

# Revised competing-risks model in screening for pre-eclampsia in twin pregnancy by maternal characteristics and medical history

Z. BENKŐ<sup>1</sup>, P. CHAVEEVA<sup>2</sup>, C. DE PACO MATALLANA<sup>3</sup>, E. ZINGLER<sup>1</sup>, D. WRIGHT<sup>4</sup>  
and K. H. NICOLAIDES<sup>1</sup>

<sup>1</sup>Fetal Medicine Research Institute, King's College Hospital, London, UK; <sup>2</sup>Dr. Shterev Hospital, Sofia, Bulgaria; <sup>3</sup>Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain; <sup>4</sup>Institute of Health Research, University of Exeter, Exeter, UK

**KEYWORDS:** calibration; competing-risks model; discrimination; first-trimester screening; performance of screening; pre-eclampsia; survival model; twin pregnancy

## CONTRIBUTION

*What are the novel findings of this work?*

In a new extension of the competing-risks model in screening for pre-eclampsia (PE) by maternal factors in twin pregnancy, the effect of twins on shifting the distribution of gestational age at delivery with PE in singletons to the left is not constant but increases with increasing prior mean.

*What are the clinical implications of this work?*

Calibration plots and calibration intercept and slope demonstrate that the new model has a superior predictive performance and provides more accurate patient-specific risk of PE than does the previous model.

## ABSTRACT

**Background** We have proposed previously that the competing-risks model for prediction of pre-eclampsia (PE) based on maternal characteristics and medical history (prior model), developed in singleton pregnancies, can be extended to risk assessment for twins; in dichorionic (DC) and monochorionic (MC) twin pregnancies with the same characteristics as in singleton pregnancies, the distribution of gestational age at delivery with PE was shifted to the left by 8 and 10 weeks, respectively. However, in a subsequent validation study, we found that, in both the training and validation datasets, the observed incidence of PE was lower than the predicted one and such overestimation of risk was particularly marked for early PE.

**Objectives** First, to develop a new extension of the competing-risks prior model in screening for PE by maternal demographic characteristics and medical history in twin pregnancies in a training dataset. Second, to examine the predictive performance of this model in screening for PE with delivery < 34 weeks (early PE), < 37 weeks (preterm PE) and at any gestational age (all PE) in twins in a validation dataset. Third, to demonstrate the application of screening in a mixed population of singleton and twin pregnancies.

**Methods** The data for this study were obtained from two prospective non-intervention multicenter screening studies for PE in twin pregnancies at 11 + 0 to 13 + 6 weeks' gestation. The training and validation datasets consisted of 2219 and 2999 women, respectively. We used the training dataset to fit a model in which the effect of twins on shifting the distribution of gestational age at delivery with PE in singletons to the left should not be the same for all gestational ages but the shift should depend on the singleton prior mean; the effect increases with increasing prior mean. We examined the predictive performance of the model in the training and validation datasets using the area under the receiver-operating characteristics curve (AUC) and calibration plots. Data on 16 747 singleton pregnancies obtained from the Screening ProgRamme for prE-Eclampsia (SPREE) study were included to examine the performance of screening in a mixed population of singleton and twin pregnancies.

**Results** Calibration plots and calibration intercept and slope demonstrate superior predictive performance of

Correspondence to: Prof. K. H. Nicolaides, Fetal Medicine Research Institute, King's College Hospital, 16–20 Windsor Walk, Denmark Hill, London SE5 8BB, UK (e-mail: kypros@fetalmedicine.com)

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the new model in the validation dataset. Although the AUC for twin pregnancies is lower than in singleton pregnancies, performance of screening in a mixed population of singleton and twin pregnancies is superior to that in singletons (AUC of 0.790 in a mixed population comprising 2% twins and 98% singletons compared to 0.775 in singletons). For the risk cut-offs likely to be used in practice, all twin pregnancies screen positive using maternal characteristics and medical history.

**Conclusions** A new competing-risks model in screening for PE by maternal risk factors in twin pregnancy has been developed and, using this model, the predicted risks for early PE, preterm PE and all PE are in relatively good agreement with the observed incidence of the disease. © 2019 The Authors. *Ultrasound in Obstetrics & Gynecology* published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.

