Competing risks model in screening for preeclampsia in twin pregnancies by maternal factors and biomarkers at 11-13 weeks' gestation

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Short title: Preeclampsia in twins

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ABSTRACT

Objective: To develop a model for preeclampsia (PE) in twin pregnancies based on maternal demographic characteristics and medical history and biomarkers at 11-13 weeks' gestation.

Methods: This was a screening study in twin pregnancies at 11-13 weeks' gestation. Bayes theorem was used to combine the *a priori* risk from maternal factors with various combinations of uterine artery pulsatility index (UTPI), mean arterial pressure (MAP), serum pregnancy associated plasma protein-A (PAPP-A) and placental growth factor (PLGF) multiple of the median (MoM) values. The performance of screening for PE requiring delivery at <32, <37 and <42 weeks' gestation was estimated in 1,100 twin pregnancies and 35,948 singleton pregnancies with complete data on UTPI, MAP, PLGF and PAPP-A.

Results: In twin pregnancies that developed PE, the values of MAP and UTPI were increased and PLGF and PAPP-A were decreased. The distributions of $\log_{10}$ multiple of the median (MoM) values of biomarkers with gestational age at delivery were similar to those that were previously reported in singleton pregnancies and it was therefore

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assumed that the same model can be used for both singleton and twin pregnancies. The performance of screening for PE by maternal factors was improved by the addition of MAP, UTPI and PLGF; there was no further improvement with the addition of PAPP-A. In a mixed population of singleton and twin pregnancies combined screening by maternal factors, MAP, UTPI and PLGF and risk cut-off of 1 in 75 for PE at <37 weeks, the detection rate of PE at <32, <37 and <42 weeks in singleton pregnancies was 91%, 77% and 57%, respectively, at screen positive rate (SPR) of 13%; the respective rates for twin pregnancies were 100%, 99% and 97%, at SPR of 75%.

Conclusions: First-trimester combined screening for PE in singleton pregnancies can be adapted for screening in twins leading to detection of nearly all affected cases but at a high SPR.

Key words: First trimester screening, Preeclampsia, Pyramid of pregnancy care, Survival model, Bayes theorem, Uterine artery Doppler, Mean arterial pressure, Pregnancy associated plasma protein-A, Placental growth factor.

Introduction

In screening for preeclampsia (PE) we proposed 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 made at different times during pregnancy.[1-8] We adopted this approach using a competing risk model for the time to delivery with PE. This model 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. The effect of maternal factors 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. The distribution of biomarkers is specified conditionally on the gestational age at delivery with PE. For any women with specific maternal factors and biomarker multiple of the median (MoM) values, the posterior distribution of the time to delivery with PE, assuming there is no other cause of delivery, is obtained from the application of Bayes theorem. Studies in singleton pregnancies have demonstrated that effective screening for PE is achieved by a combination of maternal factors, uterine artery pulsatility index (UTPI), mean arterial pressure (MAP) and serum placental growth factor (PLGF) at 11-13 weeks' gestation; serum pregnancy associated plasma protein-A (PAPP-A) did not provide significant improvement to any combination of biomarkers which included serum PLGF.[4,5]

In twin pregnancies the risk of PE is substantially higher than in singleton pregnancies.[9] In a population of singleton pregnancies in 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 was 55 weeks.[1,3] In DC and MC twin pregnancies with the same characteristics as singleton pregnancies the distribution of gestational age of delivery with PE was shifted to the left by 8 and 10 weeks, respectively.[10]

The objective of this study of twin pregnancies with data on MAP, UTPI, PLGF and PAPP-A at 11-13 weeks' gestation, is to examine the potential improvement in performance of screening by maternal factors alone with the addition of each biomarker and combinations of biomarkers.

Methods

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women with twins attending for their routine first hospital visit in pregnancy at King's College Hospital and Medway Maritime Hospital, UK between January 2006 and December 2015. This visit, which was held at 11^{+0} -13^{+6} weeks' gestation, included first, recording of maternal characteristics and medical history,[3,9] second, measurement of MAP by validated automated devices and standardized protocol,[11] third, measurement of the left and right UTPI by transabdominal color Doppler ultrasound and calculation of the mean UTPI,[12] and fourth, measurement of serum concentration of PLGF and PAPP-A

(DELFIA Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, USA). Gestational age was determined by the measurement of fetal crown-rump length[13] of the larger twin. Chorionicity was determined by examining the inter-twin membrane at its junction with the placenta.[14] Measurements of biomarkers were carried out only for some of the patients (UTPI, n=1,764; MAP, n=1,179; PLGF, n=1,366; PAPP-A, n=1,999; measurement of all four biomarkers were obtained from 1,100 pregnancies). The women 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 ≥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 form 35,948 singleton pregnancies, including 1,058 (2.9%) that developed PE, with complete data on UTPI, MAP, PLGF and PAPP-A that were included in a previous publication.[4]

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.[15] Outcome measures were delivery with PE at <32, <37 and <42 weeks' gestation.

