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## THE COMPETING RISK APPROACH FOR PREDICTION OF PREECLAMPSIA

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## **CONDENSATION**

The competing risks approach allows estimation of individual patient-specific risks of delivery with preeclampsia before any specified gestational age by combination of maternal factors and biomarkers.

**Short version of article title:** Competing risks model for preeclampsia

## **AJOG at a GLANCE**

### **Why was this study conducted?**

To explain the competing risks approach for prediction of patient-specific risks of delivery with preeclampsia (PE).

### **Key findings**

The competing risks approach is based on a survival-time model for the gestational age at delivery with PE. Every pregnant woman has a personalized distribution of gestational age at delivery with PE, which comes from the application of Bayes theorem to combine a prior distribution, determined from maternal demographic characteristics and medical history, with likelihoods from biomarkers. This approach allows estimation of the individual patient-specific risks of delivery with PE before any specified gestational age by maternal factors and biomarkers obtained either individually or in combination at any stage in pregnancy.

### **What does this add to what is known?**

The competing risks approach is superior to the established method of classifying women as high- or low-risk based on the presence or absence of risk factors from maternal demographic characteristics and medical history.

**ABSTRACT**

The established method of assessing the risk for development of preeclampsia (PE) is to identify risk factors from maternal demographic characteristics and medical history; in the presence of such factors the patient is classified as high-risk and in their absence as low-risk. Although this approach is simple to perform, it has poor performance of predicting PE and does not provide patient-specific risks. This review describes a new approach which allows estimation of patient-specific risks of delivery with PE before any specified gestational age by maternal demographic characteristics and medical history with biomarkers obtained either individually or in combination at any stage in pregnancy. In the competing risks approach every woman has a personalized distribution of gestational age at delivery with PE and whether she develops PE or not before a specified gestational age depends on competition between delivery before or after development of PE. The personalized distribution comes from the application of Bayes theorem to combine a prior distribution, determined from maternal factors, with likelihoods from biomarkers. As new data become available, what were posterior probabilities take the role as the prior and data collected at different stages are combined by repeating the application of Bayes theorem to form a new posterior at each stage allowing for dynamic prediction of PE. The competing risk model can be used for precision medicine and risk stratification at different stages of pregnancy. In the first-trimester, the model has been applied to identify a high-risk group that would benefit from preventative therapeutic interventions. In the second-trimester, the model has been used to stratify the population into high- intermediate- and low-risk groups in need of different intensities of subsequent monitoring thereby minimizing unexpected adverse perinatal events. The competing risks model can also be used in surveillance of women presenting to specialist clinics with signs or symptoms of hypertensive disorders; combination of maternal factors and biomarkers provide patient-specific risks for PE leading to personalized stratification of the intensity of monitoring with risks updated on each visit on the basis of biomarker measurements.

**Key words:** Preeclampsia, Survival model, Bayes theorem, Personalized medicine, Biomarkers, Mean arterial pressure, Uterine artery Doppler, Placental growth factor, Soluble fms-like tyrosine kinase-1.

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## INTRODUCTION

Identification of pregnancies at high-risk of developing preeclampsia (PE) is beneficial because therapeutic interventions in such pregnancies, including prophylactic use of aspirin, closer surveillance and earlier delivery can reduce the incidence of the disease and / or its associated maternal and perinatal complications.<sup>1-3</sup>

This review describes a new approach of assessing the risk for development PE. The competing risks approach is based on a survival-time model which allows estimation of the individual patient-specific risks of delivery with PE before any specified gestational age by a combination of maternal demographic characteristics and medical history with biomarkers obtained either individually or in combination at any stage in pregnancy.

## PREDICTION OF PREECLAMPSIA

### Prediction by risk scoring systems

The established method of assessing the risk for development of PE is to identify risk factors from maternal demographic characteristics and medical history; in the presence of such factors the patient is classified as high-risk and in their absence as low-risk.<sup>4,5</sup> In the UK, according to guidelines by the National Institute for Health and Clinical Excellence (NICE) women should be considered to be at high-risk of developing PE if they have any one high-risk factor or any two moderate-risk factors.<sup>4</sup> The high-risk factors are history of hypertensive disease in previous pregnancy, chronic kidney disease, autoimmune disease, diabetes mellitus or chronic hypertension and the moderate-risk factors are first pregnancy, age  $\geq 40$  years, inter-pregnancy interval  $>10$  years, body mass index (BMI) at first visit of  $\geq 35$  kg/m<sup>2</sup> or family history of PE. A similar approach was recently recommended by The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal–Fetal Medicine; the high-risk factors were identical to those of NICE and the moderate-risk factors were first pregnancy, age  $\geq 35$

years, inter-pregnancy interval >10 years, BMI >30 kg/m<sup>2</sup>, family history of PE, Black race or low socioeconomic status and previous history of low birthweight or adverse pregnancy outcome.<sup>5</sup>

The advantage of these approaches is that they are simple to perform but the disadvantages are first, they have poor performance of predicting PE<sup>6,7</sup> and second, they do not quantify individual patient-specific risks.

