Proposed clinical management of pregnancies after combined screening for preeclampsia at 19-24 weeks' gestation

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Running head: Second-trimester screening for preeclampsia

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ABSTRACT

Objective: To estimate the patient-specific risk of preeclampsia (PE) at 19-24 weeks' gestation by a combination of maternal characteristics and medical history with multiple of the median (MoM) values of mean arterial pressure (MAP), uterine artery pulsatility index (UTPI), serum placental growth factor (PLGF) and serum soluble fms-like tyrosine kinase-1 (sFLT-1) and stratify women into high-, intermediate- and low-risk management groups. The high-risk group, which would contain almost all cases of PE at <32 weeks, would require close monitoring for high blood pressure and proteinuria at 24-31 weeks. The intermediate-risk group together with the undelivered pregnancies from the high-risk group, which would contain most cases of PE at 32^{+0} - 35^{+6} weeks would have reassessment of risk for PE at 32 weeks to identify those that would require close monitoring for high blood pressure and proteinuria at 32-35 weeks. All pregnancies would have reassessment of risk for PE at 36 weeks to define the plan for further monitoring and delivery.

Methods: This was a prospective observational study in women attending for an ultrasound scan at 19-24 weeks as part of routine pregnancy care. Patient-specific risks of delivery with PE at <32 and at <36 weeks' gestation were calculated using the competing risks model to combine the *prior* risk from maternal characteristics and medical history with MoM values of MAP, UTPI, PLGF and sFLT-1. On the basis of these risks the population was stratified into high-, intermediate- and low-risk groups. Different risk cut-offs were used to vary the proportion of the population stratified into each risk category and the performance of screening for delivery with PE at <32 weeks' gestation, at 32-35 weeks and at ≥36 weeks was estimated. In addition to empirical performance we also derived model-based performance because the number of cases of PE at <32 weeks was small.

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Results: The study population of 7,748 singleton pregnancies included 268 (3.5%) that subsequently developed PE. Using a risk cut-off of 1 in 100 for PE at <32 weeks' gestation and risk cut-off of 1 in 300 for PE at <36 weeks the proportion of the population stratified into high-, intermediate- and low-risk was 0.9%, 17.2% and 81.9%, respectively. The high-risk group contained 97% of pregnancies with PE at <32 weeks and 45% of those with PE at 32-35 weeks. The intermediate-risk group contained a further 46% of women with PE at 32-35 weeks. The low-risk group contained only 0.03% of pregnancies with PE at <32 weeks and 9% of those with PE at 32-35 weeks.

Conclusion: Risk stratification of PE by the combined test at 19-24 weeks' gestation can identify first, a group which constitutes <1% of the total and contains >95% of those that develop PE at <32 weeks, in need of intensive monitoring at 24-31 weeks, and second, a group which constitutes <20% of the total and contains >90% of those with PE at 32-35 weeks, in need of reassessment at 32 weeks.

Introduction

Screening and diagnosis of PE is traditionally based on the demonstration of elevated blood pressure and proteinuria during a routine clinical visit in the late second- or third-trimester of pregnancy. In a proposed new pyramid of pregnancy care,[1] it is aimed to firstly, identify a high-risk group at 11-13 weeks gestation and through pharmacological intervention in this group reduce the prevalence of the disease [2,3] and secondly, to minimize adverse perinatal events for those that develop PE by determining the appropriate time and place for delivery [4]. The second objective can be potentially achieved through risk stratification in the second and / or third-trimester of pregnancy. Such risk stratification at 36 weeks' gestation is effective in identifying women that develop PE at ≥37 weeks, but inevitably misses PE at earlier gestations.[5] Risk stratification at 32 weeks' gestation is effective in identifying women that develop PE at 32-36 weeks, but not so for PE at ≥37 weeks.[6]

The objective of this study is to estimate the patient-specific risk of PE at 19-24 weeks' gestation by a combination of maternal characteristics and medical history with mean arterial pressure (MAP), uterine artery pulsatility index (UTPI), serum placental growth factor (PLGF) and serum soluble fms-like tyrosine kinase-1 (sFLT-1) and stratify women into high-, intermediate- and low-risk management groups (Figure 1). The high-risk group, which should ideally be very small and contain almost all cases of PE at <32 weeks, would require close monitoring for high blood pressure and proteinuria at 24-31 weeks. The intermediate-risk group together with the undelivered pregnancies from the high-risk group, which would contain most cases of PE at 32-35 weeks would have reassessment of risk for PE at 32 weeks to identify those that would require close monitoring for high blood pressure and proteinuria at 32-35 weeks. The low-risk group, should be large and contain very few pregnancies that develop PE at <36 weeks' gestation. All pregnancies would have reassessment of risk for PE at 36 weeks to define the plan for further monitoring and delivery.

Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for a second-trimester routine hospital visit at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK. In this visit at 19+0 – 24+6 weeks' gestation we first, recorded maternal demographic characteristics and medical history, second, carried out an ultrasound examination for fetal anatomy and growth, third, measured the left and right UTPI by transvaginal color Doppler ultrasound and calculated the mean value of the two arteries,[7] fourth, measured the MAP by validated automated devices

and a standardized protocol [8] and fifth, measured serum concentration of PLGF and sFLT-1 by an automated biochemical analyzer within 10 minutes of blood sampling (Cobas e411 system, Roche Diagnostics, Penzberg, Germany). Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks.[9,10]

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 were singleton pregnancies delivering a non-malformed live birth or stillbirth at ≥30 weeks' gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities. The study population is the same as in our previous publication on competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19-24 weeks' gestation.[11]

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.[12]

Statistical analysis

Empirical performance

Patient-specific risks of delivery with PE at <32 and at <36 weeks' gestation were calculated using the competing risks model to combine the *prior* risk for PE from maternal characteristics and medical history with MoM values of MAP, UTPI, PLGF and sFLT-1.[13-17] The risk calculator is freely available at the website of the Fetal Medicine Foundation. Pregnancies were allocated to the high-risk group if their risk for PE at <32 weeks was above a specific high-risk threshold and they were allocated to the low-risk group if their risk for PE at <36 weeks was below a specified low-risk threshold. Otherwise, they were allocated to the intermediate risk group. Performance was assessed in terms of the distribution of pregnancy outcomes by risk group.

Model-based estimates of performance

In view of the small number of cases with PE, particularly those with PE at <32 weeks' gestation, we produced model-based estimates of proportions allocated to each risk strata by outcome group. This was achieved using the following Monte-Carlo simulation approach. We first sampled, with replacement, 10,000 records from each outcome group; PE at <32 weeks, PE at 32^{+0} - 35^{+6} weeks, PE at ≥36 weeks and no PE. Conditionally on outcome, we then simulated the $\log_{10}$ MoM values from multivariate Gaussian using previously published parameter estimates.[11] These data were combined with the maternal history to produce risks. For each outcome group, these risks were then used to estimate the proportions allocated to each strata. To obtain the allocation to risk strata overall, the proportions for each risk group were weighted according to the proportions in each risk group of the original sample. The sample of 10,000 was chosen to provide limit imprecision in the Monte-Carlo simulations to a relative standard error of below 10%. It should be recognised that this approach fails to capture inaccuracies due to assumptions about the distribution of MoM values and other aspects of the risk model.

The statistical software package R was used for data analyses.[18]

Results

The study population of 7,748 singleton pregnancies included 268 (3.5%) that subsequently developed PE. Maternal and pregnancy characteristics of the study population are summarized in Table 1. Receiver operating characteristic curves for prediction of delivery with PE at <32, 32-35 and ≥36 weeks' gestation by combined screening at 19 - 24 weeks' gestation are shown in Figure 2; identification of affected cases was more effective for PE at <32 and 32-35 than ≥36 weeks' gestation.

The proportion of the population stratified into high- intermediate- and low-risk groups for risk cut-offs of 1 in 5, 1 in 10, 1 in 50 and 1 in 100 for PE at <32 weeks' gestation and cut-off of 1 in 100, 1 in 200 and 1 in 300 for PE at <36 weeks' gestation and the percentage of cases of PE with delivery at <32, 32-35 and ≥36 weeks in each strata is shown in Table 2. In general, the empirical results were compatible with those derived from modeling.

