Ultrasound Obstet Gynecol 2016; **47**: 554–559
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.15807

Contingent screening for preterm pre-eclampsia

D. WRIGHT*, D. M. GALLO†, S. GIL PUGLIESE†, C. CASANOVA† and K. H. NICOLAIDES†

**Institute of Health Research, University of Exeter, Exeter, UK; †Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK*

KEYWORDS: Bayes' theorem; contingent screening; mean arterial pressure; placental growth factor; pre-eclampsia; pyramid of pregnancy care; survival model; uterine artery Doppler

ABSTRACT

Objective *Effective screening for pre-eclampsia resulting in delivery < 37 weeks' gestation (preterm PE) is provided by assessment of a combination of maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PlGF) at 11–13 or 19–24 weeks' gestation. This study explores the possibility of carrying out routine screening for preterm PE by maternal factors and MAP in all pregnancies and reserving measurements of UtA-PI and PlGF for a subgroup of the population, selected on the basis of the risk derived from screening by maternal factors and MAP alone.*

Methods *Study data were derived from prospective screening for adverse obstetric outcomes in women attending their routine hospital visit at 11–13 and/or 19–24 weeks' gestation. Bayes' theorem was used to derive the* a-priori *risk for preterm PE from maternal factors and MAP. The posterior risk was obtained by the addition of UtA-PI and PlGF. We estimated the detection rate (DR) of preterm PE, at an overall false-positive rate (FPR) of 10%, from a policy in which first-stage screening by a combination of maternal factors and MAP defines screen-positive, screen-negative and intermediate-risk groups, with the latter undergoing second-stage screening by UtA-PI and PlGF.*

Results *At 11–13 weeks' gestation, the model-based DR of preterm PE, at a 10% FPR, when screening the whole population by maternal factors, MAP, UtA-PI and PlGF was 74%. A similar DR was achieved by two-stage screening, with screening by maternal factors and MAP in the first stage and reserving measurement of UtA-PI and PlGF for the second stage and for only 50% of the population. If second-stage screening was offered to 30% of the population, there would be only a small reduction in DR from 74% to 71%. At 19–24 weeks, the model-based DR of preterm PE, at a 10% FPR, when screening the whole population by maternal factors, MAP, UtA-PI and PlGF was 84%. A similar DR was achieved by two-stage screening with measurements of UtA-PI and PlGF in only 70% of the population; if second-stage screening was offered to 40% of the population, the DR would be reduced from 84% to 81%.*

Conclusions *High DR of preterm PE can be achieved by two-stage screening in the first and second trimesters with maternal factors and MAP in the whole population and measurements of UtA-PI and PlGF in only some of the pregnancies.*

INTRODUCTION

In screening for pre-eclampsia (PE), we advocate use of Bayes' theorem to combine the *a-priori* risk from maternal demographic characteristics and medical history (maternal factors) with the results of various combinations of biophysical and biochemical measurements[1–4]. This approach of screening, which allows estimation of individual patient-specific risks of PE requiring delivery before any specified gestational age, has a performance which is by far superior to that of risk-scoring systems based on maternal factors alone[3–6].

We reported recently that screening for PE at 11–13 or 19–24 weeks' gestation by a combination of maternal factors and mean arterial pressure (MAP) can predict about 60% of preterm PE, requiring delivery < 37 weeks, but only about 45% of PE delivering ≥ 37 weeks, at a false-positive rate (FPR) of 10%[3,4]. Addition of uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PlGF) improved the detection rate (DR) of preterm PE to about 75% at 11–13 weeks and 85% at 19–24 weeks[3,4]. Recording of maternal history and measurement of blood pressure are universally carried out as part of routine pregnancy care. In contrast, measurement of UtA-PI requires specific training by sonographers and quality assurance of their results; nevertheless this test can be undertaken within a few minutes by the same sonographers and machines as part of the routine second-trimester scan. Measurement of serum PlGF can be

Correspondence to: Prof. K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK (e-mail: kypros@fetalmedicine.com)

Accepted: 27 October 2015

undertaken on the same machines as for free beta-human chorionic gonadotropin and pregnancy-associated plasma protein A, which are widely used in screening for Down syndrome, but there is an inevitable increase in cost.

