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ASPRE trial: incidence of preterm pre-eclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm

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KEYWORDS: ACOG guidelines; Bayes' theorem; first-trimester screening; mean arterial pressure; NICE guidelines; placental growth factor; pre-eclampsia; pregnancy-associated plasma protein-A; uterine artery Doppler

ABSTRACT

Objective *To report the incidence of preterm pre-eclampsia (PE) in women who are screen positive according to the criteria of the National Institute for Health and Care Excellence (NICE) and the American College of Obstetricians and Gynecologists (ACOG), and compare the incidence with that in those who are screen positive or screen negative by The Fetal Medicine Foundation (FMF) algorithm.*

Methods *This was a secondary analysis of data from the ASPRE study. The study population consisted of women with singleton pregnancy who underwent prospective screening for preterm PE by means of the FMF algorithm, which combines maternal factors and biomarkers at 11–13 weeks' gestation. The incidence of preterm PE in women fulfilling the NICE and ACOG criteria was estimated; in these patients the incidence of preterm PE was then calculated in those who were screen negative relative to those who were screen positive by the FMF algorithm.*

Results *A total of 34 573 women with singleton pregnancy delivering at ≥ 24 weeks' gestation underwent prospective screening for preterm PE, of which 239 (0.7%) cases developed preterm PE. At least one of the ACOG criteria was fulfilled in 22 287 (64.5%) pregnancies and the incidence of preterm PE was 0.97% (95% CI, 0.85–1.11%); in the subgroup that was screen positive by the FMF algorithm the incidence of preterm PE was 4.80% (95% CI, 4.14–5.55%), and in those that were screen negative it was 0.25% (95% CI, 0.18–0.33%), with a relative incidence in FMF screen negative to FMF screen positive of 0.051 (95% CI, 0.037–0.071). In 1392 (4.0%) pregnancies, at least one of the NICE high-risk criteria was fulfilled, and in this group the incidence of preterm PE was 5.17% (95% CI, 4.13–6.46%); in the subgroups of screen positive and screen negative by the FMF algorithm, the incidence of preterm PE was 8.71% (95% CI, 6.93–10.89%) and 0.65% (95% CI, 0.25–1.67%), respectively, and the relative incidence was 0.075 (95% CI, 0.028–0.205). In 2360 (6.8%) pregnancies fulfilling at least two of the NICE moderate-risk criteria, the incidence of preterm PE was 1.74% (95% CI, 1.28–2.35%); in the subgroups of screen positive and screen negative by the FMF algorithm the incidence was 4.91% (95% CI, 3.54–6.79%) and 0.42% (95% CI, 0.20–0.86%), respectively, and the relative incidence was 0.085 (95% CI, 0.038–0.192).*

Conclusion *In women who are screen positive for preterm PE by the ACOG or NICE criteria but screen negative by the FMF algorithm, the risk of preterm PE is reduced to within or below background levels. The results provide further evidence to support the personalized risk-based screening method that combines maternal factors and biomarkers.* Copyright © 2018 ISUOG. *Published by John Wiley & Sons Ltd.*

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INTRODUCTION

The current approach to screening for pre-eclampsia (PE) is to identify risk factors from maternal demographic characteristics and medical history (maternal factors)[1,2]. According to the National Institute for Health and Care Excellence (NICE), in the UK, women should be considered to be at high risk of developing PE if they have any one high-risk factor (hypertensive disease in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus or autoimmune disease) or any two moderate-risk factors (nulliparity, age $\geq$ 40 years, body mass index (BMI) $\geq$ 35 kg/m^2, family history of PE or interpregnancy interval > 10 years)[1]. In the USA, according to the American College of Obstetricians and Gynecologists (ACOG), women are at high-risk of developing PE if they fulfill any of the following factors: PE in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus, systemic lupus erythematosus or thrombophilia, nulliparity, age > 40 years, BMI $\geq$ 30 kg/m^2, family history of PE or conception by *in-vitro* fertilization[2]. Consequently, the approach recommended by NICE and ACOG essentially treats each risk factor as a separate screening test with additive detection rate (DR) and screen-positive rate.