## INTRODUCTION

In screening for pre-eclampsia (PE) in singleton pregnancy, we proposed the competing-risks approach, which is based on a survival-time model for gestational age at delivery with PE<sup>1–3</sup>. Each woman has a personalized distribution of gestational age at delivery with PE and the risk of delivery with PE before a specified gestational age, assuming no other cause of delivery, is given by the area under the probability-density curve. In this approach, it is assumed that, if the pregnancy was to continue indefinitely, all women would develop PE, and whether they do so or not before a specified gestational age depends on competition between delivery due to PE or other causes. The personalized distribution is obtained by applying Bayes' theorem to combine a prior distribution determined from maternal characteristics and medical history with a likelihood function determined from biomarkers. The effects of variables from maternal factors and biomarkers is to modify the distribution of gestational age at delivery with PE so that, in pregnancies at low risk for PE, gestational age at delivery with PE is increased, with the implication that, in more pregnancies, delivery from other causes occurs before development of PE. In high-risk pregnancies, gestational age at delivery with PE is decreased so delivery with PE occurs more often.

In twin pregnancies, the rate of PE is about 9%, which is 3-times higher than in singleton pregnancies, but twins are delivered at an earlier gestational age than are singletons and, consequently, comparison of the overall rates of PE between twin and singleton pregnancies underestimates the relative risk of preterm PE in twins, which is 9-times higher<sup>4</sup>. In a study of 2219 twin pregnancies, we proposed that the same competing-risks model developed in singleton pregnancies can be adapted for use in twins; in dichorionic (DC) and monochorionic (MC) twin pregnancies with the same characteristics as in singleton pregnancies, the distribution of gestational age at delivery with PE was shifted to the left by 8 and

10 weeks, respectively<sup>5</sup>. In a subsequent validation study involving 2999 twin pregnancies, we found that the predictive performance for PE was consistent with that in the training set used for development of the model; however, calibration plots of the predictive performance of the competing-risks model demonstrated that, in both the training and validation datasets, the observed incidence of PE was lower than the predicted one and such overestimation of risk was particularly marked for early PE<sup>6</sup>. This suggested the need for a model in which the effect of twins relative to singletons in decreasing the gestational age at delivery with PE should increase with gestational age.

The objectives of this study were, first, to develop a new extension of the competing-risks prior model in screening for PE in twin pregnancies in the original training dataset<sup>5</sup>, second, to examine the predictive performance of this model in screening for PE with delivery < 34 weeks (early PE), < 37 weeks (preterm PE) and at any gestational age (all PE) in twins in a validation dataset<sup>6</sup>, and, third, to demonstrate the application of screening in a mixed population of singleton and twin pregnancies.

## METHODS

### Study population

Three datasets were used for this study. First, 2219 twin pregnancies (training dataset) that were examined at King's College Hospital and Medway Maritime Hospital, UK, between January 2006 and December 2015<sup>5</sup>. Second, 2999 twin pregnancies (validation dataset) that were examined at five hospitals in England (King's College Hospital and Medway Maritime Hospital, between December 2015 and April 2018; Homerton University Hospital, between January 2014 and April 2018; North Middlesex University Hospital, between May 2015 and April 2018; and Southend University Hospital, between June 2015 and April 2018), one hospital in Bulgaria (Dr. Shterev Hospital in Sofia, between January 2013 and April 2018) and one hospital in Spain (Hospital Clínico Universitario Virgen de la Arrixaca in Murcia, between March 2009 and April 2018)<sup>6</sup>. Third, the validation dataset of 16 747 singleton pregnancies from the Screening ProgRamme for prE-Eclampsia (SPREE) study; this was a prospective multicenter study in seven National Health Service (NHS) maternity hospitals in England<sup>7</sup>. This study was approved by the NHS Research Ethics Committee in England and the Hospital Ethics Committees of the participating hospitals in Bulgaria and Spain.

In all three datasets, women had a routine hospital visit at 11 + 0 to 13 + 6 weeks' gestation, which included recording of maternal demographic characteristics and medical history, measurement of maternal weight and height and ultrasound examination to, first, determine if the fetuses were alive and had any major abnormalities, second, estimate gestational age from the measurement of fetal crown–rump length<sup>8</sup> (in twin pregnancies, the measurement from the larger twin was used), and, third,

determine chorionicity in twin pregnancies by examining the intertwin membrane at its junction with the placenta<sup>9</sup>.

Patient characteristics recorded included maternal age, racial origin (white, black, South Asian, East Asian or mixed), method of conception (spontaneous or assisted requiring *in-vitro* fertilization or the use of ovulation drugs), cigarette smoking during pregnancy, history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, family history of PE in the mother of the patient and obstetric history including parity (parous or nulliparous if no previous pregnancy at  $\geq 24$  weeks), previous pregnancy with PE, gestational age at delivery and birth weight of the neonate in the last pregnancy and interval in years between delivery of the last child and estimated date of conception of the current pregnancy.

