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Proposed clinical management of pregnancies after combined screening for pre-eclampsia at 30–34 weeks' gestation

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KEYWORDS: mean arterial pressure; placental growth factor; pre-eclampsia; pyramid of antenatal care; soluble fms-like tyrosine kinase-1; uterine artery pulsatility index

ABSTRACT

Objective *To estimate the patient-specific risk of pre-eclampsia (PE) at 30–34 weeks' gestation by a combination of maternal characteristics and medical history with multiples of the median (MoM) values of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), 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.*

Methods *This was a prospective observational study in women attending a third-trimester ultrasound scan at 30–34 weeks as part of routine pregnancy care. Patient-specific risks of delivery with PE at < 4 weeks from assessment and at < 40 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, UtA-PI, 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 < 4 weeks from assessment and delivery with PE from 4 weeks after assessment and up to 40 weeks' gestation was estimated.*

Results *The study population of 8128 singleton pregnancies included 234 (2.9%) that subsequently developed PE. Using a risk cut-off of 1 in 50 for PE delivering at < 4 weeks and a risk cut-off of 1 in 150 for PE delivering at < 40 weeks' gestation, the proportion of the population stratified into high, intermediate and low risk was about 3%, 26% and 71%, respectively. The high-risk group contained 90% of pregnancies with PE at < 4 weeks and 40% of those with PE at 4 weeks from assessment to 40 weeks' gestation. The intermediate-risk group contained a further 49% of women with PE at 4 weeks from assessment to 40 gestational weeks. In the low-risk group, none of the women developed PE at < 4 weeks and only 0.3% developed PE at 4 weeks to 40 gestational weeks.*

Conclusion *The study presents risk stratification of PE by the combined test at 30–34 weeks, aiming to identify a high-risk group in need of intensive monitoring from the time of the initial assessment and up to 40 weeks' gestation and an intermediate-risk group in need of monitoring from 4 weeks after the initial assessment and up to 40 weeks' gestation. All pregnancies would need to be reassessed at 40 weeks' gestation. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

The objectives of screening for pre-eclampsia (PE) are first, to reduce the prevalence of the disease through pharmacological intervention in the high-risk group identified in the first trimester of pregnancy[1,2] and second, to minimize adverse perinatal events for those that develop PE by determining the appropriate time and place for delivery[3]. The second objective can potentially be achieved through risk stratification in the second and/or third trimester of pregnancy.

A study in 8128 pregnancies at 30–34 weeks' gestation reported that screening by a combination of maternal factors with multiples of the median (MoM) values of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFlt-1) predicted 98% of pregnancies that developed PE and delivered at < 37 weeks' gestation and 49% of those with PE delivering ≥ 37 weeks, at a 5% false-positive rate[4].

The objective of this study was to estimate the patient-specific risk of PE at 30–34 weeks' gestation by

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a combination of maternal characteristics and medical history with MAP, UtA-PI, PlGF and sFlt-1 and stratify women into high-, intermediate- and low-risk management groups.

METHODS

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending a third-trimester routine hospital visit at King's College Hospital, London, or Medway Maritime Hospital, Gillingham, UK, between March 2012 and January 2014. In this visit at 30 + 0 to 34 + 6 weeks' gestation we, first, recorded maternal demographic characteristics and medical history, second, carried out an ultrasound examination of fetal anatomy and growth, third, measured the left and right UtA-PI by transabdominal color Doppler ultrasound and calculated the mean value of the two arteries[5], fourth, measured the MAP by validated automated devices using a standardized protocol[6] and fifth, measured serum concentration of PlGF and sFlt-1 by an automated biochemical analyzer within 10 min 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 fetal head circumference at 19–24 weeks[7,8].

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 pregnancy delivering a non-malformed live birth or stillbirth at ≥ 30 weeks' gestation. We excluded pregnancies with aneuploidy or major fetal abnormality. The study population is the same as in our previous report[4].

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[9].

