

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

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**Short title:** Screening for preeclampsia in twins

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## ABSTRACT

**Objective:** A survival-time regression model for the gestational age at delivery with preeclampsia (PE) in singleton pregnancies using maternal demographic characteristics and medical history was previously reported. The objective of this paper is to extend this model for dichorionic (DC) and monochorionic (MC) twin pregnancies.

**Methods:** The study population included 1,789 DC and 430 MC twin pregnancies and 93,297 singleton pregnancies. A survival-time model for the gestational age at delivery with PE was developed from variables of maternal characteristics and history. The risk of PE with delivery at <37 and <42 weeks' gestation in twin pregnancies was determined and compared to singleton pregnancies.

**Results:** In singleton pregnancies comprising women of Caucasian racial origin, weight of 69 kg at 12 weeks' gestation, height of 164 cm, nulliparous, with spontaneous conception, no family history of PE and no history of diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, the mean of the Gaussian distribution of gestational age at delivery with PE was 55 weeks. In DC twins with PE the mean gestational age at delivery was shifted to the left by 8.2 (95% CI 7.2-9.1) weeks and in MC twins it was shifted to the left by 10.0 (95% CI 8.5-11.4) weeks. The risk of delivery with PE occurring at or before a

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specified gestational age is given by the area under the fitted distribution curve and for a reference population with the above characteristics the estimated risk of PE at <37 weeks' gestation, assuming no other cause of delivery, was 0.6% for singletons, 9.0% for DC twins and 14.2% for MC twins; the respective values for PE at <42 weeks were 3.6%, 27.0% and 36.5%.

Conclusions: A model based on maternal characteristics and history has been developed for estimation of patient-specific risks for PE in DC and MC twin pregnancies. Such estimation of the *a priori* risk for PE 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:** First trimester screening, Preeclampsia, Twin pregnancy, Pyramid of pregnancy care, Survival model, Bayes theorem

## Introduction

In singleton pregnancies, effective screening for preeclampsia (PE) can be achieved with the use of 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.<sup>1-5</sup> A fundamental component of this approach is adoption of a survival-time model for the gestational age at delivery with PE. This approach assumes that if the pregnancy was to continue indefinitely all women would develop PE and whether they do so or not before a specified gestational age depends on competition between delivery before or after development of PE. In this model the mean gestational age for delivery with PE for a reference population (Caucasian racial origin, weight 69 kg, height 164 cm, nulliparous, spontaneous conception, no family history of PE and no history of diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome) is 55 weeks with estimated standard deviation of 6.88 weeks (Figure 1).<sup>3</sup> The effects of variables from maternal characteristics and history and biomarkers is to modify the mean of the distribution of gestational age at delivery with PE so that 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 development of PE. In high-risk pregnancies the distribution is shifted to the left and the smaller the mean gestational age the higher is the risk for PE. Variables from maternal factors which shift the Gaussian distribution of the gestational age at delivery with PE to the left, include 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 PE and conception by *in vitro* fertilization.<sup>1,3</sup> The risk for PE decreases with increasing maternal height and in parous women with no previous PE; in the later, the protective effect, which is inversely related to the inter-pregnancy interval, persists beyond 15 years.<sup>1,3</sup>

In twin pregnancies, the rate of PE is about 10%,<sup>6-15</sup> which is 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 underestimate the relative risk of preterm-PE in twins which is 9-times higher; the rates of both total and preterm-PE for dichorionic (DC) and monozygotic (MC) twins are similar.<sup>16</sup>

The objective of this study is to modify the survival-time model for the gestational age at delivery with PE, based on maternal demographic characteristics and medical history, which was developed from the study of singleton pregnancies to include adjustments for DC and MC twin pregnancies.

