Effect of routine first trimester combined screening for pre-eclampsia on small for gestational age birth: a secondary interrupted time series analysis

Short title: First trimester combined preeclampsia screening SGA

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ABSTRACT

Objective: Evaluate the effect of first trimester combined Fetal Medicine Foundation (FMF) based pre-eclampsia screening on rates of fetal small for gestational age (SGA) birth and adverse pregnancy outcome.

Methods: A retrospective cohort study in a London tertiary hospital between January 2017 to March 2019. Secondary analysis of first trimester screening for pre-eclampsia: 7720 screened according to NICE risk-based approach and 4841 by FMF multimodal approach combining risk factors, blood pressure, PAPP-A and uterine Doppler indices. Package of care for FMF screened group included 150mg aspirin prophylaxis, ultrasound at 28 and 36 weeks and scheduled delivery at 40 weeks' gestation. Outcome measures include SGA at birth, admission to neonatal unit (NNU), intrauterine death, neonatal death and hypoxic ischaemic encephalopathy by interrupted time series (ITS) analysis.

Results: There was no significant change in the rates of intrauterine demise, neonatal death and hypoxic ischaemic encephalopathy. ITS analysis showed a significant reduction in term SGA birth <10th centile at 21 months post implementation, with a relative effect reduction of 45.1% (p=0.004) - but not for SGA birth <5th or 3rd centile.

Conclusions: First trimester FMF combined screening for pre-eclampsia with elective birth from 40 weeks' gestation resulted in a significant relative 45% effect reduction for term SGA birth at <10th centile, but not SGA at <5th or 3rd centile. Further screening strategies to detect and improve outcomes for SGA <5th centile birth need to be considered.

INTRODUCTION

The Fetal Medicine Foundation (FMF) first trimester combined screening algorithm for prediction of pre-eclampsia effectively identifies women who subsequently develop preterm pre-eclampsia because of early uteroplacental dysfunction. The efficacy of a screening programme based on this algorithm for primary prevention of preterm pre-eclampsia with targeted low dose aspirin was established in a large randomised controlled trial and subsequently externally validated in a routine healthcare setting[1-3]. As uteroplacental dysfunction is acknowledged to cause both pre-eclampsia and fetal growth restriction (FGR), women at high-risk of preterm pre-eclampsia were also offered serial ultrasound at 28- and 36-weeks' gestation[4]. In addition, induction of labour was offered from 40 weeks' gestation, given that the effect of aspirin prophylaxis is to delay the onset of pre-eclampsia, but has not been shown to prevent the development of FGR or small for gestational age (SGA) birth[5]. FGR, of which many are SGA, can result in stillbirth, significant short-term and long-term morbidity and adversely impact quality of life[6,7]. It is therefore important to understand the impact of the combined pre-eclampsia screening algorithm on the prevalence of SGA and/or FGR. In previous publications, the latter was examined using conventional odds ratio analysis and failed to show any significant differences[3,5]. A criticism of this statistical approach is that it does not account for temporal confounding due to potential underlying trends in access to clinical resources and changes to delivery of care[8,9]. This can be overcome by undertaking an interrupted time series analysis, which is a statistical approach that involves tracking outcomes before and after a point of intervention to control for possible trends and other confounders. The aim of this study is to undertake a detailed interrupted time series analysis to evaluate the impact of the FMF pre-eclampsia screening programme on rates of FGR, SGA birth and adverse pregnancy outcome.

