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Implementation of routine first trimester combined screening for pre-eclampsia: a clinical effectiveness study

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Objective Evaluate clinical effectiveness of the first trimester combined (FMF) pre-eclampsia screening programme when implemented in a public healthcare setting.

Design Retrospective cohort study.

Setting London tertiary hospital from January 2017 to March 2019.

Methods 7720 women screened for pre-eclampsia according to National Institute for Health and Care Excellence (NICE) risk-based guidance and 4841 by the Fetal Medical Foundation (FMF) algorithm which combined maternal risk factors, blood pressure, PAPP-A and uterine artery Doppler indices in the first trimester. High risk was defined by standard NICE criteria in the pre-intervention cohort (prescribed 75 mg aspirin) or a risk of ≥1:50 for preterm pre-eclampsia from the FMF algorithm in the post-intervention cohort (prescribed 150 mg aspirin).

Main outcome measures Screening effectiveness, rates of pre-eclampsia.

Results The FMF screening programme resulted in a significant reduction in the screen-positive rate (16.1 versus 8.2%, odds ratio [OR] 0.50, 95% confidence interval [CI] 0.41–0.53) with a concurrent increase in targeted aspirin use in women classified as high risk for pre-eclampsia (28.9 versus 99.0%, OR 241.6, 95% CI 89.6–652.0). Screening indices were uniformly improved for the FMF algorithm with receiver operating characteristic (ROC) analysis demonstrating excellent discrimination for preterm pre-eclampsia (area under the curve [AUC] = 0.846, 95% CI 0.778–0.915, *P* value <.001). Interrupted time series analysis showed that the FMF screening programme resulted in a significant 21-month relative effect reduction of 80% (*P* = .025) and 89% (*P* = .017), for preterm and early pre-eclampsia, respectively.

Conclusions First trimester combined screening for pre-eclampsia is both feasible and effective in a public healthcare setting. Such an approach results in a two-fold de-escalation of risk, doubling of pre-eclampsia detection, near total physician compliance of aspirin use and a significant reduction in the prevalence of preterm pre-eclampsia.

Keywords Aspirin, blood pressure, Doppler, first trimester, PAPP-A, pre-eclampsia, screening.

Tweetable abstract Implementation of 1st trimester combined pre-eclampsia screening effectively reduces prevalence of the disorder.

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Introduction

Current screening recommendations for pre-eclampsia utilise a medical, social and obstetric history-based approach for the majority of international institutions such as the American College of Obstetrics and Gynecology (ACOG),[1] International Society for the Study of Hypertension in Pregnancy (ISSHP)[2] and National Institute for Health and Care Excellence (NICE).[3] For example, NICE recommends that women are considered screen-positive for developing pre-eclampsia if one major risk factor or any two moderate factors are present. These recommendations for routine

population screening for pre-eclampsia are made on the basis of medical legacy rather than from an evidence base of prospective studies, despite such an approach being generally considered to be clinically ineffective.[4] Although the majority of the risk factors used are statistically associated with an increased risk of developing pre-eclampsia,[5] criticisms of the latter approach include low likelihood ratios of the individual risk factors, lack of consideration for the interactions between risk factors that might further weaken likelihood ratios, and the inability to de-escalate pre-eclampsia risk when protective factors are apparent, such as previous normotensive pregnancy or average weight. As a consequence of these limitations, the use of risk factor-based approach results in high screen-positive rates and a numerically indeterminate level of risk of pre-eclampsia in the screen-positive group.

A recent National Institute of Health Research (NIHR) funded study undertook a multi-centre head-to-head comparison of NICE risk-based versus first trimester Fetal Medicine Foundation (FMF) algorithm-based screening programmes for pre-eclampsia.[4] The authors demonstrated that multifactorial algorithm-based screening using maternal history, blood pressure, uterine Doppler and maternal serum biochemistry was superior, with both a significant reduction in screen-positive rate and an increase in detection for pre-eclampsia. The same FMF algorithm-based screening tool was used to guide first trimester low-dose aspirin prophylaxis and was subsequently assessed in the Aspirin for Evidence-Based Pre-eclampsia Prevention (ASPRE) randomised controlled trial.[6] This randomised controlled trial (RCT) established the efficacy of such a screening programme in a research setting by demonstrating a 62% (95% CI 26–80%) reduction in the incidence of preterm pre-eclampsia. The aim of this study is to evaluate the clinical effectiveness of the FMF algorithm-based screening programme when implemented in a routine NHS healthcare setting by assessing prediction of pre-eclampsia, rates of pre-eclampsia and maternal/fetal outcomes.

