OBSTETRICS

# Competing risks model in screening for preeclampsia by maternal characteristics and medical history

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**OBJECTIVE:** The purpose of this study was to develop a model for preeclampsia based on maternal demographic characteristics and medical history.

**STUDY DESIGN:** This was a screening study of 120,492 singleton pregnancies at 11-13 weeks' gestation, including 2704 pregnancies (2.2%) that experienced preeclampsia. A survival-time model for the gestational age at delivery with preeclampsia was developed from variables of maternal characteristics and history. This approach assumes that, if the pregnancy was to continue indefinitely, all women would experience preeclampsia and that whether they do so or not before a specified gestational age depends on competition between delivery before or after development of preeclampsia. A 5-fold cross validation study was conducted to compare the performance of the new model with the National Institute for Health and Clinical Excellence (NICE) guidelines.

**RESULTS:** In the new model, increased risk for preeclampsia, with a consequent shift in the Gaussian distribution of the gestational age at delivery with preeclampsia to the left, is provided by advancing maternal age, increasing weight, Afro-Caribbean and South Asian racial origin, medical history of chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome, family history and personal history of preeclampsia, and conception by in vitro fertilization. The risk for preeclampsia decreases with increasing maternal height and in parous women with no previous preeclampsia; in the latter, the protective effect, which is related inversely to the interpregnancy interval, persists beyond 15 years. At a screen-positive rate of 11%, as defined by NICE, the new model predicted 40%, 48%, and 54% of cases of total preeclampsia and preeclampsia requiring delivery at <37 and <34 weeks' gestation, respectively, which were significantly higher than the respective values of 35%, 40%, and 44% achieved by application of NICE guidelines.

**CONCLUSION:** A new model that is based on maternal characteristics and medical history has been developed for the estimation of patient-specific risks for preeclampsia. Such estimation of the a priori risk for preeclampsia is an essential first step in the use of Bayes theorem to combine maternal factors with biomarkers for the continuing development of more effective methods of screening for the disease.

**Key words:** Bayes theorem, preeclampsia, pregnancy, screening, survival-time model

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Preeclampsia is a major cause of maternal and perinatal morbidity and death that affects 2-3% of all pregnancies.[1-3] In the last decade extensive research has been devoted to screening for preeclampsia with the aims of reducing the prevalence of the disease through pharmacologic intervention in the high-risk group[4,5] and minimizing adverse perinatal events for those women who experience preeclampsia by determining the appropriate time and place for delivery.[6] The traditional approach to screening for preeclampsia is to identify risk factors from maternal demographic characteristics and medical history. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) has issued guidelines recommending that women should be considered to be at high risk of the development of preeclampsia if they have any 1 high-risk factor or any 2 moderate-risk factors.[7] The high-risk factors are a history of hypertensive disease in a previous pregnancy, chronic kidney disease, autoimmune disease, diabetes mellitus, or chronic hypertension; the moderate-risk factors are first pregnancy, ≥40 years old, interpregnancy interval of >10 years, body mass index (BMI) at first visit of ≥35 kg/m$^2$ or

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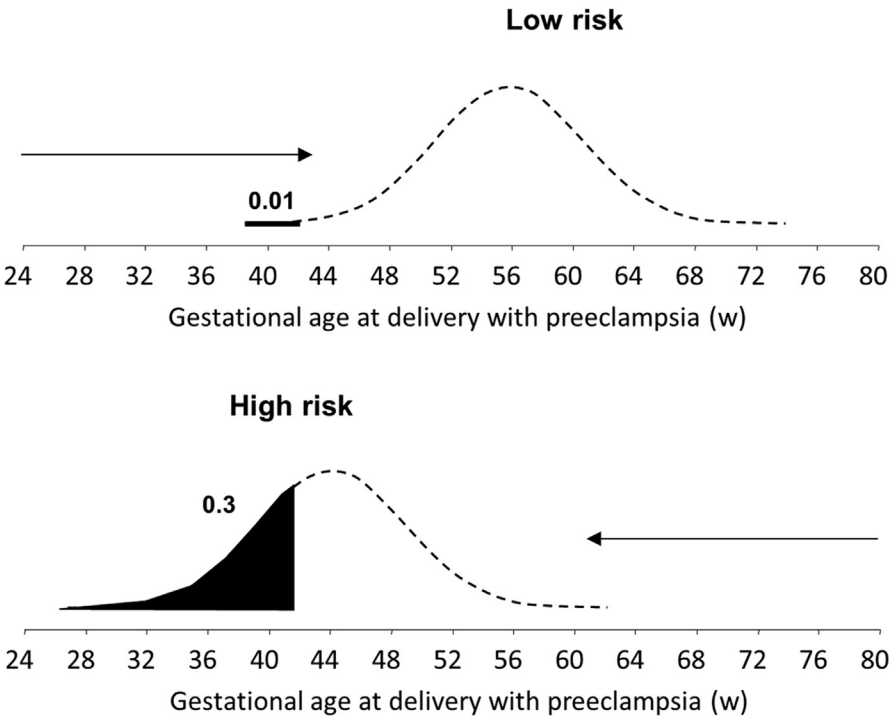
FIGURE 1
**Distribution of gestational age at delivery for preeclampsia**




In pregnancies that are at low risk for preeclampsia, the gestational age distribution is shifted to the right; in most pregnancies, delivery will occur before the development of preeclampsia. In pregnancies at high risk for preeclampsia, the distribution is shifted to the left. The risk of preeclampsia occurring at or before a specified gestational age is given by the area under the distribution curve (*black*). In the low-risk group, the risk of preeclampsia at ≤34 weeks' gestation is 0.01 (1%); in the high-risk group, the risk is 0.3 (30%).