The objective of this study was to explore the possibility of carrying out routine screening by maternal factors and MAP in all pregnancies and reserving measurements of UtA-PI and PlGF for only a subgroup of the population, selected on the basis of the risk derived from screening by maternal factors and MAP.

METHODS

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending their routine first- and/or second-trimester hospital visits at King's College Hospital, University College London Hospital and Medway Maritime Hospital, UK. These visits, which were held at 11 + 0 to 13 + 6 and 19 + 0 to 24 + 6 weeks' gestation, included first, recording of maternal characteristics and medical history, second, measurement of the left and right UtA-PI by color Doppler ultrasound and calculation of the mean PI by transabdominal ultrasound in the first trimester and by transvaginal ultrasound in the second trimester[7,8], third, measurement of MAP by validated automated devices and standardized protocol[9] and fourth, measurement of serum concentration of PlGF by an automated biochemical analyzer within 10 min of blood sampling (Cobas e411 system, Roche Diagnostics, Penzberg, Germany).

Gestational age was determined from measurement of fetal crown–rump length at 11–13 weeks or the fetal head circumference at 19–24 weeks[10,11]. The women were screened between March 2006 and July 2014 and gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

The inclusion criteria for this study were singleton pregnancy delivering a morphologically normal live birth or stillbirth at or after 24 weeks' gestation. Pregnancies with aneuploidy or major fetal abnormality and those ending in termination, miscarriage or fetal death < 24 weeks were excluded.

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners 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, as defined by the International Society for the Study of Hypertension in Pregnancy[12]. The outcome measure for this study was preterm PE.

Statistical analysis

Our competing-risks model for gestational age at delivery with PE is defined by two components: first, the prior distribution based on maternal factors[1] and second, the conditional distribution of multiples of the median (MoM) values of UtA-PI, MAP and PlGF[13–15] given the gestational age with PE and maternal factors[4]. Model-based estimates of screening performance were obtained as follows. Samples of 500 000 records with preterm PE and 500 000 without PE or pregnancy-induced hypertension were sampled with replacement from a population of 123 406 pregnancies with available data on maternal factors. For each record, the prior distribution of time to delivery was obtained from a competing-risks model[1]. MAP, UtA-PI and PlGF MoM values were simulated from the fitted multivariate Gaussian distribution for log-transformed MoM values[3,4]. Posterior distributions of time to delivery with PE were obtained by combining the prior risk[1] and the likelihoods of the biomarkers using Bayes' theorem. Risks of PE were obtained by calculating the area under the posterior distribution. The different contingent screening policies were then applied to the risks to provide model-based estimates of screening performance.

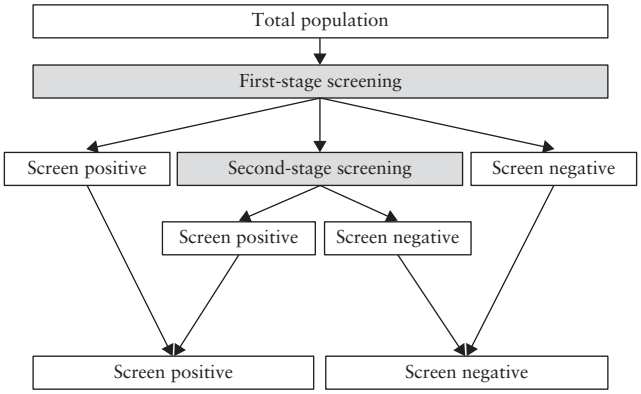

Figure 1 Two-stage screening strategy for preterm pre-eclampsia in which the whole population undergoes first-stage screening by maternal factors and mean arterial pressure and a selected proportion of those considered to be at intermediate risk undergo second-stage screening by uterine artery pulsatility index and placental growth factor.

We examined the performance of screening for preterm PE by a two-stage strategy (Figure 1). In the first stage, which is applied to the whole population, the risk of preterm PE was derived from maternal factors and MAP. On the basis of the results of first-stage screening, the population was divided into a low-risk group considered to be screen negative, a high-risk group considered to be screen positive and an intermediate-risk group in need of further testing with UtA-PI and PlGF; after such testing, the patients were again classified as screen negative or screen positive. The screen-positive rate in the normal-outcome group (same as FPR for the whole population) is the sum of the screen-positive groups from first- and second-stage screening and was fixed at 10%.