On the basis of the modelled results, use of a risk cut-off of 1 in 100 for PE at <32 weeks' gestation and risk cut-off of 1 in 300 for PE at <36 weeks resulted in stratification of 0.9%, 17.2% and 81.9% of the population into high-, intermediate- and low-risk, respectively. The high-risk group contained 97% of pregnancies with PE at <32 weeks and 45% of those with PE at 32-35 weeks. The intermediate-risk group contained a further 46% of women with PE at 32-35 weeks. The low-risk group contained only 0.03% of pregnancies with PE at <32 weeks and 9% of those with PE at 32-35 weeks; consequently, the negative predictive value for PE at <32 weeks was >99.99% and for PE at 32-35 weeks it was >99.96%.

Discussion

Main findings

The study has demonstrated an approach for stratification of the population into three management groups based on the estimated risk for PE at <32 and <36 weeks' gestation by a combination of maternal factors, MAP, UTPI, PLGF and sFLT-1 at 19-24 weeks' gestation. In view of the small number of cases with PE at <32 weeks' gestation, modelling was carried out and the performance was compatible with that of the empirical results.

The proportion of the population stratified into high- intermediate- and low-risk groups and the percentage of cases of PE with delivery at <32, 32-35 and ≥36 weeks in each strata inevitably depends on the risk cut-offs used for defining the groups. A pragmatic approach is to use a risk cut-off of 1 in 100 for PE at <32 weeks' gestation and risk cut-off of 1 in 300 for PE at <36 weeks. With such cut-offs, first, the high-risk group in need of intensive monitoring at 24-31 weeks constitutes <1% of the total and contains >95% of those that deliver with PE at <32 weeks, second, about 20% of the population, arising from a combination of the intermediate-risk group and those of the high-risk group that remain pregnant will require reassessment of risk at 32 weeks and this group contains >90% of those that deliver with PE at 32-35 weeks and third, about 80% of the population are stratified into the low-risk group which can be reassured that development of PE at <36 weeks is very unlikely.

Strengths and limitations

The strengths of this study are first, examination of a large population of pregnant women attending for routine care in a gestational age range which is widely used for assessment of fetal anatomy and growth, second, recording of data on maternal characteristics and medical history to define the *prior* risk, third, use of a specific methodology and appropriately trained doctors to measure MAP and UTPI, fourth, use of automated machines to provide accurate measurement within 40 minutes of sampling of maternal serum concentration of PLGF and

sFLT-1, 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 stratify women into high-, intermediate- and low-risk management groups.

A limitation of the study is that fitting of the risk model[4] and development and assessment of risk stratification were on the same data, which induces a degree of optimistic bias into the results. Consequently, prospective evaluation using an independent test data set is needed to validate the results.

Comparison with previous studies

In a previous study at 19-24 weeks' gestation we presented the results on the performance of screening in a routine population by maternal factors and MAP, UTPI, PLGF and sFLT-1.[11] This study investigated a policy whereby pregnancies assessed for PE at 19-24 weeks are stratified into risk groups for subsequent pregnancy management.

Clinical implications of the study

In the proposed new pyramid of pregnancy care, the timing and content of clinical visits should be defined by the patient-specific risk of developing PE.[1] This study provides the framework for stratification of risk for PE based on screening at 19-24 weeks' gestation. The very small high-risk group can be monitored at 24-31 weeks by measurement of blood pressure and urinalysis on a weekly basis and the women can be advised to report any of the symptoms associated with severe PE, such as visual disturbance and epigastric pain. The intermediate-risk group and those of the high-risk group that remain pregnant will require reassessment of risk at 32 weeks to define the need for intensive monitoring at 32-35 weeks. The low-risk group, which constitutes the great majority of the population, can be reassured that PE at <36 weeks is very unlikely, but all women together with those from the high- and intermediate-risk groups that remain pregnant will require reassessment of risk at 36 weeks to define the plan for further monitoring and delivery.[5]

The cut-offs in risks to define the proportion of the population stratified into each of the three management groups and the protocols for such management will inevitably vary according to local preferences and health economic considerations. Future studies will examine whether the implementation of such protocols could improve perinatal outcome.