*w*, week.

*Wright. Competing risks model in screening for preeclampsia. Am J Obstet Gynecol 2015.*

family history of preeclampsia. However, the performance of such an approach, which essentially treats each risk factor as a separate screening test with additive detection rate (DR) and screen positive rate, has not been evaluated.

An alternative approach to screening for preeclampsia, which allows estimation of individual patient-specific risks of preeclampsia that require delivery before a specified gestation, is to use Bayes theorem to combine the a priori risk from maternal characteristics and medical history with the results of various combinations of biophysical and biochemical measurements made at different times during pregnancy. A fundamental component of this approach is a previous distribution. In this study, we adopted a survival-time model for the gestational age at delivery with preeclampsia.[8,9] This approach assumes that, if the pregnancy was to continue indefinitely, all women would experience preeclampsia, and whether they do so or not before a specified gestational age depends on competition between delivery before or after the development of preeclampsia (Figure 1). The effect of variables from maternal characteristics and history and biomarkers is to modify the mean of the distribution of gestational age at delivery with preeclampsia so that, in pregnancies at low risk for preeclampsia, the gestational age distribution is shifted to the right with the implication that, in most pregnancies, delivery actually will occur before the development of preeclampsia. In high-risk pregnancies, the distribution is shifted to the left, and the smaller the mean gestational age the higher is the risk for preeclampsia. We previously examined 58,884 singleton pregnancies at 11-13 weeks' gestation, which included 1426 pregnancies (2.4%) that subsequently experienced preeclampsia, and we reported that variables that shift the Gaussian distribution of the gestational age at delivery with preeclampsia to the left, include advancing maternal age, increasing weight, Afro-Caribbean and South Asian racial origin, previous pregnancy with preeclampsia, conception by in vitro fertilization, and a medical history of chronic hypertension, diabetes mellitus, and systemic lupus erythematosus or antiphospholipid syndrome.[8,9]

The objectives of this study of 120,492 singleton pregnancies, which included 2704 pregnancies (2.2%) that experienced preeclampsia, are to update our previous model for preeclampsia and compare its performance with the method recommended by NICE.[7]

## Methods

### Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women who attended their routine first hospital visit in pregnancy at University College London Hospital, King's College Hospital, and Medway Maritime Hospital, United Kingdom. In this visit, at $11^{+0}$ $-13^{+6}$ weeks' gestation, we recorded maternal characteristics and medical history and performed combined screening for aneuploidies.[10] Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks' gestation.[11] The women were screened between January 2006 and March 2014 and gave written informed consent to participate in the study, which was approved by the UK National Health Service Research Ethics Committee. The inclusion criteria for this study on screening for preeclampsia were singleton pregnancy undergoing first-trimester combined screening for aneuploidy and subsequently delivering a phenotypically normal live birth or stillbirth at or after 24 weeks' gestation.

We excluded pregnancies with aneuploidies and major fetal abnormalities and those ending in termination, miscarriage, or fetal death at <24 weeks' gestation.

## Patient characteristics

Patient characteristics included maternal age, racial origin (white, Afro-Caribbean, South Asian, East Asian, and mixed), method of conception (spontaneous or assisted conception that required the use of ovulation drugs), cigarette smoking during pregnancy (yes or no), history of chronic hypertension (yes or no), history of preexisting diabetes mellitus (yes or no), history of systemic lupus erythematosus or antiphospholipid syndrome, family history of preeclampsia in the mother of the patient (yes or no) and obstetric history that included parity (parous or nulliparous if no previous pregnancies at or after 24 weeks' gestation), previous pregnancy with preeclampsia (yes or no), gestational age at delivery and birthweight of the neonate in the last pregnancy, interval in years between birth of the last child, and estimated date of conception of the current pregnancy. Maternal weight and height were measured, and the BMI was calculated.

## 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 preexisting or pregnancy-associated hypertension were examined to determine whether the condition was chronic hypertension, preeclampsia, or nonproteinuric gestational hypertension.

The definitions of *gestational hypertension* and *preeclampsia* were those of the International Society for the Study of Hypertension in Pregnancy.[12] In gestational hypertension, the systolic blood pressure should be ≥140 mm Hg and/or the diastolic blood pressure should be ≥90 mm Hg on at least 2 occasions 4 hours apart that developed after 20 weeks' gestation in previously normotensive women. In preeclampsia, there should be gestational hypertension with proteinuria of ≥300 mg in 24 hours or 2 readings of at least ++ on dipstick analysis of midstream or catheter urine specimens, if no 24-hour collection is available. In preeclampsia superimposed on chronic hypertension, significant proteinuria (as defined earlier) should develop after 20 weeks' gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit at <20 weeks' gestation in the absence of trophoblastic disease).