Statistical analyses

Our model for the gestational age at delivery with PE was defined by two components: firstly, the prior distribution based on maternal factors and secondly, the conditional distribution of biomarker values given the gestational age with PE and maternal factors. We have previously reported the *prior* distribution for twins by modifying the one for singletons.[10] In this paper we extend the singleton model for the distribution of biomarker values to include twins. Our aim was to do this as simply as possible whilst achieving good screening performance. For the distribution of biomarkers in unaffected twin pregnancies, we assumed the same relationships with gestational age, maternal weight and other factors at the time of measurement as for singleton pregnancies [16-18] and estimated twin effects that can be applied to produce MoM values for twins. In the case of PAPP-A, MoM values were obtained using our previously published algorithm which provides MoM values for both singleton and twin pregnancies.[19] In twin pregnancies with PE the distributions of MoM values, conditionally on gestational age at delivery, were compared with those previously reported for singleton pregnancies.[4] The performance of screening for delivery with PE at <32, <37 and <42 weeks' gestation in a mixed population of singleton and twin pregnancies was determined; 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.[20] The survival package[21] was used for fitting the maternal factors model and the package pROC[22] was used for the receiver operating characteristic (ROC) curve analysis.

Results

Maternal and pregnancy characteristics of the population of 1,100 twin and 35,948 singleton pregnancies with available data for all four biomarkers are summarized in Table 1.

Twin pregnancies unaffected by PE, compared to singleton pregnancies, had lower UTPI and higher MAP, PLGF and PAPP-A (Table 2, Figure 1). In twin pregnancies that developed PE the dependencies of $\log_{10}$ MoM values of UTPI, MAP and PLGF on gestational age at delivery were similar to those previously described for singleton pregnancies (Figure 2)[4] and they all showed significant associations with gestational age at delivery ($P<0.05$) . In the case of PAPP-A, in twins there was little evidence of any substantive difference between PE and unaffected pregnancies and no evidence of association with gestational age at delivery.

Estimates of standard deviations $\log_{10}$ MoM values were similar to those previously described for singletons[4]. The largest discrepancy occurred with PLGF where the standard deviation of $\log_{10}$ MoM was some 25% higher in twins than in singletons; 0.2222 (95% CI: 0.2142 to 0.2309) in twins compared to 0.1772 (95% CI: 0.1760 to 0.1785)[4]. Correlations between $\log_{10}$ MoM values in twins were consistent with those from singletons. With the exclusion of PAPP-A, the similarity between the distributional characteristics of marker MoM values in twins and in singletons, suggests that the distributional parameters for singleton pregnancies could also be applied in twin pregnancies. We therefore propose as an initial model for twins using the twin specific *prior* model[10] with the singleton model[4] for the distributional characteristics for singletons[4] applied to MoM values adjusted by the effects given in Table 2.

Performance of screening for PE in twins by maternal factors and biomarkers, using this initial model, is shown in the ROC curves in Figure 3 and the areas under the ROC curves in Table 3. The performance of screening for PE by maternal factors was improved by the addition of each biomarker and the performance was further improved by the combination of maternal factors, MAP, UTPI and PLGF (triple test); addition of PAPP-A did not improve the performance of the triple test. The performance of screening by the triple test using distributional parameters fitted to twins performed slightly better than the initial model (Table 3).

Table 4 provides the 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 and DR were higher for twin than singleton pregnancies. In combined screening by maternal factors, MAP, UTPI and PLGF and risk cut-off of 1 in 75, the DR of PE at <32, <37 and <42 weeks in singleton pregnancies was 91%, 77% and 57%, respectively, at SPR of 13%; the respective rates for twin pregnancies were 100%, 99% and 97%, at SPR of 75%.