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Figure legends

Figure 1. Stratification of pregnancies into high-, intermediate- and low-risk management groups based on the estimated risk for preeclampsia at 19-24 weeks' gestation. The high-risk group, would require close monitoring for high blood pressure and proteinuria at 24-31 weeks. The intermediate-risk group together with the undelivered pregnancies from the high-risk group, would have reassessment of risk for PE at 32 weeks to identify those that would require close monitoring at 32-35 weeks. All pregnancies would have reassessment of risk for PE at 36 weeks to define the plan for further monitoring and delivery.

Figure 2. Receiver operating characteristic curves for prediction of delivery with preeclampsia at <32 weeks' gestation (red curve), at 32^{+0} - 35^{+6} weeks (blue curve) and at $\geq$36 weeks (black curve) by combined screening at 19 - 24 weeks' gestation.

Table 1. Maternal and pregnancy characteristics of the study population.

Maternal characteristics	Preeclampsia			
	None	<32 w	$32^{+0} – 35^{+6}$ w	≥36 w
	(n=7,480)	(n=13)	(n=26)	(n=229)
Age in years, median (IQR)	30.9 (26.4, 34.6)	31.1 (28.4, 34.3)	29.7 (24.3, 33.1)	31.7 (26.6, 35.8)
Weight in Kg, median (IQR)	67.0 (59.0, 78.0)	81.2 (76.0, 89.0)	71.6 (66.0, 81.7)	72.4 (63.6, 88.0)
Height in meters, median (IQR)	1.65 (1.60, 1.69)	1.66 (1.60, 1.65)	1.64 (1.60, 1.69)	1.64 (1.60, 1.69)
Racial origin				
Caucasian, n (%)	5,717 (76.4)	5 (38.5)	13 (50.0)	152 (66.4)
Afro-Caribbean, n (%)	1171 (15.7)	8 (61.5)	12 (46.2)	59 (25.8)
South Asian, n (%)	312 (4.2)	0 (0)	1 (3.8)	8 (3.5)
East Asian, n (%)	136 (1.8)	0 (0)	0 (0)	6 (2.6)
Mixed, n (%)	144 (1.9)	0 (0)	0 (0)	4 (1.7)
Conception				
Spontaneous, n (%)	7224 (96.6)	13 (100)	24 (92.3)	216 (94.3)
Assisted conception, n (%)	256 (3.4)	0 (0)	2 (7.7)	13 (5.7)
Cigarette smoking, n (%)	755 (10.1)	1 (7.7)	1 (3.8)	19 (8.3)
Chronic hypertension, n (%)	80 (1.1)	2 (15.4)	3 (11.5)	25 (10.9)
SLE / APS, n (%)	11 (0.2)	0 (0)	0 (0)	0 (0)
Diabetes mellitus, n (%)	74 (1.0)	2 (15.4)		5 (2.2)
Parity				
Nulliparous, n (%)	3556 (47.5)	5 (38.5)	14 (53.8)	150 (65.5)
Parous no previous PE, n (%)	3672 (49.1)	6 (46.2)	6 (23.1)	50 (21.8)
Parous previous PE, n (%)	252 (3.4)	2 (15.4)	6 (23.1)	29 (12.7)
Family history of PE, n (%)	226 (3.0)	3 (23.1)	1 (3.8)	12 (5.2)
Pregnancy interval in years, median (IQR)*	3.2 (2.0, 5.1)	3.5 (1.7, 6.1)	3.4 (3.3, 3.9)	4.5 (2.6, 6.7)

Table 2. Proportion of the population stratified into high- intermediate- and low-risk groups based on the risk for preeclampsia (PE) at <32 and at <36 weeks' gestation by a combination of maternal factors, MAP, UTPI, PLGF and sFLT-1 at 19-24 weeks' gestation. The first row in each group gives the empirical data with 95% confidence interval and the second row gives the model-based results.

