate sensitivity analysis by presenting the 10 model parameters with the largest impact on results. The model results were most sensitive to the probability of pre-eclampsia cases being preterm. Costs and health-state utility values did not have a substantial impact on findings.

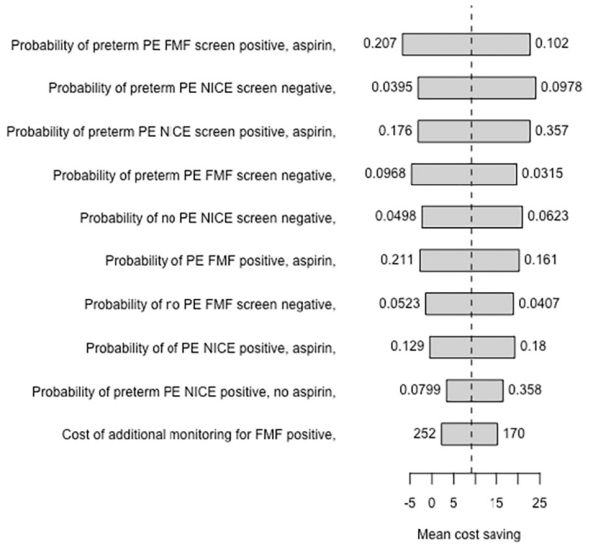

FIGURE 1 Univariate sensitivity analysis presenting the 10 model parameters with the largest impact on results.

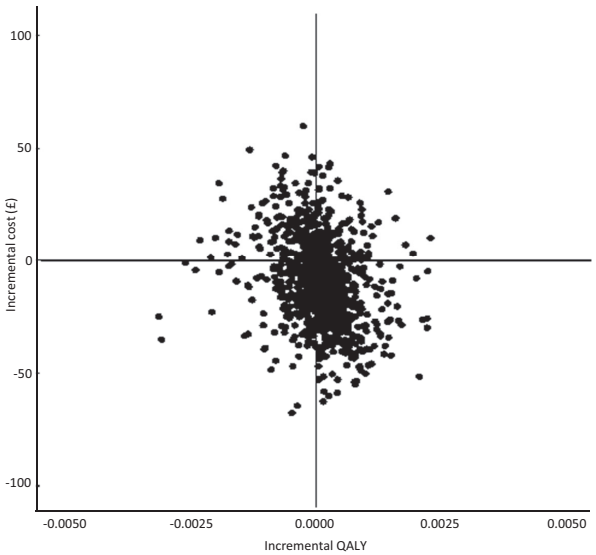

FIGURE 2 Results of the probabilistic sensitivity analysis in a cost-effectiveness plane comparing the incremental cost and QALY outcomes for the FMF algorithm and standard care.

Figure 2 illustrates the distribution of incremental cost and QALY outcomes from the probabilistic sensitivity analysis on a cost-effectiveness plane, with each dot representing a simulation of the model accounting for parameter uncertainty. The values predominantly fall within the north-western quadrant where FMF screening is associated with greater cost-savings and health gains when compared with the NICE method. The FMF screening method is cost-saving in 67% of simulations (Figure 1).

4 | DISCUSSION

4.1 | Main findings

In our study, 12.8% and 15.9% of women were identified as high risk for the development of PE using the NICE and FMF methods, respectively. Preterm PE was associated with a significantly higher rate of emergency caesarean delivery and neonatal admission to and duration of stay in NICU when compared with uncomplicated pregnancies and those with term PE. Use of the FMF algorithm was associated with seven fewer cases of preterm PE, an estimated cost-saving of £9.06 and a QALY gain of 0.00006 per pregnancy screened.