## 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 at King's College Hospital and Medway Maritime Hospital, UK. In this visit, at 11<sup>+0</sup> –13<sup>+6</sup> weeks' gestation, we record maternal characteristics and medical history and perform combined screening for aneuploidies.<sup>17</sup> Gestational age was determined by the measurement of fetal crown-rump length<sup>18</sup> of the larger twin. Chorionicity was determined by examining the inter-twin membrane at its junction with the placenta.<sup>19</sup> The women were screened between January 2006 and December 2015 and gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

The inclusion criteria for this study on screening for PE were twin pregnancy undergoing first-trimester combined screening for aneuploidy and subsequently delivering a phenotypically normal live birth or stillbirth at  $\geq 24$  weeks' gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities, those ending in termination, miscarriage or fetal death before 24 weeks and those with an interval of more than three days between death of one fetus and live birth of the second twin. For comparison of data from twin pregnancies we obtained results from 93,297 singleton pregnancies that were examined in the same hospitals as the twins and were included in a previous publication.<sup>3</sup>

### Patient characteristics

Patient characteristics including maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous or assisted conception requiring *in vitro* fertilization or the use of ovulation drugs), cigarette smoking during pregnancy, history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, family history of PE in the mother of the patient and obstetric history including parity (parous or nulliparous if no previous pregnancies at  $\geq 24$  weeks), previous pregnancy with PE, gestational age at delivery and birth weight of the neonate in the last pregnancy and interval in years between 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 pre-existing or pregnancy associated hypertension were examined to determine if the condition was PE as defined by the International Society for the Study of Hypertension in Pregnancy.<sup>20</sup> The systolic blood pressure should be  $\geq 140$  mm Hg and/or the diastolic blood pressure should be  $\geq 90$  mmHg on at least two occasions four hours apart developing after 20 weeks of gestation in previously normotensive women. There should also be proteinuria of  $\geq 300$  mg in 24 hours 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 the presence of hypertension at the booking visit before 20 weeks' gestation in the absence of trophoblastic disease).

### Statistical analyses

The previously developed model of a Gaussian distribution of gestational age in weeks at the time of delivery with PE based on maternal factors,<sup>3</sup> was applied to DC and MC twin pregnancies. In this model deliveries from causes other than PE were treated as censored observations. Established risk factors, including maternal age in years, weight in kg, height in cm, racial origin, inter-pregnancy interval in years, delivery in weeks of previous pregnancy with and without PE, method of conception, chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome, DC and MC twins were included as covariates. The performance of screening for delivery with PE at <32, <37 and <42 weeks' gestation in twin pregnancies was determined and compared to singleton pregnancies; the number of affected cases was too small to provide separate results for DC and MC twins.

The statistical software package R was used for data analyses.<sup>21</sup> The survival package was used for model fitting.<sup>22</sup>

## Results

The study population included 1,789 DC twin pregnancies, 430 MC twin pregnancies and 93,297 singleton pregnancies. Maternal and pregnancy characteristics are summarized in Table 1. The rate of PE was 2.3% (2,162 of 93,297) in singletons, 8.1% (145 of 1,789) in DC twins and 6.0% (26 of 430) in MC twins.

The effect of maternal and pregnancy characteristics (estimates and 95% confidence intervals) on mean time to delivery with PE is shown in Figure 2. The effects are relative to a reference population comprising women of Caucasian racial origin, weight of 69 kg at 12 weeks' gestation, height of 164 cm, nulliparous, with spontaneous conception, no family history of PE and no history of diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome. Compared to singletons, with the same maternal characteristics, DC twins delivered with PE on average 8.2 (95% CI 7.2-9.1) weeks earlier and MC twins delivered with PE on average 10.0 (95% CI 8.5-11.4) weeks earlier. The difference between the effects of DC and MC twins was significant ( $P=0.038$ ).

The Gaussian distribution of gestational age at delivery with PE in singletons, DC twins and MC twins is illustrated in Figure 3; the mean gestation was 55 weeks for singletons, 47 weeks for DC twins and 45 for MC twins. The risk of delivery with PE occurring at or before a specified gestational age is given by the area under the distribution curve and for a reference population with the above characteristics the estimated risk of PE at <32 weeks' gestation, assuming no other cause for delivery, was 0.06% for singletons, 1.9% for DC twins and 3.6% for MC twins; the respective values for PE at <37 weeks were 0.6%, 9.0% and 14.2% and for PE at <42 weeks were 3.6%, 27.0% and 36.5%.

Receiver operating characteristic (ROC) curves for prediction of all PE and PE with delivery at <32 and <37 weeks' gestation for singleton and twin pregnancies are shown in Figure 4. Table 2 provides the screen positive rate (SPR) and detection rate (DR) in screening of a mixed population of singleton and twin pregnancies at risk cut-offs of 1 in 10, 1 in 50 and 1 in 75 for delivery with PE at <37 weeks' gestation. At all risk cut-offs the SPR is much higher for twin than singleton pregnancies and at risk cut-off of 1 in 75 virtually all twins are screen positive.