Risk cut off for PE	Strata		PE with delivery at:		
	Type	Size (n=7,748)	<32 w (n=13)	32-35 w (n=26)	≥36 w (n=229)
1 in 5 for PE <32w and 1 in 100 for PE <36w	High	33 (0.4;0.3, 0.6)	11 (84.6;54.6, 98.1)	6 (23.1;9, 43.6)	3 (1.3;0.3, 3.8)
		0.3	87.27	16.0	0.2
	Intermediate	564 (7.3;6.7, 7.9)	2 (15.4;1.9, 45.4)	14 (53.8;33.4, 73.4)	68 (29.7;23.9, 36.1)
		7.9	12.49	66.2	29.2
	Low	7151 (92.3;91.7, 92.9)	0 (0;0, 24.7)	6 (23.1;9, 43.6)	158 (69;62.6, 74.9)
		91.7	0.24	17.8	70.7
1 in 5 for PE <32w and 1 in 200 for PE <36w	High	33 (0.4;0.3, 0.6)	11 (84.6;54.6, 98.1)	6 (23.1;9, 43.6)	3 (1.3;0.3, 3.8)
		0.3	87.27	16.0	0.2
	Intermediate	924 (11.9;11.2, 12.7)	2 (15.4;1.9, 45.4)	19 (73.1;52.2, 88.4)	89 (38.9;32.5, 45.5)
		13.4	12.66	72.1	40.2
	Low	6791 (87.6;86.9, 88.4)	0 (0;0, 24.7)	1 (3.8;0.1, 19.6)	137 (59.8;53.2, 66.2)
		86.2	0.07	11.9	59.6
1 in 5 for PE <32w and 1 in 300 for PE <36w	High	33 (0.4;0.3, 0.6)	11 (84.6;54.6, 98.1)	6 (23.1;9, 43.6)	3 (1.3;0.3, 3.8)
		0.3	87.27	16.0	0.2
	Intermediate	1211 (15.6;14.8, 16.5)	2 (15.4;1.9, 45.4)	19 (73.1;52.2, 88.4)	101 (44.1;37.6, 50.8)
		17.8	12.7	74.7	47.1
	Low	6504 (83.9;83.1, 84.8)	0 (0;0, 24.7)	1 (3.8;0.1, 19.6)	125 (54.6;47.9, 61.2)
		81.9	0.03	9.3	52.7
1 in 10 for PE <32w and 1 in 100 for PE <36w	High	38 (0.5;0.3, 0.7)	11 (84.6;54.6, 98.1)	7 (26.9;11.6, 47.8)	5 (2.2;0.7, 5)
		0.4	91.33	22.7	0.6
	Intermediate	559 (7.2;6.6, 7.8)	2 (15.4;1.9, 45.4)	13 (50;29.9, 70.1)	66 (28.8;23, 35.2)
		7.8	8.43	59.4	28.8
	Low	7151 (92.3;91.7, 92.9)	0 (0;0, 24.7)	6 (23.1;9, 43.6)	158 (69;62.6, 74.9)
		91.7	0.24	17.8	70.7
1 in 10 for PE <32w and 1 in 200 for PE <36w	High	38 (0.5;0.3, 0.7)	11 (84.6;54.6, 98.1)	7 (26.9;11.6, 47.8)	5 (2.2;0.7, 5)
		0.4	91.33	22.7	0.6
	Intermediate	919 (11.9;11.1, 12.6)	2 (15.4;1.9, 45.4)	18 (69.2;48.2, 85.7)	87 (38;31.7, 44.6)
		13.3	8.6	65.4	39.8
	Low	6791 (87.6;86.9, 88.4)	0 (0;0, 24.7)	1 (3.8;0.1, 19.6)	137 (59.8;53.2, 66.2)
		86.2	0.07	11.9	59.6
1 in 10 for PE <32w and 1 in 300 for PE <36w	High	38 (0.5;0.3, 0.7)	11 (84.6;54.6, 98.1)	7 (26.9;11.6, 47.8)	5 (2.2;0.7, 5)
		0.4	91.33	22.7	0.6
	Intermediate	1206 (15.6;14.8, 16.4)	2 (15.4;1.9, 45.4)	18 (69.2;48.2, 85.7)	99 (43.2;36.7, 49.9)
		17.7	8.64	68.0	46.7
	Low	6504 (83.9;83.1, 84.8)	0 (0;0, 24.7)	1 (3.8;0.1, 19.6)	125 (54.6;47.9, 61.2)
		81.9	0.03	9.3	52.7