The inclusion criteria for this study on screening for PE were delivery of a phenotypically normal liveborn or stillborn neonate at  $\geq 24$  weeks' gestation. We excluded pregnancies with aneuploidy or major fetal abnormality, those ending in termination, miscarriage or fetal death before 24 weeks and, in twin pregnancies, those with an interval of  $> 3$  days between the death of one fetus and live birth of the second twin.

### Outcome measures

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<sup>10</sup>.

### Statistical analysis

#### *Model development*

Using data on 120 492 singleton pregnancies, we developed a parametric survival model in which the distribution of gestational age at delivery with PE has a Gaussian distribution with a mean determined from maternal characteristics and a constant standard deviation<sup>2</sup>. We extended this model using data on the 2219 pregnancies in the training dataset by including effects for DC and MC twins<sup>5</sup>. Using this model, the prior distribution of gestational age at delivery with PE is the same as that in singleton pregnancy with the same maternal characteristics but with the mean reduced by 8 weeks in DC twins and 10 weeks in MC twins.

Here, we develop an alternative extension of the singleton model for twins by including the singleton prior mean as a covariate in a parametric survival model. The relationship between the singleton prior mean and gestational age at delivery with PE was examined by, first, treating the prior mean as a factor with levels determined by deciles (10 groups of equal size). Effects plots showed a linear relationship for both DC and MC twins. We

therefore fitted a model with a constant slope but different intercepts for DC and MC twins in the training dataset<sup>5</sup> and tested the model on the validation dataset<sup>6</sup>.

#### *Choice of gestational ages for risk assessment*

The model we have adopted gives risk of delivery with PE before a specified gestational age, assuming no other cause of delivery. For singleton pregnancies, we focused on risks of delivery with PE at  $< 34$ ,  $< 37$  and  $< 41 + 3$  weeks' gestation<sup>11</sup>. Of singleton pregnancies, 12% reach  $41 + 3$  weeks' gestation, but, in the case of twins,  $< 0.1\%$  reach  $41 + 3$  weeks; consequently, in the case of twins, the risk of delivery with PE  $< 41 + 3$  weeks is hypothetical and unrealistically high. Therefore, in twin pregnancies, it is more appropriate to use a risk of delivery with PE at  $< 39$  weeks, with 2.7% (95% CI, 2.1–3.5%) of those in the training dataset and 1.4% (95% CI, 1.0–1.9%) of those in the validation dataset reaching 39 weeks' gestation.

#### *Risk calibration*

Calibration was assessed visually by plotting the observed incidence against the predicted risk for PE  $< 34$ ,  $< 37$  and  $< 39$  weeks' gestation. The plots were produced by grouping the data into bins according to risk. The observed incidence in each group was then plotted against the incidence predicted by the model (i.e. the mean risk within each group). The risks produced from our competing-risks model are for delivery with PE before a specific gestational age, assuming no other cause for delivery. Because other causes of delivery are effectively censored observations, the actual incidence of PE would be expected to be lower than predicted. Consequently, we applied survival analysis (Kaplan–Meier) to estimate the incidence of delivery with PE, treating deliveries from other causes as censored observations. Statistical assessment of calibration of the fitted survival model was undertaken with calibration-in-the-large and calibration slope with correction for censoring. The calibration of the previous model and the new model, both fitted to the training dataset, is compared in the validation dataset.

#### *Screening performance in mixed population of twin and singleton pregnancies*

Performance of screening in a mixed population of twin and singleton pregnancies was examined using stratified analysis of the population of twins described above and the singleton population of 16 747 pregnancies from the SPREE study<sup>7</sup>. The strata weights for the detection rates are proportional to the incidence rates in twins and singletons in the mixed population. Those for the false-positive rate are proportional to  $1 - \text{incidence}$ , and those for the screen-positive rate are proportional to the proportions of twins and singletons.

The statistical software package R was used for data analyses<sup>12</sup>. The package pROC was used for

receiver–operating characteristics (ROC) curve analysis and the package survival was used for survival analysis<sup>13–15</sup>.

## RESULTS

Maternal and pregnancy characteristics in the training and validation datasets are provided and compared in Table 1. In the validation dataset, compared with the training dataset, median maternal age was higher, but median weight and body mass index were lower, the incidences of conception by *in-vitro* fertilization, chronic hypertension and nulliparity were higher and the incidences of diabetes mellitus, cigarette smoking and family history of PE were lower. The incidences of early PE, preterm PE and all PE in the two datasets were similar.

