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A Competing Risks Model in Early Screening for Preeclampsia

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Key Words
First-trimester screening · Preeclampsia · Uterine artery Doppler · Mean arterial pressure · Serum biochemistry

Abstract
Objective: It was the aim of this study to develop models for the prediction of preeclampsia (PE) based on maternal characteristics and biophysical markers at 11–13 weeks' gestation in which gestation at the time of delivery for PE is treated as a continuous variable. ***Methods:*** This was a screening study of singleton pregnancies at 11–13 weeks including 1,426 (2.4%) cases that subsequently developed PE and 57,458 cases that were unaffected by PE. We developed a survival time model for the time of delivery for PE in which Bayes' theorem was used to combine the prior information from maternal characteristics with the uterine artery pulsatility index (PI) and the mean arterial pressure (MAP), using multiple of the median values. ***Results:*** The risk for PE increased with maternal age, weight, Afro-Caribbean and South Asian racial origin, previous pregnancy with PE, conception by in vitro fertilization and a medical history of chronic hypertension, type 2 diabetes mellitus as well as systemic lupus erythematosus or antiphospholipid syndrome. In pregnancies with PE, there was an inverse correlation between multiple of the median values of the uterine artery PI and MAP with gestational age at delivery. Screening by maternal characteristics, uterine artery PI and MAP detected 90% of PE cases requiring delivery before 34 weeks and 57% of all PE cases at a fixed false-positive rate of 10%. ***Conclusions:*** A new model has been developed for effective first-trimester screening for PE.

Introduction

Preeclampsia (PE), which affects about 2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality [1–3]. Stimulated by evidence that the prophylactic use of aspirin starting from early pregnancy can result in halving of the prevalence of PE [4], several recent studies have proposed the introduction of a first-trimester screening for the disease by a combination of maternal demographic characteristics, including medical and obstetric history, uterine artery pulsatility index (PI), mean arterial pressure (MAP) and maternal serum biochemical markers [5, 6]. These studies have adopted the same principles as screening for aneuploidies [7], in the assessment of patient-specific risks for PE. PE has been defined as early or late on the basis of whether or not delivery oc-

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curs before 34 weeks' gestation. In general, the deviations from normal for the various proposed biomarkers have been greater in early PE than in late PE [5, 6]. This has led to the view that early and late PE may be different diseases with different biomarker profiles. An alternative view is that PE is a spectrum disorder, the degree of which is reflected in both gestation at the time of delivery and the biomarker levels.

In this paper, we propose an approach to screening for PE by a combination of maternal characteristics and biomarkers in which gestation at the time of delivery for PE is treated as a continuous variable.

Methods

Study Population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine first hospital visit in pregnancy. In this visit, which is held at 11^{+0}–13^{+6} weeks of gestation, we record maternal characteristics and medical history and perform combined screening for aneuploidies by measurement of the fetal crown-rump length and nuchal translucency thickness and maternal serum pregnancy-associated plasma protein A and free β-subunit of human chorionic gonadotropin [7, 8]. The women were screened between March 2006 and September 2010. In the second part of the study period, we also measured the maternal MAP by automated devices and used transabdominal color Doppler ultrasound to visualize the left and right uterine artery, measure the PI in each vessel and calculate the mean PI [9, 10]. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the King's College Hospital Ethics Committee.

The inclusion criteria for this study on screening for PE 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 before 24 weeks as well as pregnancies delivering small for gestational age (SGA) neonates in the absence of PE.

In this study, we developed a model for predicting PE based on maternal characteristics in the study population. We then expanded this model for prediction of PE to include uterine artery PI and MAP.

Maternal History and Characteristics

Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes or no), history of chronic hypertension (yes or no), history of type 1 or 2 diabetes mellitus (yes or no), history of systemic lupus erythematosus or antiphospholipid syndrome (yes or no), family history of PE in the mother of the patient (yes or no) and obstetric history including parity (parous or nulliparous if no previous pregnancies at or after 24 weeks) as well as previous pregnancy with PE (yes or no). The questionnaire was then reviewed by a doctor together with the patient, and the maternal weight and height were measured.

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 chronic hypertension, PE or non-proteinuric gestational hypertension.