The statistical software package R was used for data analyses[16].

RESULTS

The characteristics of the total population of 123 406 singleton pregnancies are given in Table 1. In the first

Table 1 Characteristics of study population of pregnant women screened at 11–13 weeks or 19–24 weeks' gestation for preterm pre-eclampsia (PE) (delivery < 37 weeks) according to pregnancy outcome

Characteristic	*Unaffected* (n = *117 710*)	*Preterm PE* (n = *790*)	*Term PE* (n = *1958*)	*PIH* (n = *2948*)
Maternal age (years)	31.3 (26.7–35.1)	31.8 (26.9–36.5)	31.3 (26.5–35.8)	31.8 (27.2–35.5)
Maternal weight (kg)	69.8 (62.4–79.9)	74.0 (65.0–88.0)	77.4 (67.8–91.9)	76.0 (67.0–88.0)
Maternal height (cm)	164 (160–169)	163 (158–167)	164 (160–168)	165 (160–169)
Body mass index (kg/m^2)	25.8 (23.2–29.4)	28.4 (24.6–32.8)	28.8 (25.4–33.7)	28.1 (25.0–32.4)
Gestational age (weeks)	22.1 (21.1–22.7)	22.2 (21.2–22.8)	22.2 (21.4–22.7)	22.2 (21.4–22.7)
Racial origin				
Caucasian	87 373 (74.2)	420 (53.2)	1165 (59.5)	2010 (68.2)
Afro-Caribbean	18 313 (15.6)	293 (37.1)	614 (31.4)	668 (22.7)
South Asian	6120 (5.2)	51 (6.5)	102 (5.2)	148 (5.0)
East Asian	3106 (2.6)	10 (1.3)	37 (1.9)	53 (1.8)
Mixed	2798 (2.4)	16 (2.0)	40 (2.0)	69 (2.3)
Medical history				
Chronic hypertension	1198 (1.0)	102 (12.9)	186 (9.5)	0 (0.0)
Diabetes mellitus	893 (0.8)	30 (3.8)	31 (1.6)	35 (1.2)
SLE/APS	207 (0.2)	9 (1.1)	7 (0.4)	9 (0.3)
Mode of conception				
Spontaneous	113 530 (96.5)	727 (92.0)	1868 (95.4)	2823 (95.8)
In-vitro fertilization	2632 (2.2)	43 (5.4)	68 (3.5)	83 (2.8)
Ovulation induction drugs	1548 (1.3)	20 (2.5)	22 (1.1)	42 (1.4)
Family history of PE	4243 (3.6)	67 (8.5)	134 (6.8)	220 (7.5)
Parity				
Nulliparous	57 720 (49.0)	468 (59.2)	1250 (63.8)	1888 (64.0)
Parous				
No previous PE	56 848 (48.3)	196 (24.8)	476 (24.3)	765 (26.0)
Previous PE	3142 (2.7)	126 (16.0)	232 (11.9)	295 (10.0)
Interpregnancy interval (years)	2.9 (1.9–4.8)	4.2 (2.4–7.3)	3.7 (2.3–6.7)	3.4 (2.0–5.7)

Data are given as median (interquartile range) or *n* (%). APS, antiphospholipid syndrome; PIH, pregnancy induced hypertension; SLE, systemic lupus erythematosus.

trimester, MAP was measured in 77 343 cases, UtA-PI in 92 712 and PlGF in 40 212, and the respective values in the second trimester were 31 120, 67 605 and 10 282.

Screening at 11–13 weeks' gestation

The model-based DR of preterm PE, at a FPR of 10%, when screening the whole population by maternal factors, MAP, UtA-PI and PlGF in the first trimester was 74% (Table 2 and Figure 2). A similar DR was achieved by two-stage screening; by maternal factors and MAP in the first stage and reserving measurement of UtA-PI and PlGF for the second stage and for only 50% of the population (Table 2 and Figure 2). Similarly, if second-stage screening was offered to 30% of the population, the DR with the addition of UtA-PI or PlGF would be reduced only mildly from 74% to 71%.

