First trimester screening for preeclampsia: a cost-effectiveness cohort study

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Abstract

Objective: Investigate cost effectiveness of first trimester preeclampsia screening using the Fetal Medicine Foundation (FMF) algorithm in comparison to standard care. Design: Retrospective observational study Setting: London tertiary hospital Population: 5957 pregnancies screened for preeclampsia using the National Institute for Health and Care Excellence (NICE) method. Methods: Differences in pregnancy outcomes between those who developed preeclampsia, term preeclampsia and preterm preeclampsia 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 the development of preeclampsia using the NICE and FMF methods, respectively. Of those screen positive by NICE recommendations, aspirin was not prescribed in 25%. Across the three groups: pregnancies without preeclampsia, term preeclampsia and preterm preeclampsia, respectively there was a statistically significant trend in rates of emergency caesarean (21%, 43%, 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. Use of the FMF algorithm was associated with 7 fewer cases of preterm preeclampsia, cost saving of £9.06 and a QALY gain of 0.00006/pregnancy screened. Conclusions: In our cohort, using a conservative approach, application of the FMF algorithm achieved clinical benefit and an economic cost saving.

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Running title: First trimester combined preeclampsia screening.

ABSTRACT

Objective: Investigate cost effectiveness of first trimester preeclampsia screening using the Fetal Medicine Foundation (FMF) algorithm in comparison to standard care.

Design: Retrospective observational study

Setting: London tertiary hospital

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

Methods: Differences in pregnancy outcomes between those who developed preeclampsia, term preeclampsia and preterm preeclampsia 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 the development of preeclampsia using the NICE and FMF methods, respectively. Of those screen positive by NICE recommendations, aspirin was not prescribed in 25%. Across the three groups: pregnancies without preeclampsia, term preeclampsia and preterm preeclampsia, respectively there was a statistically significant trend in rates of emergency caesarean (21%, 43%, 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. Use of the FMF algorithm was associated with 7 fewer cases of preterm preeclampsia, cost saving of £9.06 and a QALY gain of 0.00006/pregnancy screened.

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

Funding: No funding was received for this study.

Keywords: preeclampsia, preterm preeclampsia, first trimester combined screening, pregnancy associated plasma protein-A, PAPP-A, National Institute for Health and Care Excellence, NICE, cost-effectiveness, mean arterial blood pressure, Fetal Medicine Foundation, aspirin.

Introduction

Preeclampsia (PE) affects 2% 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 150mg 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] Second, 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 to current standard care recommended by NICE.

Methods

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 livebirth 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, since 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 1st trimester scan between 11^{+2} to 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 150mg until 36 weeks' gestation. Subsequent pregnancy management including the need for third trimester fetal growth surveillance or need 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 by having, in addition to hypertension, at least 1 of the following problems: renal involvement (proteinuria 300 mg/24 h and/or creatinine 90 mmol/L or 1 mg/dL), liver impairment (transaminases >70 IU/L), neurologic 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' of gestation and term PE with onset beyond 37 weeks. SGA was defined as birthweight <5thpercentile for gestational age.[14]

Statistical analysis

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 numeric parametric or nonparametric data) with the Bonferroni correction for post-hoc analysis. The Chi-square test was performed for categorical variables and for trend when the proportions between groups demonstrated an obvious trend.

The FMF algorithm was applied retrospectively. 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, whilst 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 10-15%. 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 appropriately adjust 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, was incorporated into analysis.[4]

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

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. 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 of health events of interest was based on primary data, while health utility values were based on available secondary data. All relevant inputs for the calculation of QALYs are outlined in Table 2.

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 and admission of a preterm neonate to NICU. Again, relevant probabilities were based on primary data, while 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 S1.

Incremental cost-effectiveness ratios were estimated to represent the additional cost per QALY gained from adopting the FMF screening algorithm. A probabilistic sensitivity analysis was also conducted, where variation in parameters was simultaneously modelled based on assumed distributions 1,000 times. Table S1 shows the parameters varied in the sensitivity analysis. All costs are reported in 2022 British Pounds. All cost-effectiveness analysis was conducted in R using the "rdecision" package.

Results

Population characteristics

The study population that met the inclusion criteria comprised of 5957 pregnancies who attended the hospital for assessment between 11^{+2} to 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)

The length of stay in NICU for pregnancies complicated by preterm PE was significantly longer when compared to 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 when compared to 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)

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, of which 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 to 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)

Cost effectiveness

In the base case deterministic analysis, the FMF algorithm is associated with an overall cost saving of PS9.06 per pregnancy screened and a QALY gain of 0.00006 when compared to standard care using the NICE screening method. care. With a cohort of 5957 pregnant women, the use of the FMF algorithm resulted in 7 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 PS54,000. Overall, the number of QALYs over a one-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 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 to the NICE method. The FMF screening method is cost saving in 67% of simulations (Figure 1).