In order to focus clinical resources effectively, we investigated a policy in which pregnancies assessed for PE at 30–34 weeks' gestation are stratified into three groups (Figure 1). A group at high risk of delivery with PE within 4 weeks of assessment would require intensive monitoring from the time of the initial assessment and up to 40 weeks' gestation; this group ideally should be small and contain a large proportion of pregnancies with PE at < 4 weeks. Conversely, the low-risk group, that would be reassessed only at 40 weeks' gestation, should be large and contain very few pregnancies that developed PE at < 40 weeks' gestation. The intermediate-risk group would ideally contain very few pregnancies with PE at < 4 weeks and a large proportion of pregnancies that deliver with PE after 4 weeks from assessment and up to 40 weeks' gestation; this group would require reassessment after 4 weeks or intensive monitoring starting from 4 weeks after the initial assessment and up to 40 weeks' gestation.

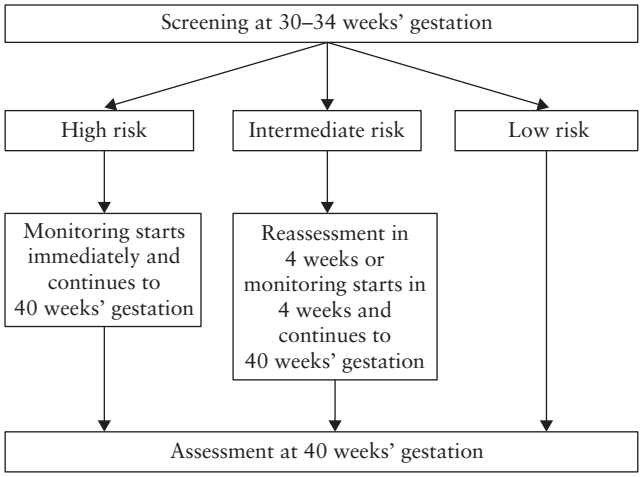

Figure 1 Stratification of pregnancies into high-, intermediate- and low-risk management groups based on estimated risk for pre-eclampsia at 30–34 weeks' gestation. High-risk group would require intensive monitoring from time of initial assessment and up to 40 weeks' gestation, intermediate-risk group would require intensive monitoring from 4 weeks after initial assessment and up to 40 weeks' gestation and low-risk group would be reassessed only at 40 weeks' gestation.

Statistical analysis

Patient-specific risks of delivery with PE at < 4 weeks from assessment and at < 40 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, UtA-PI, PlGF and sFlt-1[4,10–15]. The risk calculator is freely available on the website of The Fetal Medicine Foundation. Pregnancies were allocated to the high-risk group if their risk for PE at < 4 weeks was above a specific high-risk threshold and they were allocated to the low-risk group if their risk for PE at < 40 weeks' gestation 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.

The statistical software package R was used for data analyses[16].

RESULTS

The study population of 8128 singleton pregnancies included 234 (2.9%) that subsequently developed PE. Maternal and pregnancy characteristics of the study population are summarized in Table 1. The allocation of pregnancies to the risk group by pregnancy outcome are given in Table 2.

Delivery with PE at < 4 weeks from assessment

In the study population, there were 31 pregnancies that developed PE and were delivered within 4 weeks from

Table 1 Maternal and pregnancy characteristics in pregnancies that developed pre-eclampsia (PE) within 4 weeks from assessment, ≥ 4 weeks from assessment and up to 40 weeks' gestation and at > 40 weeks' gestation, compared with pregnancies that remained normotensive