**TABLE 1**
**Maternal and pregnancy characteristics in the screening population**

| Variable | Preeclampsia (n = 2704) | Unaffected (n = 117,788) | *P* value |
|---|---|---|---|
| Maternal age, y[a] | 31.4 (26.6–36.0) | 31.3 (26.7–35.1) | .001[b] |
| Maternal weight, kg[a] | 72.0 (62.2–85.8) | 65.8 (58.9–75.8) | < .0001[b] |
| Maternal height, cm[a] | 163 (159–167) | 164 (160–168) | < .0001[b] |
| Body mass index, kg/m$^2$[a] | 27.0 (23.5–31.9) | 24.2 (21.8–27.9) | < .0001[b] |
| Gestational age, wk[a] | 12.7 (12.3–13.1) | 12.7 (12.3–13.1) | .120 |
| Racial origin, n (%) | | | |
| White | 1557 (57.6) | 87,295 (74.1) | < .0001[b] |
| Afro-Caribbean | 894 (33.1) | 18,460 (15.7) | < .0001[b] |
| South Asian | 151 (5.6) | 6144 (5.2) | .420 |
| East Asian | 47 (1.7) | 3112 (2.6) | .004[b] |
| Mixed | 55 (2.0) | 2777 (2.4) | .301 |
| Medical history, n (%) | | | |
| Chronic hypertension | 285 (10.5) | 1153 (1.0) | < .0001[b] |
| Diabetes mellitus | 60 (2.2) | 895 (0.8) | < .0001[b] |
| Systemic lupus erythematosus/ antiphospholipid syndrome | 16 (0.6) | 207 (0.2) | < .0001[b] |
| Cigarette smokers, n (%) | 199 (7.4) | 11,543 (9.8) | < .0001[b] |
| Family history of preeclampsia, (n, %) | 197 (7.3) | 4353 (3.7) | < .0001[b] |
| Parity | | | |
| Nulliparous, n (%) | 1686 (62.4) | 58,261 (49.5) | < .0001[b] |
| Parous with previous preeclampsia and small for gestational age, n (%) | 352 (13.0) | 3360 (2.9) | < .0001[b] |
| Pregnancy interval, y[a] | 3.9 (2.3–6.9) | 2.9 (1.9–4.8) | < .0001[b] |
| Gestation of last birth, wk[a] | 39.0 (37.0–40.0) | 40.0 (39.0–40.0) | < .0001[b] |
| Conception, n (%) | | | |
| Spontaneous | 2555 (94.5) | 113,552 (96.4) | < .0001[b] |
| Ovulation induction | 42 (1.6) | 1587 (1.3) | .405 |
| In vitro fertilization | 107 (4.0) | 2649 (2.2) | < .0001[b] |

Comparisons between outcome groups were by $\chi^2$ or Fisher exact test for categoric variables and Mann Whitney *U* test for continuous variables.

[a] Data are given as median (interquartile range); [b] Significance value: $P < .05$.

*Wright. Competing risks model in screening for preeclampsia. Am J Obstet Gynecol 2015.*

TABLE 2
**Fitted regression model for the mean gestational age at delivery with preeclampsia**

| Term | Coefficient | Standard error | 95% confidence interval |
|---|---|---|---|
| For all women | | | |
| Constant | 54.3637 | 0.24355 | 53.9–54.8 |
| Age (y) −35 if age ≥35 y<br>Age (y) −0 if age <35 y | −0.206886 | 0.03003 | −0.27 to −0.145 |
| Height in cm − 164 | 0.117110 | 0.00969 | 0.098–0.136 |
| Afro-Caribbean racial origin | −2.6786 | 0.14373 | −2.96 to −2.40 |
| South Asian racial origin | −1.1290 | 0.26584 | −1.65 to −0.61 |
| Chronic hypertension | −7.2897 | 0.29379 | −7.87 to −6.71 |
| Systemic lupus erythematosus or antiphospholipid syndrome | −3.0519 | 0.95407 | −4.92 to −1.18 |
| Conception by in vitro fertilization | −1.6327 | 0.32653 | −2.27 to −0.99 |
| Parous with previous preeclampsia | −8.1667 | 0.54937 | −9.24 to −7.09 |
| Parous with previous preeclampsia (previous gestation in weeks, −24)$^2$ | 0.0271988 | 0.00261 | 0.0221–0.032 |
| Parous with no previous preeclampsia | | | |
| Intercept | −4.3350 | 0.75195 | −5.81 to −2.86 |
| Interval$^{-1}$ | −4.15137651 | 1.30364 | −6.71 to −1.60 |
| Interval$^{-0.5}$ | 9.21473572 | 1.8435 | 5.60–12.83 |
| (Previous gestation in weeks, −24)$^2$ | 0.01549673 | 0.00186 | 0.0119–0.0191 |
| For women without chronic hypertension | | | |
| Weight in kg − 69 | −0.0694096 | 0.00405 | −0.0773 to −0.0615 |
| Family history of preeclampsia | −1.7154 | 0.26093 | −2.23 to −1.20 |
| Diabetes mellitus (type 1 or 2) | −3.3899 | 0.52072 | −4.41 to −2.37 |

Effects are in weeks relative to the reference group (white racial origin, nulliparous, spontaneous conception, no family history of preeclampsia and no history of diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome). Weight and height have been centered so that the constant is the estimated mean gestational age at delivery for the reference group with a weight of 69 kg and height of 164 cm. Please note that some of the effects apply only in the women without chronic hypertension.