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [11]. The systolic blood pressure should be ≥140 mm Hg and/or the diastolic blood pressure should be ≥90 mm Hg on at least two occasions 4 h apart developing after 20 weeks of gestation in previously normotensive women and there should be proteinuria of ≥300 mg in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In PE superimposed on chronic hypertension, significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or presence of hypertension at the booking visit before 20 weeks of gestation in the absence of trophoblastic disease). The definition of SGA was a birth weight <5th percentile for gestational age of a reference range derived from our population [12].

Statistical Analysis

The proposed new approach for early screening for PE was based on a survival time model for the time of delivery for PE. Bayes' theorem was used to combine the prior information from maternal characteristics with biomarker multiple of the median (MoM) values. We used a competing risk model [13].

In this model, it is assumed that if the pregnancy was to continue indefinitely, all women would have developed PE and, in this respect, there is a competition between delivery before or after development of PE. We applied a model to represent the distribution of gestational age at delivery with PE (fig. 1). In pregnancies at low risk for PE, the gestational age distribution is shifted to the right with the implication that in most pregnancies, delivery will actually occur before the development of PE. In pregnancies at high risk for PE, the gestational age distribution is shifted to the left with the implication that in many pregnancies, delivery will actually occur after the development of PE. Given maternal characteristics and biomarker levels, the risk of PE occurring at or before a specified gestational age was given by the area under the distribution curve (fig. 1).

The distribution of gestational age at delivery with PE was defined by two components: firstly, the prior distribution based on maternal characteristics, and secondly, the distribution of MoM biomarker values with gestational age in pregnancies affected by PE. Although such model fitting was complicated because of the censoring in situations when delivery occurred before PE, fitting regression models to censored data was carried out routinely with standard statistical software.

The values of uterine artery PI and MAP were $\log_{10}$ transformed to make their distribution Gaussian. In the unaffected pregnancies, multiple regression analysis was used to determine

which of the factors amongst the maternal characteristics and fetal crown-rump length were significant predictors of each biomarker. In each case of PE, the measurements were converted into a MoM, and regression analysis was used to determine the relationship between $\log_{10}$ MoM values and gestational age at delivery.

In the estimation of screening performance, the values of uterine artery PI and MAP in the whole screened population were simulated based on the mean and standard deviation (SD) of the $\log_{10}$ transformed marker values in the unaffected and the PE pregnancies. In the PE group, the mean and SD values used for simulation were specific for each gestational week at delivery, which were estimated from the regression analysis of the $\log_{10}$ MoM values of available data with gestational age at delivery.

Results

Characteristics of the Study Population

First-trimester combined screening for aneuploidies was carried out in 65,960 singleton pregnancies. We excluded 7,076 cases because they had missing outcome data (n = 2,133), the pregnancies resulted in miscarriage, termination or the birth of babies with major defects (n = 1,775) or the birth of SGA neonates in the absence of PE (n = 3,168).

In the remaining 58,884 cases, there were 1,426 (2.4%) that developed PE and 57,458 that were unaffected by PE. We had measurements of uterine artery PI in 45,885 of the 58,884 pregnancies, including 1,245 (2.7%) that developed PE, and we had measurements of MAP in 35,215 of the 58,884 pregnancies, including 979 (2.8%) that developed PE.

The maternal characteristics and history in the PE and unaffected pregnancies in the screening population are compared in table 1. In the PE group, compared to unaffected pregnancies, there was a higher mean maternal weight and a prevalence of Afro-Caribbean racial origin, family and personal history of PE, chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome as well as a lower prevalence of cigarette smokers.

Table 1. Maternal and pregnancy characteristics in the outcome groups

Characteristic	No PE (n = 57,458)	PE (n = 1,426)
Median maternal age, years	32.0 [27.7–35.6]	31.6 [27.0–36.4]
Median maternal weight, kg	65.5 [59.0–75.0]	71.6 [62.4–85.0]*
Median fetal crown-rump length mm	63.4 [58.4–68.9]	62.6 [58.1–68.4]
Racial origin		
Caucasian	42,514 (74.0)	751 (52.7)
Afro-Caribbean	9,268 (16.1)	525 (36.8)*
South Asian	2,757 (4.8)	87 (6.1)*
East Asian	1,462 (2.6)	27 (1.9)
Mixed	1,457 (2.5)	36 (2.5)
Parity		
Nulliparous	28,231 (49.1)	877 (61.5)
Parous with no previous PE	27,609 (48.1)	346 (24.3)*
Parous with previous PE	1,618 (2.8)	203 (14.2)*
Cigarette smoker	4,498 (7.8)	86 (6.0)*
Family history of PE	2,506 (4.4)	123 (8.6)*
Conception		
Spontaneous	55,358 (96.3)	1,347 (94.5)
Assisted	2,100 (3.7)	79 (5.5)*
History of chronic hypertension	545 (0.9)	140 (9.8)*
History of type 1 diabetes mellitus	237 (0.4)	14 (1.0)*
History of type 2 diabetes mellitus	146 (0.3)	14 (1.0)*
History of SLE or APS	117 (0.2)	8 (0.6)*