### **Prediction by probability models**

Another approach of assessing the risk for development of PE is to use probabilistic models treating PE as a binary outcome. This approach involves different models for early, late or all PE and includes the use of logistic regression models. These models use maternal characteristics and medical history alone or in combination with biomarkers to quantify the individual patient-specific risk for PE, rather than just classifying women into high- and low-risk groups.<sup>8-16</sup> However, they do not allow the flexibility of selecting different gestational age cut-offs for categorizing the severity of PE, they do not take into account the increasing effect size on biomarkers with severity of the disease and they cannot be easily expanded to include additional biomarkers measured at different stages in pregnancy.

### **Prediction by the competing risks approach**

#### Personalized distribution of gestational age at delivery with PE

Whilst other approaches to prediction treat PE as a binary outcome, the competing risk model<sup>6,17-19</sup> treats PE as an event in time. Risks, of delivery with PE, assuming no other cause delivery, are determined from a personalized distribution of gestational age at delivery with PE as illustrated in Figure 1. These are given by the area under the probability density curve, as illustrated in the left panel of Figure 1 or the height of the cumulative risk curve shown on the middle panel of Figure 1. The cumulative risk curve shows the area under the probability density curve as a function of gestational

age at delivery. The panel on the right shows the survival curve which gives the probability of the pregnancy continuing without delivery due to PE. For any given gestation, the cumulative risk and the survival probabilities add to 1.0. It is notable that the distribution in the left panel of Figure 1 attaches probabilities well beyond the gestational ages at which pregnancies are delivered. This reflects the fact that most pregnancies deliver without PE due to other causes, predominantly normal delivery, that compete with PE. The part of the distribution beyond 41<sup>+3</sup> weeks is irrelevant to the calculation of risks.

### Model Specification

For implementation, we adopt the same approach to that taken in risk assessment for aneuploidies,<sup>20</sup> the prediction model is specified in terms of a prior distribution from maternal characteristics and likelihood functions from biomarker measurements. Data from biomarker measurements are used to update the prior distribution using Bayes theorem to produce a posterior distribution. Whilst risk assessment for aneuploidies concerns prediction of an unknown karyotype, the competing risk model for PE concerns the prediction of gestation at delivery with PE.

By chaining Bayes theorem, the posterior distribution can be updated as new information becomes available at different stages in pregnancy. This way of specifying the model therefore provides a framework for dynamic prediction. It also allows the different marker combinations to be used within the same underlying model and new markers to be included without the need for a completely new model.

### Prior model based on maternal factors

The prior model, based on maternal characteristics and medical history, was derived from a study of 120,492 singleton pregnancies undergoing a routine ultrasound examination at 11-13 weeks' gestation.<sup>6</sup> The model was fitted to data on gestational age in weeks at the time of delivery with PE using a parametric survival model<sup>21</sup> in which deliveries from other causes were

treated as censored observations. Various parametric models for the time to delivery with PE were considered and a Gaussian model was chosen on the basis of goodness of fit and simplicity of interpretation. In this model, the mean gestational age at delivery with PE for a reference population [White race, age <35 years, weight 69 kg, height 164 cm, nulliparous, spontaneous conception, no family history of PE and no history of diabetes mellitus, systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS)], is 54.4 weeks. The standard deviation is 6.8833. The risks of delivery with PE at <34, <37 and <42 weeks' gestation are 0.15%, 0.58% and 3.6%, respectively (Figure 1).

Risk of development of PE was increased with advancing maternal age, increasing weight, Black and South Asian racial origin, medical history of chronic hypertension, diabetes mellitus and SLE or APS, conception by *in vitro* fertilization (IVF), family history of PE and personal history of PE (Figure 2); in the latter group the risk was inversely related to the gestational age at delivery of the previous pregnancy.<sup>6</sup> The risk for PE decreased, with consequent shift in the distribution of the gestational age at delivery with PE to the right, with increasing maternal height and in parous women with no previous PE; in the latter group, the maximum protective effect was when the interval between the current and previous pregnancy was 1-2 years, but the beneficial effect persisted for more than 15 years.

