Multicenter screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation: comparison to NICE guidelines and ACOG recommendations

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Screening for preeclampsia

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ABSTRACT

Objective: To compare the performance of screening for preeclampsia (PE) based on risk factors from the medical history, as recommended by NICE and ACOG, with the method proposed by the Fetal Medicine Foundation (FMF), which 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.

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Methods: This was a prospective multicenter study of screening for PE in 8,775 singleton pregnancies at 11-13 weeks' gestation. A previously published FMF algorithm was used for the calculation of patient-specific risk of PE in each patient. The detection rates (DR) and false positive rates (FPR) for delivery with PE at <32, <37 and ≥37 weeks were estimated and compared to those derived from application of NICE guidelines and ACOG recommendations. According to NICE, all high-risk pregnancies should be offered low-dose aspirin. According to ACOG, use of aspirin should be reserved for women with history of PE in ≥2 previous pregnancies or PE requiring delivery at <34 weeks' gestation.

Results: In the study population there were 239 (2.7%) cases that developed PE, including 17 (0.2%), 59 (0.7%) and 180 (2.0%) at <32, <37 and ≥37 weeks, respectively. Screening with use of the FMF algorithm and the combination of maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UTPI) and serum placental growth factor (PLGF) detected 100% (95% CI 80-100) of PE at <32 weeks, 75% (95% CI 62-85) of PE at <37 weeks and 43% (95% CI 35-50) of PE at ≥37 weeks, at 10.0% FPR. Screening with use of NICE guidelines detected 41% (95% CI 18-67) of PE at <32 weeks, 39% (95% CI 27-53) of PE at <37 weeks and 34% (95% CI 27-41) of PE at ≥37 weeks, at 10.2% FPR. Screening with use of ACOG recommendations detected 94% (95% CI 71-100) of PE at <32 weeks, 90% (95% CI 79-96) of PE at <37 weeks and 89% (95% CI 84-94) of PE at ≥37 weeks, at 64.2% FPR. Screening based on the ACOG recommendations for use of aspirin detected 6% (95% CI 1-27) of PE at <32 weeks, 5% (95% CI 2-14) of PE at <37 weeks and 2% (95% CI 0.3-5) of PE at ≥37 weeks, at 0.2% FPR.

Conclusion: Performance of screening for PE at 11-13 weeks' gestation by the FMF algorithm and combination of maternal factors, MAP, UTPI and PLGF is by far superior to the methods recommended by NICE and ACOG.

Key words: First trimester screening, Preeclampsia, Pyramid of pregnancy care, Survival model, Bayes theorem, Uterine artery Doppler, Mean arterial pressure, Pregnancy associated plasma protein-A, Placental growth factor.

Introduction

The traditional approach to screening for preeclampsia (PE) is to identify risk factors from maternal demographic characteristics and medical history (maternal factors).[1,2] In the UK, the National Institute for Health and Clinical Excellence (NICE) has issued guidelines recommending that women should be considered to be at high-risk of developing PE if they have any one high-risk factor or any two moderate-risk factors; the high-risk factors are history of hypertensive disease in previous pregnancy, chronic kidney disease, autoimmune disease, diabetes mellitus or chronic hypertension and the moderate-risk factors are first pregnancy, age ≥40 years, inter-pregnancy interval >10 years, body mass index (BMI) at first visit of ≥35 kg/m^2 or family history of PE.[1] In the USA, according to the American College of Obstetricians and Gynecologists (ACOG) taking a medical history to evaluate for risk factors is currently the best and only recommended screening approach for PE; the risk factors are nulliparity, age >40 years, body mass index ≥30 kg/m^2, conception by *in vitro* fertilization, history of previous pregnancy with PE, family history of PE, chronic hypertension, chronic renal disease, diabetes mellitus, systemic lupus erythematosus or thrombophilia.[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. According to NICE all high-risk pregnancies should be offered low-dose aspirin. According to ACOG use of aspirin should be reserved for women with history of PE in ≥2 previous pregnancies or PE requiring delivery at <34 weeks' gestation.[3]