## Discussion

### Principal findings of this study

In twin pregnancies the risk of PE is substantially higher than in singleton pregnancies and this is reflected in the distribution of gestational age of delivery with PE. In a population of women of Caucasian racial origin, weight of 69 kg, height of 164 cm, nulliparous, with spontaneous conception, no family history of PE and no history of diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, the mean gestational age of delivery with PE is 55 weeks. In DC and MC twin pregnancies with the same characteristics as singleton pregnancies the distribution of gestational age of delivery with PE is shifted to the left by 8 and 10 weeks, respectively. The estimated risk of PE at <37 weeks' gestation was 0.6% for singletons, 9.0% for DC twins and 14.2% for MC twins.

In screening of a mixed population of singleton and twin pregnancies for PE at <37 weeks' gestation at risk cut-off of 1 in 75, when the SPR for singleton pregnancies was 13%, virtually all twins were screen positive. This is not surprising because in any screening programme certain maternal characteristics may be associated with such high-risk that irrespective of how favourable are all other factors the *posterior* risk is above a cut-off used for stratification of the population into high- and low-risk groups. For example, in the context of first-trimester combined screening for trisomy 21 the *prior* risk increases exponentially with maternal age and for a woman aged 50 years the *posterior* risk will remain above the screen positive cut-off irrespective of how favourable are the measurements of fetal nuchal translucency thickness and serum free  $\beta$ -hCG and PAPP-A.

### Strengths and limitations

The major strengths of the study are firstly, prospective examination of twin and singleton pregnancies in which specific questions were asked to identify known factors associated with PE, secondly, the use of multivariable survival analysis to identify the factors and define their contribution in the prediction of PE and thirdly, the development of a survival-time model which allows estimation of individual patient-specific risks of PE requiring delivery before any specified gestation.

A limitation of the study is that the number of twin pregnancies examined relative to that of singleton pregnancies is inevitably small. Another limitation is that the performance of screening by a model derived and tested using the same dataset is overestimated. External validation on independent data from different sources is required.

### Comparison with previous studies

In previous studies we established a competing risk model for the prediction of PE in singleton pregnancies based on maternal factors and expanded to include biomarkers.<sup>1-5</sup> In this study the maternal factor based model has been extended to include twin pregnancies. Previous studies in twin pregnancies merely reported that the rate of PE is about 3-times higher than in singleton pregnancies.<sup>6-15</sup>

Clinical implications of the study

The proposed competing risk model allows estimation of patient-specific *a priori* risk for PE in twins, which 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. Bayes theorem also provides a framework for updating the risk at different stages during pregnancy forming the basis for stratified surveillance policies as has been achieved for singleton pregnancies.<sup>23-25</sup>



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### Figure legends

**Figure 1:** Gestational age distribution at delivery with PE. In pregnancies that are at low-risk for PE the distribution is shifted to the right and in most cases 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); the risk of PE at <42 weeks' gestation is 1% for the low-risk group and 30% for the high-risk group.

**Figure 2:** Effect of maternal and pregnancy characteristics (estimates and 95% confidence intervals) on mean time to delivery with PE. The effects are relative to the reference levels of singleton pregnancy, Caucasian racial origin, weight 69 kg, height 164 cm, nulliparous, spontaneous conception, no family history of PE and no history of diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome. For the parous without PE the effect is for the interval of one year from the birth of an unaffected pregnancy at 41 weeks' gestation and for parous with PE the effect is for a previous affected pregnancy delivering with PE at 34 weeks' gestation. \* these terms apply to pregnancies without chronic hypertension.

**Figure 3:** Distribution of gestational age at delivery with preeclampsia for a population of singleton, DC twin and MC twin pregnancies with reference characteristics of Caucasian racial origin, weight 69 kg, height 164 cm nulliparous, spontaneous conception, no family history of PE and no history of diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome.

**Figure 4:** Receiver operating characteristic (ROC) curves for prediction of PE requiring delivery at <32 weeks' gestation (left), at <37 weeks (middle) and all PE (right) in singleton (black lines) and twin (red lines) pregnancies according to the competing risks model.