### *Twin pregnancies*

In twin pregnancies, the incidence of PE is about 9%, 3-times higher than in singleton pregnancies. However, twins are delivered at an earlier gestational age than 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 than in singletons.<sup>22</sup> We have extended the prior model to include twins by lowering the prior mean for singletons by a twin effect that increases in magnitude with the singleton prior mean.<sup>23-25</sup>

### Biomarkers

Several studies have investigated the value of potential biomarkers for the prediction of PE. Those found to be useful at 11-13 and 19-24 weeks' gestation are MAP, UtA-PI and PLGF, in the early third trimester MAP, UtA-PI, PLGF and serum soluble fms-like tyrosine kinase-1 (sFLT-1) and in late third trimester MAP, PLGF and sFLT-1.<sup>19,26-32</sup>

#### *Standardization: Multiples of the median*

In general, biomarker levels depend on gestational age, weight and race, method of conception, medical conditions and elements from the obstetric history associated with the individual on whom they are measured. They are also affected by the instrument used for measurement. The conventional method of standardization applied in screening is to express the measurements as multiples of the median (MoM) values specific to the gestational age, weight etc. of the individual from which the measurements were taken.<sup>31</sup> For MAP, UtA-PI, PLGF and sFLT-1, MoM values are obtained from regression models of log transformed biomarker measurements.<sup>34-37</sup> They are therefore the antilogarithm of the errors or residuals from the fitted regression model.

#### *Distribution of marker MoM values in unaffected pregnancies*

We illustrate the distributions of MoM values for first trimester markers MAP, UtA-PI and PLGF using data on 35,948 singleton pregnancies including 1058 (2.9%) that developed PE.<sup>19</sup> As shown in Figure 3, for first trimester the distribution of MAP, UtA-PI and PLGF, biomarker MoM values is fitted by a log-Gaussian distribution. Figure 4 shows estimated median MoM values in unaffected pregnancies and in pregnancies that developed PE. For unaffected pregnancies, there is little evidence of any substantive dependency on gestational age, maternal weight, racial origin, smoking status or history of chronic hypertension.

#### *Distribution of marker MoM values in pregnancies that develop PE*

In pregnancies that develop PE, MoM values of MAP, UtA-PI and sFLT-1 tend to be higher and PLGF tends to be lower than in normal pregnancies (Figure 4). The effect sizes increase with increasing severity of the disease, quantified by the gestational age at delivery; Figure 5 shows  $\log_{10}$  MoM values at 11-13 weeks' gestation for pregnancies with PE by the gestational age at delivery with PE. The means of the  $\log_{10}$  transformed MoM values are represented by the broken stick regression lines shown in Figure 5. For early gestations, the means deviate from zero according to a linear regression relationship. As the gestational age at delivery with PE increases, the linear relationship continues until the regression line intersects zero beyond which the mean is zero corresponding to a normal outcome for which the median MoM value is 1.0. The decreasing effect with gestational age at delivery explains to some extent why screening performance is superior for early and preterm PE than for term PE.<sup>19</sup>

In the univariate case, with only one biomarker, for a given MoM value of a biomarker the likelihood of a particular value of gestational age at delivery with PE is given by the height of the Gaussian curve as illustrated for UtA-PI in Figure 6. In the multivariate case, with two or more biomarkers, the likelihood is a multivariate Gaussian density with correlations between log transformed MoM values reflecting the association between markers. In principle, risks can be obtained from any combination of biomarkers measured at different visits. It is important to recognize that attendance at a visit at a particular gestational age makes the likelihood of delivery before that gestation zero so that, even if no measurements are taken, the presence at the visit is informative.

### Posterior distribution

The *posterior* distribution of gestational age at delivery with PE is obtained using Bayes theorem by multiplying the *prior* probability density from maternal factors by the likelihood function from biomarker MoM values (Figure 7). To complete the *posterior* density, the area under the curve is made 1.0 by

multiplying by a normalizing constant. The area defining the risk can be computed for other gestational ages to produce a cumulative distribution of risks that can be used as an individualized risk profile (Figure 7).

Further details and parameter estimates can be found in the Appendix. The risk calculator is available free of charge at fetalmedicine.org

## **CLINICAL IMPLEMENTATION OF THE COMPETING RISKS APPROACH**

The competing risk model can be used for precision medicine and risk stratification at different stages of pregnancy. The objective of screening in the first trimester is identification of a high-risk group that would benefit from preventative therapeutic interventions. The objective of screening in the second and third trimesters is identification of a high-risk group that would benefit from close monitoring for early diagnosis of PE thereby minimizing unexpected adverse perinatal events.