Methods

Following the publication of the ASPRE RCT results in August 2017, St George's University Hospitals NHS Foundation Trust implemented the first trimester FMF multifactorial algorithm-based screening programme for pre-eclampsia in March 2018, having previously routinely used NICE risk factor-based assessment.[3] In keeping with the intervention in the ASPRE study, the use of aspirin prophylaxis in the high risk for pre-eclampsia group was also changed from 75 to 150 mg once daily at that time. Implementation was undertaken without any additional financial support. The change of practice process included a formal application for NICE exemption and multi-professional education of midwives, sonographers, obstetricians, pharmacists and general practitioners. Sonographers who routinely undertook second trimester uterine artery Doppler in high-risk pregnancy were trained to do this in the first trimester. Time to undertake this assessment was enabled by the reduced screen-positive rate and reduced numbers of follow-up scans required with the new screening protocol. All singleton pregnancies booked at St George's hospital prior to 14 weeks' gestation were included. Exclusion criteria included multiple pregnancy, fetal abnormalities, miscarriages, terminations and those lost to follow up (see Figure S1 for participant flow information).

RRisk for pre-eclampsia was defined as high in the NICE screening cohort if one major risk factor (previous hypertensive disorder of pregnancy, chronic hypertension, diabetes mellitus, chronic kidney disease or autoimmune disease) or any two moderate factors (nulliparity, maternal age ≥40 years, body mass index [BMI] at booking ≥35 kg/m^2, inter-pregnancy interval >10 years or family history of pre-eclampsia) were present. Subsequent pregnancy management was scheduled as dictated by NICE guidance. A risk cut-off of ≥1:50 for preterm pre-eclampsia was considered high risk using an FMF algorithm combining maternal factors, mean arterial pressure (MAP), first trimester uterine artery pulsatility index (UtA-PI) Doppler and pregnancy-associated plasma protein A (PAPP-A). The risk cut-off of ≥1:100 for preterm pre-eclampsia used in the ASPRE trial resulted in a high screen-positive rate of 18% in our population, hence a pragmatic decision was taken to reduce the cut-off to ≥1:50 with an expected screen-positive rate of approximately 10%. Given the use of maternal serum PAPP-A (taken routinely for trisomy screening) rather than placental growth factor (PlGF) in the algorithm, we anticipated a detection rate of 76% for preterm pre-eclampsia at a 10% screen-positive rate.[4] If either PAPP-A or UtA-PI was not available, the FMF algorithm was run with the other parameters on the basis that the SPREE study[4] demonstrated that even without one of these measurements, first trimester FMF combined pre-eclampsia screening remained more effective than conventional NICE screening. All women with a risk of ≥1:50 for preterm pre-eclampsia were offered serial scans (28 and 36 weeks) and induction of labour from 40 weeks' gestation.

Outcome measures

Patients were not involved in the development of the research, as the data for this study were derived from a retrospective analysis of routinely collected information from the maternity birth registry and ultrasound databases between January 2017 and March 2019. These databases are used routinely in healthcare service delivery and are subject to regular clinical governance review. In addition, all hypertensive outcomes and 500 non-hypertensive pregnancies were cross-checked with individual maternity records to confirm database accuracy and reliability. Details collected included maternal demographic/pregnancy characteristics and