*Wright. Competing risks model in screening for preeclampsia. Am J Obstet Gynecol 2015.*

## Statistical analyses

A model was fitted to data on gestational age in weeks at the time of delivery with preeclampsia. In this model, deliveries from causes other than preeclampsia were treated as censored observations.[13] Established risk factors (which included maternal age in years, weight in kilograms, height in centimeters, racial origin, interpregnancy interval in years, delivery in weeks of previous pregnancy with and without preeclampsia, method of conception, chronic hypertension, diabetes mellitus and systemic lupus erythematosus, or antiphospholipid syndrome) were included as covariates.

Gaussian, log-Gaussian, and Weibull distributions were considered for the time to delivery with preeclampsia. The Gaussian model was chosen on the basis of goodness of fit and simplicity of interpretation. During the initial stages of model development, continuous variables were grouped to define factor levels. Plots of the effects were then used to identify suitable functional forms. For maternal height and weight, linear relationships were assumed; for maternal age, a broken stick relationship with a change point at 35 years was used, and for the interpregnancy interval fractional polynomials[14] was adopted. In the main effects-only model, chronic hypertension had the largest effect on the mean time to delivery with preeclampsia. Because chronic hypertension itself is associated with other risk factors in the model, the additivity of effects with chronic hypertension was considered to be implausible. Consequently, we examined the interactions between the effect of chronic hypertension and that of other covariates in the model that led to the separation of other covariates into 2 groups: those with similar effects in patients with and without chronic hypertension and those that only applied to patients without chronic hypertension.

Five-fold cross validation was used to compare the performance of the new model with the NICE guidelines.[7] The data were divided into 5 equal subgroups; the model was then fitted 5 times to different combinations of 4 of the 5 subgroups and used to predict the risk of preeclampsia in the remaining one-fifth of the data. The predicted risks that resulted from the 5-folds were then used to define a screen-positive group by comparing them with a risk cutoff determined to give the same false-positive rate (FPR) as NICE, separately for all women, for nulliparous and parous women. McNemar's test was used to assess the evidence of differences in DRs of the risk-based approach and the NICE guidelines. Receiver operating characteristic curves were produced using the risks from the cross validation, and areas under the receiver operating characteristic curve were computed.

The statistical software package R was used for data analyses.[15] The survival package was used for model fitting.[16]

# RESULTS

## Characteristics of the study population

During the period, there were 120,492 singleton pregnancies that fulfilled the

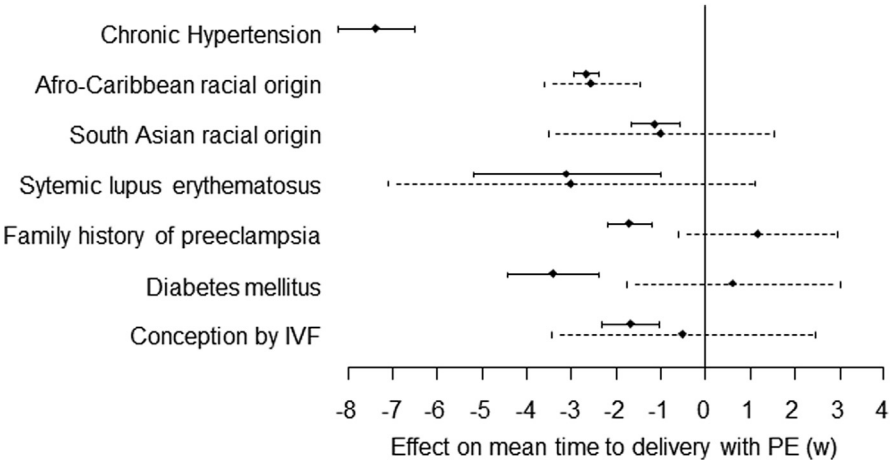
inclusion criteria. These included 2704 pregnancies (2.2%) that experienced preeclampsia and 117,788 pregnancies that were unaffected by preeclampsia. The initial description of our competing risk model for preeclampsia was derived from the first 58,884 cases included in the current study.[8]

The maternal and pregnancy characteristics of the preeclampsia and unaffected groups are compared in Table 1. In the preeclampsia group, compared with the unaffected group, there was a higher median maternal age, weight, BMI, and interpregnancy interval and lower height and gestational age at delivery in the last pregnancy. In the preeclampsia group, there was a higher prevalence of Afro-Caribbean racial origin, a history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus, or anti-phospholipid syndrome, nulliparous women, parous women with a history of preeclampsia, family history of preeclampsia and women who conceived with in vitro fertilization. In the preeclampsia group, there was a lower prevalence of white and East Asian racial origin, cigarette smokers, parous women without a history of preeclampsia, and women who conceived spontaneously.

## Model for gestational age at delivery with preeclampsia, given maternal characteristics

The final model for mean time to delivery with preeclampsia is given in Table 2. In this model, the mean gestational age for delivery with preeclampsia for a reference population (white racial origin; weight, 69 kg; height, 164 cm; nulliparous; spontaneous conception; no family history of preeclampsia; and no history of diabetes mellitus, systemic lupus erythematosus; or antiphospholipid syndrome) is 55 weeks. The estimated standard deviation (SD) was 6.8833 (95% confidence interval [CI], 6.6716−7.1015) weeks. Risks of preeclampsia that required delivery between 2 time intervals (x and y) are estimated by the area under the Gaussian distribution, with the mean determined from the regression model and this SD between x and y.