Using NICE criteria, 12.8% of women in our booking cohort were screen-positive. Physician compliance with prescribing aspirin to this high-risk cohort was 75%, approximately three times higher than the rate reported in other UK studies.[6,9] This may be explained by introduction at the study site of a mandatory checklist for PE risk assessment in 2019. Despite this improvement, 25% of high-risk women were still not prescribed aspirin. Physician compliance of 96–99% has meanwhile been demonstrated with implementation of the FMF algorithm.[9,11]

Although we did not assess patient compliance in this study, it is clear that physician compliance with prescribing aspirin does not equate with patient compliance. In an observational cohort study, 44% of women identified as high-risk using maternal characteristics alone, were not compliant with the use of aspirin.[16] When compared with those who took aspirin as prescribed, women with low compliance had a higher incidence of early-onset (odds ratio [OR] 1.9, 95% confidence interval [CI] 1.1–8.7; $P=0.04$) and late-onset PE (OR 4.2, 95% CI 1.4–19.8; $P=0.04$).[16]

Similarly, in a multicentre RCT, the efficacy of aspirin in reducing the risk of preterm PE in women identified as high risk, using the FMF algorithm, was less than in those with lower compliance. In research settings, patient compliance with aspirin prescribed based on FMF criteria is favourable compared with when NICE screening is employed. In one recent study, 71% of trial participants were compliant with the use of aspirin when screened using the FMF algorithm.[17] Therefore, improving the robustness of the screening process is likely not only to improve physician compliance but also patient concordance with aspirin prophylaxis.

Several studies have compared the cost-effectiveness of implementing the FMF algorithm for first trimester prediction of PE to the current method that involves maternal characteristics alone.[18–22] Only one of these studies included the UK.[20] In contrast to our study, which modelled cost on real data, that study used a theoretical population of 100 000 pregnancies and compared the two screening methods using input data from published literature. The authors demonstrated that the FMF algorithm, independent of the sensitivity and specificity of the new test, was associated with lower total costs and more PE cases were averted.[20] Similarly, in Belgium and Switzerland, cost-savings of €28.67 (£24.74)[18] and CHF42 (£33.32),[19] respectively, per patient screened using the FMF algorithm have been reported. In contrast, in other European countries (Sweden, Ireland and Germany) implementation of the FMF algorithm has incurred higher costs.[19,20] These inconsistencies in the literature are the result of variations both in PE prevalence and healthcare costs across different countries. For example, in Sweden, where the prevalence of PE is 1.7%, and in Ireland where healthcare costs are comparatively less than the UK, use of the FMF algorithm was more expensive.[20]

4.2 | Implications of the findings on clinical practice and future research

The largest study to date on the clinical effectiveness of first trimester screening using the FMF algorithm has shown that screen-positive women were significantly more likely to develop PE at any gestation (5.7% versus 2.4%, risk ratio [RR] 2.33, 95% CI 2.05–2.65, $P<0.001$), preterm PE (2.1% versus 0.7%, RR 3.04, 95% CI 2.46–3.77, $P<0.001$) and deliver an small for gestational age (SGA) infant <3rd centile when compared with the general population (4.5% versus 2.1%, RR 2.10, 95% CI 1.82–2.42, $P<0.001$). Conversely, screen-negative women had comparatively lower rates of the reported outcomes.[23] Finally, the potential benefit of the FMF algorithm has been demonstrated to result in relative effect reductions of 80% ($P=0.025$) and 45% ($P=0.004$) in preterm PE and delivery of an SGA infant <10th centile, respectively.[9,10]

Despite these studies demonstrating clinical superiority of the FMF algorithm in comparison with maternal characteristic-based screening for PE, barriers to its more widespread implementation persist. Most notably, these include concerns regarding the cost of not only the test but also the package of care it involves, such as training to measure first trimester uterine Doppler indices. When considering the clear benefit of aspirin and these perceived barriers to implementation, particularly in healthcare settings that are not well resourced, some authors have advocated universal aspirin prophylaxis.[24,25]

In this study, we did not incorporate the universal aspirin strategy into our cost analysis for two reasons. First, the benefit of aspirin must be balanced against the risk of causing harm. Outside of pregnancy, the relation between low dose aspirin and major bleeding events is well established and, therefore, aspirin is no longer recommended for the primary prevention of cardiovascular disease.[26,27]