previous medical history. Gestational age was determined by crown–rump length (CRL) measurement performed at the routine 11- to 13-week ultrasound scan.[7] The MAP and UtA-PI were assessed according to standardised protocols at the same visit.[8,9] Core outcome sets were not used. The primary outcomes were defined as the rates of pre-eclampsia at various gestational ages at delivery, before and after introduction of the FMF screening programme, and evaluation of screening performance. Secondary outcomes included evaluation of prescription of aspirin prophylaxis, rates of small-for-gestational-age birth and severity of pre-eclampsia. Pre-eclampsia was defined according to the criteria in the NICE hypertension in pregnancy guidelines.[3] Small for gestational age was defined as a birthweight <10th centile, adjusted for gestational age at birth. Fetal growth restriction was defined as any of the following: abnormal fetal Doppler (umbilical artery pulsatility index >95th centile and/or middle cerebral artery pulsatility index <5th centile); or birthweight <10th centile with abnormal fetal Doppler; or birthweight <3rd centile; or intrauterine or neonatal death secondary to uteroplacental insufficiency. Severity of pre-eclampsia was defined by the following criteria: two or more abnormal bloods and/or polymerase chain reaction (PCR), according to the NICE cut-off criteria for pre-eclampsia diagnosis[3] (i.e. any maternal biochemistry or haematology results outside the expected reference range); use of magnesium sulphate for treatment of severe pre-eclampsia; eclampsia or haemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome; neonatal unit admission and hypertensive treatment needing two or more agents. The latter was chosen, as rescue therapy with a second (or more) antihypertensive medication to control hypertension is a good clinical proxy of severe hypertension and is more strongly associated with adverse pregnancy outcome[10] Maternal, fetal and neonatal outcomes of the overall population are shown in Table S1.

Statistical analysis

Descriptive data were presented in median and interquartile range for continuous variables and in numbers and percentages for categorical variables. To detect whether the intervention had a significantly greater effect than any temporal confounding due to an underlying secular trend, an interrupted time series (ITS) analysis using ARIMA modelling of the primary outcomes of pre-eclampsia rates at various gestational age at delivery was performed[11] and reported as the relative effect change at 21 months post-intervention. In short, data were organised as per the methods described in Cochrane: Effective Practice and Organisation of Care.[11] Estimates for regression coefficients correlated with two standardised effect sizes were calculated including a change in level (also called 'step change') and a change in trend before and after the intervention (Table S4).[11] In the pre-intervention period, the coefficient for 'time' gives the slope of the regression line pre-intervention; the coefficient for 'phase' is the point on the *y*-axis when projecting back the line for the post-slope to the *y*-axis; and the coefficient for 'interact' is the difference between the pre-slope and post-slope. Post intervention, in each 3-monthly period, the coefficient for 'phase' is the level effect at 3, 6, 12, 15, 18 and 21 months, respectively. The model was then used to calculate the relative effect change at each interval by the method described by Cochrane,[11] which included the 'phase' coefficient and predicted value. This was reported at the 21-month post implementation interval to interrogate the maximal effect of the new screening programme. Comparisons between groups were performed using the Mann–Whitney *U*-test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Odds ratios

Table 1. Maternal demographic and risk factor characteristics of the study population managed with NICE or first trimester FMF algorithm-based pre-eclampsia screening. Data shown as median (interquartile range) or number (%)

Characteristic	NICE screened (*n* = 7720)	Combined (FMF) screened (*n* = 4841)	*P*-value
Weight (kg)	65.3 (58.0–75.0)	65.9 (58.6–75.4)	0.158
Height (cm)	163.5 (159–168)	164 (164–168)	0.287
Age (years)	33 (29–36)	32 (29–35)	0.223
MAP (mmHg)	86.7 (81.3–92.0)	86 (81.3–91.2)	0.344
Nulliparous	3890 (50.4%)	2484 (51.3%)	0.323
Ethnicity			
White	5036 (65.5%)	3165 (65.4%)	0.882
Black	930 (12.0%)	547 (11.3%)	0.216
South Asian	1291 (16.7%)	814 (16.8%)	0.913
East Asian	269 (3.5%)	195 (4.0%)	0.128
Mixed	201 (2.6%)	120 (2.5%)	0.709
Smoker	321 (4.2%)	201 (4.2%)	0.216
Previous pre-eclampsia	174 (2.3%)	122 (2.5%)	0.370
ART (IVF/ICSI/ other)	322 (4.2%)	179 (3.7%)	0.203
Renal disease	29 (0.4%)	29 (0.6%)	0.097
Autoimmune disease	79 (1.0%)	69 (1.4%)	0.052
SLE/APLS	21 (0.3%)	17 (0.4%)	0.536
Pre-pregnancy diabetes	54 (7.0%)	42 (8.7%)	0.343
Chronic hypertension	94 (1.2%)	56 (1.2%)	0.825

