Accuracy of competing risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation

Neil O'Gorman,[1] David Wright,[2] Liona C. Poon,[1,3]# Daniel L. Rolnik,[1] Argyro Syngelaki,[1] Alan Wright,[2] Ranjit Akolekar,[1,4] Simona Cicero,[5] Deepa Janga,[6] Jacques Jani,[7] Francisca S. Molina,[8] Catalina de Paco Matallana,[9] Nikos Papantoniou,[10] Nicola Persico,[11] Walter Plasencia,[12] Mandeep Singh,[13] Kypros H. Nicolaides[1]#

1. King's College Hospital, London, UK.
2. University of Exeter, Exeter, UK.
3. Chinese University of Hong Kong, Hong Kong, China
4. Medway Maritime Hospital, Gillingham, UK
5. Homerton University Hospital, London, UK,
6. North Middlesex University Hospital, London, UK,
7. Centre Hospitalier Universitaire Brugmann, Université Libre de Bruxelles, Brussels, Belgium
8. Hospital Universitario San Cecilio, Granada, Spain
9. Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain
10. Attikon University Hospital, Athens, Greece
11. Ospedale Maggiore Policlinico, Milan, Italy
12. Hospiten Group, Tenerife, Canary Islands, Spain
13. Southend University Hospital, Essex, UK

L. C. P and K. H. N are joint senior authors.

Competing risks model in screening for preeclampsia

Correspondence to: Prof. K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK.
Tel: 00 44 2032998256, email: kypros@fetalmedicine.com

ABSTRACT

Objective: To examine the diagnostic accuracy of a previously developed model for prediction of preeclampsia (PE) by a combination of maternal factors and biomarkers at 11-13 weeks' gestation.

Methods: This was a prospective first-trimester multicenter study of screening for PE in 8,775 singleton pregnancies. A previously published 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 in the dataset used for development of the algorithm.

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. In combined screening by maternal factors, mean arterial pressure, uterine artery pulsatility index and serum placental growth factor the DR was 100% (95% CI 80-100) for PE at <32 weeks, 75% (95% CI 62-85) for PE at <37 weeks and 43% (95% CI 35-50) for PE at ≥37 weeks, at 10%

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.17399

FPR. These DRs were similar to the estimated rates in the dataset used for development of the model: 89% (95% CI 79-96) for PE at <32 weeks, 75% (95% CI 70-80) for PE at <37 weeks and 47% (95% CI 44-51) for PE at ≥37 weeks.

Conclusion: Combination of maternal factors and biomarkers provides effective first-trimester screening for preterm-PE.

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

Scientific and clinical background

Effective screening for preterm preeclampsia (PE) can be provided at 11-13 weeks' gestation by a combination of maternal characteristics and medical history (maternal factors) with multiple of the median (MoM) values of mean arterial pressure (MAP), uterine artery pulsatility index (UTPI) and serum placental growth factor (PLGF) and pregnancy associated plasma protein-A (PAPP-A). 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.[1] Bayes theorem was used to combine the *a priori* risk from maternal factors[2] with various combinations of MAP, UTPI, PAPP-A and PLGF.[1] In pregnancies with PE the deviation from normal for each biomarker was inversely related to the gestational age at delivery and consequently the performance of screening was greater for early than late PE. The performance of each biomarker in combination with maternal factors was superior to that of screening by maternal factors alone. Similarly, the performance by a combination of two or more biomarkers was superior to that of screening by individual biomarkers. The only exception was serum PAPP-A, which did not provide significant improvement to any combination of biomarkers which included serum PLGF. In combined screening by maternal factors, MAP, UTPI and PLGF the detection rate (DR) of delivery with PE at <32, <37 and ≥37 weeks was 89%, 75% and 47%, respectively, at false positive rate (FPR) of 10%. A limitation of the study is that the performance of screening by a model derived and tested using the same dataset may be overestimated.

Study objectives and hypothesis

The objective of this study is to report the accuracy of the previously reported first-trimester model of screening for PE [1] in a prospective, non-intervention, multicenter study in 8,775 singleton pregnancies. The hypothesis is that the performance of screening would be similar to that estimated from the original model [1].

The Standards for Reporting Diagnostic accuracy studies (STARD) [3] were adhered to.

METHODS

Study design and participants

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 at 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. 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 eligibility criteria were maternal age ≥18 years, no serious mental illness or learning difficulties, singleton pregnancy with live fetus demonstrated on the 11-13 weeks scan and subsequent delivery of a phenotypically normal live birth or stillbirth at ≥24 weeks' gestation.

We excluded multiple pregnancies, those with aneuploidies or major fetal abnormalities and those ending in termination or miscarriage.