Figures in parentheses are percentages; figures in brackets are interquartile ranges. SLE = Systemic lupus erythematosus; APS = antiphospholipid syndrome. Comparisons between each outcome group and unaffected controls: χ^2 test or Fisher's exact test for categorical variables and Mann-Whitney test for continuous variables.

Gestational Age at Delivery with PE Given Maternal Characteristics

A standard Gaussian regression model for gestation at delivery was fitted by treating deliveries in which PE did not occur as censored observations (table 2). This specified the mean gestational age at delivery with PE for given variables from maternal demographic characteristics, medical and obstetric history; the smaller the mean gestational age, the higher the risk for PE (fig. 2).

In this model, the mean gestational age for delivery with PE is 55 weeks, with an estimated SD of 7.11 weeks (table 2). Certain variables, including advancing maternal age >30 years, increasing weight, Afro-Caribbean and South Asian racial origin, previous pregnancy with PE, conception by in vitro fertilization and a medical history of chronic hypertension, type 2 diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome increase the risk for development of PE. The consequence of this increased risk is a shift to the left of the Gaussian distribution of the gestational age at delivery with PE (fig. 1).

Uterine Artery PI and MAP in Unaffected Pregnancies

Multiple regression analyses demonstrated that significant independent contributions for the prediction of

Table 2. Fitted regression model for posited gestational age in weeks at delivery with PE

	Coefficient	Standard error	95% confidence limits	p
Intercept	55.0081	0.3465	54.3289 to 55.6873	0.00000
Age >30 years	–0.10367	0.02319	–0.14912 to –0.05822	0.00001
Weight ≤69 kg	–0.07259	0.00551	–0.08339 to –0.06180	0.00000
Height ≤1.64 m	12.4007	1.3263	9.801129 to 15.0003	0.00000
Ethnicity				
Black	–3.0357	0.2040	–3.4355 to –2.6360	0.00000
South Asian	–1.7709	0.3737	–2.5034 to –1.0384	0.00000
Previous history				
Parous with PE	–3.0333	0.3174	–3.6554 to –2.4112	0.00000
Parous with no PE	3.1440	0.2033	2.7455 to 3.5424	0.00000
Mother had PE	–1.8841	0.3262	–2.5234 to –1.2448	0.00000
Conception by in vitro fertilization	–1.7895	0.4782	–2.7268 to –0.8523	0.00018
SLE or APS	–4.0613	1.3186	–6.6459 to –1.4768	0.00207
Chronic hypertension	–6.2415	0.4179	–7.0606 to –5.4223	0.00000
Type 1 diabetes mellitus	–3.8525	0.9732	–5.7600 to –1.9450	0.00008

In this model, the mean gestational age for delivery with PE is 55 weeks, with a residual SD of 7.11 weeks. SLE = Systemic lupus erythematosus; APS = antiphospholipid syndrome.