APLS, antiphospholipid syndrome; ART, artificial reproductive technology; BP, blood pressure; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation; MAP, mean arterial pressure; SLE, systemic lupus erythematosus.
Comparisons between outcome groups were by Chi-square or Fisher exact test for categorical variables and Mann–Whitney *U*-test for continuous variables.

for each variable were calculated. Screening test evaluation included sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy. The statistical software packages SPSS 22.0 (SPSS Inc., Chicago, IL, USA), GraphPad (GraphPad Software, San Diego, CA, USA) and MedCalc (MedCalc Software, Mariakerke, Belgium) were used for data analyses.

Results

Between January 2017 and March 2019, a total of 12 561 women attended the unit with singleton pregnancies prior to 14 weeks' gestation: 7720 underwent screening for pre-eclampsia according to NICE guidance and 4841 using the FMF screening algorithm. There were no significant differences in the maternal demographic characteristics or medical history between the two groups, with maternal age, BMI, parity, ethnicity and pre-eclampsia risk factors being comparable between both groups (Table 1).

Comparison of the NICE and FMF screening tests

There was a significant reduction in the screen-positive rate (8.2 versus 16.1%, OR 0.50, 95% CI 0.41–0.53) with a concurrent increase in targeted aspirin use in women classified as high risk for pre-eclampsia (99.0 versus 28.9%, OR 241.6, 95% CI 89.6–652.0) in the FMF compared with the NICE screened cohorts (Table 2). The rate of aspirin prophylaxis in women who developed pre-eclampsia was also significantly higher in women screened using the FMF algorithm (39.0 versus 24.5%, OR 1.97, 95% CI 1.27–3.06). The detection rates for preterm pre-eclampsia after routine aspirin prophylaxis using NICE and FMF screening algorithms are also shown in Table 2—screening indices were uniformly improved for FMF compared with NICE screening. The ROC analysis for FMF screening demonstrated excellent discrimination for preterm pre-eclampsia (Figure S2: AUC = 0.846, 95% CI 0.778–0.915, SE 0.035, $P < 0.001$). The screening characteristics for different risk cut-offs to detect preterm and term pre-eclampsia are shown in Tables S2 and S3.

Effect of the FMF screening programme on pregnancy outcomes

With conventional odds ratio analysis, there was an apparent 23% reduction in the prevalence of pre-eclampsia in the cohort managed with the FMF screening programme (2.8

Table 2. Comparison of screening performance, targeting use of aspirin prescription, pre-eclampsia rates and pregnancy outcomes in the NICE and first trimester FMF algorithm-based pre-eclampsia screened cohorts. There were 65 (0.84%) and 27 (0.56%) preterm pre-eclampsia cases in the NICE and FMF cohorts, respectively. Data presented as number (%) or screening test evaluation results

Outcome	NICE screened (*n* = 278)	Combined (FMF) screened (*n* = 136)	Odds ratio (95% CI)	*P*-value	21 months' relative effect change (ITS analysis)	*P*-value
Pre-eclampsia rates						
Overall pre-eclampsia rate	278 (3.6)	136 (2.8)	0.774 (0.628–0.953)	**0.016**	−44.3%	0.308
Pre-eclampsia at term (≥37 weeks)	213 (2.7)	109 (2.3)	0.812 (0.643–1.026)	0.080	−20.2%	0.739
Pre-eclampsia <37 weeks	65 (0.84)	27 (0.56)	0.661 (0.421–1.036)	0.071	−80.0%	**0.025**
Pre-eclampsia <34 weeks	18 (0.23)	7 (0.14)	0.620 (0.259–1.485)	0.283	−89.9%	**0.017**
Pre-eclampsia <30 weeks	8 (0.10)	0 (0)	0.094 (0.005–1.624)	0.104	–	–
Screening and aspirin						
Screen-positive (high-risk)	1242 (16.1)	397 (8.2)	0.496 (0.414–0.525)	**<0.001**	–	–
Screen-positive on aspirin	359 (28.9)	393 (99.0)	241.66 (89.56–652.04)	**<0.001**	–	–
Pre-eclampsia cases on aspirin	68 (24.5)	53 (39.0)	1.972 (1.270–3.062)	**0.003**	–	–
Screening performance for preterm (<37 weeks) pre-eclampsia						
Sensitivity	36.9% (25.3–49.8)	55.6% (35.3–74.5)	2.135 (0.859–5.311)	0.103	–	–
Specificity	84.1% (83.6–84.9)	92.0% (91.2–92.8)	2.195 (1.945–2.478)	**<0.001**	–	–
Positive LR	2.3 (1.9–3.2)	7.0 (4.9–9.9)	–	–	–	–
Negative LR	0.75 (0.62–0.90)	0.48 (0.32–0.74)	–	–	–	–
Positive PV	1.9% (1.4–2.7)	3.8% (2.7–5.3)	–	–	–	–
Negative PV	99.4% (99.2–99.5)	99.7% (99.6–99.8)	–	–	–	–
Accuracy	83.7% (82.9–84.5)	91.8% (91.0–92.6)	–	–	–	–