Discussion

Principal findings of this study

In DC twin pregnancies that did not develop PE, compared to singleton pregnancies, UTPI was lower, PLGF was higher and MAP was not significantly different. In MC twins, UTPI was lower, MAP was higher and PLGF was not significantly different. In a previous study we found that at 11-13 weeks' gestation the estimated median MoM of PAPP-A was about 2.0 for DC twins and 1.6 for MC twins.[19]

In twin pregnancies that developed PE, MAP and UTPI at 11-13 weeks' gestation were increased and serum PLGF was decreased. The distribution of biomarkers with gestational age at delivery was similar to the previously reported fitted regression relationships for singleton pregnancies with PE[4] and it was therefore assumed that the same model can be used for both singleton and twin pregnancies. We propose an initial model using a twin specific prior[10] with biomarker MoM values adjusted for twins, but singleton distributional parameters for biomarkers. The results obtained using this model are marginally worse than that using twin specific parameters. However, this may be the consequence of the optimistic bias introduced from fitting and testing on the same data.

The performance of screening for PE by maternal factors was improved by the addition of MAP, UTPI and PLGF. In screening for PE by the combined test and use of risk cut-off of 1 in 75 to define the high-risk group in a mixed population of singleton and twin pregnancies, the estimated SPR and DR of preterm PE for singletons were 13% and 77%, respectively; the estimated SPR and DR of preterm PE for singletons were 13% and 77%, respectively and the values for twins were 75% and 99%.

Strengths and limitations

The strengths of the study are firstly, prospective examination of twin pregnancies attending for routine care in a gestational age range which is widely used for assessment of gestational age, determination of chorionicity, diagnosis of major fetal defects and screening for trisomies, second, recording of data on maternal characteristics and medical history to identify known risk factors associated with PE and use of multivariable logistic model to define the *prior* risk, third, use of a specific methodology and appropriately trained doctors to measure UTPI and MAP, fourth, use of automated machines to provide accurate measurement within 40 minutes of sampling of maternal serum concentration of PLGF and PAPP-A, fifth, expression of the values of the biomarkers as MoMs after adjustment for factors that affect the measurements, and sixth, use of Bayes theorem to combine the *prior* risk from maternal factors with biomarkers to estimate patient-specific risks and the performance of screening for PE delivering at different stages of pregnancy.

A limitation of the study is that the number of twin pregnancies examined relative to that of singleton pregnancies was inevitably small and we adopted the pragmatic view of using the model that was previously described for singleton pregnancies to examine both singleton and twin pregnancies. This model requires validation and possible adjustments from the study of larger datasets of twins.

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 biomarkers.[2,4] In this study the model has been extended to include twin pregnancies.

Studies on uterine artery Doppler during the second and third trimesters reported that UTPI in twin pregnancies is significantly lower than in singleton pregnancies, but the value is increased in pregnancies that develop PE.[23-26] A study in 421 twin and 500 singleton pregnancies at 11-13 weeks' gestation measured UTPI and converted the values to MoM after correction for maternal body mass index, ethnicity and gestational age; the study reported that first, median UTPI MoM was similar between MC and DC twins, second UTPI in twins was lower than in singletons and third, in twin pregnancies that developed PE at <34 weeks' gestation, but not in those with PE at ≥34 weeks, UTPI was increased.[27] Another first-trimester study in 147 twin and 110 singleton pregnancies converted the values to MoM after correction for maternal weight and gestational age; the study reported that first, UTPI in twins was lower than in singletons, second, UTPI was higher in MC than DC twins and third, in 12 twins that developed PE median UTPI was significantly reduced. [28] This study also measured MAP, converted the values to MoM after correction for maternal weight and gestational age and reported that first, MAP in twins was not significantly different from that in singletons, second, MAP was unrelated to chorionicity and third, in the twin pregnancies that developed PE median MAP was increased.[28]

A study in 144 twin and 109 singleton pregnancies at 11-13 weeks' gestation measured serum PAPP-A and PlGF, converted the values to MoM and reported that first, in twin pregnancies PAPP-A and PlGF were approximately twice as high compared to singletons, and second, in 12 twin pregnancies that developed PE median PLGF was decreased but PAPP-A was increased.[29] A study in 74 twin and triplet pregnancies and 698 singleton pregnancies measured serum PLGF at 12-18 weeks' gestation and reported that first, in multiple pregnancies the levels were higher than in singletons and second, in 5 multiple pregnancies that developed PE median PLGF was decreased.[30]

Clinical implications of the study

In singleton pregnancies effective screening for preterm PE can be provided at 11-13 weeks' gestation by a combination of maternal factors, MAP, UTPI and PLGF.[4,5] Such early identification of high-risk pregnancies is useful because the rate of PE may be reduced by the prophylactic use of low-dose aspirin and / or pravastatin.[31-33] This study has demonstrated that the same model of screening can be adapted for the use in mixed populations of singleton and twin pregnancies.