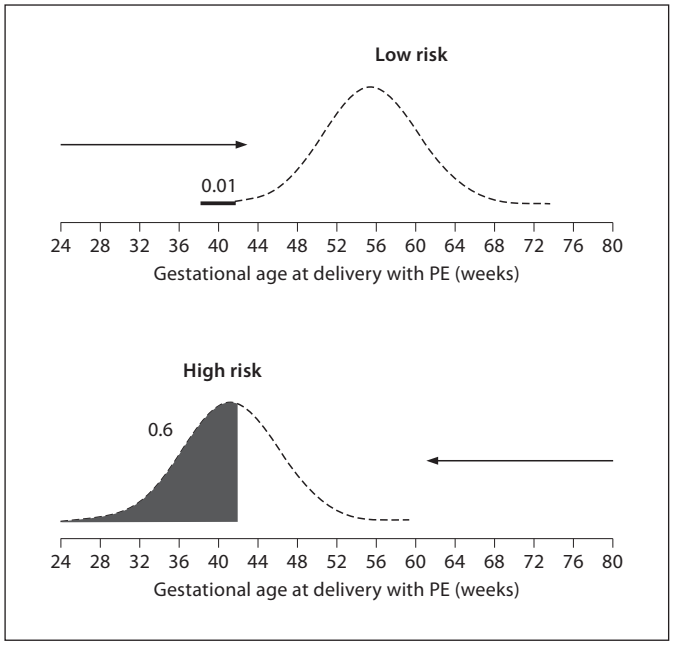

Fig. 1. Distribution of gestational age at delivery for PE. In pregnancies at low risk for PE, the gestational age distribution is shifted to the right, and in most pregnancies, delivery will occur before the development of PE. In pregnancies at high risk for PE, the distribution is shifted to the left. The risk of PE 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 PE at or before 34 weeks' gestation is 0.01 or 1%, and in the high-risk group, the risk is 0.6 or 60%.

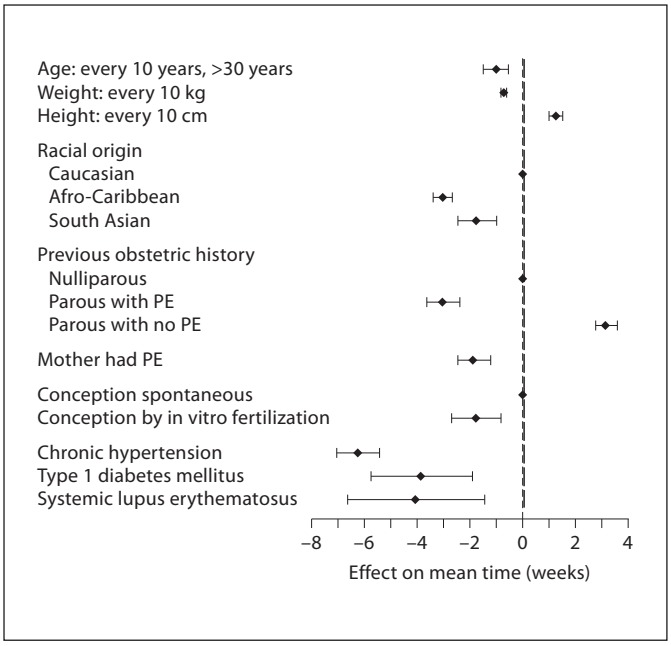

Fig. 2. Effects of maternal characteristics (with 95% confidence intervals) on gestational age at delivery for PE. This effect is expressed as gestational weeks by which the expected gestational age at delivery for PE is altered.

Table 3. Fitted regression model for $\log_{10}$ uterine artery PI in unaffected pregnancies

Variable	Coefficient	Standard error	95% confidence limits	p
Intercept	0.2556871303969	0.0016856952435	0.2523831547569 to 0.2589911060369	<0.0001
Gestation ≤77 days	–0.0045660653454	0.0001297279461	–0.0048203331174 to –0.0043117975734	<0.0001
Weight ≤69 kg	–0.0007582673888	0.0000455428109	–0.0008475316484 to –0.0006690031293	<0.0001
(Weight ≤69 kg)^2	0.0000081480441	0.0000014554139	0.0000052954217 to 0.0000110006665	<0.0001
Afro-Caribbean racial origin	0.0236442656264	0.0014622000327	0.0207783423182 to 0.0265101889346	<0.0001

Table 4. Fitted regression model for $\log_{10}$ MAP in unaffected pregnancies

Variable	Coefficient	Standard error	95% confidence limits	p
Intercept	1.933065465937210	0.000225794634398	1.932622902665880 to 1.933508029208530	<0.0001
Weight ≤69 kg	0.001144342904429	0.000016591134737	0.001111823855055 to 0.001176861953802	<0.0001
(Weight ≤69 kg)^2	–0.000007788699012	0.000000543008054	–0.000008853008718 to –0.000006724389307	<0.0001

Table 5. Fitted regression model for marker $\log_{10}$ MoM values on gestation at time of delivery for pregnancies with PE