LR, likelihood ratio; PV, predictive value.
Primary outcomes of pre-eclampsia rates were compared by interrupted time series (ITS) analysis. Comparisons between secondary outcome groups were by Chi-square or Fisher exact test for categorical variables or Mann–Whitney *U*-test for continuous variables.
P-values for signficant findings shown in bold.

versus 3.6%, OR 0.774, 95% CI 0.628–0.953). Although not reaching statistical significance, there was a trend evident with reductions of 38, 34 and 19% in early, preterm and term pre-eclampsia, respectively—and no cases of pre-eclampsia before 30 weeks' gestation in the FMF screened cohort (Table 2, Figure 1). When analysed using ITS method, after confirming rates of pre-eclampsia at various gestations of delivery that were stable in the NICE (pre-intervention) period, there were now significant reductions in both the preterm (<37 weeks) and early pre-eclampsia (<34 weeks) rates at 21 months post implementation, with relative effective reductions of 80% ($P = 0.025$) and 89% ($P = 0.017$), respectively (Tables 2 and S4, Figures 2, S3–S5). ITS analysis for pre-eclampsia delivering at <30 weeks revealed invalid results due to the lack of cases that inherently affect the analysis. There was a 45% overall reduction in women with pre-eclampsia needing more than

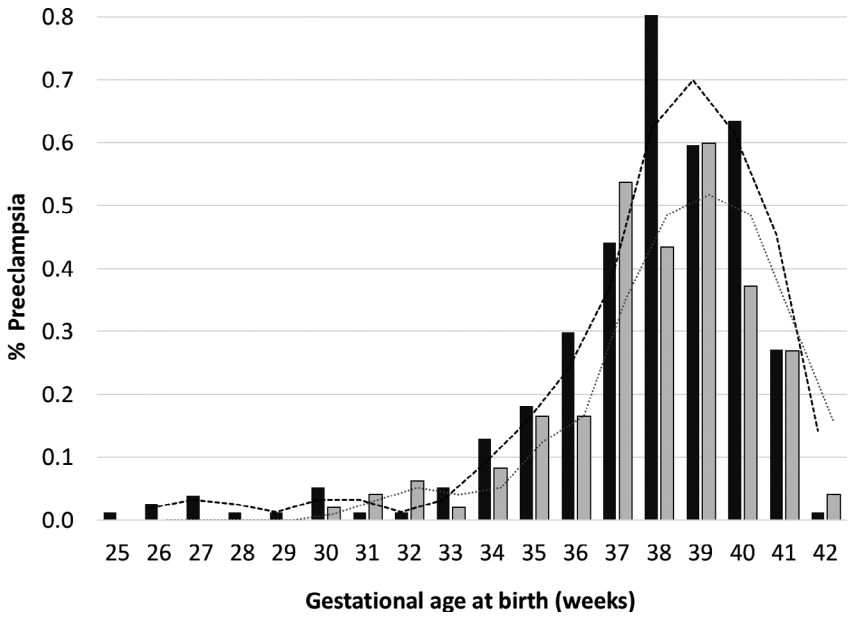

Figure 1. Graph showing the proportion of women developing pre-eclampsia in weekly gestational epochs in the NICE- and FMF-screened cohorts (NICE cohort—black bars and dashed line, FMF cohort—grey bars and dotted line).