### Model development

Estimates for the effect of twins (DC and MC grouped together) on gestational age at delivery with PE, grouped according to decile of the mean of the Gaussian distribution for gestational age at delivery with PE in singletons,

are shown in Figure 1. The effect of twins in reducing gestational age at delivery with PE is not uniform but increases with increasing singleton prior mean. On the basis of this, a model in which the effect of twins depends linearly on the singleton prior mean with a common slope but different intercepts for DC and MC twins was fitted to the training dataset. Table 2 shows the coefficients of the regression model fitted to the training dataset alone and the training and validation datasets combined. The fitted regression lines for DC and MC twins with 95% CI are shown in Figure 2. The regression lines have the same slope but different intercepts; in MC twin pregnancies, delivery with PE was an estimated 1.48 (95% CI, 0.51–2.46) weeks earlier than in DC twins ( $P = 0.0028$ ).

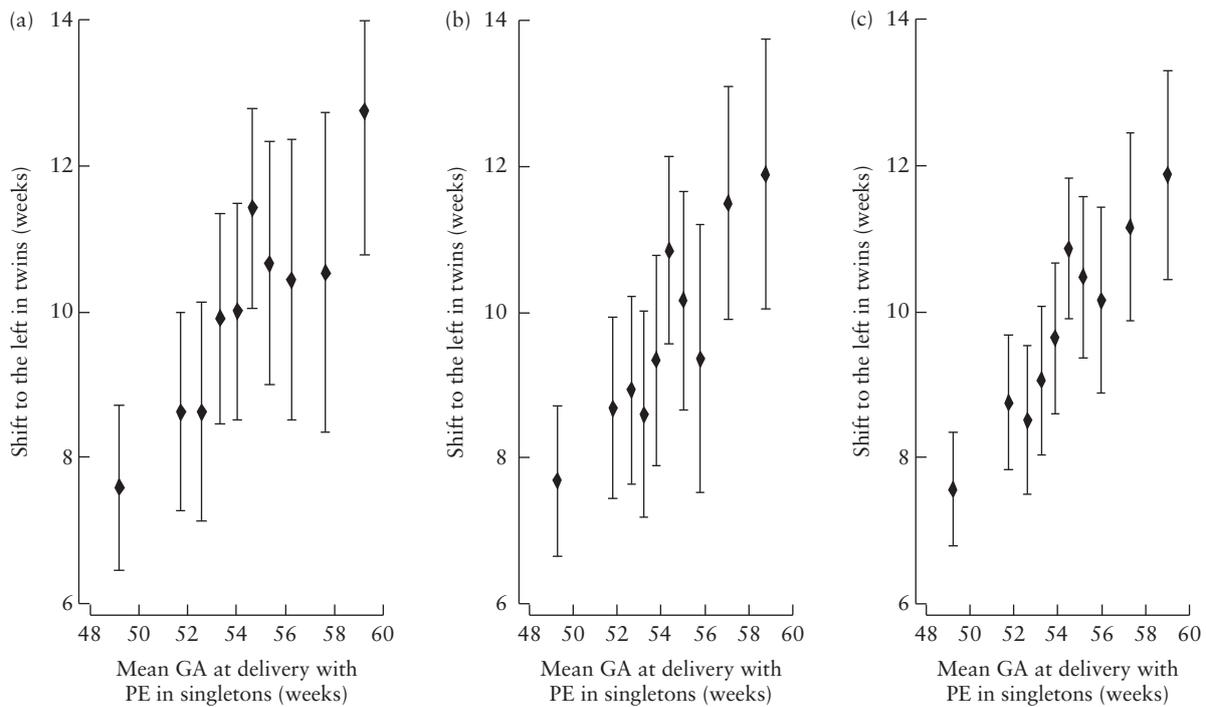
### Risk calibration

Calibration intercept and slope statistics for the predictive performance for early PE, preterm PE and all PE of the previous model and the new model are given in Table 3. The corresponding calibration plots showing the predictive performance for early PE and preterm PE are shown in Figure 3. Using the new model, the