FIGURE 2
**Effect on mean time to delivery with preeclampsia**



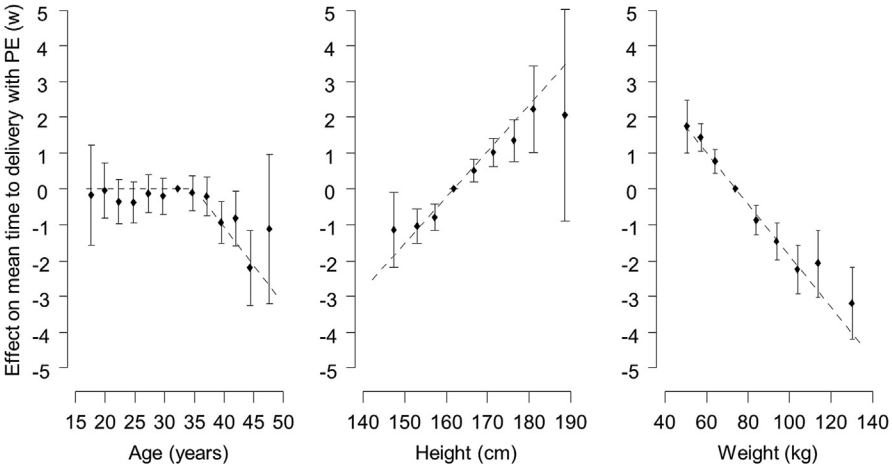

Effect (estimates and 95% confidence intervals) on mean time to delivery with preeclampsia, stratified by chronic hypertension (*interrupted lines*). The effects are relative to the reference levels of white racial origin, nulliparous, spontaneous conception, no family history of preeclampsia, and no history of diabetes mellitus, systemic lupus erythematosus, or antiphospholipid syndrome. The effect of chronic hypertension is for a woman who weighs 69 kg without diabetes mellitus and no family history of preeclampsia.

*IVF*, in vitro fertilization; *PE*, preeclampsia; *w*, week.

*Wright. Competing risks model in screening for preeclampsia. Am J Obstet Gynecol 2015.*

The effect on the time to delivery with preeclampsia for categoric variables is shown in Figure 2 and for continuous variables in Figures 3-5. We found that maternal age, height, Afro-Caribbean and South Asian racial origin, and history of systemic lupus erythematosus or antiphospholipid syndrome had similar

FIGURE 3
**Effect of maternal age, height, and weight**




Effect (estimates and 95% confidence intervals) of maternal age, height, and weight on mean time to delivery with preeclampsia. The effects shown for weight are for women without chronic hypertension.

*cm*, centimeter; *kg*, kilogram; *PE*, preeclampsia; *w*, week.

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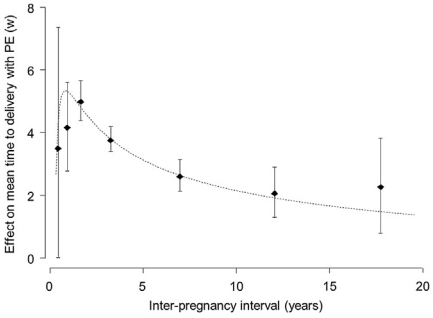
FIGURE 4

**Effect on mean time to delivery with preeclampsia of a previous pregnancy unaffected by preeclampsia**




Estimates and 95% confidence intervals for data are grouped by interpregnancy intervals of <0.5, 0.5-1, 1-2, 2-5 5-10, 10-15, and >15 years. *Horizontal axes points* are shown at the mean pregnancy interval for these groups. The *interrupted curve* is the fitted fractional polynomial.

*PE*, preeclampsia; *w*, week.

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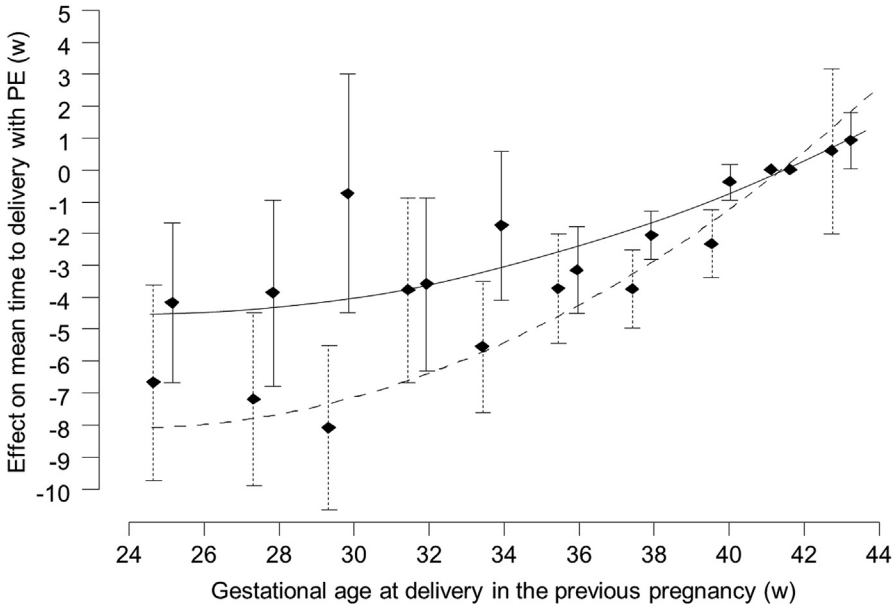
FIGURE 5

**Effect on mean time to delivery with preeclampsia in the current pregnancy**




Effect (estimates and 95% confidence intervals) on mean time to delivery with preeclampsia in the current pregnancy of gestational age at delivery of the previous pregnancy with preeclampsia (*interrupted lines* and *curve*) and without preeclampsia (*solid lines* and *curve*).