In pregnancy, the evidence to date has been more conflicting. Data from a large registry study[28] and two randomised controlled trials[25,29] have reported a higher incidence of gastrointestinal bleeding,[29] vaginal spotting,[25,29] postpartum haemorrhage,[25,28] postpartum haematoma[28] and possibly neonatal intracranial haemorrhage[28] among women taking between 75 and 100 mg aspirin.[28] However, these findings were not supported by two recent meta-analyses.[30,31] Should aspirin be given to the entire maternity population, inevitably these adverse effects would become more frequent, the risk of which currently remains undefined, particularly when the dose is increased to 150 mg. Secondly, the strong beneficial effect of aspirin in the prevention of preterm PE in high-risk populations may be diluted when given on an 'opt out' basis. Earlier studies have reported a lower adherence to treatment and no clear impact on the rate of preterm PE when aspirin is given to women either for being pregnant or nulliparous.[29,32] More recently, a randomised controlled trial and post-hoc analysis demonstrated that routine use of aspirin in nulliparous women from low- to middle-income countries was a cost-effective strategy that resulted in an 11% and 14% reduction in preterm delivery and perinatal death, respectively.[33,34] Further prospective studies are clearly warranted to address the paucity of data on aspirin adherence in a low-risk population and clarify the potential benefits of a universal aspirin strategy with not just preterm PE but other adverse pregnancy outcomes.

Finally, the findings of our study do not support a greater cost associated with use of the FMF algorithm. The cost-savings demonstrated here are modest, but we have adopted a conservative approach and, nonetheless, confirmed that even when higher rates of physician compliance are achieved, FMF screening algorithms can be implemented without additional cost to the healthcare system. This would ultimately enable greater individualisation of antenatal care through the identification of a high-risk cohort that requires not just aspirin prophylaxis but also evidence-based third trimester fetal growth surveillance and earlier induction of labour.

4.3 | Strengths and limitations

The strength of our study is the input of actual data, such as physician compliance with aspirin prophylaxis, into the model structure and probabilities for the cost analysis. We recognise that the use of input parameters derived from a local population in a local healthcare setting means that caution should be used when generalising these results to other populations or healthcare settings without the appropriate adjustment for the characteristics or costs.

Due to the retrospective application of the FMF algorithm, a proportion of those who were screen-positive using the FMF algorithm received aspirin. Therefore, the input data had to be estimated in this group while adjusting for the possible effect of aspirin. However, as we have only considered the effect of the intervention on preterm, rather than total PE, of which a possible benefit has been demonstrated,[23] our estimates of cost-savings can only represent an underestimate.

We did not evaluate the cost-effectiveness of other maternal characteristic-based screening algorithms such as the recent broader strategy published by the American College of Obstetricians and Gynecologists (ACOG).[35] In addition to the characteristics specified by NICE, ACOG recommendations incorporate socio-demographic factors, which we were unable to account for due to the retrospective nature of the study.[35]

Finally, neither PLGF nor UtA-PI were incorporated into the FMF algorithm in our study. Through clinical effectiveness studies, incorporation of these biomarkers would only improve the performance of the screening method and, therefore, an even greater reduction in the rate of preterm PE could be anticipated.[8,36]

Despite a high physician compliance rate in prescribing aspirin prophylaxis, using a maternal characteristic-based screening method still results in a high clinical and economic burden from preterm PE. In our cohort, using a conservative approach, application of the FMF algorithm achieved both clinical benefit and an economic cost-saving.

AUTHOR CONTRIBUTIONS

DN and SH contributed to conceptualisation, data curation, methodology, formal analysis, and writing. TP was involved in the methodology, formal analysis of the data, review and editing of the paper. DS contributed to conceptualisation, review and editing of the paper. CA contributed to data curation. PP, RN and DC all contributed to project administration, review and editing of the paper.

ACKNOWLEDGEMENTS

We would like to acknowledge Yu-Chieh Baldwinson, Sobia Sharif and Sarah Trompeter for her tremendous help in data collection.

FUNDING INFORMATION

No funding was received for this study.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL

The study is part of our routine clinical management; the local Research and Development Committee advised that formal consideration was not required.

