Ultrasound Obstet Gynecol 2015; **45**: 707–714
Published online 23 April 2015 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.14777

Prediction of small-for-gestational-age neonates: screening by uterine artery Doppler and mean arterial pressure at 30–34 weeks

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KEYWORDS: mean arterial pressure; pre-eclampsia; pyramid of antenatal care; small-for-gestational age; third-trimester screening; uterine artery Doppler

ABSTRACT

Objective *To investigate the potential value of uterine artery (UtA) pulsatility index (PI) and mean arterial pressure (MAP) at 30–34 weeks' gestation in the prediction of small-for-gestational-age (SGA) neonates, in the absence of pre-eclampsia (PE).*

Methods *This was a screening study in singleton pregnancies at 30–34 weeks' gestation, including 1727 that delivered SGA neonates with a birth weight < 5th percentile and 29 122 that were unaffected by SGA, PE or gestational hypertension (normal group). Multivariable logistic regression analysis was used to determine if measuring the UtA-PI and MAP improved the prediction of SGA neonates provided by screening with maternal characteristics and medical history (maternal factors), and estimated fetal weight (EFW) calculated from fetal head circumference, abdominal circumference and femur length.*

Results *Combined screening by maternal factors and EFW Z-scores predicted 79%, 87% and 92% of SGA neonates delivering < 5 weeks following assessment, with a birth weight < 10th, < 5th and < 3rd percentiles, respectively, at a false-positive rate of 10%. The addition of UtA-PI and MAP improved the respective detection rates to 83%, 91% and 93%. Screening by maternal factors and EFW Z-scores predicted 53%, 58% and 61% of SGA delivering ≥ 5 weeks following assessment and these rates increased to 53%, 60% and 63% with the addition of UtA-PI and MAP.*

Conclusion *Combined testing by maternal factors, fetal biometry, UtA-PI and MAP at 30–34 weeks' gestation could identify a high proportion of pregnancies that deliver SGA neonates.*

INTRODUCTION

The increased risk of perinatal mortality and morbidity associated with small-for-gestational-age (SGA) neonates can be reduced substantially in cases identified prenatally, through close monitoring, timely delivery and prompt neonatal management, compared with those detected after birth[1]. A study involving 30 849 singleton pregnancies undergoing routine prenatal care examined the performance of screening for delivery of SGA neonates by a combination of maternal characteristics and medical history (maternal factors) and estimated fetal weight (EFW) from the measurements of fetal head circumference, abdominal circumference and femur length at 30–34 weeks' gestation[2]. Combined screening predicted 79%, 87% and 92% of SGA neonates delivering at < 5 weeks following assessment with a birth weight < 10th, < 5th and < 3rd percentiles, respectively, at a 10% false-positive rate (FPR). The respective detection rates for the prediction of SGA neonates delivering at ≥ 5 weeks after assessment were 53%, 58% and 61%.

Histological studies have reported that in pregnancies complicated by pre-eclampsia (PE), and in those delivering SGA neonates in the absence of PE, there is evidence of impaired placentation characterized by inadequate trophoblastic invasion of the maternal spiral arteries[3,4]. Extensive screening studies at 11–13, 20–24 and 30–34 weeks' gestation have reported that, in pregnancies that develop PE, the uterine artery pulsatility index

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Accepted: 29 December 2014

(UtA-PI) is increased before the onset of clinical signs of the disease[5–11]. There is also evidence that in such pregnancies the mean arterial pressure (MAP) at 11–13, 20–24 and 30–34 weeks is also increased before the onset of clinical signs of PE[5,6,11–14]. Screening studies in the first and second trimesters have reported that in pregnancies that deliver SGA neonates in the absence of PE, the UtA-PI is increased[15,16]. Although, in the first trimester MAP is not significantly altered in pregnancies that deliver SGA neonates in the absence of PE[15,16], two longitudinal studies have reported that an increase in blood pressure between the second and early third trimesters of pregnancy is associated with a decrease in birth weight[17,18].

The objectives of this study were first, to determine the distribution of UtA-PI and MAP levels at 30–34 weeks' gestation in pregnancies that deliver SGA neonates in the absence of PE and second, to examine the potential value of these biomarkers in improving the performance of screening for SGA by maternal factors and fetal biometry.

METHODS

The data for this study were derived from the prospective screening for adverse obstetric outcomes in women attending their routine hospital visit in the third trimester of pregnancy at King's College Hospital or University College London Hospital, London, UK, or Medway Maritime Hospital, Kent, UK, between May 2011 and April 2014.

This visit, which is attended at 30 + 0 to 34 + 6 weeks' gestation, included recording maternal characteristics and medical history and deriving the EFW from the transabdominal ultrasound measurement of fetal head circumference, abdominal circumference and femur length. Gestational age was calculated from measurement of the fetal crown–rump length at 11–13 weeks or the fetal head circumference at 19–24 weeks[19,20]. Transabdominal color Doppler ultrasound was used to visualize the left and right UtAs at the apparent crossover with the external iliac arteries[21]. Pulsed-wave Doppler was then used to obtain waveforms and when three similar waveforms had been obtained consecutively the PI was measured, and the mean PI of the two vessels was calculated. The scans were carried out by sonographers who had received the Certificate of Competence in Doppler of The Fetal Medicine Foundation (http://www.fetalmedicine.com).

In the second part of the study, we measured MAP in addition to UtA-PI. The MAP was measured by validated automated devices (3BTO-A2, Microlife, Taipei, Taiwan), which were calibrated before, and at regular intervals during, the study. The recordings were made by doctors who had received appropriate training in the use of these machines. The women undergoing the examination were in the sitting position, their arms supported at the level of their heart, and a small (22 cm), normal (22–32 cm) or large (33–42 cm) adult cuff was used, depending on the mid-arm circumference. After the women had rested for 5 min, two recordings of blood pressure were made in both arms simultaneously. We calculated the final MAP as the average of all four measurements[12].