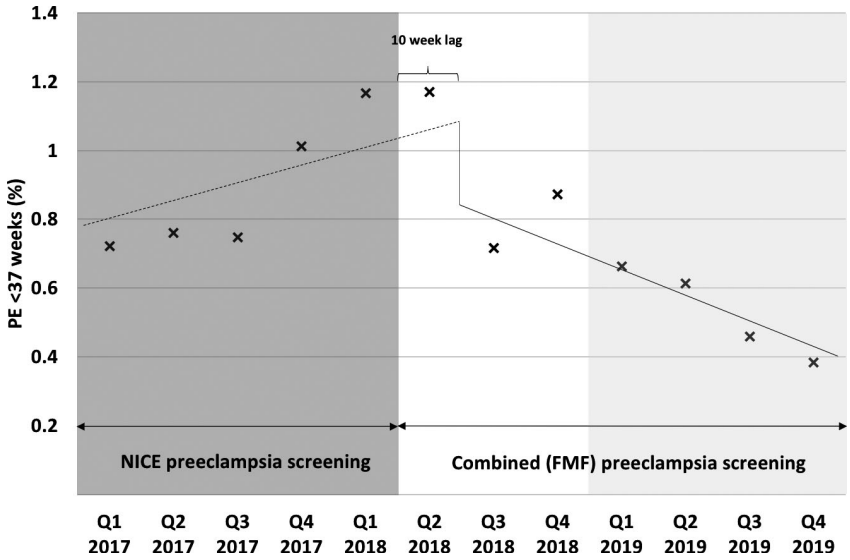

Figure 2. Graph showing the change in percentage of births complicated by preterm (<37 weeks) pre-eclampsia in quarter-year epochs before (NICE screened) and after implementation of the FMF screening programme with reference to the general elements of an interrupted time series (ITS) analysis (pre-slope—dashed lines; change in level—dotted lines; post-slope—solid lines). Dark grey—births with exclusive NICE screening; white—births containing both NICE and FMF screening; light grey—births with exclusive FMF screening; 10-week lag—pre-viability period (14–24 weeks' gestation) of the first FMF-screened pregnancies.

one antihypertensive drug to control blood pressure in the FMF cohort (Table S5) (15.4 versus 24.8%, OR 0.553, 95% CI 0.323–0.948). This reduction was most evident in the term pre-eclampsia group, with a three-fold decrease in hypertension needing treatment with more than one antihypertensive (16.9 versus 6.4%, $P = 0.015$). The rates of abnormal haematology, biochemistry, urine PCR, magnesium sulphate use, HELLP syndrome and eclampsia were not significantly different between the cohorts. There were also no significant differences in the prevalence of small-for-gestational-age birth, fetal growth restriction, admission to the neonatal intensive care unit or perinatal mortality (Table S5).

Discussion

Main findings

This study demonstrates the clinical effectiveness of multimodal first trimester pre-eclampsia screening and contingent aspirin prophylaxis. We have shown that this screening programme can be implemented in a state-funded, national healthcare setting and confers a significant improvement in clinical outcomes compared with current routine practice by effectively decreasing the screen-positive rate, improving the targeted use of aspirin prophylaxis and reducing the prevalence of preterm pre-eclampsia—all achieved without worsening of pre-eclampsia clinical severity (Video S1).

Strengths and limitations of the study

This study evaluates the effectiveness of an FMF pre-eclampsia screening programme in a large population of women receiving routine care in a public health setting. The comparisons of demographic and medical characteristics, as well as comprehensive outcome analysis are among the strengths of this study. Although we externally validated the ASPRE trial findings, by implication, a retrospective analysis limits the internal validity of our study findings. As such, we cannot rule out the possibility that other concurrent changes in clinical practice, health environment or population may have contributed to the study findings. However, by performing the ITS analysis, we have accounted for the effects of temporal confounders on our primary outcomes. We acknowledge that the improved targeting of aspirin and its effect on reducing pre-eclampsia prevalence would have led to an underestimation of the screening efficiency of the FMF algorithm because of treatment paradox, but avoiding this effect by withholding aspirin prophylaxis from such high-risk women would have been unethical.