**Table 1** Maternal and pregnancy characteristics in training and validation datasets of twin pregnancies

Variable	Training set (n = 2219)	Validation set (n = 2999)	P
Maternal age (years)	32.9 (28.7–36.3)	33.7 (30.1–36.9)	< 0.00001
Maternal weight (kg)	68.0 (60.0–79.0)	66.0 (58.8–76.0)	< 0.00001
Maternal height (cm)	165 (160–170)	165 (161–170)	0.739
Body mass index (kg/m <sup>2</sup> )	24.9 (22.3–28.6)	23.9 (21.6–27.7)	< 0.00001
Gestational age (weeks)	12.9 (12.5–13.3)	12.6 (12.1–13.1)	< 0.00001
Racial origin			< 0.00001
White	1710 (77.1)	2627 (87.6)	
Black	353 (15.9)	240 (8.0)	
South Asian	80 (3.6)	78 (2.6)	
East Asian	33 (1.5)	20 (0.7)	
Mixed	43 (1.9)	34 (1.1)	
Conception			< 0.00001
Natural	1547 (69.7)	1619 (54.0)	
Assisted by use of ovulation drugs	55 (2.5)	63 (2.1)	
<i>In-vitro</i> fertilization	617 (27.8)	1317 (43.9)	
Medical history			
Chronic hypertension	30 (1.4)	57 (1.9)	< 0.00001
Diabetes mellitus	23 (1.0)	17 (0.6)	< 0.00001
SLE/APS	4 (0.2)	12 (0.4)	0.243
Cigarette smoker	203 (9.1)	190 (6.3)	< 0.001
Family history of PE	97 (4.4)	35 (1.2)	< 0.00001
Parity			< 0.00001
Nulliparous	1184 (53.4)	1877 (62.6)	
Parous with no previous PE	967 (43.6)	1095 (36.5)	
Parous with previous PE	68 (3.1)	27 (0.9)	
Chorionicity			0.103
Dichorionic	1789 (80.6)	2472 (82.4)	
Monochorionic	430 (19.4)	527 (17.6)	
PE			
Total	171 (7.7)	215 (7.2)	0.497
Delivery < 37 weeks	124 (5.6)	167 (5.6)	1
Delivery < 34 weeks	41 (1.8)	43 (1.4)	0.288

Data are given as median (interquartile range) or  $n$  (%). Comparisons between outcome groups were by chi-square or Fisher's exact test for categorical variables and Mann–Whitney  $U$ -test for continuous variables. APS, antiphospholipid syndrome; PE, pre-eclampsia; SLE, systemic lupus erythematosus.



**Figure 1** Estimates with 95% CI for effect of twins on gestational age (GA) at delivery with pre-eclampsia (PE) in training (a), validation (b) and combined (c) datasets, according to decile of mean of Gaussian distribution for GA at delivery with PE in singletons.

**Table 2** Fitted regression model for prediction of pre-eclampsia in dichorionic and monochorionic twin pregnancies in training dataset alone and in training and validation datasets combined

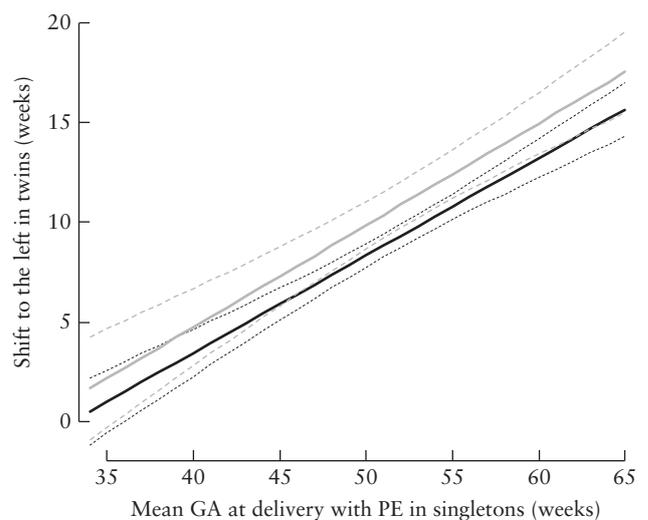
	Value (95% CI)	P
<b>Training data</b>		
Singleton mean*	0.487 (0.3588–0.6158)	< 0.00001
Dichorionic	17.268 (10.634–23.902)	< 0.00001
Monochorionic	15.783 (8.989–22.578)	< 0.00001
SD	4.5058 (4.0073–5.0663)	
<b>Combined data</b>		
Singleton mean*	0.492 (0.4036–0.5811)	< 0.00001
Dichorionic	17.115 (12.532–21.698)	< 0.00001
Monochorionic	15.768 (11.059–20.477)	< 0.00001
SD	4.6019 (4.2557–4.9761)	

\*Singleton mean obtained from Wright *et al.*<sup>2</sup>.

observed incidence of early PE and preterm PE is close to that predicted, and it is substantially better than the previous model. Calibration of the 39-week risk, when used for prediction of PE at any gestational age, is also satisfactory.