### **First trimester**

In the first-trimester, the competing risks approach utilizing maternal factors, MAP, UtA-PI and PLGF (triple test) was used to identify women at high-risk of developing preterm-PE; at a 10% screen positive rate, 90% of cases of early-PE and 75% of cases with preterm-PE were predicted in both a training and two validation datasets.<sup>7,19,38-40</sup> It was then demonstrated through a randomized trial that in women at high-risk of PE the administration of aspirin (150 mg / day from 11-4 until 36 weeks' gestation) reduces the risk of early-PE and preterm-PE by about 90% and 60%, respectively and length of stay in neonatal intensive care by about 70%.<sup>1,41</sup>

Recording maternal characteristics and medical history, measurement of blood pressure and hospital attendance at 11-13 weeks' gestation for an ultrasound scan are an integral part of routine antenatal care in many countries. In contrast, measurements of serum PLGF and UtA-PI are not part of routine care and would be associated with an additional cost. We examined

the possibility of carrying out first-stage screening in the whole population by some of the components of the triple test and proceeding to second-stage screening by the triple test only for a subgroup of the population selected on the basis of the risk derived from first-stage screening (Figure 8).<sup>42,43</sup> On the basis of the results of first-stage screening the population was divided into a low-risk, screen negative group, and a higher-risk group in need of further testing. After such testing the patients were again classified as screen-negative and screen-positive. We found that a similar screen positive rate and detection rate can be achieved with a two-stage strategy of screening, at substantially lower costs, than with carrying out screening with all biomarkers in the whole population.

### **Second or third trimester**

The competing risks approach can be used for stratification into high-, intermediate- and low-risk management groups.<sup>44-48</sup> For example, women attending for a routine hospital visit at 20 weeks' gestation, were allocated to the high-risk group if their risk for PE at <32 weeks was above a high-risk threshold and they were allocated to the low-risk group if their risk for PE at <36 weeks was below a low-risk threshold (Figure 9).<sup>45</sup> The high-risk group, which should be very small (about 1% of the total population) and contain almost all cases of PE at <32 weeks, would require close monitoring for high blood pressure, proteinuria and hepatic, renal and hematological disturbance at 24-31 weeks. The intermediate-risk group together with the undelivered pregnancies from the high-risk group (about 10% of the total population), which would contain about 90% of PE at 32-35 weeks would have reassessment of risk at 32 weeks' gestation to identify those that would require close monitoring at 32-35 weeks. The low-risk group (about 90% of the total population), can be reassured that they are unlikely to develop PE at <36 weeks' gestation. However, all women that remain pregnant will require reassessment of risk at 36 weeks because the performance of screening at 20 weeks' gestation for PE at  $\geq 36$  weeks is poor.

### **Surveillance of high-risk pregnancies**

Development of PE is preceded by decrease in the maternal serum concentration of the angiogenic PLGF and increase in the level of antiangiogenic sFLT-1.<sup>49-59</sup> In women presenting to specialist clinics with signs or symptoms of hypertensive disorders use of cut-offs on the concentration of PLGF or the ratio of the concentrations of sFLT-1 and PLGF have been used to predict the development of PE within the subsequent 1-4 weeks.<sup>53,54,57,58</sup> This approach has the advantage of simplicity in clinical implementation. However, it does not take into account the *prior* risk of the individual patient in the study population, or the measurement of blood pressure at presentation, which is a prerequisite in the diagnosis of PE, and ignores the effects of maternal characteristics and gestational age on the measured serum concentrations.

An alternative approach for the prediction of PE at predefined intervals from assessment is use of the competing risks model to derive patient-specific risks for PE by various combinations of maternal factors with MoM values of biomarkers, including PLGF, sFLT-1 and MAP.<sup>46-48,56,59,60</sup> In a large prospective observational study we found that the performance of such approach is superior to that of PLGF alone or the sFLT-1 / PLGF ratio.<sup>60</sup> The competing risks model provides a personalized risk for delivery with PE that could lead to personalized stratification of the intensity of monitoring with risks updated on each visit on the basis of biomarker measurements.

## VALIDATION

The competing risk model for use in first trimester screening has been prospectively validated in two studies.<sup>40</sup> In these studies risks were produced, blinded to outcome using a pre-specified algorithm in 25,226 pregnancies, including 712 with PE of which 201 were delivered before 37 weeks and 84 were delivered before 34 weeks. Performance was assessed by first, the ability of the model to discriminate between the PE and no-PE groups and second, calibration, which assesses agreement between predicted risks and outcomes; for a well-calibrated model, among those women with a risk of 1 in

n, the incidence should be 1 in n. Performance in the validation data sets were consistent with those from the training data set<sup>19</sup> (Figure 10) and there was good agreement between predicted risk and observed incidence (Figure 11).