Interpretation

Clinical implications of study findings

Randomised controlled trials are considered to be the gold standard in evaluating the effects of treatment, and in this regard the ASPRE RCT established the efficacy of multimodal first trimester pre-eclampsia screening with contingent aspirin prophylaxis in managing pre-eclampsia. To be clinically meaningful, the external validity (or generalisability) of the ASPRE study findings must be established to determine whether it can overcome the limitations of 'real world' practical implementation, such as differing patient characteristics, doctor preferences, patient compliance, comorbidities and other concomitant interventions. Effectiveness studies measure the degree of beneficial effect of an intervention in a pragmatic clinical setting. The introduction of FMF combined screening improved detection of both preterm and term pre-eclampsia despite a two-fold reduction in the proportion of women identified as at high risk of pre-eclampsia. The former findings contributed to effective de-escalation of risk and also led to improved physician compliance, with 99% of women being prescribed aspirin—a six-fold improvement on the cohort with NICE screening. The latter findings of more accurate screening and improved physician compliance are consistent with a recent study undertaken to validate the FMF screening algorithm.[4]

On conventional OR analysis, the FMF screening programme resulted in a significant overall 23% reduction in the prevalence of pre-eclampsia—similar to the 27% reduction reported in the ASPRE trial.[6] The reduction in pre-eclampsia rates was most evident at preterm gestations, with no cases being reported before 30 weeks and a 38% reduction in early pre-eclampsia requiring scheduled birth before 34 weeks' gestation. The ITS analysis performed to reduce the influence of temporal confounding factors revealed significant reductions in both preterm and early pre-eclampsia after introduction of the FMF screening programme, with a 21-months relative effect reduction of 80 and 89%, respectively. Conversely, the term pre-eclampsia rate reduction was not significant by ITS analysis and therefore is most likely due to confounding factors rather than the FMF screening programme. This was not unexpected, as the ASPRE trial did not demonstrate reduction in term pre-eclampsia and because there was an overall trend to increasing induction of labour in our cohort (Table S1). A recent RCT, where elective birth at 39 weeks' gestation resulted in a 35% lower chance of developing hypertensive disorders of pregnancy compared with expectant management, provides evidence for this effect.[12] In addition to reducing the prevalence of pre-eclampsia, the severity of the disease appeared not to worsen, with all maternal markers of maternal and fetal complications (such as pre-eclampsia markers and poor fetal growth) appearing unchanged in the FMF cohort. Our findings are consistent not only with a reduction in pre-eclampsia prevalence but also with a 'right shift' in the clinical presentation of pre-eclampsia to a later gestational age (Figure 1)—a finding in keeping with a secondary analysis of the ASPRE efficacy trial.[13]

Public health implications of study findings

This study demonstrates that a first trimester combined pre-eclampsia screening programme is feasible, pragmatic and effective in a public healthcare setting. Implementation of this screening programme resulted in de-escalation of risk for many women with half as many being labelled as high risk. The manageable screen-positive rate of 8% is likely to have contributed to the six-fold improvement in physician compliance, such that 99% of high-risk women were prescribed aspirin prophylaxis at 150 mg. It is important to note that the dosage of aspirin used in this study has not been universally adopted by international societies. Aside from the findings of the ASPRE RCT, the optimal timing and dosage of aspirin prophylaxis were recently reviewed with the observation that there was a dose-response effect resulting in 150 mg aspirin conferring the most beneficial effect in preventing pre-eclampsia.[14] This finding is readily explained by several studies demonstrating a 30–40% rate of aspirin resistance in pregnancy that is not evident in the non-pregnant state.[15–17] The near total initiation of effective aspirin prophylaxis as a result of an individualised risk and a universal 'one-stop' screening approach is important given the previously poor rates. This is echoed in the most recent MBRRACE report, where a number of women at increased risk were never offered aspirin prophylaxis.[18]