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 gestation, with the use of 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.[4,5] In a previous study we used data from prospective screening in 35,948 singleton pregnancies at 11-13 weeks to develop an algorithm for the calculation of patient-specific risk of PE.[5] Combined screening by maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UTPI) and serum placental growth factor (PLGF) achieved detection rates (DR) of delivery with PE at <32, <37 and ≥37 weeks of 89%, 75% and 47%, respectively, at false positive rate (FPR) of 10%.[5] A limitation of the study is that the performance of screening by a model derived and tested using the same dataset may be overestimated. However, a recent multicentre study in 8,775 singleton pregnancies has confirmed the validity of the algorithm[5] and reported DRs of 100% (95% CI 80-100), 75% (95% CI 62-85) and 43% (95% CI 35-50) for PE at <32, <37 and ≥37 weeks, respectively, at 10% FPR.[6]

The objective of this study is to examine the performance of screening based on risk factors from the medical history, as recommended by NICE[1] and ACOG[2,3] with the method proposed by the FMF.

Methods

This was a prospective, non-intervention, multicenter study in singleton pregnancies at 11^{+0} - 13^{+6} weeks' gestation in women booking for routine pregnancy care in one of 12 maternity hospitals in five different countries: King's College Hospital, London, UK, Medway Maritime Hospital, Gillingham, UK, Homerton University Hospital, London, UK, North Middlesex University Hospital, London, UK, Southend University Hospital, Essex, UK, Lewisham University Hospital, London, UK, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain, Hospital Universitario San Cecilio, Granada, Spain, Hospiten Sur, Tenerife, Spain, Centre Hospitalier Universitaire Brugmann, Brussels Belgium, Attikon University Hospital, Athens, Greece and Ospedale Maggiore Policlinico, Milan, Italy.[6] The women were screened between February and September 2015 and gave written informed consent to participate in

the study, which was approved by the NHS Research Ethics Committee in the UK and the Ethics Committee of each participating hospital in other countries. The results from screening were not made available to the patients or their physicians.

Maternal factors were recorded,[4] MAP and UTPI were measured by standardized protocols[7,8] 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, P.O.Box 10, 20101 Turku, Finland). Measured values of MAP, UTPI, PAPP-A and PLGF were expressed as a MoM adjusting for those characteristics found to provide a substantive contribution to the $\log_{10}$ transformed value including the maternal factors in the prior model.[9-12]

The outcome measure was PE, as defined by the International Society for the Study of Hypertension in Pregnancy.[13] 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 FMF algorithm was used for the calculation of patient-specific risk of delivery with PE at <32, <37 and ≥37 weeks' gestation by maternal factors and various combinations of maternal factors and biomarkers[4,5] and DR, with 95% CI, at FPR of 10% was estimated. Similarly, the maternal characteristics and medical history of each patient were examined to determine whether they were screen positive or negative according to the NICE[1] and ACOG[2,3] guidelines; the DR, with 95% CI, of delivery with PE at <32, <37 and ≥37 weeks' gestation and FPR were then estimated.

The statistical software package R was used for data analyses.[14]

Results

In the study population, there were 239 (2.7%) cases that developed PE, including 17 (0.2%), 59 (0.7%) and 180 (2.0%) at <32, <37 and >37 weeks, respectively and 8,536 cases without PE. Baseline demographic and clinical characteristics of participants are shown in Table 1

The performance of screening by the FMF algorithm,[4,5] and the methods advocated by NICE[1] and ACOG[2,3] are summarized in Table 2. Combined screening by maternal factors, MAP, UTPI and PLGF[4,5] detected 100% (95% CI 80-100) of PE at <32 weeks, 75% (95% CI 62-85) of PE at <37 weeks and 43% (95% CI 35-50) of PE at ≥37 weeks, at 10.0% FPR. The receiver operating characteristics curve is shown in Figure 1.

Screening with use of NICE guidelines[1] detected 41% (95% CI 18-67) of PE at <32 weeks, 39% (95% CI 27-53) of PE at <37 weeks and 34% (95% CI 27-41) of PE at ≥37 weeks, at 10.2% FPR. Screening with use of ACOG recommendations[2] detected 94% (95% CI 71-100) of PE at <32 weeks, 90% (95% CI 79-96) of PE at <37 weeks and 89% (95% CI 84-94) of PE at ≥37 weeks, at 64.2% FPR. Screening based on the ACOG recommendations for use of aspirin[3] detected (1/17) 6% (95% CI 1-27) of PE at <32 weeks, (3/59) 5% (95% CI 2-14) of PE at <37 weeks and (3/180) 2% (95% CI 0.3-5) of PE at ≥37 weeks, at (19/8,536) 0.2% FPR. The results of the methods advocated by NICE[1] and ACOG[2,3] are illustrated in Figure 1.