An alternative approach to screening, developed by The Fetal Medicine Foundation (FMF), allows estimation of individual patient-specific risks of PE requiring delivery before a specified gestational age. The approach uses Bayes' theorem to combine the *a-priori* risk from maternal factors, derived by a multivariable logistic model, with the results of various combinations of biophysical and biochemical measurements[3,4]. In a previous study, we used data from prospective screening in 35 948 singleton pregnancies at 11–13 weeks' gestation to develop an algorithm for the calculation of patient-specific risk of PE[4]. Combined screening by maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum pregnancy-associated plasma protein-A (PAPP-A) achieved DR of delivery with PE at < 37 (preterm PE) and $\geq$ 37 weeks (term PE) of 75% and 47%, respectively, at a false-positive rate (FPR) of 10%. This prediction algorithm was validated prospectively in a multicenter study of 8775 singleton pregnancies and reported DRs of 75% for preterm PE and 43% for term PE, at 10% FPR[5]. In the same cohort, the performance of the FMF algorithm was compared with those of the screening methods recommended by NICE and ACOG[6]. In screening with use of NICE guidelines, the DR was 39% for preterm PE and 34% for term PE, at 10.3% FPR, and the respective DRs with use of ACOG recommendations were 90% and 89%, at 64.3% FPR.

The Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial reported that in women identified by first-trimester screening as being at high risk for PE, use of aspirin (150 mg/day from the first to the third trimester), compared with placebo, reduced the incidence of preterm PE, which was the primary outcome, by 62% (95% CI, 26–80%), but had no significant effect on the rate of term PE[7]. Since the performance of screening for preterm PE by the FMF algorithm is superior to the methods recommended by NICE and ACOG, the best method of selecting patients that would benefit from prophylactic use of aspirin is the method recommended by the FMF. However, obstetricians may be reluctant to withhold treatment from women who are screen positive by the NICE or ACOG methods but screen negative by the FMF method.

The objective of this study was to report the incidence of preterm PE in women who are screen positive according to the criteria of NICE and ACOG and compare the incidence with that in those who are screen positive or screen negative by the FMF algorithm, in the total screened population of the ASPRE study.

METHODS

Study design and participants

This was a secondary analysis of a prospective, multicenter study in singleton pregnancies at 11 + 0 to 13 + 6 weeks' gestation in women booking for routine pregnancy care at 13 maternity hospitals in the UK, Spain, Italy, Belgium, Greece and Israel[5,7]. Approval for the trial was obtained from the relevant research ethics committee and competent authority of each country in which the trial was conducted. Quality control of screening and verification of adherence to protocol were performed by the University College London Comprehensive Clinical Trials Unit (UCL-CCTU).

The study population consisted of women recruited during the two phases of the ASPRE study: in the first phase, participants underwent screening by the FMF algorithm but no intervention (screening quality study)[5], and in the second phase, women in the high-risk group were invited to participate in a randomized control trial (RCT) of use of aspirin *vs* placebo for prevention of preterm PE[7]. Eligibility criteria for the trial were maternal age $\geq$ 18 years, no serious mental illness or learning difficulty and singleton pregnancy with live fetus without major abnormality demonstrated on the 11–13-week scan. In this study, we included pregnancies delivered at $\geq$ 24 weeks' gestation. During the screening quality study, 8775 women were evaluated, and 59 subsequently developed preterm PE. During the second phase, 25 798 women were screened and 159 developed preterm PE.

FMF test

The FMF test is the previously reported algorithm for first-trimester assessment of risk for PE by maternal factors, MAP, UtA-PI, PAPP-A and PlGF[4]. Maternal factors were recorded as described previously[3] and MAP was measured using validated automated devices and standardized protocol[8]. Left and right UtA-PI were measured by transabdominal color Doppler ultrasound

and the average value was recorded[9], and serum PAPP-A and PlGF concentrations were measured by an automated device (PAPP-A and PlGF 1-2-3™ kits, DELFIA® Xpress random access platform; PerkinElmer Inc. (Wallac Oy), Turku, Finland). All operators undertaking the Doppler studies had received the appropriate Certificate of Competence from the FMF. Measured values of MAP, UtA-PI, PAPP-A and PlGF were expressed as multiples of the median (MoM) adjusting for those characteristics found to provide a substantive contribution to the $\log_{10}$ transformed value, including maternal factors in the prior model[10–13]. Gestational age was determined from the measurement of fetal crown–rump length[14].