The results of a policy in which the population is divided after first-stage screening into screen-positive, screen-negative and intermediate-risk groups, with the latter undergoing second-stage screening, is shown in Figure 2 and Table S1. If the selected population for second-stage screening is > 30%, the maximum DR is achieved without the need for identifying a screen-positive group in first-stage screening. In contrast, if the selected population for second-stage screening is ≤ 30%, the DR is higher if a screen-positive group is introduced. For example, if after first-stage screening 0% of the population is classified as screen-positive and 20% is selected for second-stage screening, the DR, at a 10% FPR, would be 66.7%; if after first-stage screening 5% of the population is classified as screen positive and 20% is selected for second-stage screening, the DR, at a 10% FPR, would be 68.7%.

The DR for preterm PE, at a 10% FPR, of two-stage screening at 11–13 weeks' gestation in the population, subdivided according to racial origin and obstetric history is shown in Table S2. In these calculations, a policy was selected whereby, after first-stage screening, 2% of the population was classified as screen positive, 68% as screen negative and 30% were selected for second-stage screening. The FPR was lower and DR higher in parous than in nulliparous women, in parous women with PE in a previous pregnancy than in parous women without PE in a previous pregnancy and in those of Afro-Caribbean racial origin than in those of Caucasian racial origin.

Screening at 19–24 weeks' gestation

The model-based DR of preterm PE, at a FPR of 10%, when screening the whole population by maternal factors, MAP, UtA-PI and PlGF in the second trimester was 84% (Table 2 and Figure 2). A similar DR was achieved by two-stage screening; by maternal factors and MAP in the first stage and reserving measurements of UtA-PI and PlGF for the second stage and for only 70% of the population (Table 2 and Figure 2). Similarly, if second-stage screening was offered to 40% of the population, the DR with the addition of UtA-PI or PlGF would be reduced only mildly from 84% to 81%.

The results of a policy in which the population is divided after first-stage screening into screen-positive, screen-negative and intermediate-risk groups, with the

Table 2 Model-based detection rate (DR) of preterm pre-eclampsia (PE), at overall false-positive rate of 10%, by two-stage screening with maternal factors and mean arterial pressure at the first stage and uterine artery pulsatility index and serum placental growth factor at the second stage, at 11–13 or 19–24 weeks' gestation

Screening at 11–13 weeks				*Screening at 19–24 weeks*			
Proportion undergoing second-stage screening (%)				*Proportion undergoing second-stage screening (%)*			
All	*Unaffected*	*Preterm PE*	*DR (%)*	*All*	*Unaffected*	*Preterm PE*	*DR (%)*
15	13.8	64.3	62.8	15	13.7	66.7	66.1
20	18.7	71.1	66.7	20	18.6	73.3	71.2
25	23.6	76.6	69.3	25	23.5	78.4	74.7
30	28.6	81.0	70.9	30	28.5	82.4	77.2
35	33.6	84.6	72.0	35	33.5	85.8	79.1
40	38.6	87.6	72.7	40	38.5	88.6	80.5
45	43.6	90.2	73.3	45	43.5	90.9	81.5
50	48.6	92.3	73.6	50	48.6	92.8	82.3
55	53.7	94.0	73.8	55	53.7	94.4	82.9
60	58.8	95.5	74.0	60	58.7	95.8	83.4
65	63.9	96.7	74.0	65	63.8	96.9	83.8
70	69.0	97.6	74.1	70	69.0	97.8	84.0
75	74.1	98.4	74.1	75	74.1	98.5	84.2
80	79.3	99.0	74.1	80	79.2	99.0	84.3
85	84.4	99.4	74.1	85	84.4	99.4	84.4
90	89.6	99.7	74.1	90	89.6	99.6	84.4
95	94.8	99.9	74.1	95	94.8	99.8	84.4
100	100	100	74.1	100	100	100	84.4

In the first stage, applied to the whole population, risk of preterm PE is assessed by maternal factors and mean arterial pressure, defining a higher risk group that continues to the second stage. In the second stage, uterine artery pulsatility index and serum placental growth factor are measured and the combined risk is used to identify a screen-positive group. The risk cut-off in the first stage is determined to achieve the proportion continuing to the second stage. The second-stage risk cut-off is determined so that the two stages combined have a false-positive rate of 10%.

latter undergoing second-stage screening, is shown in Figure 2 and Table S3. If the selected population for second-stage screening is $> 40\%$, the maximum DR is achieved without the need for identifying a screen-positive group in first-stage screening. In contrast, if the selected population for second-stage screening is $\leq 40\%$, the DR is higher if a screen-positive group is introduced. For example, if after first-stage screening 0% of the population is classified as screen positive and 20% is selected for second-stage screening, the DR, at a 10% FPR, would be 71.6%; if after first-stage screening 7% of the population is classified as screen positive and 20% is selected for second-stage screening, the DR, at a 10% FPR, would be 74.9%.