METHODS

The data for this study were derived from a secondary analysis of the implementation cohort of first trimester FMF multifactorial algorithm-based screening programme for pre-eclampsia at St George's University Hospitals NHS Foundation Trust between January 2017 to March 2019[3]. This cohort study included all women who booked prior to 14 weeks' gestation, as identified by the maternity booking database. The pre-intervention cohort were screened for pre-eclampsia risk and offered 75mg aspirin prophylaxis according to NICE guidance[10]. The succeeding FMF screening programme was introduced in March 2018 and included an algorithm-based risk assessment using maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and pregnancy-associated plasma protein A (PAPP-A). Those with a risk of ≥ 1:50 for preterm pre-eclampsia were classified as high risk and offered 150mg of prophylactic aspirin, as previously described[3]. Those women with a high risk ≥1:50 for preterm pre-eclampsia were offered serial growth scans (28- and 36-weeks' gestation) due to the associated risk of growth restriction and a recommendation for induction of labour from 40 weeks to reduce the risk of late-onset placental insufficiency[5]. The cut-off differed to the ASPRE trial as ≥1:100 resulted in a resource overwhelming high screen positive rate of 18% in our population and a pragmatic decision was taken to reduce the cut-off to ≥1:50 with an expected screen positive rate of approximately 10%[1]. In the pre-intervention (NICE screened) cohort compliance to prescription of aspirin was <25%, rising to >99% in the post-intervention (FMF screened) cohort[3]. Women's adherence to aspirin prescription was not measured. All singleton pregnancies booked at St George's hospital prior to 14 weeks' gestation were included to allow for FMF algorithm assessment. Exclusion criteria included miscarriages, terminations, multiple pregnancy and those lost to follow-up (see Figure S1 for patient stream information).

Outcome Measures

Data for this study originated from a retrospective evaluation of information from the ultrasound database and maternity birth registry for those booked between January 2017 and March 2019. The data is routinely collected for the provision of healthcare and has systematic clinical governance evaluation. To confirm database fidelity, every

hypertensive and 500 non-hypertensive pregnancies were validated against the hospital case notes. Maternal demographics, obstetric and past medical history were obtained. Gestational age was established by crown-rump length (CRL) dimension completed at the routine 11-to-13-week ultrasound scan[11]. The UtA-PI and MAP were measured in accordance with systematic protocols at the same visit[12,13]. Using the Society for Maternal-Fetal Medicine (SMFM) criteria, FGR was defined as a sonographic estimated fetal weight (EFW) below the 10th percentile for gestational age. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) on the other hand, highlight that fetuses with birth weight below the 3rd percentile are at the highest risk of stillbirth and perinatal mortality[14, 15], and for this reason, EFW below the 3rd percentile can be used as an isolated criterion to define FGR at any gestation[16]. The primary outcomes were the rates of birth of a SGA infant at the 10th, 5th and 3rd centile cut-offs at <37 weeks (preterm), ≥37 weeks (term) and any gestation (overall). Rates of adverse fetal and neonatal outcomes were also collected including admission to neonatal unit (NNU), intrauterine demise (IUD), early neonatal death (NND), hypoxic ischaemic encephalopathy (HIE) grade 2/3 and a composite measure of IUD, NND and HIE due to their rare occurrence individually and combined importance in pregnancy outcome. Pre-eclampsia cases were not excluded from the secondary analysis. Additionally, the gestation used for SGA determination for these cases included those that were delivered because of pre-eclampsia.

Statistical analysis

Descriptive data were presented in median and interquartile range for continuous variables and in numbers and percentages for categorical variables. Comparisons between groups were performed using the Mann–Whitney U-test for continuous variables and the $\chi 2$ test or Fisher's exact test for categorical variables. Odds ratios for each variable were calculated. The interrupted time series analysis (ITSA) method includes generating a time series of outcome rates for an intervention before and after its implementation and testing statistically the intervention effect on the change in outcome. The advantages of this method include the ability to control temporal confounding due to an underlying secular trend and provide clear graphical representation of results[17]. An approach to ITSA is the use of Autoregressive integrated moving average (ARIMA) modelling that predicts future values based on