*PE*, preeclampsia; *w*, week.

*Wright. Competing risks model in screening for preeclampsia. Am J Obstet Gynecol 2015.*

TABLE 3

**Comparisons of performance of screening from the 5-fold cross validation study**

| Delivery for preeclampsia | Total, n | Preeclampsia, n (%) | False positive rate (%) | Detection rate, % (95% confidence interval) | | |
|---|---|---|---|---|---|---|
| | | | | National Institute for Health and Clinical Excellence guidelines | New model | *P* value |
| Any gestation | | | | | | |
| Nulliparous | 59,947 | 1686 (2.81%) | 11.5 | 24.8 (22.7–26.9) | 31.0 (28.8–33.3) | < .0001 |
| Parous | 60,545 | 1018 (1.68%) | 9.8 | 51.3 (48.2–54.4) | 54.9 (51.8–58.0) | .0015 |
| Total | 120,492 | 2704 (2.24%) | 10.6 | 34.8 (33.0–36.6) | 40.3 (38.5–42.2) | < .0001 |
| Before 37 wks' gestation | | | | | | |
| Nulliparous | 59,947 | 465 (0.78%) | 11.5 | 29.0 (24.9–33.4) | 35.9 (31.5–40.5) | .0061 |
| Parous | 60,545 | 321 (0.53%) | 9.8 | 55.8 (50.1–61.3) | 61.7 (56.1–67.0) | .0087 |
| Total | 120,492 | 786 (0.65%) | 10.6 | 39.9 (36.5–43.5) | 47.6 (44.0–51.1) | < .0001 |
| Before 34 wks' gestation | | | | | | |
| Nulliparous | 59,947 | 214 (0.36%) | 11.5 | 32.7 (26.5–39.4) | 41.6 (34.9–48.5) | .0117 |
| Parous | 60,545 | 156 (0.26%) | 9.8 | 58.3 (50.2–66.2) | 66.7 (58.7–74.0) | .0139 |
| Total | 120,492 | 370 (0.31%) | 10.6 | 43.5 (38.4–48.7) | 53.5 (48.3–58.7) | < .0001 |

Results are presented for all folds combined. The screen-positive rate in each group was the one that was derived from the National Institute for Health and Clinical Excellence guidelines.[7]

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effects in those women with and those without chronic hypertension. In contrast, maternal weight, family history of preeclampsia, diabetes mellitus, and conception by in vitro fertilization had a significant effect in those women without chronic hypertension, but very little or no effect in the group with chronic hypertension.

Chronic hypertension was present in 10.5% of women who experienced preeclampsia, compared with only 1.0% of women without preeclampsia (Table 1), which reflects the importance of this categoric variable as a risk factor for preeclampsia. However, the effects of chronic hypertension in the model are complicated because of interactions with other factors. In the fitted regression model (Table 2), the regression coefficient of −7.3 (95% CI, −7.9 to −6.7) for chronic hypertension means that, in women with chronic hypertension who weighed 69 kg, without diabetes mellitus, and no family history of preeclampsia, the mean gestation for delivery with preeclampsia is reduced by 7.3 weeks. For those women with a family history of preeclampsia or diabetes mellitus or weight in excess of 69 kg, the effect of chronic hypertension is <7.3 weeks. Conversely, for those without a family history of preeclampsia and with weights <69 kg, the effect of chronic hypertension is >7.3 weeks. In extreme cases that occur in <0.01% of the records the model predicts that those with a family history of preeclampsia, diabetes mellitus, and weight in excess of 100.5 kg will be protected by chronic hypertension. From the clinical perspective, this is implausible, and in practical applications, it should be avoided by taking the minimum of the means from the model with and without chronic hypertension.

Compared with nulliparous women, in those women with a previous pregnancy that was unaffected by preeclampsia, the risk of preeclampsia in the current pregnancy is reduced; the maximum benefit occurs when the interval is 1-2 years, but a significant beneficial effect persists for >15 years (Figure 4). In parous women, the risk of preeclampsia in the current pregnancy is related inversely to the gestational age at delivery of the previous pregnancy, and the risk is more marked in those with a previous preeclampsia (Figure 5).

### Comparison of performance of the new model with NICE guidelines

The screen-positive rate with the NICE guidelines[7] was 11.2%; the DR of all preeclampsia and preeclampsia that required delivery at <37 and at <34 weeks' gestation was 35%, 40%, and 44%, respectively. Table 3 shows the comparisons of DRs of preeclampsia at any gestation and preeclampsia that required delivery at <37 and at <34 weeks for the new model and the NICE guidelines[7] from the 5-fold cross validation study. The FPR was determined by NICE guidelines[7] separately for nulliparous and multiparous women and all women; for these FPRs, the DRs within each group are significantly higher by the new model, compared with those achieved by the NICE guidelines.