The DR for preterm PE, at a 10% FPR, of two-stage screening at 19–24 weeks' gestation in the population subdivided according to racial origin and obstetric history is shown in Table S4. In these calculations, a policy was selected whereby, after first-stage screening, 2% of the population was classified as screen positive, 58% as screen negative and 40% were selected for second-stage screening. The FPR and DR were higher in nulliparous than in parous women, in parous women with PE in a previous pregnancy than in women without PE in a previous pregnancy and in those of Afro-Caribbean racial origin than in those of Caucasian racial origin.

DISCUSSION

Principal findings of the study

The findings of this study demonstrate that, in screening the whole population for preterm PE at 11–13 or 19–24 weeks' gestation by a combination of maternal factors, MAP, UtA-PI and PlGF, the DR, at a 10% FPR, is about 75% and 85%, respectively. A similar performance can be achieved by a two-stage strategy with screening by maternal factors and MAP in the whole population in the first stage and reserving measurement of UtA-PI and PlGF for the second stage and for only some of the population; 50% of the population when screening at 11–13 weeks and 70% of the population when screening at 19–24 weeks. Further reduction in the proportion of the population undergoing second-stage screening to 30% at 11–13 weeks and 40% at 19–24 weeks would result in only a small decrease in DR.

We propose a methodology and provide data on the estimated overall DR based on the proportion of the population selected for second-stage screening, and this could form the basis for heath economic evaluations that would define the most appropriate strategy for different healthcare systems.

In the application of Bayes' theorem, the maternal-factor derived prior risk has a strong influence on the posterior risk and therefore the performance of screening. This is well recognized in the case of screening for Down syndrome for which the maternal-age derived prior risk is combined with the measurement of first- and or second-trimester biomarkers to derive the posterior risk; at a fixed risk cut-off, both the DR and FPR increase with maternal age and therefore the overall performance of screening depends on the maternal age distribution of a given study population. In screening for PE, important contributors to the prior risk are racial origin, maternal weight and height, method of conception as well as