past values[8]. ITSA analysis of the primary outcomes of small for gestational age rates at various cut-offs and gestational age at delivery was performed and reported as the relative effect change at 21 months post-intervention, which was the latest time point in our data series. In summary, data was prepared as per the methods described in Cochrane: Effective Practice and Organisation of Care. Estimates for regression coefficients correlated with two standardised effect sizes were calculated including a change in level (step change) and a change in trend before and after the intervention (Table S1). 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, the coefficient for 'phase' is the level effect in each subsequent three-monthly period. The model was then used to calculate the relative effect change at each interval by the method described by Cochrane[8] that included the 'phase' coefficient and predicted value. This was reported at the 21-month post implementation interval so to interrogate the maximal effect of the new screening programme. ITS analysis was only undertaken when the number of events in each epoch was greater than 10, in view of the unreliability inherent to low event rates[6]. The statistical software packages SPSS 22.0 (SPSS Inc., Chicago, IL), GraphPad (GraphPad Software, San Diego, CA) and MedCalc (MedCalc Software, Mariakerke, Belgium) were used for data analyses.

RESULTS

Between January 2017 and March 2019, 12,561 women attended the unit with singleton pregnancies prior to 14 weeks' gestation: 7720 underwent screening for preeclampsia according to standard NICE guidance and 4841 using the FMF screening algorithm. There were no significant differences in the maternal demographic characteristics and medical history between the two groups with maternal age, BMI, parity, ethnicity and preeclampsia risk factors being comparable between both groups as previously reported (Table S2).[3]

Effect of the FMF screening programme on pregnancy outcomes

The overall stillbirth rate in the screened population during the entire period of study was 2.78 per 1000 births (35 stillbirths in 12,561 pregnancies). The equivalent neonatal death and hypoxic ischaemic encephalopathy rates were 1.03 and 1.43 per 1000 births, respectively (Table 1). With conventional odds ratio analysis, there was no significant change in the rates of preterm or term intrauterine demise, neonatal death, hypoxic ischaemic encephalopathy and composite outcome of all three outcomes when the NICE and FMF screening programme were compared (Table 1). There was no change in the admission rate to the neonatal unit in the two screening programmes. Very low event rates (<10) in each epoch precluded an ITS analysis to evaluate step and relative effect changes of modifying the screening programme.

Fetal monitoring for SGA with FMF screening

Conventional odds ratio analysis did not show significant change in the rates of preterm or term SGA birth at <10th, <5th and <3rd birthweight centiles when NICE and FMF screening programmes were compared (Table 1). Event rates permitted ITS analysis for term and preterm SGA birth at <10th, <5th and <3rd birthweight centiles. When analysed using ITS analysis, there was a significant reduction only for term SGA birth (<10th birthweight centile) at 21 months post implementation, with a relative effect reduction of 45.1%, p=0.004 (Table 2, Figures 1 and S2).

DISCUSSION

Main findings

We have previously shown that the implementation of routine first trimester FMF screening results in an 80% relative effect reduction in preterm pre-eclampsia at the 21-month interval using interrupted time series analysis (ITSA).[3] The secondary analysis presented here shows that this screening programme also resulted in a 45% relative effect reduction in SGA <10th centile birth at term. The study was not powered to evaluate much rarer pregnancy adverse outcomes, but there was no evidence of an increase in stillbirth, neonatal death, hypoxic ischaemic encephalopathy or admissions to the neonatal unit with implementation of routine first trimester FMF pre-eclampsia screening.

Strengths and limitations of the study

This is a retrospective effectiveness study, so measured outcomes may be prone to other/concurrent changes in clinical resources or practices. We have mitigated some of the biases of retrospective analysis by adopting an ITS analysis. Importantly, the pre-eclampsia analysis demonstrated outcomes consistent with efficacy RCT studies[1,2] showing that the ITS analysis produced accurate data consistent with previous publications. Furthermore, secondary analysis may be subject to bias from intervention such as aspirin prophylaxis, ultrasound assessment and induction of labour. However, even though aspirin prophylaxis, ultrasound assessment and induction of labour may improve pregnancy outcomes, there is no evidence that they can themselves reduce SGA rates. Finally, given the impact of interventions such as ultrasound monitoring and elective birth, this dataset is of limited value in establishing screening effectiveness for either SGA or FGR.