## CONCLUSIONS

The defining features of our approach to prediction of PE are the use of a time to event model for the gestational age at delivery with PE and the application of Bayes theorem to update the personalized distribution of gestational age at delivery with PE. Treating delivery with PE as an event in time allows prediction of PE before different gestational ages to be accommodated into the same model, it is a natural way of allowing for deliveries due to causes other than PE, and it allows the effect of disease severity, as reflected by the gestational age of delivery, to be included in the model. The application of Bayes theorem to combine prior probabilities with data to produce posterior probabilities is ubiquitous and operationally easy to implement. As new data become available, what were posterior probabilities take the role as the prior and data collected at different stages are combined by repeating the application of Bayes theorem to form a new posterior at each stage. This chaining of Bayes theorem can be applied for dynamic prediction of PE.

In addition to PE there are many conditions in pregnancy that require risk assessment and clinical management is considerably facilitated if the risk can be quantified. Such risks can vary considerably between individuals and different parameters may be used at different times in pregnancy to evaluate them. Therefore, a general method that can deal with all these situations on an individualized basis is needed. The same competing risks approach can be applied to fetal growth restriction, spontaneous preterm birth, gestational diabetes and other pregnancy complications so that prediction before different gestational ages can be accommodated into the same model.

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**FIGURE LEGENDS**

**Figure 1.** Personalized distribution of gestational age of delivery with PE. The risk of delivery with PE <32, <36 and <40 weeks' gestation is shown in the shaded area under the probability density (left) and the height of the cumulative distribution (right).

**Figure 2.** Prior distribution of gestational age of delivery with PE in a low-risk and a high-risk pregnancy and the effect of maternal factors in shifting the distribution to the left or right.

**Figure 3.** Distributions of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PLGF) multiple of the median ( $\log_{10}$  MoM scale) values measured at 11-13 weeks' gestation in unaffected singleton pregnancies.<sup>19</sup>

**Figure 4.** Medians and 95% confidence interval of mean arterial pressure, uterine artery pulsatility index and serum placental growth factor multiple of the median (MoM) values measured at 11-13 weeks' gestation in pregnancies that developed preeclampsia (solid circles and lines) and those that did not (open circles and interrupted lines) according to maternal characteristics.<sup>19</sup> The dark grey band and light grey bands correspond to  $\pm 0.1$  and  $\pm 0.2$  standard deviations respectively ( $\log_{10}$  MoM scale). Effects outside  $\pm 0.2$  standard deviations are considered substantial.

**Figure 5.** Scatter diagram and broken stick regression line for the relationship between mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PLGF) multiple of the median ( $\log_{10}$  MoM) measured at 11-13 weeks' gestation and gestational age at delivery in pregnancies with preeclampsia.

**Figure 6.** Distribution of  $\log_{10}$  MoM values of uterine artery pulsatility index in pregnancies with preeclampsia (PE) according to gestational age at delivery (grey dots) and regression line of this relationship. The black Gaussian curves show the distribution of  $\log_{10}$  MoM UtA-PI conditionally on gestational age at delivery with PE at 26, 32 and 38 weeks. The grey histograms show the distribution of values in pregnancies without PE. The broken horizontal line corresponds to a  $\log_{10}$  MoM of 0.3 (MoM = 2.0). Likelihoods of PE at 26, 32 and 38 weeks given this measurement are the full horizontal lines under the Gaussian curves. Relative to pregnancies without PE, the likelihood ratio decreases with gestational age at delivery with PE for as shown by the decreasing line lengths. The figure on the right shows the likelihood ratio function of gestational age at delivery with PE relative to no PE for an observed value 0.3 ( $\log_{10}$  MoM).

**Figure 7.** Application of Bayes theorem in a case with uterine artery pulsatility index (UtA-PI) MoM of 2.0 ( $\log_{10}$  MoM = 0.3) modifying a prior distribution of gestational age at delivery with PE. The prior risk of delivery with PE <37 weeks is 0.05 or 1 in 20. This is increased to 0.2 or 1 in 5 with the measurement.

**Figure 8.** Two stage screening for preterm preeclampsia at 11-13 weeks' gestation.

**Figure 9.** Stratification of pregnancies into high-, intermediate- and low-risk management groups based on the estimated risk for preeclampsia at 19-24 weeks' gestation.