Discussion

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. Of those who screened positive by NICE, aspirin prophylaxis was not prescribed in 25%, with the majority having a least one major risk factor for the development of PE. 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 to uncomplicated pregnancies and those with term PE.

Use of the FMF algorithm was associated with 7 fewer cases of preterm PE, an estimated cost saving of PS9.06 and a QALY gain of 0.00006 per pregnancy screened.

Interpretation

The benefit of prophylactic aspirin in women at high risk of PE is well established.[4] 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 recent changes to the maternity notes at our centre. In 2019, the maternity notes were digitalised at the study site and a mandatory checklist for PE risk assessment was introduced. Despite this improvement, 25% of high-risk women were still not prescribed aspirin. Physician compliance of 96 to 99% has meanwhile been demonstrated with implementation of the FMF algorithm.[9, 11]

Although we didn't assess patient compliance in this study, it's 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.[15] When compared to 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).[15]

Similarly, in a multicentre randomised controlled trial, the efficacy of aspirin in women identified as high risk using the FMF algorithm in reducing the risk of PE was less in those with lower compliance (OR, 0.24 (95% CI, 0.09-0.65) vs 0.59 (95% CI 0.23-1.53). In research settings, patient compliance with aspirin prescribed based on FMF criteria is favourable compared to 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.[16]Therefore, improving the robustness of the screening process is likely to not only 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.[17-21]Only one of these studies included the UK. In contrast to our study that modelled cost on real data, this 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 averted.[19] Similarly, in Belgium and Switzerland, cost savings of \euro28.67 (PS24.74)[17] and CHF42 (PS33.32)[18], respectively, per patient screened using the FMF algorithm have been reported. In contrast, in other European countries that include Sweden, Ireland, and Germany implementation of the FMF algorithm has incurred higher costs.[18, 19]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.[19]

Implications of the findings on clinical practice and future research

The largest study to date on the clinical effectiveness of first trimester PE using the FMF algorithm, showed that screen positive women were significantly more likely to develop PE at any gestation (5.7% vs 2.4%, risk ratio (RR) 2.33, 95% CI 2.05-2.65, p<0.001), preterm PE (2.1% vs. 0.7%, RR 3.04, 95% CI 2.46–3.77, P < 0.001) and other adverse pregnancy outcomes that include birthweight <3rd centile when compared to the general population (4.5% vs. 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.[22] 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 to 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 1st trimester uterine Doppler indices and additional growth scans for screen positive women. The findings of our study do not support this. 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 require not just aspirin prophylaxis but also evidence-based third trimester fetal growth surveillance and earlier induction of labour.

To enable re-evaluation of the current national recommendations of maternal characteristic based screening, larger prospective studies are clearly needed to further demonstrate the cost-effectiveness of the FMF algorithm.

Strengths and limitations

The strengths of this study are inclusion of a large cohort of pregnancies with retrospective application of the FMF algorithm. This allowed for the input of actual data, such as physician compliance with aspirin prophylaxis, into the model structure and probabilities for the cost analysis.

Due to the retrospective application of the FMF algorithm, a proportion of those who were screen positive using the FMF algorithm received aspirin. Therefore, a limitation of this study was that the input data had to be estimated in this group 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[22], our estimates of cost-savings can only represent an under-estimate.

Finally, neither PLGF or 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. Again, this emphasises the conservative approach adopted in this study to avoid an inflation in the expected cost-savings.[8, 23]

Conclusion

We have shown that, 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.

Disclosure of interests

The authors have no conflicts of interest to disclose.

Contribution to authorship

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 manuscript. DS contributed to conceptualisation, review and editing of the manuscript. CA contributed to data curation. PP, RN and DC all contributed to project administration, review and editing of the manuscript.

Details of 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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Table and figure captions

Table 1: Maternal, pregnancy and screening characteristics of the overall cohort. Numerical data is presented as median (interquartile range) and categorical data as proportions.

Table 2: Health outcome input values

Figure 1: 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.

Table S1: Unit costs

Figure S1: Decision tree for first trimester preeclampsia screening

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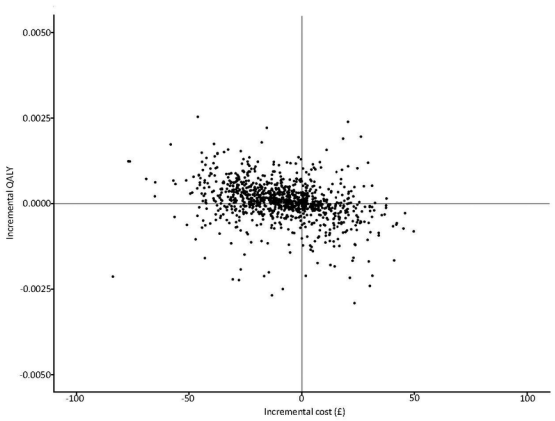

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