Marker	Intercept	Standard error	p	Slope	Standard error	p
Uterine artery PI	0.642102	0.038479	<0.0001	–0.015173	0.0010191	<0.0001
MAP	0.114859	0.014798	<0.0001	–0.002115	0.0003917	<0.0001

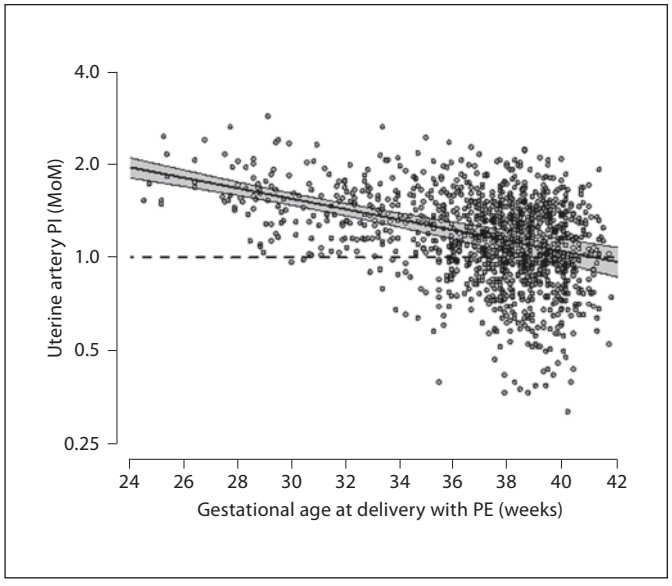

Fig. 3. Scatter diagram and regression line with 95% confidence limits for the relationship between uterine artery PI MoM and gestational age at delivery in pregnancies with PE.

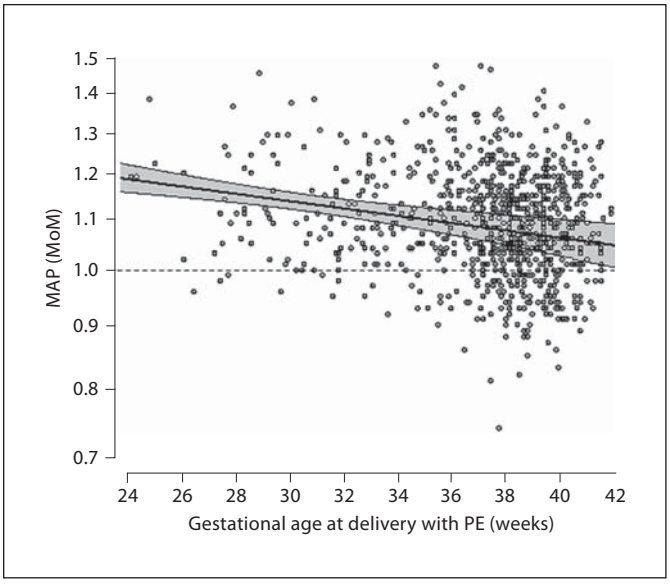

Fig. 4. Scatter diagram and regression line with 95% confidence limits for the relationship between MAP MoM and gestational age at delivery in pregnancies with PE.

Table 6. SDs and correlations, with 95% confidence limits, for log10 multiples of the median (MoM) values for uterine artery PI and MAP

	No PE	PE
SD Uterine artery PI	0.1242215 (0.122254 to 0.127840)	0.1409539 (0.122250 to 0.158148)
SD MAP	0.0386549 (0.037002 to 0.040257)	0.0426263 (0.032693 to 0.053506)
Correlation	–0.0724816 (–0.075278 to –0.070882)	0.0093204 (–0.004507 to 0.014433)

Table 7. Estimated detection rates of PE requiring delivery before 34, 37 and 42 weeks' gestation at false-positive rates (FPR) of 5 and 10%

Screening test	PE <34 weeks (n = 214)		PE <37 weeks (n = 568)		PE <42 weeks (n = 1,426)	
	FPR 5%	FPR 10%	FPR 5%	FPR 10%	FPR 5%	FPR 10%
Maternal characteristics	35.5	50.5	32.7	43.3	29.4	40.3
Maternal characteristics plus						
Uterine artery PI	59.3	75.2	40.0	55.1	31.2	42.2
MAP	58.4	72.9	44.0	59.3	37.3	53.5
Combined testing	79.9	89.7	54.6	71.5	34.9	56.6

$\log_{10}$ uterine artery PI were provided by gestational age as well as by maternal weight and racial origin ($R^2 = 0.031$, $p < 0.0001$; table 3).