**Figure 10.** Detection rate for preterm preeclampsia, at fixed screen positive rate of 10%, in the three databases and the combined results.<sup>40</sup>

**Figure 11.** Calibration plots. The diagonal gray line is the line of perfect agreement. The overall mean risk is shown by the vertical interrupted line and the overall incidence by the horizontal interrupted line. The numbers in red are the cases that developed preeclampsia and those in black are the cases with a given predicted risk.  
<sup>40</sup>

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## APPENDIX

### Competing risk approach for prediction of PE: algorithm specification

#### Calculation of prior mean gestational age at delivery with PE

##### Inputs

<b>age</b>	Maternal age at estimated date of delivery (years)
<b>wt</b>	Maternal weight at the first trimester visit (kg)
<b>ht</b>	Maternal height (cm)
<b>race</b>	Maternal racial origin (White, Black, South Asian, East Asian)
<b>prev</b>	Previous obstetric history (nullip, parous with or without previous PE)
<b>interval</b>	Previous pregnancy interval (years)
<b>last.ga</b>	Gestational age at delivery of previous pregnancy (weeks)
<b>f.hist</b>	Family history of PE (mother)
<b>conception</b>	Method of conception (natural, IVF, ovulation drugs)
<b>ch</b>	History of chronic hypertension
<b>db</b>	History of diabetes mellitus
<b>sle</b>	History of systemic lupus erythematosus or antiphospholipid syndrome
<b>twins</b>	Singleton, twins dichorionic or monochorionic

##### Parameters

See tables 1 and 2

##### **Truncation limits**

Age	upper and lower truncation
Weight	upper and lower truncation
Height	upper and lower truncation
Interval	upper and lower truncation
Previous GA	upper and lower truncation

##### **Regression coefficients**

###### For all pregnancies:

Constant  
 Age in years -35 if age >35  
 Height in cm - 164  
 Black racial origin  
 South Asian racial origin  
 Chronic hypertension  
 Systemic lupus erythematosus or antiphospholipid syndrome  
 Conception by in vitro fertilization

Parous with previous PE: Intercept  
 Parous with previous PE: (Previous ga (weeks) -24)<sup>2</sup>  
 Parous with no previous PE: intercept  
 Parous with no previous PE: interval<sup>-1</sup>  
 Parous with no previous PE: interval<sup>-0.5</sup>  
 Parous with no previous PE: (Previous ga (weeks) -24)<sup>2</sup>

For pregnancies without chronic hypertension:

(Weight in kg - 69)\*(not CH)  
 (Family history of PE) \* (not CH)  
 (Diabetes mellitus (type 1 or 2))\*(not CH)

For twin pregnancies:

Twin factor  
 Dichorionic twin (DC.coeff)  
 Monochorionic twin (MC.coeff)

**Computation**

wt = max(wt, Weight truncation lower)  
 wt = min(wt, Weight truncation upper)  
 ht = max(ht, Height truncation lower)  
 ht = min(ht, Height truncation upper)  
 ma = max(ma, Age truncation lower)  
 ma = min(ma, Age truncation upper)  
 interval = max(interval, Interval truncation lower)  
 interval = min(interval, Interval truncation upper)  
 last.ga = max(last.ga, Last GA truncation lower)  
 last.ga = min(last.ga, Last GA truncation upper)

For singleton pregnancies (Table 1):

prior.mean.pe = sum(coeff\*value)  
 prior.sd.pe = sd\_singleton

For twin pregnancies (Table 2):

prior.mean.pe = sum(coeff\*value)  
 prior.sd.pe = sd\_twin

## Risk calculation

### Inputs

#### MoM values

Markers (length=p) found to be useful (\*)

Marker	Visit			
	12 weeks	22 weeks	32 weeks	36 weeks
MAP	*	*	*	*
UtA-PI	*	*		
PIGF	*	*	*	*
sFLT-1			*	*

Where each visit is defined by the below gestational age (GA) limits

Visit	Lower GA limit (days)	Upper GA limit (days)
12 weeks	77	99
22 weeks	133	174
32 weeks	210	244
36 weeks	245	265

#### Prior mean and standard deviation

prior.mean.pe  
prior.sd.pe

#### Likelihood parameters

See tables 3-5

#### Regression coefficients for gestation at delivery g with PE in weeks

b0 vector ( $p \times 1$ ) of constant coefficients for specified markers  
b1 vector ( $p \times 1$ ) of coefficients of gestation for specified markers

#### Covariance matrix

sigma.pe covariance matrix ( $p \times p$ ) for PE outcome for the specified markers

(Note: in the current configuration sigma.pe is also used for normals)

#### Truncation limits

lower vector ( $p \times 1$ ) of lower truncation limits for the specified marker  $\log_{10}$  MoM values  
upper vector ( $p \times 1$ ) of upper truncation limits for the specified marker  $\log_{10}$  MoM values