The performance of the new model in the prediction of preeclampsia at any gestation and preeclampsia that requires delivery at <37 and at <34 weeks' gestation is shown in Figure 6; the performance for nulliparous and parous women of different racial origins are given in Table 4. For a given risk cutoff, the FPR and DR of preeclampsia are higher in nulliparous women than in parous women and in those of Afro-Caribbean than white racial origin.

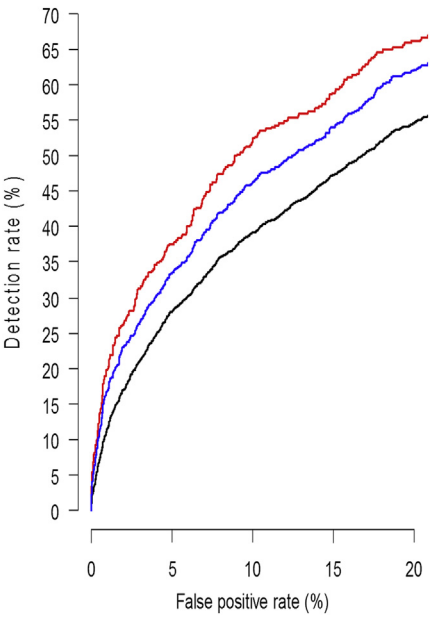
## COMMENT

### Principal findings of this study

Screening for preeclampsia by maternal characteristics and obstetric history is associated with a higher DR for a given FPR, if the maternal factors are combined into a multivariable logistic model rather than treating each one as an independent screening test as recommended by NICE.[7] At a screen-positive rate of approximately 11%, according to the NICE guidelines, the new model can predict 40%, 48%, and 54% of cases of preeclampsia at any gestation and preeclampsia that requires delivery at <37 and at <34 weeks' gestation, respectively, which is higher than the respective values of 35%, 40%, and 44%, respectively, that are achieved by the application of the NICE guidelines.

In the new model, increased risk for preeclampsia, with the consequent shift to the left in the Gaussian distribution of the gestational age at delivery with preeclampsia, is provided by advancing maternal age, increasing weight, Afro-Caribbean and South Asian racial origin, medical history of chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome, family history and personal history of preeclampsia, and conception by in vitro fertilization. The risk for preeclampsia decreases with increasing maternal height and in parous women with no previous preeclampsia; in the latter, the protective effect, which is related inversely to the interpregnancy interval, persists >15 years.

FIGURE 6
**Receiver operating characteristic curves**




Receiver operating characteristic curves for the prediction of all preeclampsia (*black curve*) and preeclampsia that required delivery at <37 (*blue curve*) and at <34 weeks' gestation (*red curve*) according to the competing risks model. Areas under the receiver operating characteristic curves are respectively 0.7562, 0.7920, and 0.8106.

*Wright. Competing risks model in screening for preeclampsia. Am J Obstet Gynecol 2015.*

TABLE 4
**Screening performance of the new model in the prediction of preeclampsia**

| Pregnancy group | Total, n | Preeclampsia, n | Risk cutoff for preeclampsia at <37 wks' gestation, % | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 1 in 50 | | 1 in 75 | | 1 in 100 | |
| | | | False-positive rate | Detection rate | False-positive rate | Detection rate | False-positive rate | Detection rate |
| Preeclampsia at <34 wks' gestation | | | | | | | | |
| All pregnancies | 120,492 | 370 | 6.1 | 40 | 12.1 | 55 | 17.9 | 65 |
| Nulliparous | 59,947 | 214 | 6.6 | 29 | 15.7 | 48 | 24.5 | 62 |
| Parous | 60,545 | 156 | 5.6 | 56 | 8.7 | 65 | 11.5 | 68 |
| Afro-Caribbean racial origin | | | | | | | | |
| All pregnancies | 19,354 | 149 | 22.5 | 60 | 43.6 | 81 | 56.6 | 87 |
| Nulliparous | 7721 | 61 | 33.6 | 56 | 73.4 | 90 | 92.8 | 97 |
| Parous | 11,633 | 88 | 15.4 | 64 | 24.1 | 75 | 33.0 | 80 |
| White racial origin | | | | | | | | |
| All pregnancies | 88,852 | 187 | 2.9 | 27 | 5.9 | 39 | 9.9 | 51 |
| Nulliparous | 45,991 | 129 | 2.7 | 18 | 6.9 | 31 | 13.3 | 50 |
| Parous | 42,861 | 58 | 3.2 | 48 | 4.9 | 55 | 6.3 | 55 |
| Preeclampsia at <37 wks' gestation | | | | | | | | |
| All pregnancies | 120,492 | 786 | 6.1 | 36 | 12.1 | 50 | 17.9 | 60 |
| Nulliparous | 59,947 | 465 | 6.6 | 25 | 15.7 | 42 | 24.5 | 57 |
| Parous | 60,545 | 321 | 5.6 | 51 | 8.7 | 60 | 11.5 | 64 |
| Afro-Caribbean racial origin | | | | | | | | |
| All pregnancies | 19,354 | 291 | 22.5 | 57 | 43.6 | 77 | 56.6 | 84 |
| Nulliparous | 7721 | 129 | 33.6 | 53 | 73.4 | 84 | 92.8 | 95 |
| Parous | 11,633 | 162 | 15.4 | 60 | 24.1 | 70 | 33.0 | 75 |
| White racial origin | | | | | | | | |
| All pregnancies | 88,852 | 418 | 2.9 | 23 | 5.9 | 33 | 9.9 | 44 |
| Nulliparous | 45,991 | 289 | 2.7 | 15 | 6.9 | 26 | 13.3 | 41 |
| Parous | 42,861 | 129 | 3.2 | 40 | 4.9 | 48 | 6.3 | 50 |
| Preeclampsia any gestation | | | | | | | | |
| All pregnancies | 120,492 | 2704 | 6.1 | 30 | 12.1 | 42 | 17.9 | 52 |
| Nulliparous | 59,947 | 1686 | 6.6 | 22 | 15.7 | 37 | 24.5 | 49 |
| Parous | 60,545 | 1018 | 5.6% | 44 | 8.7 | 52 | 11.5 | 57 |
| Afro-Caribbean racial origin | | | | | | | | |
| All pregnancies | 19,354 | 894 | 22.5 | 56 | 43.6 | 76 | 56.6 | 84 |
| Nulliparous | 7721 | 437 | 33.6 | 54 | 73.4 | 87 | 92.8 | 97 |
| Parous | 11,633 | 457 | 15.4 | 57 | 24.1 | 66 | 33.0 | 72 |
| White racial origin | | | | | | | | |
| All pregnancies | 88,852 | 1557 | 2.9 | 17 | 5.9 | 25 | 9.9 | 35 |
| Nulliparous | 45,991 | 1086 | 2.7 | 11 | 6.9 | 19 | 13.3 | 31 |
| Parous | 42,861 | 471 | 3.2 | 31 | 4.9 | 38 | 6.3 | 44 |