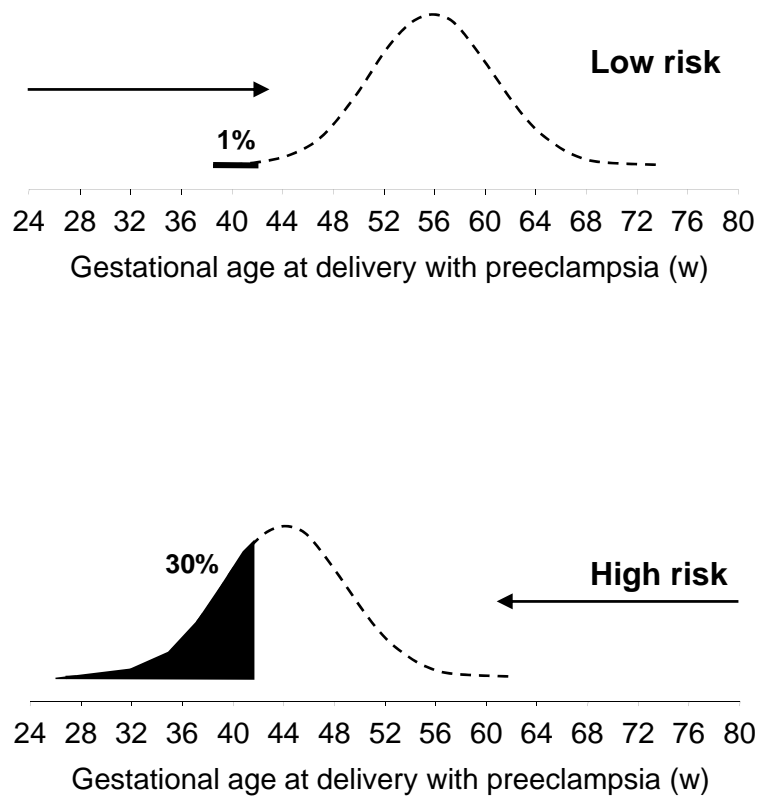
**Table 1.** Maternal and pregnancy characteristics in the screening population.

Variable	Singleton pregnancies		Dichorionic twin pregnancies		Monochorionic twin pregnancies	
	All (n=93,297)	PE (n=2,162)	All (n=1,789)	PE (n=145)	All (n=430)	PE (n=26)
Maternal age in years	31.0 (26.4-35.0)	31.1 (26.4-35.6)	33.2 (29.1-36.5)	34.0 (30.3-37.3)	31.5 (27.0-35.8)	31.0 (28.0-36.6)
Maternal weight in kg	66.5 (59.0-77.0)	72.65 (63-86.5)	69.0 (60.5-79.0)	72.0 (63.1-84.0)	65.3 (58.7-77.0)	71.9 (60.0-84.0)
Maternal height in cm	164 (160-169)	163 (159-168)	165 (161-170)	165 (160-168)	164 (160-168)	163 (159-169)
Gestational age in weeks	12.7 (12.3-13.1)	12.7 (12.3-13.1)	12.9 (12.5-13.3)	12.8 (12.4-13.2)	12.8 (12.5-13.3)	13.0 (12.5-13.5)
Racial origin						
Caucasian	70,380 (75.4)	1,273 (58.9)	1,390 (77.7)	104 (71.7)	320 (74.4)	20 (76.9)
Afro-Caribbean	15,211 (16.3)	716 (33.1)	287 (16.0)	33 (22.8)	66 (15.3)	4 (15.4)
South Asian	3761 (4)	97 (4.5)	57 (3.2)	4 (2.8)	23 (5.3)	2 (7.7)
East Asian	1,790 (1.9)	31 (1.4)	22 (1.2)	3 (2.1)	11 (2.6)	0
Mixed	2,155 (2.3)	45 (2.1)	33 (1.8)	1 (0.7)	10 (2.3)	0
Medical history						
Chronic hypertension	1,203 (1.3)	245 (11.3)	27 (1.5)	13 (9.0)	3 (0.7)	0
Diabetes mellitus	799 (0.9)	46 (2.1)	18 (1.0)	4 (2.8)	5 (1.2)	0
SLE/APS	148 (0.2)	12 (0.6)	4 (0.2)	1 (0.7)	0	0
Cigarette smokers	10,087 (10.8)	166 (7.7)	160 (8.9)	8 (5.5)	43 (10.0)	0
Family history of PE	4,047 (4.3)	175 (8.1)	77 (4.3)	7 (4.8)	20 (4.7)	2 (7.7)
Parity						
Nulliparous	44,145 (47.3)	1,319 (61)	968 (54.1)	101 (69.7)	216 (50.2)	13 (50.0)
Parous: previous PE	3,143 (3.4)	300 (13.9)	52 (2.9)	11 (7.6)	16 (3.7)	1 (3.8)
Parous: no previous PE	46,009 (49.3)	543 (25.1)	769 (43.0)	33 (22.8)	198 (46.0)	12 (46.0)
Pregnancy interval in years	3.0 (2.0-5.0)	4.1 (2.5-7.1)	3.1 (2.0-5.3)	4.1 (3.0-7.2)	3.0 (1.7-4.9)	3.4 (2.1-4.6)
Gestation of last birth in weeks	40 (39-40)	39 (37-40)	40 (39-40)	40 (38-40)	40 (39-40)	40 (38-41)
Conception						
Spontaneous	90,275 (96.8)	2,048 (94.7)	1,162 (65.0)	90 (62.1)	385 (89.5)	24 (92.3)
Ovulation induction	1,281 (1.4)	32 (1.5)	52 (2.9)	5 (3.4)	3 (0.7)	0
In-vitro fertilization	1,741 (1.9)	82 (3.8)	575 (32.1)	50 (34.5)	42 (9.8)	2 (7.7)