Test methods

The index test, or test whose accuracy has been evaluated, is the previously reported algorithm for first-trimester assessment of risk for PE by maternal factors and various combinations of MAP, UTPI, PAPP-AS and PLGF.[1] Maternal factors were recorded,[2] MAP was measured by validated automated devices and standardized protocol,[4] transabdominal color Doppler ultrasound was used to measure the left and right UTPI and the average value was recorded,[5] serum PAPP-A and PLGF concentrations were measured by an automated device (PAPP-A and PlGF 1-2-3^{TM} kits, DELFIA® Xpress random access platform; PerkinElmer Inc. Wallac Oy, P.O.Box 10, 20101 Turku, Finland). All operators undertaking the Doppler studies had received the appropriate Certificate of Competence from the Fetal Medicine Foundation. 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.[6-9]

The index test was carried out prospectively in consecutive singleton pregnancies at 11^{+0} - 13^{+6} weeks' gestation; gestational age was determined from the measurement of fetal crown-rump length.[10] The results from screening were not made available to the patients or their physicians.

The target condition was PE, as defined by the International Society for the Study of Hypertension in Pregnancy.[11] The systolic blood pressure should be $\geq$140 mm Hg and/or the diastolic blood pressure should be $\geq$90 mmHg on at least two occasions four hours apart developing after 20 weeks of gestation in previously normotensive women. Hypertention should be accompanied by proteinuria of $\geq$300 mg in 24 hours or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour 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 the 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

Analysis

The previously described algorithm was used for the calculation of patient-specific risk of delivery with PE at <32, <37 and $\geq$37 weeks' gestation.[1] The pre-specified analyses for performance of screening for maternal factors and any combinations of maternal factors with MAP, UTPI, PAPP-A and PLGF were estimation of areas under the receiver operating characteristic curve (AUC) and DR, with 95% CI, at FPR of 5% and 10%.

The statistical software package R was used for data analyses.[12]

RESULTS

Participants

During the study period, 9,041 pregnancies meeting the inclusion criteria underwent screening for PE. We subsequently excluded 266 (2.9%) cases because they had a major

fetal defect (n=33), the pregnancy resulted in termination (n=39) or miscarriage (n=88) or there was no follow up (n=106).

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. Baseline demographic and clinical characteristics of participants are shown in Table 1. In total, 12 maternity hospitals in five different countries were involved in patient recruitment, 127 doctors participated in the measurement of UTPI and 152 doctors or nurses were involved in the measurement of MAP.

Test results

The AUC and DR at FPR of 5% and 10% of delivery with PE at <32, <37 and ≥37 weeks' gestation in screening by maternal factors and biomarkers using the previously reported algorithm[1] are given in Table 2 and compared to previously reported values in Figures 1-3. The DRs in the validation dataset were very similar to the estimated rates in the dataset used for development of the model.

The performance of screening for PE at <37 weeks was superior to that of PE at ≥37 weeks. The best performance of screening was achieved by a combination of maternal factors, MAP, UTPI and PLGF and this was not improved by addition of PAPP-A.

DISCUSSION

Main findings

This prospective multicenter validation study demonstrates the feasibility of incorporating first-trimester screening for PE into routine clinical practice. The findings demonstrate that the performance of screening for PE at 11-13 weeks by a combination of maternal factors and biomarkers is similar to that estimated from the original model.[1] The DR of screening by maternal factors, MAP, UTPI and PLGF, at 10% FPR, was 100% (95% CI 80-100) for PE at <32 weeks, 75% (95% CI 62-85) for PE at <37 weeks and 43% (95% CI 35-50) for PE at ≥37 weeks; the estimated rates in the dataset used for development of the model were 89% (95% CI 79-96), 75% (95% CI 70-80) and 47% (95% CI 44-51), respectively.[1]

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 used for development of the algorithm.

Implications for practice

Screening and diagnosis of PE is traditionally based on the demonstration of elevated blood pressure and proteinuria during a routine clinical visit in the late second- or third-trimester of pregnancy. In a proposed new pyramid of pregnancy care,[13] 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 prevalence of these complications.[14,15]

The findings of the validation study confirm that screening at 11-13 weeks identifies a high proportion of cases that will develop PE at <37 weeks, but the performance of screening at this stage for PE at ≥37 weeks is poor.[1] This is particularly important because the

prophylactic use of low-dose aspirin is effective in the prevention of preterm-PE rather than term-PE.[16] We have previously reported that effective prediction of PE at ≥37 weeks requires screening at 35-36 weeks.[17]

Sources of Funding: The study was supported by grants from the Fetal Medicine Foundation (Charity No: 1037116) and by the European Union 7th Framework Programme - FP7-HEALTH-2013-INNOVATION-2 (ASPRE Project # 601852).