Outcome

The outcome measure was preterm PE and the diagnosis of PE was based on the criteria of the International Society for the Study of Hypertension in Pregnancy[15]. The systolic blood pressure should be ≥ 140 mmHg and/or the diastolic blood pressure should be ≥ 90 mmHg on at least two occasions 4 h apart developing after 20 weeks of gestation in previously normotensive women. Hypertension should be accompanied by proteinuria of ≥ 300 mg in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection is available. In PE superimposed on chronic hypertension, significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or presence of hypertension at the booking visit before 20 weeks' gestation in the absence of trophoblastic disease).

Data on pregnancy outcome were collected from the hospital maternity records of the women. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was PE.

The incidence of preterm PE in patients fulfilling the NICE and ACOG criteria was calculated. In the subgroup of patients participating in the ASPRE trial and allocated to aspirin, an adjustment was made for the incidence of preterm PE based on the finding that aspirin was associated with a 62% reduction in the incidence of preterm PE[7]. In the ACOG and NICE screen-positive patients, the incidence of preterm PE was estimated separately for those who were screen positive and those who were screen negative by the FMF algorithm, using a risk cut-off of 1 in 100 for preterm PE, and the relative incidence of preterm PE in the screen-negative to the screen-positive group was calculated. Medcalc (Medcalc Software, Mariakerke, Belgium) was used for all data analyses.

RESULTS

The study population consisted of 34 573 pregnancies that were screened during the first or second phase of the ASPRE study, of which an estimated 239 (0.7%) cases developed preterm PE and 630 (1.8%) term PE.

ACOG criteria

In 22 287 (64.5%) of the 34 573 pregnancies, at least one of the ACOG criteria was fulfilled and this group included 732 women on aspirin prophylaxis as part of the ASPRE RCT (Table 1). In this group, the incidence of preterm PE was 0.97% (95% CI, 0.85–1.11%). Of the 22 287 ACOG screen-positive pregnancies, 3566 (16.0%) were screen positive by the FMF algorithm and in this group the incidence of preterm PE was 4.80% (95% CI, 4.14–5.55%), whereas 18 721 (84.0%) pregnancies were screen negative by the FMF algorithm and in this group the incidence of preterm PE was 0.25% (95% CI, 0.18–0.33%). The relative incidence of preterm PE in FMF negative to FMF positive pregnancies was 0.051 (95% CI, 0.037–0.071). The incidence of preterm PE for each risk factor in the total group and subgroups of screen-positive and screen-negative women by the FMF algorithm is presented in Table 1.

NICE criteria

In 1392 (4.0%) of the 34 573 pregnancies, at least one of the NICE high-risk criteria was fulfilled and this group included 142 women on aspirin prophylaxis as part of the ASPRE RCT. In this group the incidence of preterm PE was 5.17% (95% CI, 4.13–6.46%). Of the women who were screen positive by the NICE high-risk criteria, 781 (56.1%) were screen positive by the FMF algorithm and in this group the incidence of preterm PE was 8.71% (95% CI, 6.93–10.89%), whereas in the 611 (43.9%) pregnancies that were screen negative by the FMF algorithm the incidence was 0.65% (95% CI, 0.25–1.67%) (Table 1). The relative incidence of preterm PE in FMF screen-negative to FMF screen-positive pregnancies was 0.075 (95% CI, 0.028–0.205).

In 2360 (6.8%) pregnancies, at least two of the NICE moderate-risk criteria were fulfilled and in this group the incidence of preterm PE was 1.74% (95% CI, 1.28–2.35%). Of these, 692 (29.3%) pregnancies were screen positive by the FMF algorithm and in this group the incidence of preterm PE was 4.91% (95% CI, 3.54–6.79%), whereas in the 1668 (70.7%) pregnancies that were screen negative by the FMF algorithm the incidence was 0.42% (95% CI, 0.20–0.86%). The relative incidence of preterm PE in FMF screen-negative to FMF screen-positive pregnancies was 0.085 (95% CI, 0.038–0.192) (Table 1).