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Figure legends

Figure 1. Box and whisker plots of MAP, UTPI, PLGF and PAPP-A multiple of the median (MoM) values in singleton (white box), DC twin (dark grey box) and MC twin (light grey box) pregnancies that did not develop PE.

Figure 2. Scatter diagram of MAP, UTPI, PLGF and PAPP-A MoM values in twin pregnancies with PE and red regression lines with gestational age at delivery. The blue regression lines are derived from a previous study in singleton pregnancies.[4]

Figure 3. Receiver operating characteristic curves for prediction of delivery with PE at <32 weeks' gestation (left), <37 weeks (middle) and <42 weeks (right) by maternal factors (black) and combination of maternal factors with MAP (blue), UTPI (green), PLGF (purple) and their combination (red). The brown curves represent the performance of screening by the combined test in singleton pregnancies.

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

Variable	Singleton pregnancies		Twin pregnancies	
	All (n=35,948 **)**	**PE (n=1,058)**	**All (n=1,200)**	**PE (n=93)**
Maternal age in years	31.3 (26.8, 35.0)	31.45 (27, 35.58)	33.1 (28.8, 36.6)	34.2 (29.0, 37.3)
Maternal weight in kg	66.7 (59.0, 77.2)	72.1 (63.0, 86.7)	69 (60.3, 80.0)	73.4 (62.6, 84.0)
Maternal height in cm	165 (160, 169)	163 (159, 168)	165 (161, 170)	164 (160, 168)
Gestational age in weeks	12.7 (12.3, 13.1)	12.7 (12.3, 13.08)	12.8 (12.5, 13.2)	12.8 (12.4, 13.2)
Racial origin				
Caucasian	25,879 (72.0)	564 (53.3)	812 (73.8)	61 (65.6)
Afro-Caribbean	6,681 (18.6)	394 (37.2)	199 (18.1)	25 (26.9)
South Asian	1,623 (4.5)	56 (5.3)	43 (3.9)	4 (4.3)
East Asian	846 (2.4)	17 (1.6)	18 (1.6)	2 (2.2)
Mixed	919 (2.6)	27 (2.6)	28 (2.5)	1 (1.1)
Medical history				
Chronic hypertension	561 (1.6)	140 (13.2)	19 (1.7)	9 (9.7)
Diabetes mellitus	325 (0.9)	22 (2.1)	12 (1.1)	2 (2.2)
SLE/APS	53 (0.1)	5 (0.5)	2 (0.2)	1 (1.1)
Cigarette smokers	3,263 (9.1)	68 (6.4)	85 (7.7)	2 (2.2)
Family history of PE	1518 (4.2)	90 (8.5)	46 (4.2)	5 (5.4)
Parity				
Nulliparous	17,361 (48.3)	622 (58.8)	538 (48.9)	60 (64.5)
Parous: previous PE	1,276 (3.5)	153 (14.5)	35 (3.2)	7 (7.5)
Parous: no previous PE	17,311 (48.2)	283 (26.7)	527 (47.9)	26 (28.0)
Pregnancy interval in years	3 (2, 5)	4.1 (2.4, 7.4)	3.1 (2.0, 5.4)	4.1 (2.4, 6.4)
Gestation of last birth in weeks	40 (39, 40)	39 (37, 40)	40 (39, 40)	40 (38.0, 40)
Conception				
Spontaneous	34,743 (96.6)	998 (94.3)	779 (70.8)	65 (69.9)
Ovulation induction	349 (1.0)	19 (1.8)	20 (1.8)	0 (0)
In-vitro fertilization	856 (2.4)	41 (3.9)	301 (27.4)	28 (30.1)
Dichorionic twins			885 (80.5)	77 (82.8)
Monochorionic twins			215 (19.5)	16 (17.2)

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

PE = preeclampsia; IQR = interquartile range; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; PE = preeclampsia.