Multiple regression analyses demonstrated that significant independent contribution for the prediction of $\log_{10}$ MAP was provided by maternal weight ($R^2 = 0.132$, $p < 0.0001$; table 4).

Distribution of Uterine Artery PI and MAP in Pregnancies with PE

In pregnancies with PE, there was an inverse correlation between MoM values of uterine artery PI and MAP with gestational age at delivery (fig. 3, 4). The fitted regression models for $\log_{10}$ MoM values on gestational age at delivery are presented in table 5 and the estimated parameters for the assumed bivariate Gaussian distributions for log MoM values are given in table 6.

Performance of Screening for PE

Estimated detection rates of PE requiring delivery before 34, 37 and 42 weeks' gestation, at false-positive rates of 5 and 10% in screening by maternal factors, uterine artery PI, MAP and their combination are given in table 7.

Discussion

This study has demonstrated a new approach to screening for PE in which gestation at the time of delivery for PE is treated as a continuous rather than a categorical variable. This approach, which is based on a survival time model, assumes that if the pregnancy was to continue indefinitely, all women would develop PE and whether they do or not before a specified gestational age depends on a competition between delivery before or after development of PE. In the traditional approach to screening, the effects of variables from maternal characteristics and history are expressed as odds ratios and the effect of biomarker MoMs are expressed as likelihood ratios for early, late or total PE. In our new approach, the effect of various risk factors is to modify the mean of the distribution of gestational age at delivery with PE. In pregnancies at low risk for PE, the gestational age distribution is shifted to the right with the implication that in most pregnancies, delivery will actually occur before the development of PE. In high-risk pregnancies, the distribution is shifted to the left, and the smaller the mean gestational age, the higher the risk for PE.

There is evolving evidence that the incidence of adverse fetal and maternal short- and long-term conse-

quences of PE is inversely related to the gestational age at onset of the disease [14–18]. Similarly, studies reporting on early screening for PE by a combination of maternal characteristics and biomarkers have demonstrated that both the odds ratios for the factors in maternal history which define the a priori risk for PE and the deviations from normal for the various proposed biomarkers are inversely proportional to gestation at delivery [5, 6]. Consequently, the endpoint in screening for PE should not be total PE but the condition should be subdivided according to gestational age at delivery. In our previous studies aiming to capture this gestational age-related severity of disease, we have subdivided the condition into early PE and late PE. However, such a subdivision could lead to the erroneous conclusion that early and late PE are different diseases with different biomarker profiles. As demonstrated by the MoM values of uterine artery PI and MAP in pregnancies with PE, the distribution with gestational age is not bimodal. Consequently, PE could be considered a single pathophysiological entity with a wide spectrum of severity manifested in gestational age at which delivery becomes necessary for maternal and or fetal indications.

Evidence from randomized studies suggests that in women at high risk for PE, the prophylactic use of low-dose aspirin, started at or before 16 weeks' gestation, reduces the prevalence of the disease by about 50% [4]. Such therapy may reduce the prevalence of preterm PE by about 90% but has no significant effect on the risk of term PE [19]. These findings are compatible with the competing risk model for PE proposed in this study. Early administration of low-dose aspirin may improve placentation resulting in a shift to the right in the gestation for PE with a consequent overall reduction in the prevalence of PE which is more marked for early-onset disease. Such hypothesis could be tested by randomized studies in which the outcome measure would not merely be the prevalence of PE but also the distribution of gestational age at delivery for PE.

The performance of screening for PE by maternal characteristics, uterine artery PI and MAP is inversely related to gestational age at delivery. At the fixed false-positive rates of 5 and 10%, the competing risk model detected 80 and 90% of cases of PE requiring delivery before 34 weeks and 36 and 56% of all cases of PE. These results are compatible with those of previous studies, and the performance is likely to improve with the addition of biochemical markers, including pregnancy-associated plasma protein A and placental growth factor [5, 6]. The major advantage of the new compared to our previous models [5, 6] is that gestational age at delivery for PE is treated as a continuous rather than an arbitrary categorical variable. Clinicians and researchers can use the new model to select their own gestational age cut-off to define the high-risk group that could potentially benefit from therapeutic interventions starting from the first trimester of pregnancy [20].

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