DISCUSSION

Main findings

This study demonstrates that, in the screened population of the ASPRE trial, the incidence of preterm PE was 0.7% and this was increased in subgroups of women with risk factors described by ACOG and NICE. The highest risk factors were chronic hypertension, history of PE in a previous pregnancy and diabetes mellitus, which were associated with a 15-fold, 7-fold and 7-fold, respectively,

Table 1 Incidence of preterm (< 37 weeks) pre-eclampsia (PE) by risk factors of the American College of Obstetricians and Gynecologists (ACOG)[2] criteria and high- and moderate-risk factors of the National Institute of Health and Care Excellence (NICE)[1] criteria, in the total group ($n = 34\,573$) of women screened during the ASPRE study and subgroups of screen positive and screen negative women by the FMF algorithm[4]

	*ACOG/NICE screen positive**			
Screening criteria	*Total*	*FMF screen positive*	*FMF screen negative*	*Relative incidence*
ACOG risk factors				
Any one risk factor	217/22287 (0.97, 0.85–1.11)	171/3566 (4.80, 4.14–5.55)	46/18721 (0.25, 0.18–0.33)	0.051 (0.037–0.071)
Previous PE	35/708 (4.94, 3.58–6.80)	33/410 (8.05, 5.79–11.09)	2/298 (0.67, 0.18–2.41)	0.083 (0.020–0.345)
Chronic hypertension	44/419 (10.50, 7.92–13.80)	43/321 (13.40, 10.10–17.56)	1/98 (1.02, 0.18–5.56)	0.076 (0.011–0.546)
Diabetes mellitus	14/275 (5.09, 3.06–8.36)	12/124 (9.68, 5.62–16.16)	2/151 (1.32, 0.36–4.70)	0.137 (0.031–0.600)
APS/SLE	3/107 (2.80, 0.96–7.92)	3/29 (10.34, 3.58–26.39)	0/78 (0.00, 0.00–4.69)	0.000 (0.000–0.470)
Nulliparity	151/17161 (0.88, 0.75–1.03)	115/2686 (4.28, 3.58–5.11)	36/14475 (0.25, 0.18–0.34)	0.058 (0.040–0.084)
Age > 40 years	13/1486 (0.87, 0.51–1.49)	11/303 (3.63, 2.04–6.38)	2/1183 (0.17, 0.05–0.61)	0.047 (0.010–0.209)
BMI ≥ 30 kg/m^2	81/6225 (1.30, 1.05–1.61)	66/1241 (5.32, 4.20–6.71)	15/4984 (0.30, 0.18–0.50)	0.057 (0.032–0.099)
Family history of PE	23/1613 (1.43, 0.95–2.13)	19/368 (5.16, 3.33–7.92)	4/1245 (0.32, 0.13–0.82)	0.062 (0.021–0.182)
In-vitro fertilization	12/991 (1.21, 0.69–2.10)	8/195 (4.10, 2.09–7.89)	4/796 (0.50, 0.20–1.28)	0.123 (0.037–0.403)
NICE high-risk factors†				
Any one factor	72/1392 (5.17, 4.13–6.46)	68/781 (8.71, 6.93–10.89)	4/611 (0.65, 0.25–1.67)	0.075 (0.028–0.205)
NICE moderate-risk factors‡				
Any two or more factors	41/2360 (1.74, 1.28–2.35)	34/692 (4.91, 3.54–6.79)	7/1668 (0.42, 0.20–0.86)	0.085 (0.038–0.192)
Any two or more factors including:				
Nulliparity	34/1888 (1.80, 1.29–2.51)	28/548 (5.11, 3.56–7.29)	6/1340 (0.45, 0.21–0.97)	0.088 (0.037–0.211)
Age ≥ 40 years	10/768 (1.30, 0.71–2.38)	8/212 (3.77, 1.92–7.27)	2/556 (0.36, 0.10–1.30)	0.095 (0.020–0.445)
BMI ≥ 35 kg/m^2	21/976 (2.15, 1.41–3.27)	17/339 (5.01, 3.15–7.88)	3/637 (0.47, 0.16–1.38)	0.094 (0.028–0.318)
Family history of PE	18/928 (1.94, 1.23–3.05)	15/263 (5.70, 3.49–9.20)	3/665 (0.45, 0.15–1.32)	0.079 (0.023–0.271)
Interpregnancy interval > 10 years	2/276 (0.72, 0.20–2.60)	2/75 (2.67, 0.73–9.21)	0/201 (0.00, 0.00–1.88)	0.075 (0.004–1.550)