Clinical implications of study findings

This study demonstrates that the introduction of routine first trimester combined pre-eclampsia screening results in a relative effect 45% reduction in SGA <10th centile birth at term without a concomitant increase in neonatal unit admission rate from iatrogenic preterm or early term birth. There was also no evidence of an increase in stillbirth, neonatal death or hypoxic ischaemic encephalopathy (or composite of all three) with implementation of routine first trimester FMF pre-eclampsia screening.

Previous analysis of trials and studies evaluating the effect of low-dose aspirin in high-risk women has shown amelioration of pre-eclampsia fails to confer a beneficial effect on SGA birth at term[9]. Therefore, we do not believe that reduction in pre-eclampsia rates in the intervention group influenced the incidence of SGA in this study. Additionally, serial ultrasound assessment of fetal growth may detect, but should not have the therapeutic potential to prevent the development of fetal SGA in pregnancy. Given the demonstrable lack of effect of aspirin prophylaxis and ultrasound assessment on fetal size, the most plausible explanation for reduced prevalence of term of SGA birth is that a policy of routine scheduled birth at 40 weeks in women identified at high risk from combined first trimester pre-eclampsia screening may have influenced (and prevented) subsequent post-dates SGA <10th centile birth. Consistent with this presumed mechanism, a similar effect on the development of term pre-eclampsia was observed in the index study[3].

Public health implications of study findings

Implementation of an effective screening programme aimed at reducing the burden of preterm pre-eclampsia also resulted in a demonstrable reduction in the rate of SGA birth at term. Similar to the 25% trend reduction in term pre-eclampsia[3], the 40% trend reduction in SGA birth was an unexpected beneficial pregnancy outcome that had not been demonstrated in previous efficacy studies. It is likely that both of these desirable outcomes are related to the different policy of elective schedule birth at 40 week's gestation in the screen-positive high-risk cohort. It is however, important to note that the first trimester combined pre-eclampsia FMF screening programme did not influence rates of SGA <5th and <3rd birth, which are at increased risk of adverse outcomes. Although it may be argued that the smaller numbers of <5th and <3rd centile outcomes precluded demonstration of improved outcome, the majority of these births occurred in the FMF-screened low-risk population. These findings suggest that it is important to consider a screening strategy to identify these SGA <5th centile pregnancies in this population. As routine first trimester FMF pre-eclampsia screening halves the screen-positive rate compared to NICE-screening[3], hospital units will have spare scanning capacity that previously would have been used for assessment of women judged high-risk based on NICE screening. Two potential strategies to detect SGA <5th centile would be a selective approach using a lower FMF risk threshold to signal the need for ultrasound fetal growth assessment to a larger proportion of women

or introduce a routine policy of routine ultrasound near term for all women irrespective of their first trimester FMF risk assessment. Given the demonstrable improved clinical impact on fetal SGA detection and additional cost-effectiveness in diagnosis of breech presentation at term[18, 19], the latter option should be given serious consideration.

Conclusions

The first trimester FMF algorithm-based screening programme for pre-eclampsia accompanied by a policy offering scheduled birth at 40 weeks' gestation for high-risk women resulted in a significant relative effect reduction for term SGA birth <10th centile by 45%, but not for SGA birth <5th centile. Further screening strategies, such as using a lower FMF risk threshold to signal the need for a term ultrasound assessment or routine universal term ultrasound to identify and reduce the risk of adverse pregnancy outcomes in SGA <5th centile babies need to be considered.

Disclosure of interests: None

Contribution to authorship: Conceptualisation: BT, GPG; Methodology: BT, GPG; Data collection: GPG, DDG, KL, KF, EB; Statistical analysis: GPG; Data interpretation: GPG, BT; Manuscript draft: GPG, BT; Manuscript review & editing: GPG, KL, DDG, KF, EB, AB, BT.