		Pre-eclampsia at:		
Characteristic	*Normotensive* (n = *7894*)	*< 4 weeks* (n = *31*)	*≥ 4 weeks to 40 GW* (n = *141*)	*> 40 GW* (n = *62*)
Age (years)	31.0 (26.7–34.7)	31.0 (26.3–34.2)	31.7 (27.5–35.2)	31.0 (24.8–34.8)
Weight (kg)	67.2 (59.4–78.0)	70.4 (60.0–86.0)	76.0 (64.5–89.9)	69.0 (60.2–84.9)
Height (m)	1.65 (1.60–1.69)	1.60 (1.58–1.65)	1.65 (1.60–1.69)	1.64 (1.60–1.69)
Racial origin				
Caucasian	5923 (75.0)	20 (64.5)	80 (56.7)	42 (67.7)
Afro-Caribbean	1353 (17.1)	9 (29.0)	50 (35.5)	17 (27.4)
South Asian	297 (3.8)	2 (6.5)	6 (4.3)	2 (3.2)
East Asian	145 (1.8)	0 (0)	3 (2.1)	1 (1.6)
Mixed	176 (2.2)	0 (0)	2 (1.4)	0 (0)
Mode of conception				
Spontaneous	7631 (96.7)	29 (93.5)	136 (96.5)	60 (96.8)
Assisted	263 (3.3)	2 (6.5)	5 (3.5)	2 (3.2)
Cigarette smoker	798 (10.1)	1 (3.2)	8 (5.7)	4 (6.5)
Chronic hypertension	90 (1.1)	6 (19.4)	23 (16.3)	3 (4.8)
APS/SLE	15 (0.2)	0 (0)	0 (0)	0 (0)
Diabetes mellitus	77 (1.0)	0 (0)	3 (2.1)	0 (0)
Parity				
Nulliparous	3871 (49.0)	20 (64.5)	68 (48.2)	48 (77.4)
Parous no previous PE	3752 (47.5)	8 (25.8)	42 (29.8)	13 (21.0)
Parous previous PE	271 (3.4)	3 (9.7)	31 (22.0)	1 (1.6)
Family history of PE	235 (3.0)	1 (3.2)	6 (4.3)	2 (3.2)
Interpregnancy interval (years)*	3.1 (2.1–5.1)	7.1 (3.5–8.2)	3.6 (2.4–5.3)	6.6 (2.7–9.0)

Data are given as median (interquartile range) or *n* (%). *Interpregnancy interval reported for parous women. APS, antiphospholipid syndrome; GW, gestational weeks; SLE, systemic lupus erythematosus.

assessment. At a risk cut-off of 1 in 3 for PE delivering at < 4 weeks from assessment, 77.4% of pregnancies with PE at < 4 weeks were allocated to the high-risk group which comprised 0.9% of all pregnancies. The respective values for risk cut-off of 1 in 10 were 83.9% and 1.6%, for a cut-off of 1 in 50 they were 90.3% and 3.1%, for cut-off of 1 in 100 they were 90.3% and 3.9% and for cut-off of 1 in 150 they were 93.5% and 4.5%.

Consequently, the proportion of the population that would require intensive monitoring from the time of the initial assessment and up to 40 weeks' gestation would increase from 0.9% if the risk cut-off was 1 in 3 to 4.5% if the cut-off was 1 in 150 and the proportion of pregnancies with PE at < 4 weeks in the high-risk group would increase from 77.4% to 93.5%

Delivery with PE at ≥ 4 weeks from assessment up to 40 gestational weeks

In the study population, there were 141 pregnancies that delivered with PE at ≥ 4 weeks from assessment to 40 gestational weeks. The allocation of these cases into the high-, intermediate- and low-risk groups is shown in Table 2.

For example, the high-risk group defined by a risk cut-off of 1 in 50 for PE at < 4 weeks constituted 3.1% of the population and contained 40.4% (57/141) of pregnancies with PE delivering at ≥ 4 weeks from assessment to 40 gestational weeks. Using this risk cut-off of 1 in 50 for PE at < 4 weeks and a risk cut-off of 1 in 150 for PE at < 40 weeks' gestation, 26.4% of pregnancies were allocated to the intermediate-risk group which contained 48.9% (69/141) of pregnancies with PE at ≥ 4 weeks from assessment to 40 gestational weeks. Consequently, for these particular risk cut-offs, 29.5% of pregnancies were allocated to the high- or intermediate-risk groups and the combination of these groups contained a total of 89.4% (126/141) of pregnancies with PE at ≥ 4 weeks from assessment to 40 gestational weeks.