1 in 50 for PE <32w and 1 in 100 for PE <36w	High	55 (0.7;0.5, 0.9)	11 (84.6;54.6, 98.1)	9 (34.6;17.2, 55.7)	6 (2.6;1, 5.6)
		0.8	96.1	38.1	1.9
	Intermediate	542 (7;6.4, 7.6)	2 (15.4;1.9, 45.4)	11 (42.3;23.4, 63.1)	65 (28.4;22.6, 34.7)
		7.5	3.66	44.1	27.4
	Low	7151 (92.3;91.7, 92.9)	0 (0;0, 24.7)	6 (23.1;9, 43.6)	158 (69;62.6, 74.9)
		91.7	0.24	17.8	70.7
1 in 50 for PE <32w and 1 in 200 for PE <36w	High	55 (0.7;0.5, 0.9)	11 (84.6;54.6, 98.1)	9 (34.6;17.2, 55.7)	6 (2.6;1, 5.6)
		0.8	96.1	38.1	1.9
	Intermediate	902 (11.6;10.9, 12.4)	2 (15.4;1.9, 45.4)	16 (61.5;40.6, 79.8)	86 (37.6;31.3, 44.2)
		13.0	3.83	50.0	38.4
	Low	6791 (87.6;86.9, 88.4)	0 (0;0, 24.7)	1 (3.8;0.1, 19.6)	137 (59.8;53.2, 66.2)
		86.2	0.07	11.9	59.6
1 in 50 for PE <32w and 1 in 300 for PE <36w	High	55 (0.7;0.5, 0.9)	11 (84.6;54.6, 98.1)	9 (34.6;17.2, 55.7)	6 (2.6;1, 5.6)
		0.8	96.1	38.1	1.9
	Intermediate	1189 (15.3;14.6, 16.2)	2 (15.4;1.9, 45.4)	16 (61.5;40.6, 79.8)	98 (42.8;36.3, 49.5)
		17.3	3.87	52.6	45.4
	Low	6504 (83.9;83.1, 84.8)	0 (0;0, 24.7)	1 (3.8;0.1, 19.6)	125 (54.6;47.9, 61.2)
		81.9	0.03	9.3	52.7
1 in 100 for PE <32w and 1 in 100 for PE <36w	High	72 (0.9;0.7, 1.2)	11 (84.6;54.6, 98.1)	11 (42.3;23.4, 63.1)	7 (3.1;1.2, 6.2)
		0.9	97.36	44.7	3.3
	Intermediate	525 (6.8;6.2, 7.4)	2 (15.4;1.9, 45.4)	9 (34.6;17.2, 55.7)	64 (27.9;22.2, 34.2)
		7.3	2.4	37.5	26.1
	Low	7151 (92.3;91.7, 92.9)	0 (0;0, 24.7)	6 (23.1;9, 43.6)	158 (69;62.6, 74.9)
		91.7	0.24	17.8	70.7
1 in 100 for PE <32w and 1 in 200 for PE <36w	High	72 (0.9;0.7, 1.2)	11 (84.6;54.6, 98.1)	11 (42.3;23.4, 63.1)	7 (3.1;1.2, 6.2)
		0.9	97.36	44.7	3.3
	Intermediate	885 (11.4;10.7, 12.2)	2 (15.4;1.9, 45.4)	14 (53.8;33.4, 73.4)	85 (37.1;30.8, 43.7)
		12.8	2.57	43.4	37.1
	Low	6791 (87.6;86.9, 88.4)	0 (0;0, 24.7)	1 (3.8;0.1, 19.6)	137 (59.8;53.2, 66.2)
		86.2	0.07	11.9	59.6
1 in 100 for PE <32w and 1 in 300 for PE <36w	High	72 (0.9;0.7, 1.2)	11 (84.6;54.6, 98.1)	11 (42.3;23.4, 63.1)	7 (3.1;1.2, 6.2)
		0.9	97.36	44.7	3.3
	Intermediate	1172 (15.1;14.3, 15.9)	2 (15.4;1.9, 45.4)	14 (53.8;33.4, 73.4)	97 (42.4;35.9, 49)
		17.2	2.61	46.0	44.0
	Low	6504 (83.9;83.1, 84.8)	0 (0;0, 24.7)	1 (3.8;0.1, 19.6)	125 (54.6;47.9, 61.2)
		81.9	0.03	9.3	52.7