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

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FIGURE LEGENDS

Figure 1. Graph showing the change in percentage of births complicated by small for gestational age at various centile cut-offs 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 (ITSA) analysis (pre-slope - dashed 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.

Figure S1. Patient flow information with regards to screening, eligibility, allocation, follow-up and analysis[3].

Figure S2. Colour version of figure 1. Graph showing the change in percentage of births complicated by small for gestational age at various centile cut-offs 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). Red – births with exclusive NICE screening; Yellow – births containing both NICE and FMF screening; Green – births with exclusive FMF screening; 10-week lag – pre-viability period (14-24 weeks' gestation) of the first FMF-screened pregnancies.

Table 1. Fetal and neonatal outcomes of those pregnancies delivering preterm (<37 week' gestation) and at term (≥ 37 weeks' gestation) as managed by NICE risk factor or FMF first trimester algorithm-based screening programme for pre-eclampsia prevention. Data shown as number (%).

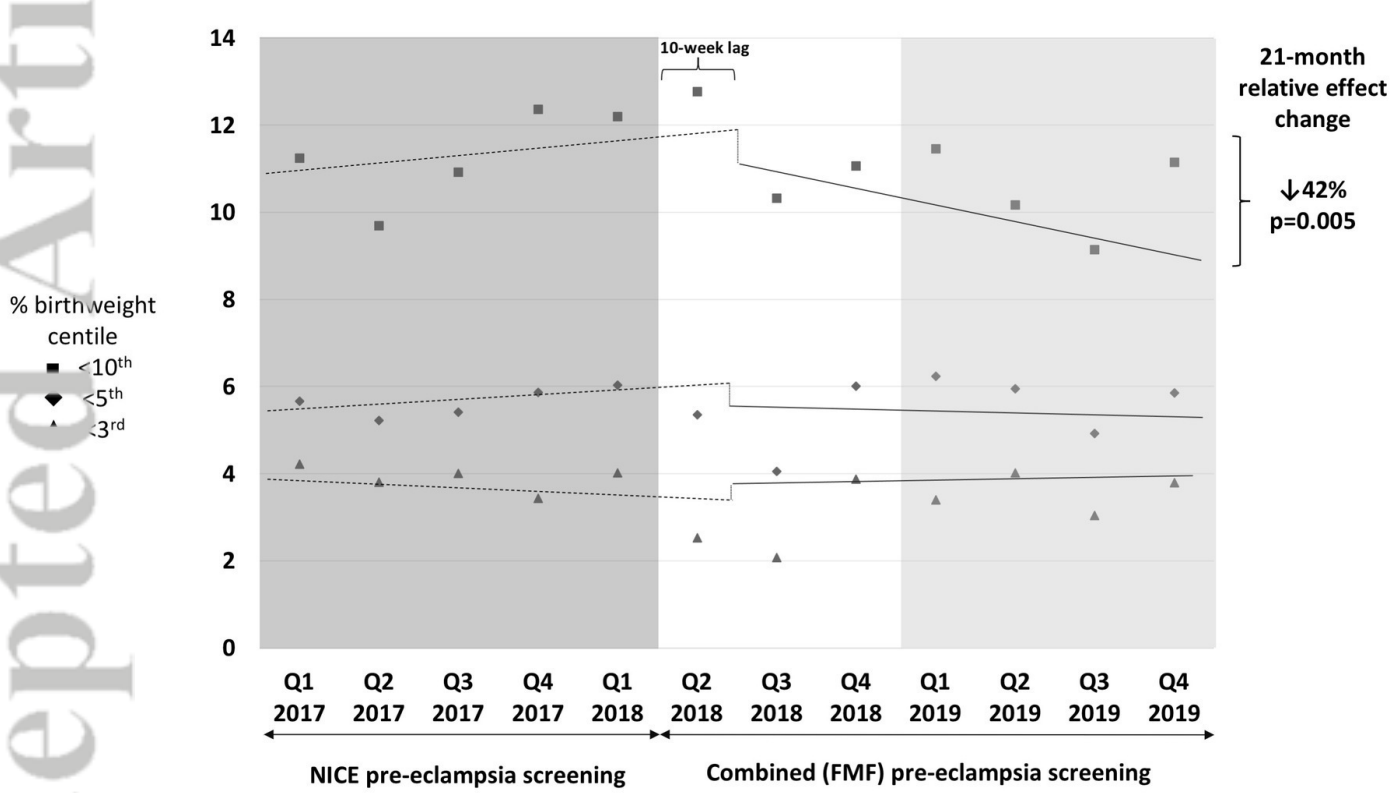
	Preterm (<37w)				**Term (≥37w)**			
Outcome	**NICE screened (n=395)**	**FMF screened (n=237)**	**Odds Ratio (95%CI)**	**p-value**	**NICE screened (n=7325)**	**FMF screened (n=4604)**	**Odds Ratio (95% CI)**	**p-value**
SGA <10th	103 (26.1%)	60 (25.3%)	0.961 (0.664 – 1.390)	0.833	769 (10.5%)	444 (9.6%)	0.910 (0.805 – 1.029)	0.133
SGA <5th	72 (18.2%)	46 (19.4%)	1.080 (0.716 – 1.630)	0.712	342 (4.7%)	239 (5.2%)	1.118 (0.944 – 1.325)	0.197