Table 2. Estimated median multiples of the median values, with 95% confidence limits, for biomarkers in twin pregnancies derived from the algorithms used for singleton pregnancies.

Biomarker	Median multiples of the median value	
	Estimate	P*
Placental growth factor		
Dichorionic twins	1.2326 (1.1926, 1.2741)	<0.0001
Monochorionic twins	0.9968 (0.9335, 1.0644)	0.923
Uterine artery pulsatility index		
Dichorionic twins	0.8686 (0.8535, 0.8839)	<0.0001
Monochorionic twins	0.9647 (0.9320, 0.9985)	0.041
Mean arterial pressure		
Dichorionic twins	1.0030 (0.9973, 1.0088)	0.304
Monochorionic twins	1.0156 (1.0039, 1.0275)	0.009

* Effect relative to the singleton MoM where the median for each biomarker is 1.0

Table 3. Areas under the receiver operating characteristic curve with 95% confidence intervals in screening for PE by maternal factors and combination of maternal factors and biomarkers in twin pregnancies.

Screening	Areas under the receiver operating characteristic curve		
	PE <32 w	**PE <37 w**	**PE <42 w**
Maternal factors	0.6805 (0.5436, 0.8173)	0.7026 (0.6410, 0.7642)	0.6880 (0.6337, 0.7422)
MAP	0.8343 (0.7371, 0.9314)	0.7725 (0.7198, 0.8251)	0.7509 (0.7014, 0.8004)
UTPI	0.8416 (0.7618, 0.9214)	0.7354 (0.6768, 0.7941)	0.7156 (0.6619, 0.7693)
PLGF	0.8071 (0.7052, 0.9089)	0.7395 (0.6810, 0.7980)	0.7080 (0.6534, 0.7625)
PAPP-A	0.6897 (0.5389, 0.8406)	0.7149 (0.6556, 0.7741)	0.7066 (0.6526, 0.7607)
MAP, UTPI, PLGF	0.9293 (0.8851, 0.9735)	0.8122 (0.7661, 0.8583)	0.7796 (0.7342, 0.8250)
MAP, UTPI, PLGF*	*0.9400 (0.9077, 0.9723)*	*0.8172 (0.7724, 0.8621)*	*0.7857 (0.7409, 0.8306)*
MAP, UTPI, PLGF, PAPP-A	0.9227 (0.8727, 0.9727)	0.8111 (0.7649, 0.8572)	0.7804 (0.7353, 0.8254)

MAP = Mean arterial pressure; UTPI = Uterine artery pulsatility index; PLGF = Placental growth factor; PAPP-A = Pregnancy associated plasma protein-A.

* Results from regressions fitted to twin data

Table 4: Screen positive and detection rates with 95% confidence intervals in screening for PE in singleton and twin pregnancies by a combination of maternal factors, MAP, UTPI and PLGF at risk cut-offs for PE at <37 weeks of 1 in 10, 1 in 50 and 1 in 75.

	Risk cut-off 1 in 10		Risk cut-off 1 in 50		Risk cut-off 1 in 75	
	Singletons N=35,948	**Twins N=1,100**	**Singletons N=35,948**	**Twins N=1,100**	**Singletons N=35,948**	**Twins N=1,100**
Screen positive rate (%)						
Maternal factors	344 (1.0: 0.9-1.1)	559 (50.8: 47.8-53.8)	2794 (7.8: 7.5-8.1)	1069 (97.2: 96-98.1)	5231 (14.6: 14.2-14.9)	1095 (99.5: 98.9-99.9)
+MAP, UTPI, PLGF	560 (1.6: 1.4-1.7)	278 (25.3: 22.7-28.0)	3140 (8.7: 8.4-9.0)	724 (65.8: 62.9-68.6)	4541 (12.6: 12.3-13.0)	825 (75.0: 72.3-77.5)
Detection rate (%)						
Preeclampsia <32 w						
Maternal factors	11/66 (16.7: 8.6-27.9)	9/12 (75: 42.8-94.5)	32/66 (48.5: 36-61.1)	12/12 (100: 73.5-100)	60/66 (90.9: 81.3-96.6)	12/12 (100: 73.5-100)
+MAP, UTPI, PLGF	36/66 (54.5: 41.8-66.9)	12/12 (100: 73.5-100)	58/66 (87.9: 77.5-94.6)	12/12 (100: 73.5-100)	60/66 (90.9: 81.3-96.6)	12/12 (100: 73.5-100)
Preeclampsia <37 w						
Maternal factors	37/292 (12.7: 9.1-17)	51/68 (75: 63-84.7)	116/292 (39.7: 34.1-45.6)	67/68 (98.5: 92.1-100)	158/292 (54.1: 48.2-59.9)	68/68 (100: 94.7-100)
+MAP, UTPI, PLGF	104/292 (35.6: 30.1-41.4)	47/68 (69.1: 56.7-79.8)	210/292 (71.9: 66.4-77)	67/68 (98.5: 92.1-100)	226/292 (77.4: 72.2-82.1)	67/68 (98.5: 92.1-100)
Preeclampsia <42 w						
Maternal factors	92/1,044 (8.8: 7.2-10.7)	68/93 (73.1: 62.9-81.8)	355/1,044 (34: 31.1-37)	91/93 (97.8: 92.4-99.7)	474/1,044 (45.4: 42.4-48.5)	93/93 (100: 96.1-100)
+MAP, UTPI, PLGF	191/1,044 (18.3: 16-20.8)	59/93 (63.4: 52.8-73.2)	502/1,044 (48.1: 45-51.2)	88/93 (94.6: 87.9-98.2)	590/1,044 (56.5: 53.4-59.5)	90/93 (96.8: 90.9-99.3)