Delivery with PE at > 40 weeks' gestation

In the study population, there were 62 pregnancies that delivered with PE at > 40 weeks. The allocation of these cases into the high-, intermediate- and low-risk groups is shown in Table 2. For example, the high-risk group defined by a risk cut-off of 1 in 50 for PE at < 4 weeks constituted 3.1% of the population and contained 11.3% (7/62) of pregnancies with PE at > 40 weeks. Using this risk cut-off of 1 in 50 for PE at < 4 weeks and a risk cut-off of 1 in 150 for PE at < 40 weeks' gestation, 26.4% of pregnancies were allocated to the intermediate-risk group which contained 56.5% (35/62) of pregnancies with PE at > 40 weeks. Consequently, for these particular risk cut-offs, 29.5% of pregnancies were allocated to the high- or intermediate-risk groups and the combination of these groups contained a total of 67.7% (42/62) of pregnancies with PE at > 40 weeks; the remaining 70.5% of pregnancies were allocated to the low-risk

Table 2 Stratification of risk for pre-eclampsia (PE) delivering < 4 weeks from assessment, ≥ 4 weeks from assessment and up to 40 gestational weeks and at > 40 weeks' gestation

		PE with delivery at:		
Risk cut-off for PE	*All pregnancies (n = 8128)*	*< 4 w (n = 31)*	*≥ 4 w to 40 GW (n = 141)*	*> 40 GW (n = 62)*
1 in 3 for PE < 4 w	*76 (0.9; 0.7–1.2)*	*24 (77.4; 58.9–90.4)*	*25 (17.7; 11.8–25.1)*	*0 (0; 0–5.8)*
1 in 50 for PE < 40 GW	1141 (14.0; 13.3–14.8)	6 (19.4; 7.5–37.5)	81 (57.4; 48.8–65.7)	26 (41.9; 29.5–55.2)
1 in 100 for PE < 40 GW	1828 (22.5; 21.6–23.4)	7 (22.6; 9.6–41.1)	95 (67.4; 59.0–75.0)	37 (59.7; 46.4–71.9)
1 in 150 for PE < 40 GW	2325 (28.6; 27.6–29.6)	7 (22.6; 9.6–41.1)	101 (71.6; 63.4–78.9)	42 (67.7; 54.7–79.1)
1 in 200 for PE < 40 GW	2774 (34.1; 33.1–35.2)	7 (22.6; 9.6–41.1)	104 (73.8; 65.7–80.8)	44 (71.0; 58.1–81.8)
1 in 10 for PE < 4 w	*134 (1.6; 1.4–1.9)*	*26 (83.9; 66.3–94.5)*	*37 (26.2; 19.2–34.3)*	*1 (1.6; 0–8.7)*
1 in 50 for PE < 40 GW	1083 (13.3; 12.6–14.1)	4 (12.9; 3.6–29.8)	69 (48.9; 40.4–57.5)	25 (40.3; 28.1–53.6)
1 in 100 for PE < 40 GW	1770 (21.8; 20.9–22.7)	5 (16.1; 5.5–33.7)	83 (58.9; 50.3–67.1)	36 (58.1; 44.8–70.5)
1 in 150 for PE < 40 GW	2267 (27.9; 26.9–28.9)	5 (16.1; 5.5–33.7)	89 (63.1; 54.6–71.1)	41 (66.1; 53.0–77.7)
1 in 200 for PE < 40 GW	2716 (33.4: 32.4–34.5)	5 (16.1; 5.5–33.7)	92 (65.2; 56.8–73.1)	43 (69.4; 56.3–80.4)
1 in 50 for PE < 4 w	*254 (3.1; 2.8–3.5)*	*28 (90.3; 74.2–98.0)*	*57 (40.4; 32.3–49.0)*	*7 (11.3; 4.7–21.9)*
1 in 50 for PE < 40 GW	963 (11.8; 11.2–12.6)	2 (6.5; 0.8–21.4)	49 (34.8; 26.9–43.2)	19 (30.6; 19.6–43.7)