**Performance of screening**

ROC curves for twins, singletons and for a mixed population comprising 98% singletons and 2% twins are shown in Figure 4. The area under the ROC curve for the mixed population is 0.790 (95% CI, 0.755–0.826) compared to 0.775 (95% CI, 0.735–0.815) for singletons and 0.647 (95% CI, 0.604–0.690) for twins, and the performance of screening in the mixed population is superior to that in the subpopulations comprising the mixture. This is



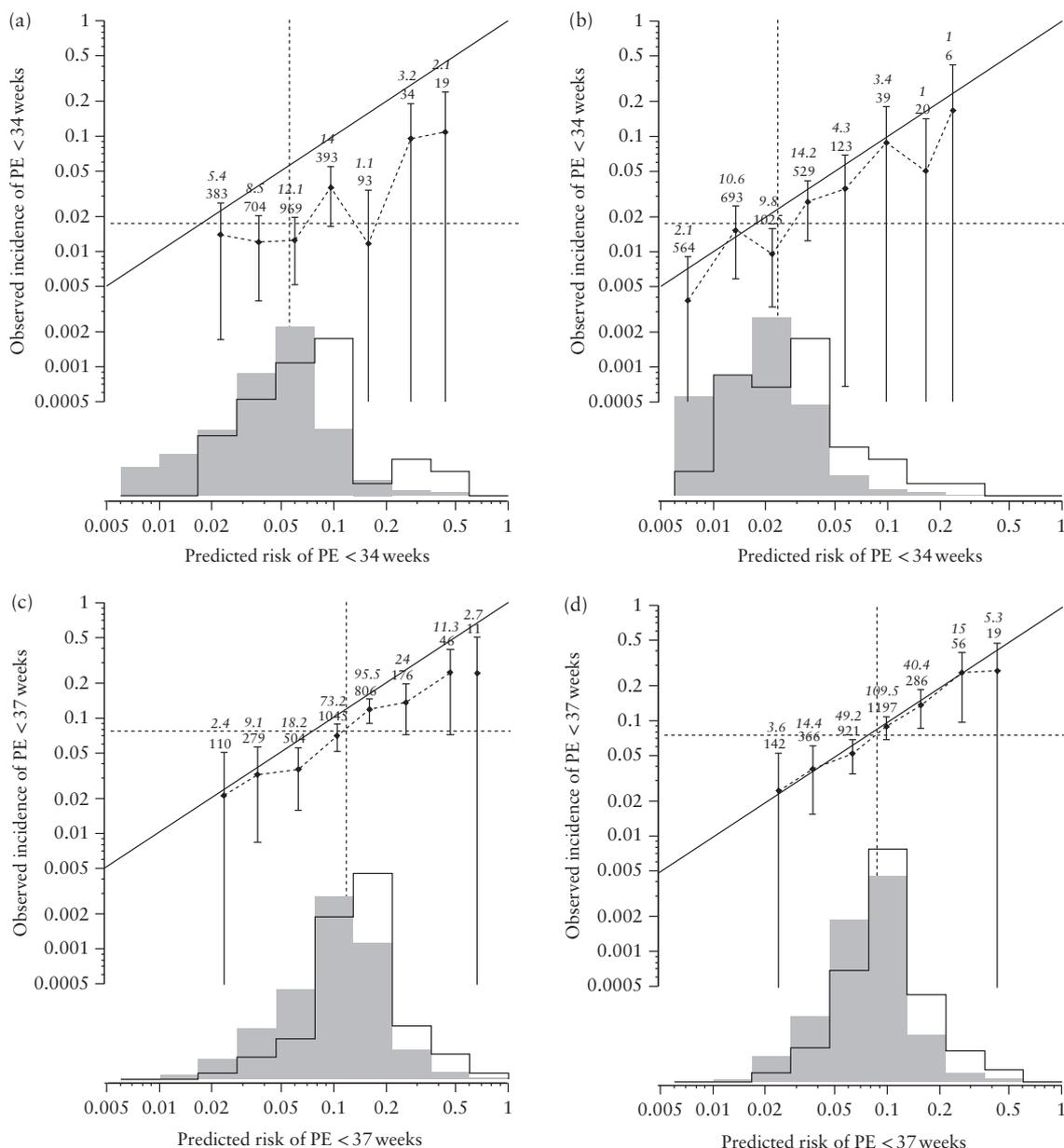
**Figure 2** Relationship between effect of dichorionic (black) and monochorionic (gray) twin pregnancy in reducing gestational age (GA) at delivery with pre-eclampsia (PE) and prior mean of GA at delivery with PE in singleton pregnancies. Dashed lines are 95% CI.