References

1. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Am J Obstet Gynecol* 2016; **214**: 103.e1-103.e12.

2. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol* 2015; **213**: 62.e1-10.

3. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, LijmerJG Moher D, Rennie D, de Vet HCW, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF, For the STARD Group. STARD 2015: An updated list of essential items for reporting diagnostic accuracy studies. *BMJ* 2015; **351**: h5527.

4. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. *Fetal Diagn Ther* 2012; **31**: 42-48.

5. Plasencia W, Maiz N, Bonino S, Kaihura C, Nicolaides KH. Uterine artery Doppler at 11+0 to 13+6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2007; **30**: 742-749.

6. Wright A, Wright D, Ispas A, Poon LC, Nicolaides KH. Mean arterial pressure in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 698-706.

7. Tayyar A, Guerra L, Wright A, Wright D, Nicolaides KH. Uterine artery pulsatility index in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 689-697.

8. Wright D, Silva M, Papadopoulos S, Wright A, Nicolaides KH. Serum pregnancy associated plasma protein-A in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **46**: 42-50.

9. Tsiakkas A, Duvdevani N, Wright A, Wright D, Nicolaides KH. Serum placental growth factor in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 591-598.

10. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length

measurements. *Br J Obstet Gynaecol* 1975; **82**: 702-710.

11. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the international society for the study of hypertension in pregnancy (ISSHP). Hypertens Pregnancy 2001;20:IX-XIV.

12. R Development Core Team. R. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2011;ISBN 3-900051-07-0, URL http://www.R-project.org/

13. Nicolaides KH. Turning the pyramid of prenatal care. *Fetal Diagn Ther* 2011; **29**: 183-196.

14. Bujold E, Roberge S, Lacasse Y, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010; **116**: 402-414.

15. Roberge S, Nicolaides K, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. *Ultrasound Obstet Gynecol* 2013; **41**: 491-499.

16. Roberge S, Villa P, Nicolaides KH, et al. Early administration of low dose aspirin for the prevention of preterm and term pre-eclampsia: a systematic review and meta-analysis. *Fetal Diagn Ther* 2012; **31**: 141-146.

17. Andrietti S, Silva M, Wright A, Wright D, Nicolaides KH. Competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 35-37 weeks' gestation. *Ultrasound Obstet Gynecol* 2016; **48**: 72-79.

Figure legends

Figure 1. Detection rate with 95% confidence interval at 10% false positive rate of screening for delivery with preeclampsia at <32 weeks' gestation by maternal factors and combinations of biomarkers. The black circles and lines represent the values obtained in the dataset used for development of the algorithm[1] and the red circles and lines represent the values obtained in the validation dataset. MAP = Mean arterial pressure; UTPI = Uterine artery pulsatility index; PAPP-A = Pregnancy associated plasma protein-A; PLGF = Placental growth factor.

Figure 2. Detection rate with 95% confidence interval at 10% false positive rate of screening for delivery with preeclampsia at <37 weeks' gestation by maternal factors and combinations of biomarkers. The black circles and lines represent the values obtained in the dataset used for development of the algorithm[1] and the red circles and lines represent the values obtained in the validation dataset. MAP = Mean arterial pressure; UTPI = Uterine artery pulsatility index; PAPP-A = Pregnancy associated plasma protein-A; PLGF = Placental growth factor.

Figure 3. Detection rate with 95% confidence interval at 10% false positive rate of screening for delivery with preeclampsia at ≥37 weeks' gestation by maternal factors and combinations of biomarkers. The black circles and lines represent the values obtained in the dataset used for development of the algorithm[1] and the red circles and lines represent the values obtained in the validation dataset. MAP = Mean arterial pressure; UTPI = Uterine artery pulsatility index; PAPP-A = Pregnancy associated plasma protein-A; PLGF = Placental growth factor.

Table 1: Characteristics of study population.