1 in 100 for PE < 40 GW	1650 (20.3; 19.4–21.2)	3 (9.7; 2.0–25.8)	63 (44.7; 36.3–53.3)	30 (48.4; 35.5–61.4)
1 in 150 for PE < 40 GW	2147 (26.4; 25.5–27.4)	3 (9.7; 2.0–25.8)	69 (48.9; 40.4–57.5)	35 (56.5; 43.3–69.0)
1 in 200 for PE < 40 GW	2596 (31.9; 30.9–33.0)	3 (9.7; 2.0–25.8)	72 (51.1; 42.5–59.6)	37 (59.7; 46.4–71.9)
1 in 100 for PE < 4 w	*314 (3.9; 3.5–4.3)*	*28 (90.3; 74.2–98.0)*	*64 (45.4; 37.0–54.0)*	*8 (12.9; 5.7–23.9)*
1 in 50 for PE < 40 GW	903 (11.1; 10.4–11.8)	2 (6.5; 0.8–21.4)	42 (29.8; 22.4–38.1)	18 (29.0; 18.2–41.9)
1 in 100 for PE < 40 GW	1590 (19.6; 18.7–20.4)	3 (9.7; 2.0–25.8)	56 (39.7; 31.6–48.3)	29 (46.8; 34.0–59.9)
1 in 150 for PE < 40 GW	2087 (25.7; 24.7–26.6)	3 (9.7; 2.0–25.8)	62 (44.0; 35.6–52.6)	34 (54.8; 41.7–67.5)
1 in 200 for PE < 40 GW	2536 (31.2; 30.2–32.2)	3 (9.7; 2.0–25.8)	65 (46.1; 37.7–54.7)	36 (58.1; 44.8–70.5)
1 in 150 for PE < 4 w	*369 (4.5; 4.1–5.0)*	*29 (93.5; 78.6–99.2)*	*68 (48.2; 39.7–56.8)*	*11 (17.7; 9.2–29.5)*
1 in 50 for PE < 40 GW	848 (10.4; 9.8–11.1)	1 (3.2; 0.1–16.7)	38 (27.0; 19.8–35.1)	15 (24.2; 14.2–36.7)
1 in 100 for PE < 40 GW	1535 (18.9; 18.0–19.8)	2 (6.5; 0.8–21.4)	52 (36.9; 28.9–45.4)	26 (41.9; 29.5–55.2)
1 in 150 for PE < 40 GW	2032 (25.0; 24.1–26.0)	2 (6.5; 0.8–21.4)	58 (41.1; 32.9–49.7)	31 (50.0; 37.0–63.0)
1 in 200 for PE < 40 GW	2481 (30.5; 29.5–31.5)	2 (6.5; 0.8–21.4)	61 (43.3; 35.0–51.9)	33 (53.2; 40.1–66.0)

Data are given as *n* (%; 95% CI). Numbers in italic represent high-risk group and those not in italic represent intermediate-risk group.
GW, gestational weeks; w, weeks.

group which contained 32.3% of pregnancies with PE at > 40 weeks.

The performance of screening for delivery with PE at > 40 weeks' gestation is poorer than that of screening for delivery with PE at < 4 weeks or at ≥ 4 weeks from assessment to 40 gestational weeks (Figure 2). This is the consequence of a smaller deviation from normal for each biomarker with an increasing interval between assessment and delivery with PE[4].

Composition of high-, intermediate- and low-risk groups

The proportion of the population stratified into high- intermediate- and low-risk groups for risk cut-offs of 1 in 3, 1 in 10, 1 in 50, 1 in 100 and 1 in 150 for PE delivering at < 4 weeks from assessment and a cut-off of 1 in 150 for PE delivering < 40 weeks' gestation and the proportion of each stratum developing PE with delivery at < 4 weeks, at ≥ 4 weeks from assessment to 40 gestational weeks and at > 40 weeks' gestation is shown in Table 3.