*Wright. Competing risks model in screening for preeclampsia. Am J Obstet Gynecol 2015.*

The factor with the highest risk for preeclampsia is chronic hypertension. Although some of the other risk factors (which include age, Afro-Caribbean and South Asian racial origin, and a history of systemic lupus erythematosus or antiphospholipid syndrome) have similar effects in those women with and without chronic hypertension, other risk factors (which include maternal weight, family history of preeclampsia, diabetes mellitus, and conception by in vitro fertilization) have a significant effect in those without chronic hypertension, but not in those with chronic hypertension. This tendency for risk factors to separate into these 2 groups leads to the conjecture that some risk factors operate through the mechanism of hypertension while others act independently with effects over and above those of hypertension.

The study has highlighted that, in screening for preeclampsia, the FPR and DR for a given risk cutoff are influenced by the characteristics of the study population. Consequently, comparison of the performance of screening between studies requires the appropriate adjustments for the characteristics of the population under investigation.

The improvement in performance of screening for preeclampsia by maternal characteristics and obstetric history with the use of our method, compared with that of NICE, is only modest. The main benefit of our method is that it provides a previous model that can be used in conjunction with likelihood ratios from biophysical and biochemical markers (measured either at the same or different gestational ages during pregnancy) to derive patient-specific risks for preeclampsia that is developing at any desired gestational age cutoff. We previously reported that screening at 11-13 weeks' gestation by a combination of maternal factors (mean arterial pressure, uterine artery pulsatility index, serum pregnancy-associated plasma protein-A and placental growth factor with the use of the competing risks model) can predict 54%, 77%, and >90% of cases of preeclampsia at any gestation and preeclampsia that requires delivery at <37 and at <34 weeks' gestation, respectively, at FPR of 10%.[9]

## Strengths and limitations

The major strengths of the study are (1) prospective examination of a large number of pregnancies in which specific questions were asked to identify known factors that are associated with preeclampsia, (2) the use of multivariable survival analysis to identify the factors and define their contribution in the prediction of preeclampsia, and (3) the development of a survival-time model that allows the estimation of individual patient-specific risks of preeclampsia that will require delivery before any specified gestation. Bayes theorem can be used to combine the information on maternal characteristics and medical history with biomarkers for risk assessment at different stages of pregnancy.

A limitation of the study is that the performance of screening by a model that is derived and tested with the use of the same dataset is overestimated. We have used cross validation to reduce this effect but acknowledge that this approach fails to capture the overestimation of performance because of model selection. It does not demonstrate the applicability of our results to other populations. External validation on independent data from different sources is required.

## Comparison with previous studies

The risk factors for preeclampsia that were incorporated in our new model have been reported extensively in the past and have been highlighted in previous clinical risk prediction models for preeclampsia.[7,17] However, screening by the NICE or World Health Organization guidelines involves dichotomization of continuous measurements,[7,17] whereas, our study has demonstrated that the observed proportions of preeclampsia depend continuously on maternal age, weight, height, and interpregnancy interval that is captured poorly by this process of dichotomization. Similarly, the effect of a previous pregnancy with or without preeclampsia is related to the gestational age at delivery. Consequently, in our model these factors are treated as continuous rather than categoric variables. Additionally, in previous scoring systems patients were classified as screen positive and screen negative for preeclampsia based on the presence or absence of specific characteristics each one of which was attributed the same independent importance. In our model, the risk factors were combined through a multivariate survival-time model that allows estimation of individual patient risk for preeclampsia at any desired gestational age cutoff or prespecified time interval from assessment. ■

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