**Computation****Mean vector**

pe.mean(t) vector ( $p \times 1$ ) of mean  $\log_{10}$  MoM values for pregnancies delivered with PE at t weeks

For each marker the mean  $\log_{10}$  MoM for gestational age at delivery t is given by

$$b_0 + b_1 \times t \quad \begin{array}{l} \text{if } t < (-b_0/b_1) \\ 0 \quad \text{else} \end{array}$$

**Posterior probability density**

$$h(t) = \text{dmvnorm}(x, \text{mean}=\text{pe.mean}(t), \text{sigma}=\text{sigma.pe}) * \text{dnorm}(t, \text{mean}=\text{prior.mean}, \text{sd}=\text{prior.sd.pe})$$

In the above  $\text{dmvnorm}(x, \text{mean}=\text{pe.mean}(t), \text{sigma}=\text{sigma.pe})$  is a multivariate Gaussian density with

x  $\log_{10}(\text{MoM}^T)$  vector ( $p \times 1$ ) of truncated  $\log_{10}$  MoM values used in the risk calculation

pe.mean Mean vector ( $p \times 1$ ) for the distribution of x (functions of t)

sigma Covariance matrix ( $p \times p$ ) for the distribution of x

$\text{dnorm}(t, \text{mean}=\text{prior.mean}, \text{sd}=\text{prior.sd.pe})$  is a univariate normal density with

t Gestation in weeks

prior.mean Mean of the prior distribution of t

prior.sd.pe Standard deviation of the prior distribution of t

**Posterior risks of PE requiring delivery gestation g**

If  $\text{integ}(h(t), a, b)$  denotes the integral of  $h(t)$  over the interval (a,b) then from the current gestation, g.current, the risk of preeclampsia requiring delivery before gestation g (weeks), assuming no other cause delivery, is given by

$$r = \text{integ}(h(t), g.\text{current}, g) / \text{integ}(h(t), g.\text{current}, \infty)$$

where  $g.\text{current} = \text{maximum}(24, \text{current gestational age in weeks})$

### **Prior risks of PE requiring delivery gestation g**

To compute prior risks, omit the `dmvnorm` factor in the above and use  
 $h(t) = \text{dnorm}(t, \text{mean}=\text{prior.mean}, \text{sd}=\text{prior.sd.pe})$

### **Result**

r        the risk of PE requiring delivery before g weeks assuming no other cause delivery

### **Values**

The current parameter estimates used in the algorithm are given at [fetalmedicine.com](http://fetalmedicine.com)

### **Disclaimer**

This specification and accompanying information is provided 'as is' with no warranty of any kind. In addition, the Fetal Medicine Foundation accepts no liability for any use of the data, including but not limited to such use as part of the provision of clinical or diagnostic services.

**Table 1:** Preeclampsia prior model: Regression coefficients, standard deviations and truncation limits

<b>Regression coefficients</b>	<b>Value</b>
Constant	54.3637
Age in years -35 if age >35; 0 if age <35	-0.206886
Height in cm - 164	0.11711
Black racial origin	-2.6786
South Asian racial origin	-1.129
Chronic hypertension	-7.2897
Systemic lupus erythematosus or antiphospholipid syndrome	-3.0519
Conception by in vitro fertilization	-1.6327
Parous with PE in previous pregnancy	-8.1667
Parous with PE in previous pregnancy: (Previous ga (weeks)-24) <sup>2</sup>	0.0271988
Parous with no previous PE: intercept	-4.335
Parous with no previous PE: interval <sup>-1</sup>	-4.1513765
Parous with no previous PE: interval <sup>0.5</sup>	9.21473572
Parous with no previous PE: (Previous ga (weeks)-24) <sup>2</sup>	0.01549673
(Weight in kg - 69)*(not CH)	-0.0694096
(Family history of PE) * (not CH)	-1.7154
(Diabetes mellitus (type 1 or 2))*(not CH)	-3.3899
<b>Singleton pregnancy SD</b>	6.8833
<b>Truncation limits</b>	<b>Lower, Upper</b>
Age (years)	12, 55
Weight (Kg)	34, 190
Height (cm)	127, 198
Interpregnancy interval (years)	0.25, 15
Gestation at delivery of last pregnancy (weeks)	24, 42

**Table 2:** Preeclampsia prior model in twin pregnancies.

<b>Regression coefficients</b>	<b>Value</b>
Singleton mean ( Obtained from Table 1)	0.492
Dichorionic twins	17.115
Monochorionic twins	15.768
<b>Twin pregnancy SD</b>	4.6019