In the low-risk group, which accounted for 70.5% of the population, there was no case of PE at < 4 weeks and only 0.3% developed PE at ≥ 4 weeks from assessment to 40 gestational weeks; therefore, the negative predictive value for PE at < 4 weeks was 100% (5727/5727) and for PE at 4 weeks to 40 gestational weeks was 99.7% (5712/5727).

The proportion of the population classified as high risk varied according to the risk cut-off for PE at < 4 weeks, from 0.9% for a cut-off of 1 in 3 to 4.5% for cut-off of 1 in 150, and the positive predictive value for PE at < 4 weeks ranged from 31.6% (24/76) to 7.9% (29/369).

The proportion of the population classified as intermediate-risk varied according to both the risk cut-off for PE at < 4 weeks and the cut-off for PE at < 40 weeks' gestation. For example, at fixed risk cut-off of 1 in 150 for PE at < 40 weeks' gestation, the proportion of the population classified as intermediate-risk varied according to the risk cut-off for PE at < 4 weeks from 28.6% for risk cut-off of 1 in 3 to 25.0% for risk cut-off of 1 in 150; the positive predictive value for PE at ≥ 4 weeks from assessment to 40 gestational weeks ranged from 4.3% (101/2325) to 2.9% (58/2032) and the negative predictive value for PE at < 4 weeks ranged from 99.7% (2318/2325) to 99.9% (2030/2032).

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 delivering at < 4 weeks from assessment and at < 40 weeks' gestation by a combination of maternal factors, MAP, UtA-PI, PlGF and sFlt-1 at 30–34 weeks' gestation. A high-risk group would require intensive monitoring from the time of the initial assessment and up to 40 weeks' gestation, an intermediate-risk group would require intensive monitoring from 4 weeks after the initial assessment and up to 40 weeks' gestation and a low-risk group would be

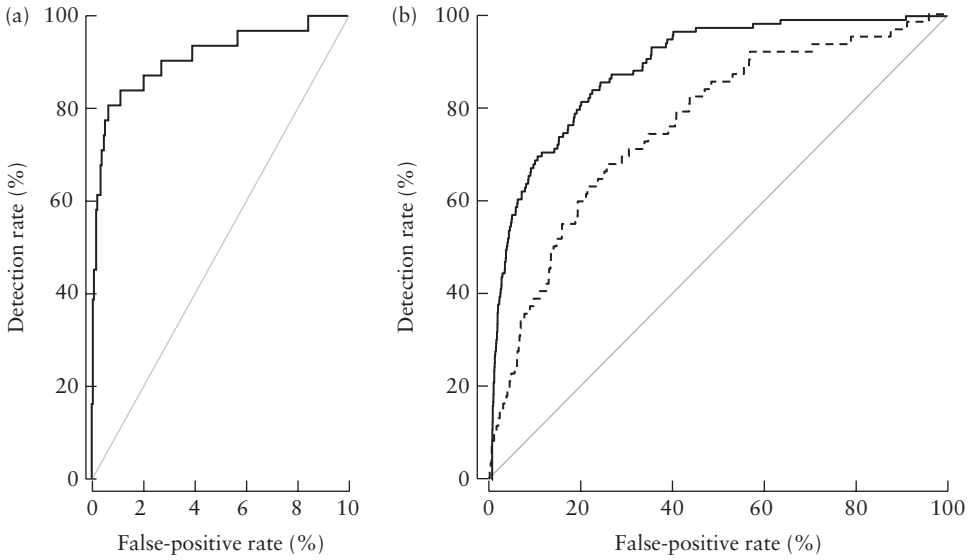

Figure 2 Receiver–operating characteristics curves for prediction of delivery with pre-eclampsia: (a) within 4 weeks of assessment, (b) from 4 weeks after assessment and up to 40 weeks' gestation (———) and after 40 weeks' gestation (- - - -), by combined screening at 30–34 weeks' gestation.

reassessed only at 40 weeks' gestation. The performance of screening at 30–34 weeks is poor for prediction of PE delivering at > 40 weeks' gestation and it would therefore be necessary to reassess all remaining pregnancies at 40 weeks to decide the best time and method of delivery.