Maternal characteristics	Delivery with preeclampsia			
	None (n=8,624)	<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, 28.3)	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	6,768 (78.5)	8 (47.1)	38 (64.4)	129 (71.7)
Afro-Caribbean	1,068 (12.4)	8 (47.1)	14 (23.7)	36 (20.0)
East Asian	154 (1.8)	0 (0.0)	0 (0.0)	1 (0.6)
South Asian	451 (5.2)	0 (0.0)	3 (5.1)	12 (6.7)
Mixed	183 (2.1)	1 (5.9)	4 (6.8)	2 (1.1)
Medical history, n (%)				
Chronic hypertension	79 (0.9)	3 (17.7)	9 (15.3)	16 (8.9)
Diabetes mellitus	64 (0.7)	2 (11.8)	3 (5.1)	2 (1.1)
SLE or APS	19 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cigarette smoking, n (%)	7,901 (91.6)	16 (94.1)	55 (93.2)	169 (93.9)
Family history of preeclampsia, n (%)	441 (5.1)	1 (5.9)	7 (11.9)	17 (9.4)
Conception, n (%)				
Spontaneous	8,340 (96.7)	17 (100)	57 (96.6)	173 (96.1)
In vitro fertilization	219 (2.5)	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	4,008 (46.5)	11 (64.7)	36 (61.0)	119 (66.1)
Parous: no previous preeclampsia	4,445 (51.5)	4 (23.5)	17 (28.8)	46 (25.6)
Parous: previous preeclampsia	171 (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. Performance of screening for delivery with preeclampsia at <32, <37 and ≥37 weeks' gestation in the validation dataset using a previously developed algorithm based on maternal factors and combinations of biomarkers.

Method of screening	Preeclampsia at <32w (n=17)			Preeclampsia at <37w (n=59)			Preeclampsia at ≥37w (n=180)		
	AUC	Detection rate at:		AUC	Detection rate at:		AUC	Detection rate at:	
		FPR 5%	FPR 10%		FPR 5%	FPR 10%		FPR 5%	FPR 10%
Maternal factors	0.8045	41 (18, 67)	53 (28, 77)	0.7583	29 (18, 42)	41 (28, 54)	0.7449	18 (13,25)	37 (30, 45)
Maternal factors plus:									
MAP	0.9071	59 (33, 82)	71 (44, 90)	0.8243	36 (24, 49)	47 (34, 61)	0.7789	26 (20, 33)	37 (30, 45)
UTPI	0.9309	71 (44, 90)	82 (57, 96)	0.8537	47 (34, 61)	61 (47, 73)	0.7539	22 (16, 29)	39 (32, 47)
PAPP-A	0.8546	47 (23, 72)	59 (33, 82)	0.7825	37 (25, 51)	47 (34, 61)	0.7504	21 (15, 28)	37 (30, 44)
PLGF	0.9506	65 (38, 86)	88 (64, 99)	0.8722	49 (36, 63)	63 (49, 75)	0.7578	20 (14, 27)	39 (32, 46)
MAP, UTPI	0.9667	82 (57, 96)	94 (71, 100)	0.8958	53 (39, 66)	71 (58, 82)	0.7875	27 (20, 34)	41 (34, 49)
MAP, PAPP-A	0.9133	65 (38, 86)	76 (50, 93)	0.8342	41 (28, 54)	49 (36, 63)	0.7827	28 (21, 35)	40 (33, 48)
MAP, PLGF	0.9674	76 (50, 93)	88 (64, 99)	0.8985	53 (39, 66)	69 (56, 81)	0.7870	29 (22, 36)	43 (36, 51)
UTPI, PAPP-A	0.9339	71 (44, 90)	82 (57, 96)	0.8583	49 (36, 63)	66 (53, 78)	0.7571	24 (18, 31)	40 (33, 48)
UTPI, PLGF	0.9772	82 (57, 96)	100 (80, 100)	0.9000	61 (47, 73)	75 (62, 85)	0.7619	22 (16, 29)	39 (32, 47)
PLGF, PAPP-A	0.9510	65 (38, 86)	88 (64, 99)	0.8741	51 (37, 64)	66 (53, 78)	0.7589	20 (14, 27)	39 (32, 47)
MAP, UTPI, PAPP-A	0.9644	88 (64, 99)	94 (71, 100)	0.8956	61 (47, 73)	69 (56, 81)	0.7892	29 (22, 36)	42 (35, 50)
MAP, PAPP-A, PLGF	0.9672	76 (50, 93)	88 (64, 99)	0.8998	54 (41, 67)	69 (56, 81)	0.7882	29 (22, 36)	43 (36, 51)
MAP, UTPI, PLGF	0.9870	94 (71, 100)	100 (80, 100)	0.9242	66 (53, 78)	75 (62, 85)	0.7916	32 (25, 39)	43 (35, 50)
UTPI, PAPP-A, PLGF	0.9769	82 (57, 96)	100 (80, 100)	0.9004	61 (47, 73)	75 (62, 85)	0.7626	23 (17, 30)	38 (31, 46)
MAP, UTPI, PAPP-A, PLGF	0.9865	94 (71, 100)	100 (80, 100)	0.9241	66 (53, 78)	80 (67, 89)	0.7923	31 (24, 38)	43 (35, 50)

AUC = area under the receiver operating characteristic curve; FPR = false positive rate; MAP = Mean arterial pressure; UTPI = Uterine artery pulsatility index; PAPP-A = Pregnancy associated plasma protein-A; PLGF = Placental growth factor