Data are given as *n*/*N* (%, 95% CI) or % (95% CI). *Incidence of preterm PE estimated after adjustment for effect of aspirin in those receiving this treatment. †NICE high-risk factors: hypertensive disease in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus, autoimmune disease. ‡NICE moderate-risk factors: nulliparity, age ≥ 40 years, BMI ≥ 35 kg/m^2, family history of PE, interpregnancy interval > 10 years. APS, antiphospholipid syndrome; BMI, body mass index; SLE, systemic lupus erythematosus.

increase in incidence of preterm PE, compared with the background levels. There was also a 2-fold increase in incidence of preterm PE associated with obesity, family history of PE and conception by *in-vitro* fertilization. In the case of nulliparity and increased maternal age, the incidence of preterm PE was not significantly higher than the background.

The study also demonstrates that, in women who were screen positive by the ACOG or NICE criteria, the incidence of preterm PE increased substantially in those who were also screen positive by the FMF algorithm, whereas in the FMF screen-negative group the incidence was reduced to within or below background levels. In the group fulfilling any one of the ACOG criteria, the incidence of preterm PE in the subgroup of FMF screen-negative pregnancies was 95% lower than in the screen-positive group. Similarly, in women fulfilling any one of the NICE high-risk criteria, the incidence of preterm PE in the subgroup of FMF screen-negative pregnancies was 92% lower than in the screen-positive group, and for those with any two or more moderate-risk factors the reduction was 91%.

Strengths and limitations

This was a large study of prospectively collected data on maternal characteristics, medical history and biomarkers in women attending for routine care in a gestational age range that is widely used for diagnosis of major fetal defects and screening for fetal trisomies. Measurement of all biomarkers was recorded in all cases and consistency in data collection was maintained throughout the study period by ensuring adequate training of all investigators based on standardized protocols, and regular UCL-CCTU monitoring.

The main limitation of the study relates to the low number of cases of women with certain risk factors, such as antiphospholipid syndrome or systemic lupus erythematosus, and the small number of cases of preterm PE leading to the inevitable wide CIs obtained for relative risks. Nevertheless, there was a major reduction in incidence of preterm PE in the FMF screen-negative group relative to that in the screen-positive group.

Implications for practice

Traditionally, screening for PE was based on a series of maternal factors and women in the high-risk group were offered aspirin (75–80 mg/day) with the aim of reducing the risk of PE by about 10%[1,2,16]. Recent evidence suggests that the target for first-trimester screening should be severe PE leading to preterm birth, rather than all types of PE. Aspirin is considerably more effective than previously thought in reducing the risk of preterm PE;

a recent meta-analysis reported that aspirin reduces the risk of preterm PE by 67%, provided the daily dose of the drug is ≥ 100 mg and the gestational age at onset of therapy is ≤ 16 weeks, whereas aspirin had no effect on the incidence of term PE[17]. The performance of screening for preterm PE, and therefore appropriate selection of the patients that would benefit from prophylactic use of aspirin, is by far superior if the FMF algorithm is used than the method advocated by ACOG and NICE[1–6].

The study confirmed that with most risk factors described by ACOG and NICE, the incidence of preterm PE is increased. However, the main issue is whether women that fulfill the ACOG or NICE screening criteria but are screen negative by the FMF method should in any case receive aspirin. We have shown that in such women the incidence of preterm PE is reduced to within or below background levels. Consequently, in screening for preterm PE, known risk factors should be combined with various biophysical and biochemical markers to determine if the patient-specific risk is high or low before deciding whether or not they should be advised to take aspirin.

Lessons can be learned from the implementation of screening for fetal trisomies. In the 1970s, the method of screening was solely dependent on maternal age, but in the subsequent decades a series of biophysical and biochemical markers were described[18]. It is now accepted that the best approach of selecting the high-risk group in need of further investigations is the use of Bayes' theorem to combine maternal age with a series of biomarkers to determine the patient-specific risk, rather than use of arbitrary cut-offs in maternal age or biomarker levels.

ACOG and NICE guidelines should be updated to reflect recent scientific evidence that the screening target should be preterm PE, the best way to identify the high-risk group is by a combination of maternal factors and biomarkers, aspirin should be started before 16 weeks' gestation and the daily dose should be higher than 100 mg.

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