PE = preeclampsia; MAP = Mean arterial pressure; UTPI = Uterine artery pulsatility index; PLGF = Placental growth factor.

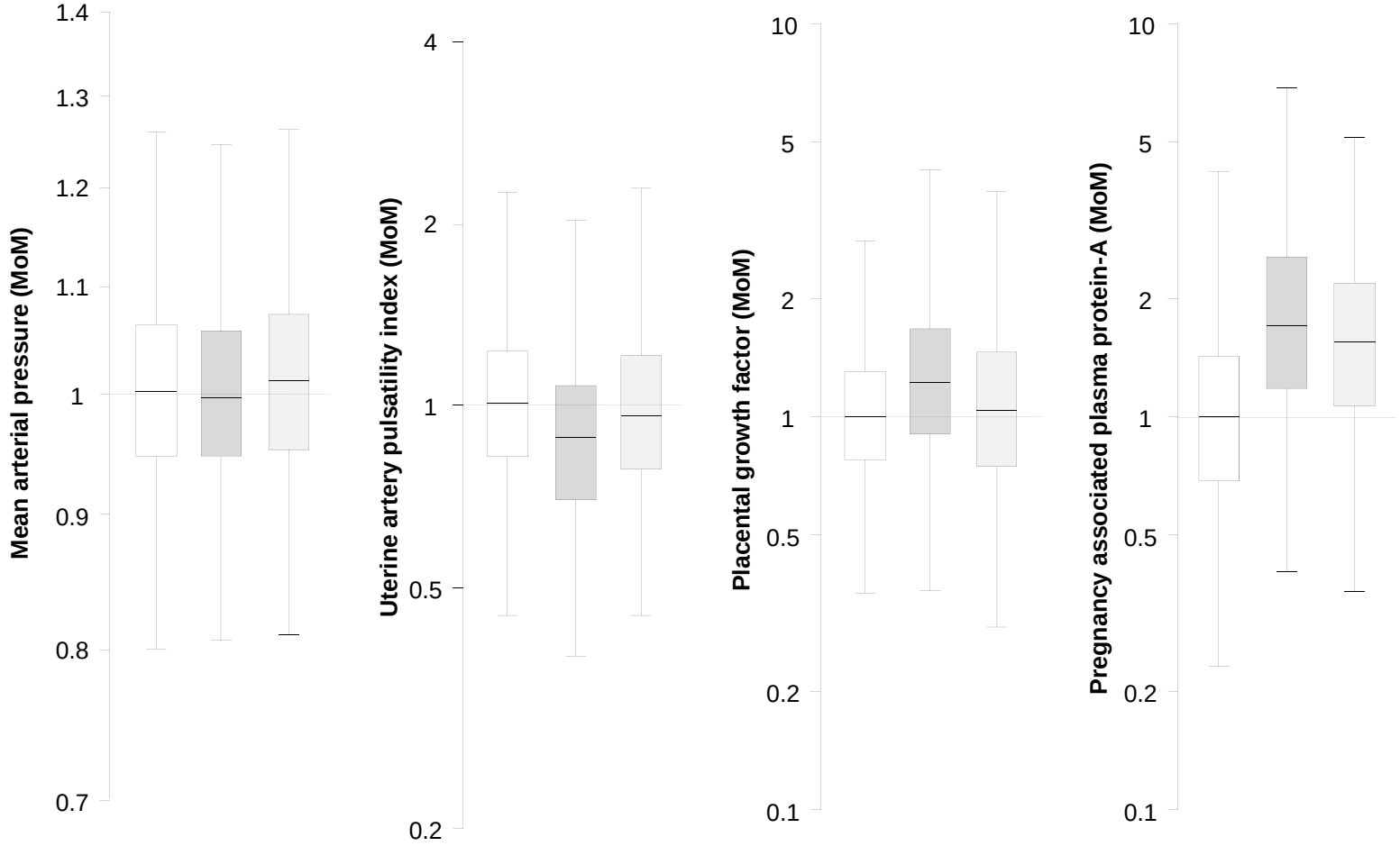

Figure 1