The proportion of the population stratified into high-, intermediate- and low-risk groups and the proportion of each stratum developing PE with delivery at < 4 weeks, at ≥ 4 weeks from assessment to 40 gestational weeks and at > 40 weeks' gestation would inevitably depend on the risk cut-offs used for defining the groups. At risk cut-offs of 1 in 50 for PE at < 4 weeks and 1 in 150 for PE at < 40 weeks' gestation, about 3% and 26% of the population would be allocated to the high- and intermediate-risk groups, respectively; the high-risk group would contain 90% of pregnancies with PE at < 4 weeks and the combined high- and intermediate-risk groups would contain 89% of PE at ≥ 4 weeks from assessment to 40 gestational weeks and 68% of PE at > 40 weeks. At these risk cut-offs the low-risk group accounted for 71% of the population and, in this group, there was no case of PE at < 4 weeks and only 0.3% developed PE at ≥ 4 weeks from assessment to 40 gestational weeks, which corresponds to a negative predictive value of 99.7%.

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 growth and wellbeing, 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 UtA-PI, fourth, use of automated machines to provide accurate measurement within 40 min 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 done using the same data, which introduces a degree of optimistic bias into the results. However, our risk model[4] is a parsimonious one with just two parameters for the mean log MoM value for each of the markers and a pooled estimate of an assumed common covariance matrix which limits the degree of bias. Nevertheless, prospective evaluation using an independent test dataset is needed to validate the results.

Comparison with previous studies

Previous studies examining biomarkers in the late second or early third trimesters of pregnancy have essentially focused on the investigation of women presenting to specialist clinics with signs of hypertensive disorders with the aim of identifying the subgroup that will develop severe disease[17–24]. In a previous study at 30–34 weeks' gestation we presented the results on the performance of screening in a routine population by maternal factors and MAP, UtA-PI, PlGF and sFlt-1[4]. This study investigated a policy in which pregnancies assessed for PE at 30–34 weeks are stratified into risk groups for subsequent pregnancy management.

Clinical implications of the study

In the traditional approach to prenatal care, screening and diagnosis of PE is based on the demonstration of elevated

Table 3 Proportion of population stratified into high-, intermediate- and low-risk groups by combined screening with risk cut-offs of 1 in 3, 1 in 10, 1 in 50, 1 in 100 and 1 in 150 for pre-eclampsia (PE) delivering at < 4 weeks (w) from assessment and a risk cut-off of 1 in 150 for PE delivering < 40 weeks' gestation and the proportion of each group developing PE with delivery at < 4 weeks, at ≥ 4 weeks from assessment to 40 gestational weeks (GW) and at > 40 weeks' gestation