Discussion

Main findings

The findings of this prospective multicentre validation study demonstrate that the performance of first-trimester screening for PE by the FMF algorithm, in which the patient-specific risk is derived from a combination of maternal factors, MAP, UTPI and PLGF,[4,5] is by far superior to the methods advocated by NICE[1] and ACOG[2,3]. In screening by the FMF algorithm the DRs of delivery with PE at <32, <37 and ≥37 weeks' gestation were 100%, 75% and 43%, respectively, at FPR of 10%. The respective DRs in screening according to NICE guidelines[1], were 41%, 39% and 34%, at FPR of 10.2%. In the case of ACOG recommendations about two-thirds of the population were classified as screen positive; the DRs of delivery with PE at <32, <37 and ≥37 weeks were 94%, 90% and 89%, respectively, at FPR of 64.2%.[2] In screening based on the ACOG recommendations for use of aspirin[3] the DRs of delivery with PE at <32, <37 and ≥37 weeks were 6%, 5% and 2%, respectively, at FPR of 0.2%.

Study limitations

The main limitation of the study relates to the low incidence of delivery with PE with the inevitable wide confidence intervals obtained for performance of screening. Nevertheless, the values obtained in the validation study are very similar to those in the dataset of 35,948 pregnancies that was used for development of the algorithm.[5]

Implications for practice

In a proposed new pyramid of pregnancy care,[15] assessment of risk at 11-13 weeks' gestation aims to identify pregnancies at high-risk of developing PE and through pharmacological intervention, with such medications as low-dose aspirin, to reduce the incidence of these complications.[16-18] Administration of low-dose aspirin from the first-trimester to those at high-risk is effective in prevention of preterm- rather than term-PE,[18] and the use of the method advocated by the FMF[4,5] is superior to those recommended by NICE[1] and ACOG[3] in identifying the group of pregnancies that could benefit from such therapy. According to FMF and NICE about 10% of the pregnant population would receive low-dose aspirin and this population would contain 75% of those that would develop preterm-PE if selection of the high-risk group was based on the FMF algorithm and only 39% if selection was based on the NICE guidelines. In the case of the ACOG recommendations 0.2% of the population would receive aspirin and only 5% of cases of preterm-PE that could potentially benefit from such therapy would be targeted.

The method of NICE[1] and ACOG[2] treat each maternal factor as a separate screening test with additive DR and FPR. In the FMF method use of a multivariable logistic model to define the *prior* risk attributes the appropriate relative importance to each maternal factor and allows estimation of the patient-specific risk of PE requiring delivery before a specified gestation.[4] The *prior* risk can then be adjusted according to the results of biophysical and biochemical testing.[5] The software for such estimation of prior and adjusted risk is freely available (www.fetalmedicine.com). Recording maternal history and measurement of blood pressure are universally carried out as part of routine pregnancy care; measurement of MAP requires adherence to a protocol,[7] but can be undertaken by healthcare assistants after minimal training, with the use of inexpensive equipment and takes a few minutes to perform. Measurement of UTPI requires specific training by sonographers and quality assurance of their results;[8] nevertheless, this test can be undertaken within a few minutes by the same sonographers and machines as part of the routine first-trimester scan. Measurement of serum PLGF can be undertaken on the same machines as for free ß-hCG and PAPP-A, which are widely used in screening for Down syndrome.

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Figure legends

Figure 1. Receiver operating characteristic curves for prediction of delivery with PE at <32, <37 and ≥37 weeks' gestation by the FMF algorithm combining maternal factors, MAP, UTPI and PLGF. Performance of screening using the methods of NICE[1] ACOG[2] and ACOG for use of aspirin[3] are shown as dots.