because twins are at higher risk than singletons, and whether a pregnancy is a singleton or twin is informative, improving screening performance over that achieved in singletons. To illustrate this, we considered screening for PE < 37 weeks with a screen-positive rate of 10%. In the mixed population, a cut-off of 1 in 60 gives an overall screen-positive rate of 10% (8.2% for singletons and 100% for twins) with an overall detection rate of 45%, including 38% for singletons and 100% for twins. In contrast, for singletons, a risk cut-off of 1 in 70 gives a screen-positive rate of 10% with a detection

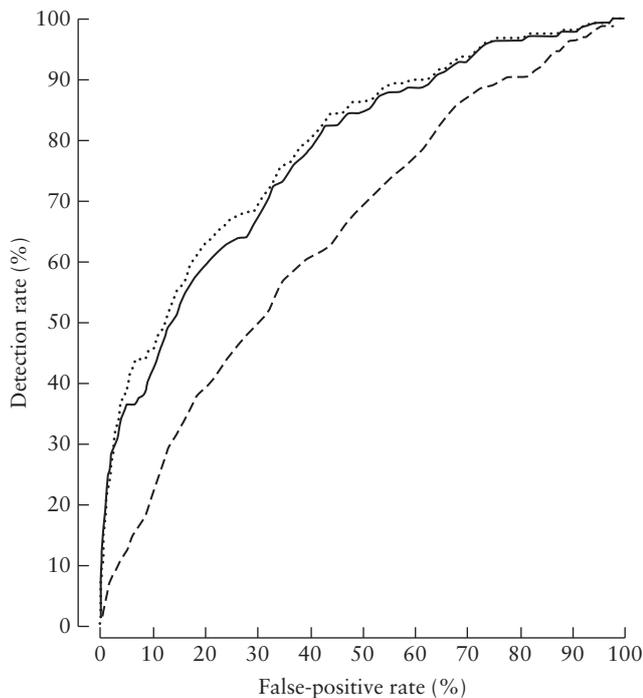
**Table 3** Risk calibration in validation dataset for prediction of pre-eclampsia (PE) in twin pregnancy

Model	Calibration intercept	Calibration slope
Early PE (< 34 weeks)		
Previous	-1.244 (-1.544 to -0.944)	0.746 (0.308 to 1.184)
New	-0.353 (-0.641 to -0.066)	0.891 (0.433 to 1.349)
Preterm PE (< 37 weeks)		
Previous	-0.464 (-0.629 to -0.300)	0.771 (0.553 to 0.988)
New	-0.100 (-0.274 to 0.074)	0.941 (0.655 to 1.228)
All PE (< 39 weeks)		
Previous	-0.293 (-0.538 to -0.047)	0.802 (0.578 to 1.026)
New	-0.263 (-0.486 to -0.039)	1.096 (0.693 to 1.500)

Results are given for our previous model<sup>5</sup> and for new model (Table 2). Perfectly calibrated model should have intercept of 0 and calibration slope of 1.0.



**Figure 3** Calibration plots for screening using competing-risks model for prediction of early (a,b) and preterm (c,d) pre-eclampsia (PE) in validation dataset, according to previous<sup>5</sup> (a,c) and new (b,d) models, after adjustment for effect of censoring due to births from causes other than PE. Diagonal line is line of perfect agreement. Overall mean risk is shown by vertical dashed line and overall incidence by horizontal dashed line. Vertical solid lines are confidence intervals. Numbers of women with PE are shown in italics above total number in that predicted-risk group. Histograms show distribution of risk in affected (□) and unaffected (■) pregnancies.



**Figure 4** Receiver–operating characteristics curves for preterm pre-eclampsia in singletons (—), twins (---) and mixed population comprising 98% singleton and 2% twin pregnancies (.....).

rate of 41% and, for twins, a risk cut-off of 1 in 7 gives a screen-positive rate of 10% and a detection rate of only 19%.

## DISCUSSION

### Main findings

In this study, we developed a new model for the prediction of PE in twin pregnancies and demonstrated relatively good calibration in an independent validation dataset. The basis of the new model is that, in twin pregnancies, the shift to the left of the distribution of gestational age at delivery with PE in singleton pregnancies is not uniform, as in our original model<sup>5</sup>, but the effect increases with increasing singleton prior mean.