			Proportion of each risk group developing PE with delivery at:			
Risk cut-off for PE	*Risk group*	*All pregnancies (n = 8128)*	*< 4 w (n = 31)*	*≥ 4 w to 40 GW (n = 141)*	*> 40 GW (n = 62)*	*No PE (n = 7894)*
1 in 3 for PE < 4w and 1 in 150 for PE < 40 GW	High	76 (0.9; 0.7–1.2)	24 (31.6; 21.4–43.3)	25 (32.9; 22.5–44.6)	0 (0; 0–4.7)	27 (35.5; 24.9–47.3)
	Inter	2325 (28.6; 27.6–29.6)	7 (0.3; 0.1–0.6)	101 (4.3; 3.6–5.3)	42 (1.8; 1.3–2.4)	2175 (93.5; 92.5–94.5)
	Low	5727 (70.5; 69.5–71.5)	0 (0; 0–0.1)	15 (0.3; 0.1–0.4)	20 (0.3; 0.2–0.5)	5692 (99.4; 99.2–99.6)
1 in 10 for PE < 4w and 1 in 150 for PE < 40 GW	High	134 (1.6; 1.4–1.9)	26 (19.4; 13.1–27.1)	37 (27.6; 20.2–36.0)	1 (0.7; 0–4.1)	70 (52.2; 43.4–60.9)
	Inter	2267 (27.9; 26.9–28.9)	5 (0.2; 0.1–0.5)	89 (3.9; 3.2–4.8)	41 (1.8; 1.3–2.4)	2132 (94.0; 93.0–95.0)
	Low	5727 (70.5; 69.5–71.5)	0 (0; 0–0.1)	15 (0.3; 0.1–0.4)	20 (0.3; 0.2–0.5)	5692 (99.4; 99.2–99.6)
1 in 50 for PE < 4w and 1 in 150 for PE < 40 GW	High	254 (3.1; 2.8–3.5)	28 (11.0; 7.5–15.5)	57 (22.4; 17.5–28.1)	7 (2.8; 1.1–5.6)	162 (63.8; 57.5–69.7)
	Inter	2147 (26.4; 25.5–27.4)	3 (0.1; 0–0.4)	69 (3.2; 2.5–4.0)	35 (1.6; 1.1–2.3)	2040 (95.0; 94.0–95.9)
	Low	5727 (70.5; 69.5–71.5)	0 (0; 0–0.1)	15 (0.3; 0.1–0.4)	20 (0.3; 0.2–0.5)	5692 (99.4; 99.2–99.6)
1 in 100 for PE < 4w and 1 in 150 for PE < 40 GW	High	314 (3.9; 3.5–4.3)	28 (8.9; 6.0–12.6)	64 (20.4; 16.1–25.3)	8 (2.5; 1.1–5.0)	214 (68.2; 62.7–73.3)
	Inter	2087 (25.7; 24.7–26.6)	3 (0.1; 0–0.4)	62 (3.0; 2.3–3.8)	34 (1.6; 1.1–2.3)	1988 (95.3; 94.3–96.1)
	Low	5727 (70.5; 69.5–71.5)	0 (0; 0–0.1)	15 (0.3; 0.1–0.4)	20 (0.3; 0.2–0.5)	5692 (99.4; 99.2–99.6)
1 in 150 for PE < 4 w and 1 in 150 for PE < 40 GW	High	369 (4.5; 4.1–5.0)	29 (7.9; 5.3–11.1)	68 (18.4; 14.6–22.8)	11 (3.0; 1.5–5.3)	261 (70.7; 65.8–75.3)
	Inter	2032 (25.0; 24.1–26.0)	2 (0.1; 0–0.4)	58 (2.9; 2.2–3.7)	31 (1.5; 1.0–2.2)	1941 (95.5; 94.5–96.4)
	Low	5727 (70.5; 69.5–71.5)	0 (0; 0–0.1)	15 (0.3; 0.1–0.4)	20 (0.3; 0.2–0.5)	5692 (99.4; 99.2–99.6)

Data are given as *n* (%; 95% CI). Inter, intermediate.

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, the timing and content of clinical visits should be defined by the patient-specific risk of developing PE[25].

This study provides the framework for stratification of risk for PE based on screening at 30–34 weeks. The high-risk group can be monitored by measurement of blood pressure and urinalysis at least on a weekly basis and the women can be advised to report any symptoms associated with severe PE, such as visual disturbance and epigastric pain. In the intermediate-risk group, intensive monitoring would begin 4 weeks after the initial assessment but these women would also be advised to report any symptoms associated with severe PE. The low-risk group can be reassured that development of PE at < 40 weeks' gestation is very unlikely. In all pregnancies, the routine ultrasound examination carried out at 30–34 weeks would have already identified any possible impairment of fetal growth and in such cases the decision on timing of delivery would be based on fetal heart rate patterns and/or Doppler findings in the umbilical artery, middle cerebral artery and ductus venosus.

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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