**Table 3:** Regression coefficients for gestation at delivery g with PE in weeks

Term	b0	b1
MAP at 12 weeks	0.088997	-0.0016711
MAP at 22 weeks	0.13131	-0.0028424
MAP at 32 weeks	0.38691	-0.0091384
MAP at 36 weeks	0.42855	-0.0098879
UtA-PI at 12 weeks	0.5861	-0.014233
UtA-PI at 22 weeks	0.81659	-0.019526
PLGF at 12 weeks	-0.92352	0.021584
PLGF at 22 weeks	-3.00329	0.078571
PLGF at 32 weeks	-4.17	0.09794
PLGF at 36 weeks	-2.53271	0.052863
sFLT-1 at 32 weeks	3.27941	-0.078654
sFLT-1 at 36 weeks	2.51128	-0.055499

**Table 4:** Truncation limits for  $\log_{10}$  MoM values

Term	lower	upper
MAP at 12 weeks	-0.1224076	0.12240759
MAP at 22 weeks	-0.1200055	0.12000551
MAP at 32 weeks	-0.1149381	0.1149381
MAP at 36 weeks	-0.1149381	0.1149381
UtA-PI at 12 weeks	-0.4216152	0.42161519
UtA-PI at 22 weeks	-0.3792332	0.37923321
PLGF at 12 weeks	-0.5655099	0.56550992
PLGF at 22 weeks	-0.6720572	0.67205718
PLGF at 32 weeks	-1.0851499	1.08514991
PLGF at 36 weeks	-1.0851499	1.08514991
sFLT-1 at 32 weeks	-0.6287209	0.62872094
sFLT-1 at 36 weeks	-0.6287209	0.62872094

**Table 5: Covariance matrix.**

Term	MAP 12 w	MAP 22 w	MAP 32 w	MAP 36 w	UtA-PI 12 w	UtA-PI 22 w	PLGF 22 w	PLGF 22 w	PLGF 32 w	PLGF 36 w	sFLT-1 32 w	sFLT-1 36 w
MAP 12 w	0.00141396	0.0005958	0.00045935	0.00036618	-0.0002726	-8.81E-05	-0.0001907	-0.0002597	-0.0006436	6.86E-05	0.00028429	0.00031047
MAP 22 w	0.0005958	0.00132521	0.00049627	0.00036157	-0.0001716	-0.0001697	-0.0001543	-0.0003954	-0.0006493	-6.59E-05	0.00035188	0.00045598
MAP 32 w	0.00045935	0.00049627	0.00119901	0.00050848	-9.39E-05	1.18E-06	-0.0003921	-0.0004258	-0.0016781	-0.0019469	0.00052444	0.00118262
MAP 36 w	0.00036618	0.00036157	0.00050848	0.00116992	-0.0001104	0.00013911	-0.0002124	0.00186098	0.01045051	-0.0025113	0.00191923	0.00125473
UtA-PI 12 w	-0.0002726	-0.0001716	-9.39E-05	-0.0001104	0.01630906	0.00690169	-0.0034539	-0.0009843	-0.0031131	-0.0042846	-0.000385	0.00017831
UtA-PI 22 w	-8.81E-05	-0.0001697	1.18E-06	0.00013911	0.00690169	0.01293826	-0.0035973	-0.0017036	-0.0053382	-0.0069074	-0.0003231	0.00125763
PLGF 12 w	-0.0001907	-0.0001543	-0.0003921	-0.0002124	-0.0034539	-0.0035973	0.03147225	0.01450618	0.01939823	0.01893804	-0.0019393	-0.0028661
PLGF 22 w	-0.0002597	-0.0003954	-0.0004258	0.00186098	-0.0009843	-0.0017036	0.01450618	0.04040798	0.03481532	0.01636539	0.00220321	0.00768529
PLGF 32 w	-0.0006436	-0.0006493	-0.0016781	0.01045051	-0.0031131	-0.0053382	0.01939823	0.03481532	0.09958536	0.03254317	-0.0094197	-0.0253335
PLGF 36 w	6.86E-05	-6.59E-05	-0.0019469	-0.0025113	-0.0042846	-0.0069074	0.01893804	0.01636539	0.03254317	0.11924898	0.06012917	-0.0291357
sFLT-1 32 w	0.00028429	0.00035188	0.00052444	0.00191923	-0.000385	-0.0003231	-0.0019393	0.00220321	-0.0094197	0.06012917	0.03760481	0.00681
sFLT-1 36 w	0.00031047	0.00045598	0.00118262	0.00125473	0.00017831	0.00125763	-0.0028661	0.00768529	-0.0253335	-0.0291357	0.00681	0.04192345

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