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REFERENCES

1. Panaitescu AM, Syngelaki A, Prodan N, Akolekar R, Nicolaides KH. Chronic hypertension and adverse pregnancy outcome: a cohort study. Ultrasound Obstet Gynecol. 2017;50(2):228–35.
2. Fox A, McHugh S, Browne J, Kenny LC, Fitzgerald A, Khashan AS, et al. Estimating the cost of preeclampsia in the healthcare system: cross-sectional study using data from SCOPE study (screening for pregnancy end points). Hypertension. 2017;70(6):1243–9.
3. Wright D, Rolnik DL, Syngelaki A, de Paco Matallana C, Machuca M, de Alvarado M, et al. Aspirin for evidence-based preeclampsia prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. Am J Obstet Gynecol. 2018;218(6):612.e1–6.
4. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med. 2017;377(7):613–22.
5. National Institute for Health and Care Excellence. Antenatal care. [NICE guideline number NG201]. 2021. https://www.nice.org.uk/guidance/ng201
6. Tan MY, Wright D, Syngelaki A, Akolekar R, Cicero S, Janga D, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. Ultrasound Obstet Gynecol. 2018;51(6):743–50.
7. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet. 2007;369(9575):1791–8.
8. O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, Wright A, et al. Accuracy of competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol. 2017;49(6):751–5.
9. Guy GP, Leslie K, Diaz Gomez D, Forenc K, Buck E, Khalil A, et al. Implementation of routine first trimester combined screening for pre-eclampsia: a clinical effectiveness study. BJOG. 2021;128(2):149–56.
10. Guy GP, Leslie K, Diaz Gomez D, Forenc K, Buck E, Bhide A, et al. Effect of routine first-trimester combined screening for pre-eclampsia on small-for-gestational-age birth: secondary interrupted time series analysis. Ultrasound Obstet Gynecol. 2022;59(1):55–60.
11. Lourenço I, Gomes H, Ribeiro J, Caeiro F, Rocha P, Francisco C. Screening for preeclampsia in the first trimester and aspirin prophylaxis: our first year. Rev Bras Ginecol Obstet. 2020;42(7):390–6.
12. National Institute for Health and Care Excellence. Economic analysis of smoking cessation in secondary care. [NICE guideline number PH45]. 2013.
13. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. Pregnancy Hypertens. 2014;4(2):97–104.
14. Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr. 1996;85(7):843–8.
15. Harmon QE, Huang L, Umbach DM, Klungsøyr K, Engel SM, Magnus P, et al. Risk of fetal death with preeclampsia. Obstet Gynecol. 2015;125(3):628–35.
16. Shanmugalingam R, Wang X, Motum P, Fulcher I, Lee G, Kumar R, et al. Clinical influence of nonadherence with prophylactic aspirin in preventing preeclampsia in high-risk pregnancies: a multicenter, prospective, observational cohort study. Hypertension. 2020;75(4):1125–32.
17. Wright D, Poon LC, Rolnik DL, Syngelaki A, Delgado JL, Vojtassakova D, et al. Aspirin for evidence-based preeclampsia prevention trial: influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia. Am J Obstet Gynecol. 2017;217(6):685.e1–5.
18. Dubon Garcia A, Devlieger R, Redekop K, Vandeweyer K, Verlohren S, Poon LC. Cost-utility of a first-trimester screening strategy versus the standard of care for nulliparous women to prevent pre-term pre-eclampsia in Belgium. Pregnancy Hypertens. 2021;25:219–24.
19. Mewes JC, Lindenberg M, Vrijhoef HJM. Cost-effectiveness analysis of implementing screening on preterm pre-eclampsia at first trimester of pregnancy in Germany and Switzerland. PLoS One. 2022;17(6):e0270490.
20. Zakiyah N, Tuytten R, Baker PN, Kenny LC, Postma MJ, van Asselt ADI. Early cost-effectiveness analysis of screening for preeclampsia in nulliparous women: a modelling approach in European high-income settings. PLoS One. 2022;17(4):e0267313.
21. Park F, Deeming S, Bennett N, Hyett J. Cost-effectiveness analysis of a model of first-trimester prediction and prevention of preterm pre-eclampsia compared with usual care. Ultrasound Obstet Gynecol. 2021;58(5):688–97.
22. Ortved D, Hawkins TL, Johnson JA, Hyett J, Metcalfe A. Cost-effectiveness of first-trimester screening with early preventative use of aspirin in women at high risk of early-onset pre-eclampsia. Ultrasound Obstet Gynecol. 2019;53(2):239–44.
23. Rolnik DL, Selvaratnam RJ, Wertaschnigg D, Meagher S, Wallace E, Hyett J, et al. Routine first trimester combined screening for preterm preeclampsia in Australia: a multicenter clinical implementation cohort study. Int J Gynaecol Obstet. 2022;158(3):634–42.
24. Mallampati D, Grobman W, Rouse DJ, Werner EF. Strategies for prescribing aspirin to prevent preeclampsia: a cost-effectiveness analysis. Obstet Gynecol. 2019;134(3):537–44.
25. Mone F, O'Mahony JF, Tyrrell E, Mulcahy C, McParland P, Breathnach F, et al. Preeclampsia prevention using routine versus screening test-indicated aspirin in low-risk women. Hypertension. 2018;72(6):1391–6.
26. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315–81.
27. Davidson KW, Barry MJ, Mangione CM, Cabana M, Chelmow D, Coker TR, et al. Aspirin use to prevent cardiovascular disease: US Preventive Services Task Force recommendation statement. JAMA. 2022;327(16):1577–84.
28. Hastie R, Tong S, Wikström AK, Sandström A, Hesselman S, Bergman L. Aspirin use during pregnancy and the risk of bleeding complications: a Swedish population-based cohort study. Am J Obstet Gynecol. 2021;224(1):95.e1–2.
29. Subtil D, Goeusse P, Puech F, Lequien P, Biausque S, Breart G, et al. Aspirin (100 mg) used for prevention of pre-eclampsia in nulliparous women: the Essai Régional Aspirine Mère-Enfant study (part 1). BJOG. 2003;110(5):475–84.
30. Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N. Aspirin use to prevent preeclampsia and related morbidity and mortality: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2021;326(12):1192–206.
31. Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2019;2019(10):CD004659.
32. Cuckle H. Strategies for prescribing aspirin to prevent preeclampsia: a cost-effectiveness analysis. Obstet Gynecol. 2020;135(1):217.
33. Hoffman MK, Goudar SS, Kodkany BS, Metgud M, Somannavar M, Okitawutshu J, et al. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. Lancet. 2020;395(10220):285–93.
34. Patterson JK, Neuwahl S, Goco N, Moore J, Goudar SS, Derman RJ, et al. Cost-effectiveness of low-dose aspirin for the prevention of preterm birth: a prospective study of the Global Network for Women's and Children's Health Research. Lancet Glob Health. 2023;11(3):e436–44.
35. ACOG Committee opinion no. 743: low-dose aspirin use during pregnancy. Obstet Gynecol. 2018;132(1):e44–52.
36. Wright D, Tan MY, O'Gorman N, Syngelaki A, Nicolaides KH. Serum PlGF compared with PAPP-A in first trimester screening for preterm