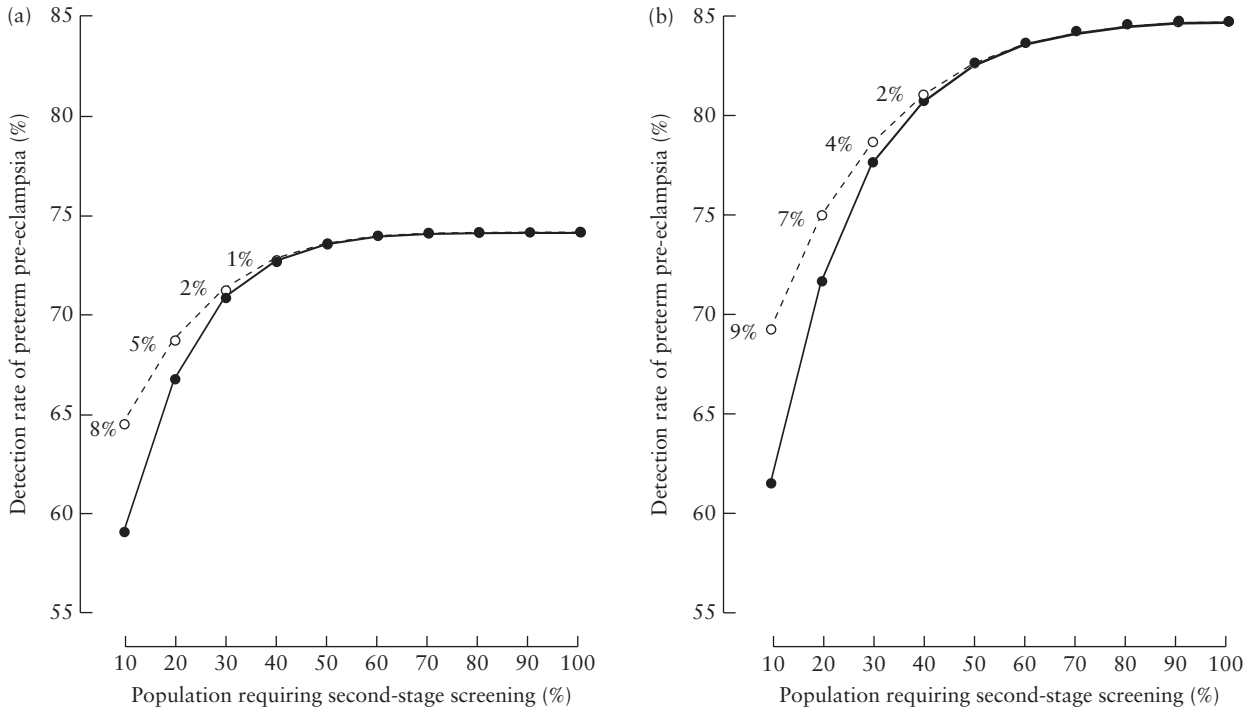

Figure 2 Relationship between the detection rate of preterm pre-eclampsia and the proportion of the population requiring second-stage screening by uterine artery pulsatility index and placental growth factor after first-stage screening by maternal factors and mean arterial pressure at: (a) 11–13 weeks; or (b) 19–24 weeks' gestation. Filled circles and solid lines represent the performance of screening if the population is divided after the first stage into a screen-negative group and a group in need of second-stage screening. Open circles and dashed lines represent the performance of screening if the population is divided after the first stage into a screen-positive group, a screen-negative group and an intermediate-risk group in need of second-stage screening. Values adjacent to the open circles are the proportion of the population classified as screen positive after the first stage.

components of family, obstetric and medical history; consequently, at a fixed FPR, the risk cut-off and DR are inevitably dependent on the distribution of maternal factors of a given study population.

Strengths and limitations

The strength of this study relies on the basic principle that first-stage screening identifies a group that is at such high risk and another that is at such low risk that further testing with additional biomarkers is unlikely to change their classification from screen positive and screen negative, respectively. Second-stage testing is restricted to an intermediate-risk group for which additional measurements are likely to make a difference to their final screening result. The first stage uses maternal factors and MAP; taking a medical history and recording blood pressure are an integral part of routine antenatal care. The second stage uses UtA-PI and PlGF; measures that incur additional costs or require specialist expertise or equipment.

Previous studies have demonstrated that contingent strategies provide a cost-effective way of screening for Down syndrome; the performance of screening by a combination of first-trimester fetal nuchal translucency thickness and first- and second-trimester serum biochemistry in all pregnancies, as in the integrated test, is similar to contingent screening in which second-trimester testing is carried out in only about 25% of the population, who were identified as being at intermediate risk by first-trimester screening[17,18].

A limitation of the study is that although a large dataset of prospectively examined patients undergoing routine pregnancy care in the first and/or second trimesters was used, the performance of screening was estimated from modeling. Prospective evaluation is required to confirm the results, after appropriate adjustments for the distribution of maternal factors in the study populations.

Comparison to alternative strategies of screening for preterm PE

In the USA, the American College of Obstetricians and Gynecologists (ACOG) recommends that the best and only approach to screening for PE should be by taking a medical history to evaluate for the following risk factors: 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 and systemic lupus erythematosus or thrombophilia[5]. However, the performance of such a strategy in screening for preterm PE is very poor, with a DR of 90% but a FPR of 67%[4]. In the UK, the National Institute for Health and Clinical Excellence (NICE) recommends that 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 ≥ 40 years, body mass index $\geq 35\,kg/m^2$, interpregnancy interval > 10 years or family history of PE)[6]. However, the performance of such a strategy in screening for preterm PE is also very poor with a DR of 40% and a FPR of 11%[1].