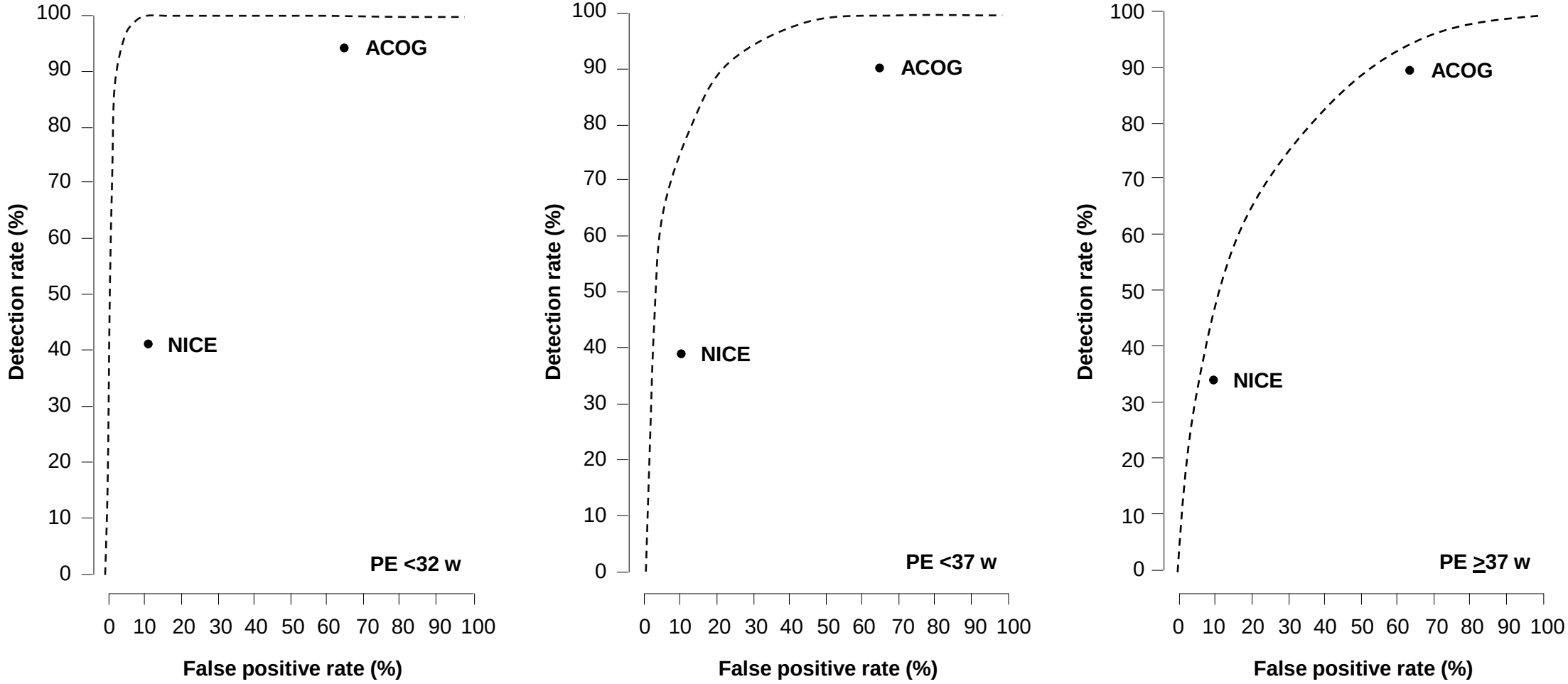

Figure 1

Table 1: Characteristics of study population.