The findings of this study raise important issues regarding the process and mechanism of policy-making for the screening of pre-eclampsia. Screening committees typically commission reviews of evidence for pre-eclampsia as a specific disorder without giving credence to the fact that pre-eclampsia is defined by signs elicited in pregnancy, where the true disease is underlying uteroplacental insufficiency with many other potential manifestations.[19] Another example of how screening may be impacted is the influence of birth, which introduces significant treatment paradox—birth today precludes the development of pre-eclampsia tomorrow, even though the woman may have been destined to develop it. Hence, conventional sensitivity/specificity and likelihood ratio analyses used for non-pregnancy conditions such as cervical cancer are invalid and should be replaced by a competing risk approach analyses.[20] Similarly, the use of arbitrary thresholds to determine whether a screening test may be useful (i.e. likelihood ratio of 10) should be replaced, as they have only been bench-marked and standardised for routine screening for conditions outside pregnancy that are well-defined and free of treatment paradox.

Conclusions

First trimester multimodal screening for pre-eclampsia with aspirin prophylaxis is feasible and effective in a public health setting. Such an approach results in a two-fold de-escalation of risk, doubling of pre-eclampsia detection, almost total physician compliance with aspirin use and reduction the prevalence of preterm and early pre-eclampsia without any worsening of pre-eclampsia clinical severity. Given the demonstration of efficacy of such a screening programme in an RCT and now a demonstration of its effectiveness in a public healthcare setting, the continued use of a risk factor-based screening must be re-evaluated.

Disclosure of interests

None declared. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

Conceptualisation: BT, GPG, KL. Methodology: BT, GPG. Data collection: GPG, DDG, KL, KF, EB. Statistical analysis: GPG. Data interpretation: GPG, BT. Manuscript draft: GPG, BT. Manuscript review and editing: GPG, KL, DDG, KF, EB, AK, BT.

Details of ethics approval

This retrospective study of routinely collected clinical data was collated from an ongoing continuous audit and was deemed not to require ethics approval or signed patient consent as per the Health Regional Authority (HRA) decision tool.

Funding

None.

Supporting Information

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

Figure S1. Study participant flow chart.

Figure S2. The receiver operator characteristic of an FMF risk ≥1:50 for the detection of preterm pre-eclampsia demonstrates excellent discrimination (AUC = 0.846, $P < 0.001$).

Figure S3. Colour version of Figure 2. Graph showing the percentage of births complicated by preterm (<37 weeks) pre-eclampsia in quarter-year epochs before (NICE screened) and after implementation of the FMF screening programme with reference to the general elements of an interrupted time series (ITS) analysis (pre-slope—dashed lines; change in level—dotted lines; post-slope—solid lines).

Figure S4. Graph showing the percentage of births complicated by early (<34 weeks) pre-eclampsia in quarter-year epochs before (NICE screened) and after implementation of the FMF screening programme with reference to the general elements of an interrupted time series (ITS) analysis (pre-slope—dashed lines; change in level—dotted lines; post-slope—solid lines).

Figure S5. Colour version of Figure S4. Graph showing the percentage of births complicated by early (<34 weeks) pre-eclampsia in quarter-year epochs before (NICE screened) and after implementation of the FMF screening programme with reference to the general elements of an interrupted time series (ITS) analysis (pre-slope—dashed lines; change in level—dotted lines; post-slope—solid lines).

Table S1. Maternal, fetal and neonatal outcomes of the study population managed with NICE or first trimester FMF algorithm-based pre-eclampsia screening.

Table S2. Screening performance for preterm pre-eclampsia delivering before 37 weeks' gestation for the NICE-screened (n = 65, 0.84%) and FMF-screened (n = 27, 0.56%) cohort at various risk cut-offs for pre-eclampsia <37 weeks.

Table S3. Screening performance for term pre-eclampsia delivering at or after 37 weeks' gestation for the NICE-screened (n = 213, 2.7%) and FMF-screened (n = 109, 2.3%) cohort at various risk cut-offs for pre-eclampsia <37 weeks.

Table S4. Interrupted time series analysis (ITS) of the % of births complicated by pre-eclampsia at birth at various gestational age at delivery using ARIMA modelling.

Table S5. Maternal, fetal and neonatal outcomes of the pre-eclamptic women managed with NICE or first trimester FMF algorithm-based pre-eclampsia screening.

Video S1. Author insights. ■

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