In our approach to screening, maternal factors are not treated as independent screening tests, as advocated by ACOG[4] and NICE[6], but rather they are combined into a multivariable logistic model which attributes the appropriate value to each factor and takes into consideration their interrelations to derive the individual patient-specific *a-priori* risk. Bayes' theorem is then used to combine the information on maternal factors with that from biomarkers to estimate the patient-specific posterior risk. We have shown that useful biomarkers in both the first and second trimesters are MAP, UtA-PI and PlGF and, when these are measured in all pregnancies, the DR of preterm PE, at a 10% FPR, is about 75% and 85%, respectively[3,4]. In this study, we have shown that a similarly high DR can be achieved by a two-stage screening strategy, at substantially lower costs than carrying out screening with all biomarkers in the whole population. The software for implementation of this approach is freely available (https://fetalmedicine.org/calculator/preeclampsia).

ACKNOWLEDGMENTS

The study was supported by a grant from The Fetal Medicine Foundation (Charity No: 1037116). The reagents and equipment for the measurement of serum placental growth factor were provided by Roche Diagnostics Limited. This paper is part of the PhD thesis of Dahiana M. Gallo for Universidad de Granada, Spain.

REFERENCES

1. 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.
2. Wright D, Akolekar R, Syngelaki A, Poon LC, Nicolaides KH. A competing risks model in early screening for preeclampsia. *Fetal Diagn Ther* 2012; **32**: 171–178.
3. 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.e1–12.
4. Gallo DM, Wright D, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19–24 weeks' gestation. *Am J Obstet Gynecol* 2015. doi: 10.1016/j.ajog.2015.11.016. [Epub ahead of print]
5. ACOG. First-trimester risk assessment for early-onset preeclampsia. Committee opinion No. 638. *Obstet Gynecol* 2015; **126**: e25–27.
6. National Collaborating Centre for Women's and Children's Health (UK). Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. London: RCOG Press, 2010.
7. 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.
8. Papageorghiou AT, Yu CKH, Bindra R, Pandis G and Nicolaides KN. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; **18**: 441–449.
9. 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.
10. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *Br J Obstet Gynaecol* 1975; **82**: 702–710.
11. Snijders RJ, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34–38.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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. http://www.R-project.org/.
17. Wright D, Bradbury I, Benn P, Cuckle H, Ritchie K. Contingent screening for Down syndrome is an efficient alternative to non-disclosure sequential screening. *Prenat Diagn* 2004; **24**: 762–766.
18. Cuckle HS, Malone FD, Wright D, Porter TF, Nyberg DA, Comstock CH, Saade GR, Berkowitz RL, Ferreira JC, Dugoff L, Craigo SD, Timor IE, Carr SR, Wolfe HM, D'Alton ME. Contingent screening for Down syndrome--results from the FaSTER trial. *Prenat Diagn* 2008; **28**: 89–94.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Model-based detection rate (DR) of preterm pre-eclampsia (PE) by two-stage screening at 11–13 weeks' gestation at a fixed overall false-positive rate of 10%

Table S2 Effects of two-stage screening for preterm pre-eclampsia (PE) (delivery < 37 weeks) at 11–13 weeks' gestation in the total population, subdivided according to racial origin and obstetric history

Table S3 Model-based detection rate (DR) of preterm pre-eclampsia (PE) by two-stage screening at 19–24 weeks' gestation at a fixed overall false-positive rate of 10%

Table S4 Effects of two-stage screening for preterm pre-eclampsia (PE) (delivery < 37 weeks) at 19–24 weeks' gestation in the total population, subdivided according to racial origin and obstetric history

Ultrasound Obstet Gynecol 2016; **47**: 554–559
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.15807

RESUMEN

Objetivo Proporcionar un cribado eficaz de la preeclampsia que causa el parto antes de la semana 37 de gestación (PE pretérmino), mediante la evaluación de una combinación de factores maternos, la presión arterial media (PAM), el índice de pulsatilidad de la arteria uterina (IP artUt) y el factor de crecimiento placentario (PlGF, por sus siglas en inglés) en las semanas de gestación 11–13 o 19–24. Este estudio explora la posibilidad de realizar cribados rutinarios para la PE pretérmino mediante factores maternos y la PAM en todos los embarazos y tan solo medir el UtA-PI y el PlGF en un subgrupo de la población, seleccionado en función del riesgo derivado del cribado empleando solo factores maternos y la PAM.