Maternal characteristics	Delivery with preeclampsia			
	None (n=8,536)	<32 (n=17)	<37 (n=59)	≥37 (n=180)
Maternal age in years, median (IQR)	31.5 (27.3, 35.0)	29.8 (26.7, 34.6)	30.6 (25.95, 34.7)	31.2 (27.8, 34.8)
Maternal weight in Kg, median (IQR)	66.2 (58.8, 76.9)	72.6 (65.6, 86.0)	69.8 (63.0, 87.8)	75.0 (64.925, 84.0)
Maternal height in cm, median (IQR)	165 (160, 169)	164 (161, 166)	164 (160, 169)	164 (159, 168)
Body mass index, median (IQR)	24.5 (21.9, 28.2)	27.3 (23.9, 31.8)	27.1 (23.6, 31.82)	27.8 (23.9, 31.5)
Gestational age in weeks, median (IQR)	12.7 (12.3, 13.1)	12.6 (12.3, 12.7)	12.7 (12.4, 13.0)	12.7 (12.3, 13.2)
Racial origin, n (%)				
Caucasian	6,716 (78.7)	8 (47.1)	38 (64.4)	129 (71.7)
AfroCaribbean	1,040 (12.2)	8 (47.1)	14 (23.7)	36 (20.0)
East Asian	153 (1.8)	0 (0.0)	0 (0.0)	1 (0.6)
South Asian	447 (5.2)	0 (0.0)	3 (5.1)	12 (6.7)
Mixed	180 (2.1)	1 (5.9)	4 (6.8)	2 (1.1)
Medical history, n (%)				
Chronic hypertension	75 (0.9)	3 (17.7)	9 (15.3)	16 (8.9)
Diabetes mellitus	63 (0.7)	2 (11.8)	3 (5.1)	2 (1.1)
SLE or APS	32 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cigarette smoking, n (%)	717 (8.4)	1 (5.9)	4 (6.8)	11 (6.1)
Family history of preeclampsia, n (%)	434 (5.1)	1 (5.9)	7 (11.9)	17 (9.4)
Conception, n (%)				
Spontaneous	8,254 (96.7)	17 (100)	57 (96.6)	173 (96.1)
In vitro fertilization	218 (2.6)	0 (0.0)	2 (3.4)	7 (3.9)
Ovulation drugs	64 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Parity, n (%)				
Nulliparous	3,972 (46.5)	11 (64.7)	36 (61.0)	119 (66.1)
Parous: no previous preeclampsia	4,396 (51.5)	4 (23.5)	17 (28.8)	46 (25.6)
Parous: previous preeclampsia	168 (2.0)	2 (11.8)	6 (10.2)	15 (8.3)
Pregnancy interval in years, median (IQR)	2.7 (1.6, 4.6)	5.4 (4.3, 7.2)	4.1 (2.4, 6.8)	3.4 (2.0, 5.4)

IQR = interquartile range; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; Comparisons between outcome groups were by chi-square or Fisher exact test for categorical variables and Mann Whitney-U test for continuous variables

Table 2. Detection rate (with 95% confidence interval), at false positive rate of 10%, in screening for delivery with preeclampsia at <32, <37 and ≥37 weeks' gestation in the validation dataset using a previously developed algorithm[5] based on maternal factors and combinations of biomarkers. Performance of screening is compared to that using the NICE[1] and ACOG[2,3] recommendations.

Method of screening	**PE <32 w**	**PE <37 w**	**PE ≥37 w**
FMF algorithm (FPR 10%)			
Maternal factors	53 (28, 77)	41 (28, 54)	37 (30, 45)
Maternal factors plus:			
MAP	71 (44, 90)	47 (34, 61)	37 (30, 45)
UTPI	82 (57, 96)	61 (47, 73)	39 (32, 47)
PAPP-A	59 (33, 82)	47 (34, 61)	37 (30, 44)
PLGF	88 (64, 99)	63 (49, 75)	39 (32, 46)
MAP, UTPI	94 (71, 100)	71 (58, 82)	41 (34, 49)
MAP, PAPP-A	76 (50, 93)	49 (36, 63)	40 (33, 48)
MAP, PLGF	88 (64, 99)	69 (56, 81)	43 (36, 51)
UTPI, PAPP-A	82 (57, 96)	66 (53, 78)	40 (33, 48)
UTPI, PLGF	100 (80, 100)	75 (62, 85)	39 (32, 47)
PLGF, PAPP-A	88 (64, 99)	66 (53, 78)	39 (32, 47)
MAP, UTPI, PAPP-A	94 (71, 100)	69 (56, 81)	42 (35, 50)
MAP, PAPP-A, PLGF	88 (64, 99)	69 (56, 81)	43 (36, 51)
MAP, UTPI, PLGF	100 (80, 100)	75 (62, 85)	43 (35, 50)
UTPI, PAPP-A, PLGF	100 (80, 100)	75 (62, 85)	38 (31, 46)
MAP, UTPI, PAPP-A, PLGF	100 (80, 100)	80 (67, 89)	43 (35, 50)
NICE[1] (FPR 10.2%)	41 (18, 67)	39 (27, 53)	34 (27, 41)
ACOG[2] (FPR 64.2%)	94 (71, 100)	90 (79, 96)	89 (84, 94)
ACOG aspirin[3] (FPR 0.2%)	6 (1, 27)	5 (2, 14)	2 (0.3, 5)

FPR = false positive rate; MAP = Mean arterial pressure; UTPI = Uterine artery pulsatility index; PAPP-A = Pregnancy associated plasma protein-A; PLGF = Placental growth factor