Variables given as mean (interquartile range) or n (%); SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; PE = preeclampsia

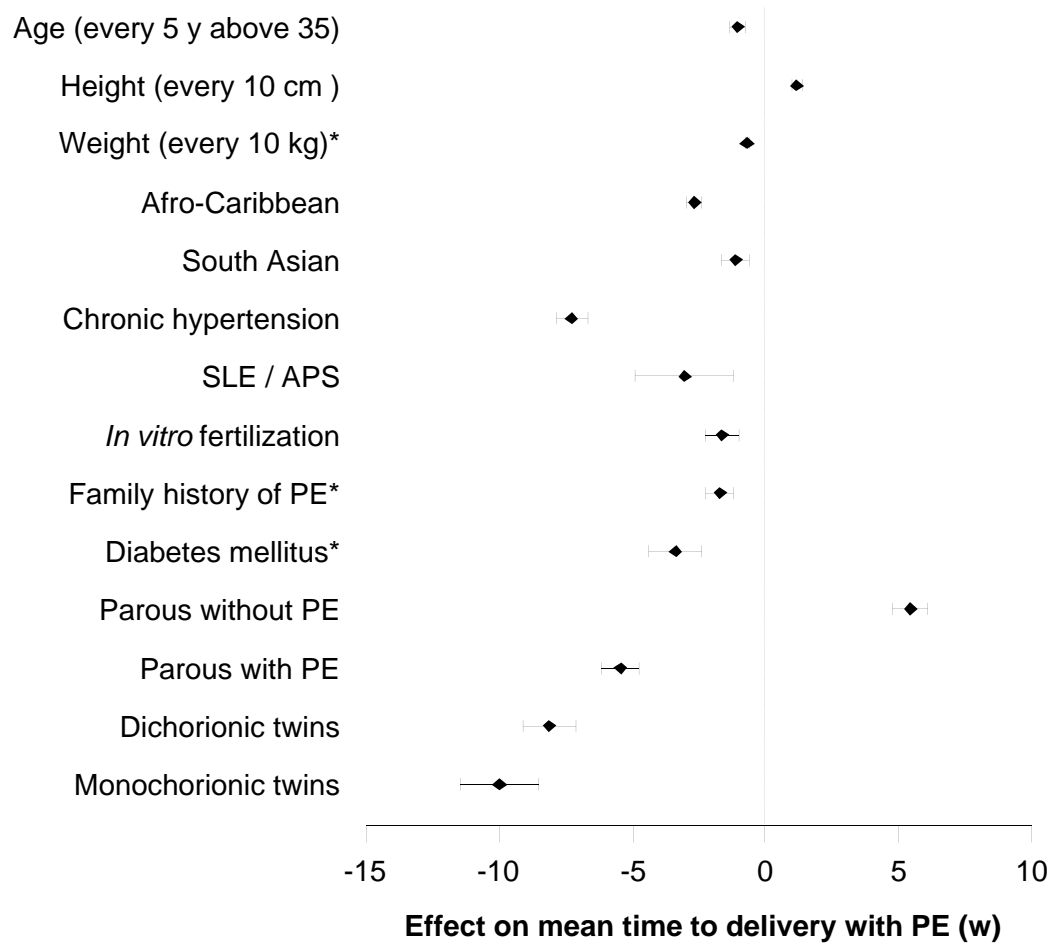
**Table 2:** Screen positive rate and detection rate with 95% confidence intervals in screening by maternal factors for PE in singleton and twin pregnancies.