The implication of this finding is that, in a woman who, on the basis of her demographic characteristics and medical history, has a very high risk of developing PE, reflected in a mean of  $\leq 34$  weeks for the gestational age at delivery with PE, the presence of a DC twin pregnancy does not increase her risk above that of a singleton pregnancy. In contrast, in a woman at very low risk of developing PE, reflected in a mean of 65 weeks for the distribution of gestational age at delivery with PE, the presence of a DC twin pregnancy results in a substantially increased risk of developing PE compared to that of a singleton pregnancy, with a shift of the distribution to the left by about 16 weeks. In a MC twin pregnancy, there is no shift to the left if the prior mean is  $\leq 28$  weeks,

but if the prior mean is 65 weeks, the shift to the left is about 18 weeks.

This finding is analogous to the effect of history of pregnancy affected by fetal Down syndrome on the maternal age-related risk for Down syndrome in the current pregnancy. On the assumption that such history increases the risk by about 1%, in a 50-year-old woman with an age-related risk of about 1 in 10, there is a 1.1-fold increase to 1.1 in 10, whereas, in a 20-year-old woman with an age-related risk of about 1 in 1000, there is a 10-fold increase to 11 in 1000; consequently, the increase in risk is inversely proportional to the prior risk.

In the prediction of PE, in a mixed population of singleton and twin pregnancies, the same risk cut-off should be used in identifying the high-risk group in need of prophylactic pharmacological interventions to prevent the development of PE and closer monitoring for early identification of the clinical signs of the disease in those that will develop PE. In this study, we have demonstrated that, at a risk cut-off that would classify 10% of a mixed population as being at high risk for preterm PE, all twins will be classified as screen positive.

### Comparison with previous studies

In a previous study, we evaluated the predictive performance for PE of the competing-risks model in singleton pregnancies using two validation datasets and demonstrated very good discrimination between affected and unaffected pregnancies and good agreement between predicted risk and observed incidence of PE<sup>3,7,16</sup>. In contrast, a validation study of our competing-risks model for twin pregnancies<sup>5</sup> found that, in both the training and validation datasets, the observed incidence of PE was lower than the predicted one, especially for early PE<sup>6</sup>. In this study, we developed a new model and demonstrated good agreement between predicted risk and observed incidence of PE  $< 34$ ,  $< 37$  and  $< 39$  weeks' gestation. Previously, we used risks of PE  $< 41 + 3$  weeks for assessment of risk for all PE in twins<sup>5,6</sup>, the same as we have adopted in singletons. Because the vast majority of twins are delivered earlier than  $41 + 3$  weeks, these risks are unrealistic and inappropriate for twin pregnancies and, therefore, in this study, we have used risks before 39 weeks for all PE in twin pregnancies.

### Clinical implications

Estimation of accurate patient-specific risk of PE can help stratify the monitoring of twin pregnancies for early identification of those that will develop the disease. In singleton pregnancies at high risk of PE, prophylactic use of aspirin (150 mg/day from 11–14 until 36 weeks' gestation) reduces the incidence of early PE by about 90% and preterm PE by 60%, with no significant effect on the incidence of term PE<sup>17,18</sup>. A systematic review on the prophylactic use of aspirin in twin pregnancies identified five trials<sup>19</sup>. Use of aspirin was not associated

with a reduction in the incidence of PE in any of the trials but a meta-analysis of the trials reported that, first, aspirin reduced the incidence of mild PE but not severe PE and, second, there was significant reduction in PE if aspirin was initiated > 16 weeks' gestation but not < 16 weeks<sup>19</sup>. These results are inconsistent with findings in singleton pregnancies and it was therefore recommended that additional studies are required before recommending that low-dose aspirin should be initiated early in pregnancy for all twin pregnancies. Our results suggest that, when such trials are carried out, all twin pregnancies should be included because they are, by comparison with singleton pregnancies, all at increased risk of developing PE.

### Strengths and limitations

The strengths of this study include, first, development of a new model for the prediction of PE in twin pregnancies in a training dataset and evaluation of discrimination and calibration in a validation dataset derived from an independent multicenter study, and, second, assessment of calibration, allowing for the effect of censoring due to births from causes other than PE. A limitation of this study is that the number of twin pregnancies, by comparison with the number of singleton pregnancies, was relatively small and the model may require further adjustments based on results of future large multicenter studies.

### Conclusions

A new competing-risks model in screening for PE by maternal risk factors in twin pregnancies has been developed and, using this model, the predicted risks for early PE, preterm PE and all PE are in good agreement with the observed incidence of the disease.

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