pre-eclampsia: adjusting for the effect of aspirin treatment. BJOG. 2022;129(8):1308–17.
37. Turner CE, Young JM, Solomon MJ, Ludlow J, Benness C, Phipps H. Vaginal delivery compared with elective caesarean section: the views of pregnant women and clinicians. BJOG. 2008;115(12): 1494–502.
38. Matthijsse S, Andersson FL, Gargano M, Yip Sonderegger YL. Cost-effectiveness analysis of carbetocin versus oxytocin for the prevention of postpartum hemorrhage following vaginal birth in the United Kingdom. J Med Econ. 2022;25(1):129–37.
39. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. [NICE guideline number NG133]. 2019. https://www.nice.org.uk/guidance/ng133
40. Campbell HE, Kurinczuk JJ, Heazell A, Leal J, Rivero-Arias O. Healthcare and wider societal implications of stillbirth: a population-based cost-of-illness study. BJOG. 2018;125(2):108–17.
41. Hunter R, Beardmore-Gray A, Greenland M, Linsell L, Juszczak E, Hardy P, et al. Cost-utility analysis of planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX). Pharmacoecon Open. 2022;6:723–33.

SUPPORTING INFORMATION

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

How to cite this article: Nzelu D, Palmer T, Stott D, Pandya P, Napolitano R, Casagrandi D, et al. First trimester screening for pre-eclampsia and targeted aspirin prophylaxis: a cost-effectiveness cohort study. BJOG. 2023;00:1–9. https://doi.org/10.1111/1471-0528.17598