	Risk cut-off 1 in 10		Risk cut-off 1 in 50		Risk cut-off 1 in 75	
	Singletons N =93,297	Twins N=2,219	Singletons N =93,297	Twins N=2,219	Singletons N =93,297	Twins N=2,219
Screen positive rate (%)	722 (0.8: 0.7-0.8)	1,113 (50.2: 48.1-52.3)	6,517 (7: 6.8-7.2)	2,152 (97: 96.2-97.7)	12,512 (13.4: 13.2-13.6)	2,211 (99.6: 99.3-99.8)
Detection rate (%)						
Preeclampsia <32 w	26/161 (16.1: 10.8-22.8)	15/21 (71.4: 47.8-88.7)	74/161 (46: 38.1-54)	21/21 (100: 83.9-100)	90/161 (55.9: 47.9-63.7)	21/21 (100: 83.9-100)
Preeclampsia <37 w	76/597 (12.7: 10.2-15.7)	88/124 (71.0: 62.1-78.8)	222/597 (37.2: 33.3-41.2)	123/124 (99.2: 95.6-100)	299/597 (50.1: 46-54.2)	124/124 (100: 97.1-100)
Preeclampsia <42 w	175/2,140 (8.2: 7.1-9.4)	116/171 (67.8: 60.3-74.8)	675/2,140 (31.5: 29.6-33.6)	169/171 (98.8: 95.8-99.9)	935/2,140 (43.7: 41.6-45.8)	171/171 (100: 97.9-100)