SGA <3rd	58 (14.7%)	38 (16.0%)	1.110 (0.711 – 1.731)	0.647	211 (2.9%)	137 (3.0%)	1.034 (0.831 – 1.286)	0.764
NNU admission	155 (39.2%)	100 (42.2%)	1.130 (0.815 – 1.568)	0.464	230 (3.1%)	157 (3.4%)	1.089 (0.886 – 1.339)	0.418
IUD	11 (2.9%)	8 (3.4%)	1.220 (0.483 – 3.077)	0.674	12 (0.1%)	4 (0.09%)	0.530 (0.171 – 1.644)	0.272
NND	4 (1.0%)	6 (2.5%)	2.539 (0.709 – 9.092)	0.152	1 (0.01%)	2 (0.04%)	3.183 (0.289 – 35.11)	0.345
HIE	2 (0.5%)	1 (0.4%)	0.833 (0.075 – 9.233)	0.881	11 (0.2%)	4 (0.1%)	0.578 (0.184 – 1.187)	0.348
Composite	17 (4.3%)	15 (6.3%)	1.502 (0.736 – 3.068)	0.264	24 (0.3%)	10 (0.2%)	0.662 (0.316 – 1.386)	0.274

Outcomes of small-for-gestational age (SGA) at birth (at various centile cut-offs), neonatal unit (NNU) admission, intrauterine death (IUD), neonatal death (NND), hypoxic ischaemic encephalopathy (HIE)

and composite adverse outcome (IUD, NND & HIE) rates were compared by Chi-square or Fisher exact test for categorical variables or Mann–Whitney U-test for continuous variables.

Table 2. Summary of the interrupted time series analysis (ITSA) at the 21-month interval of births complicated by small for gestational age at birth (SGA) at various centile cut-offs in the study population managed by NICE risk factor approach or FMF first trimester algorithm-based screening programme for pre-eclampsia. Bold text indicates significance at 95% cut-off.

	Preterm (<37 weeks)		**Term (≥37 weeks)**		**Overall**	
Outcome	**21-month relative ITSA effect change**	**p-value**	**21-month relative ITSA effect change**	**p-value**	**21-month relative ITSA effect change**	**p-value**
SGA <10th	-9.8%	0.884	**-45.1%**	**0.004**	**-42.0%**	**0.005**
SGA <5th	+16.8%	0.793	-36.2%	0.439	-25.0%	0.550
SGA <3rd	+33.5%	0.470	+10.9%	0.676	+16%	0.574



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