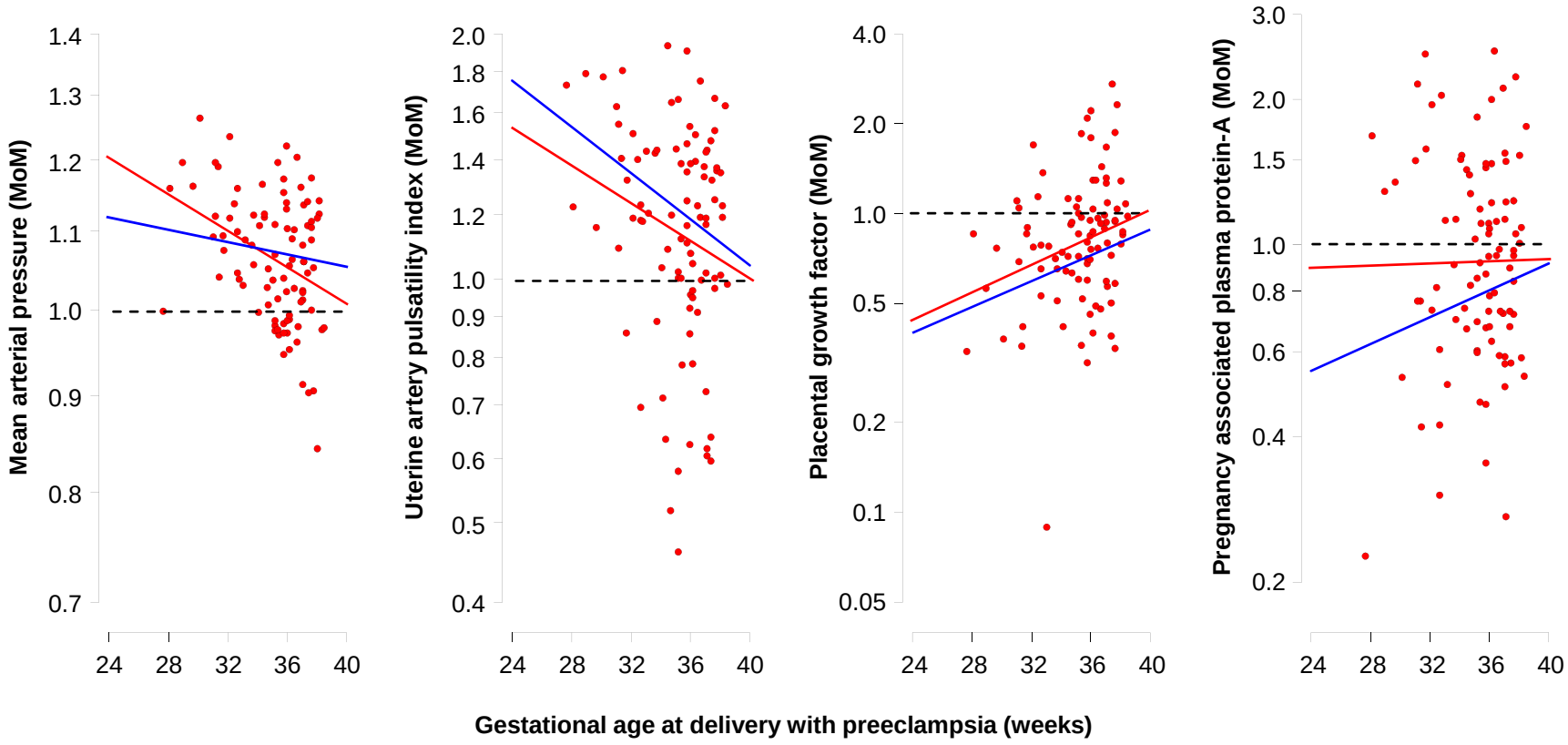

Figure 2

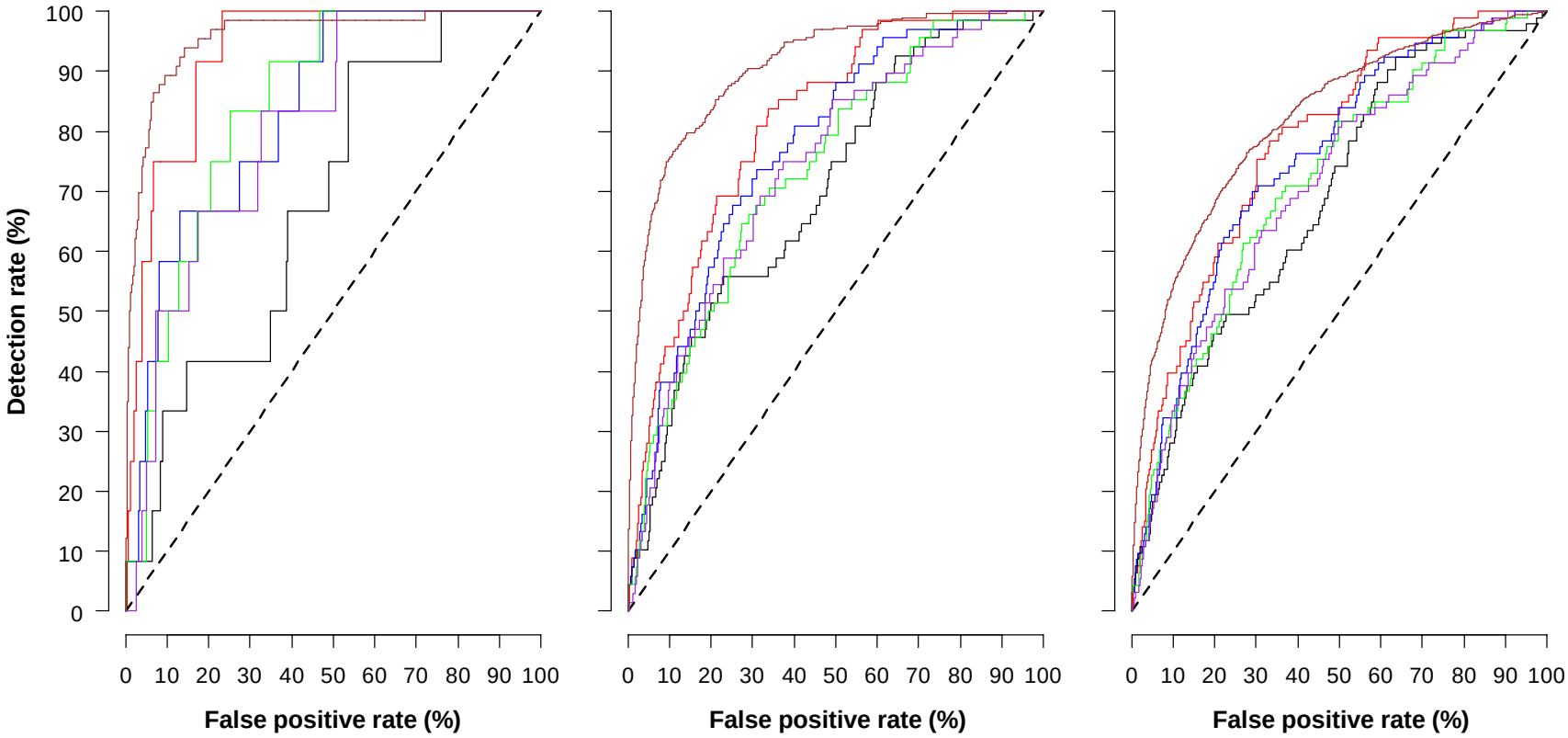

Figure 3