Métodos Los datos del estudio se obtuvieron del cribado prospectivo de resultados obstétricos adversos en mujeres que realizaron su visita rutinaria en el hospital en las semanas de gestación 11–13 y/o 19–24. Se empleó el teorema de Bayes para calcular el riesgo a priori de PE pretérmino a partir de factores maternos y la PAM. El riesgo a posteriori se obtuvo al añadir el UtA-PI y el PlGF. Se estimó la tasa de detección (TD) de PE pretérmino, con una tasa de falsos positivos (TFP) en general del 10%, a partir de una política en la que la primera etapa de cribado mediante una combinación de factores maternos y PAM define los grupos de cribado en resultados positivos, negativos y de riesgo intermedio, siendo este último al que se le aplicaría una segunda fase de cribado por UtA-PI y PlGF.

Resultados En las semanas de gestación 11–13, la TD de PE pretérmino, basada en un modelo con TFP de 10% en el que se cribó la totalidad de la población mediante factores maternos, la PAM, el UtA-PI y el PlGF, fue del 74%. Mediante el cribado de dos etapas se logró una TD similar, empleando factores maternos y PAM en la primera etapa y tan solo midiendo el UtA-PI y el PlGF durante la segunda etapa y tan sólo para el 50% de la población. Si la segunda etapa de cribado se hiciera al 30% de la población, solo habría una ligera reducción en la TD del 74% al 71%. En las semanas de gestación 19–24, la TD de PE pretérmino, basada en un modelo con TFP de 10% en el que se cribó la totalidad de la población mediante factores maternos, la PAM, el UtA-PI y el PlGF, fue del 84%. Mediante el cribado de dos etapas se logró una TD similar, midiendo el UtA-PI y el PlGF en tan sólo el 70% de la población; si la segunda etapa de cribado se hiciera al 40% de la población, la TD se reduciría del 84% al 81%.

Conclusiones Es posible lograr una elevada TD de la PE pretérmino mediante un cribado en dos etapas en el primer y el segundo trimestre, a partir de factores maternos y la PAM en toda la población y la medición del UtA-PI y el PlGF en tan sólo algunos de los embarazos.

目的：通过综合评估孕11~13周或孕19~24周时的母体因素、平均动脉压（mean arterial pressure，MAP）、子宫动脉搏动指数（uterine artery pulsatility index，UtA-PI）和血清胎盘生长因子 (PlGF)，有效筛查导致孕37周前分娩的先兆子痫。本研究探讨了对所有孕妇通过母体因素和MAP进行早产PE常规筛查，并对通过母体因素和MAP进行筛查后所确定的高风险亚组进行UtA-PI和PlGF检测的可能性。

方法：研究资料来自在孕11~13周和/或孕19~24周时，进行常规检查孕妇的不良产科结局的前瞻性筛查。应用贝叶斯法则，根据母体因素和MAP得到早产 PE的验前风险，通过增加UtA-PI和PlGF检测得到验后风险。采用母体因素和MAP进行第一阶段筛查，分为筛查阳性组、筛查阴性组和中度风险组，后者采用UtA-PI和PlGF进行第二阶段筛查，根据这一策略，我们评估在总的假阳性率（false-positive rate，FPR）为10%时早产PE的检出率（detection rate，DR）。

结果：孕11~13周时，当根据母体因素、MAP、UtA-PI和PlGF对整个人群进行筛查时，在10% FPR时，基于模型的早产PE的DR为74%。两阶段筛查所得的DR相似，第一阶段采用母体因素和MAP进行筛查，第二阶段仅对50%的人群进行UtA-PI和PlGF检测。如果对30%的人群进行第二阶段筛查，则DR从74%降至71%，下降很小。孕19~24周时，当根据母体因素、MAP、UtA-PI和PlGF对整个人群进行筛查时，在10% FPR时，基于模型的早产PE的DR为84%。仅对70%的人群进行UtA-PI 和PlGF检测的两阶段筛查所得DR相似；如果对40%的人群进行第二阶段筛查，DR将从84%降至81%。

结论：在妊娠早期和妊娠中期，通过检测整个人群的母体因素和MAP以及仅检测某些孕妇的UtA-PI和PlGF进行两阶段筛查，早产PE的DR较高。