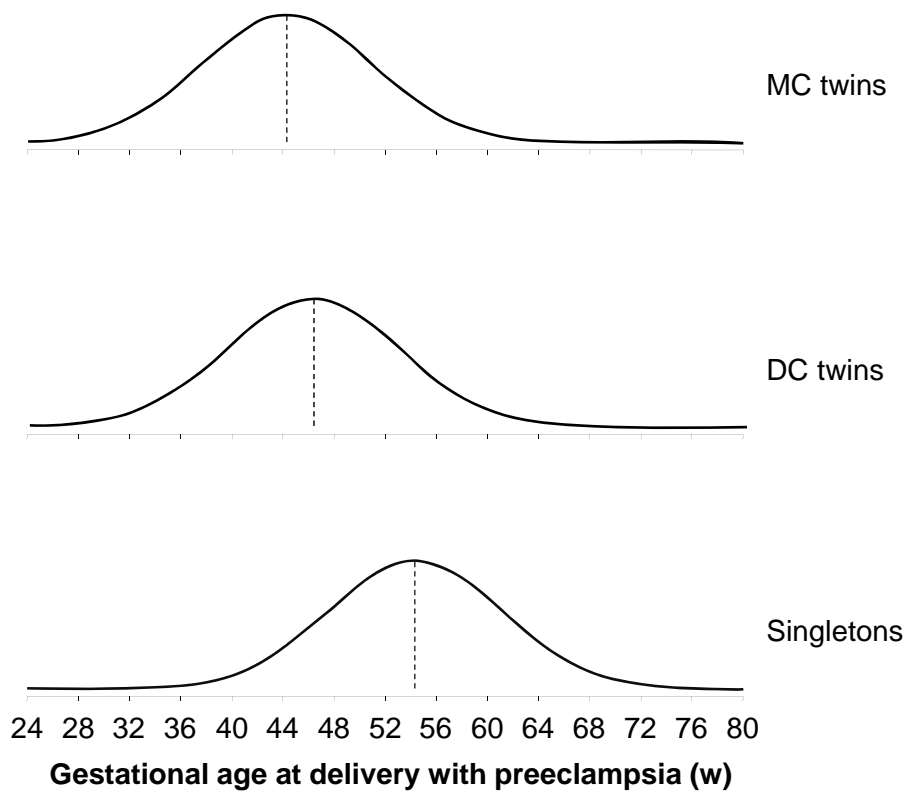
**Figure 1**

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**Figure 2**

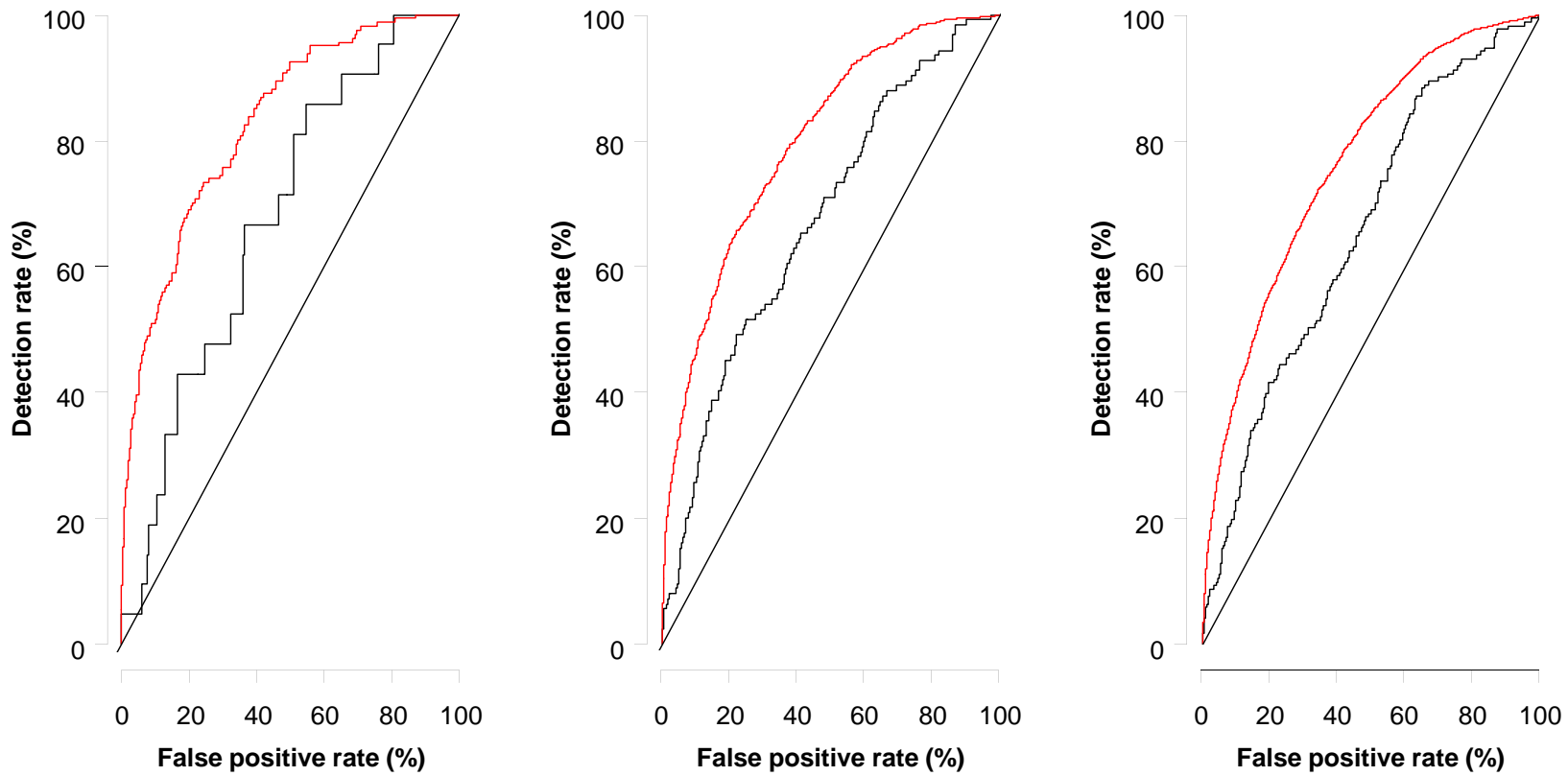
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**Figure 3**

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**Figure 4**

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