Written informed consent was obtained from the women agreeing to participate in this study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital. This study was part of a research program on the third-trimester prediction of PE and/or SGA. In this paper, we present the results on combined screening by maternal factors and biophysical markers in the prediction of delivery of SGA neonates in the absence of PE. All patients included in the study had pregnancies resulting in a live birth or a stillbirth of phenotypically normal babies.

Patient characteristics

Patient characteristics that were recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous/assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes/no), medical history of chronic hypertension (yes/no), diabetes mellitus (yes/no), systemic lupus erythematosus or antiphospholipid syndrome (yes/no), family history of PE in the mother of the patient (yes/no) and obstetric history including parity (parous/nulliparous if no previous pregnancies $\geq$ 24 weeks' gestation), previous pregnancy with PE (yes/no), previous pregnancy with SGA (yes/no) and the time interval (years) between the last delivery and conception of the current pregnancy. Maternal weight and height were also measured.

Outcome measures

Data on pregnancy outcomes were collected from the hospital maternity records or the general medical practitioners of the women. The primary outcome of the study was SGA without PE. The newborn was considered to be SGA if the birth weight was less than the 5th percentile after correcting for gestational age at delivery (SGA < 5th)[22]. The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy[23]. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to ascertain whether the condition was chronic hypertension, PE or GH.

Statistical analysis

The observed measurements of EFW were expressed as *Z*-scores, corrected for gestational age[22]. The values of UtA-PI and MAP were $\log_{10}$ transformed to make their distributions Gaussian. Each value measured in the outcome groups was expressed as a multiple of the normal median (MoM) after adjustment for the characteristics found to provide a substantial contribution

to the $\log_{10}$ transformed value[24,25]. The Mann–Whitney *U*-test was used to compare the median MoM values of UtA-PI and MAP between the outcome groups. Regression analysis was used to determine the significance of the association between the $\log_{10}$MoM of UtA-PI and MAP with the assessment-to-delivery interval and birth weight *Z*-score.

The *a-priori* risks for SGA $< 5^{th}$ delivering at < 5 weeks and ≥ 5 weeks following assessment were determined using the algorithms derived from multivariable logistic regression analysis of maternal characteristics and history, as previously described[2]. Multivariable logistic regression analysis was then used to determine if the maternal factor-derived logit (*a-priori* risks), $\log_{10}$MoM UtA-PI, $\log_{10}$MoM MAP and EFW *Z*-score had a significant contribution in predicting SGA $< 5^{th}$ delivering at < 5 and at ≥ 5 weeks following assessment. The performance of screening was determined by receiver–operating characteristics (ROC) curves. Similarly, the algorithm was used to determine the performance of screening for SGA defined by birth weight $< 10^{th}$ percentile (SGA $< 10^{th}$) and birth weight $< 3^{rd}$ percentile (SGA $< 3^{rd}$).

The statistical software packages SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analysis.

RESULTS

The study population comprised 30 849 pregnancies, including 1727 (5.6%) that delivered SGA $< 5^{th}$ neonates, in the absence of PE, and 29 122 (94.4%) pregnancies that were unaffected by these outcomes. The characteristics of the study population are presented in a previous publication[2].

Normal pregnancy outcome

The mean ± SD, 90^{th} and 95^{th} percentiles of $\log_{10}$MoM UtA-PI were 0.005 ± 0.111, 0.145 and 0.197, respectively. The mean ± SD, 90^{th} and 95^{th} percentiles of $\log_{10}$MoM MAP were 0.000 ± 0.034, 0.042 and 0.054, respectively.

There was no significant association between $\log_{10}$ MoM values of UtA-PI and MAP ($r = -0.010$; $P = 0.095$). There was a significant inverse association between $\log_{10}$MoM UtA-PI with the assessment-to-delivery interval ($r = -0.086$; $P < 0.0001$) and birth-weight *Z*-score ($r = -0.070$; $P < 0.0001$), and between $\log_{10}$MoM MAP with the assessment-to-delivery interval ($r = -0.068$; $P < 0.0001$) and birth-weight *Z*-score ($r = -0.014$; $P = 0.021$).

Small-for-gestational age

The median MoM values of UtA-PI and MAP at 30–34 weeks' gestation were significantly higher in the SGA $< 5^{th}$ group than in the group with normal outcome (Table 1).

There was a significant direct association between $\log_{10}$MoM values of UtA-PI and MAP ($r = 0.128$; $P < 0.0001$). There was a significant inverse association between $\log_{10}$MoM UtA-PI and assessment-to-delivery interval ($r = -0.239$; $P < 0.0001$; Figure 1a) and between

Table 1 Uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) at 30–34 weeks' gestation in pregnancies that delivered small-for-gestational-age (SGA) neonates with birth weight $< 5^{th}$ percentile, in the absence of pre-eclampsia, and in unaffected pregnancies

Outcome group	n *(%)*	*Median (IQR)*	*MoM (median (IQR))*	*Log_{10} MoM (mean ± SD)*	*$> 95^{th}$ percentile* (n *(%, 95% CI))*	*$> 90^{th}$ percentile* (n *(%, 95% CI))*
UtA-PI						
Normal ($n = 29\,122$)	28 620 (98.3)	0.720 (0.615–0.855)	0.996 (0.854–1.176)	0.005 ± 0.111	1431 (5.0, 4.8–5.3)	2862 (10.0, 9.7–10.4)
All SGA ($n = 1727$)	1683 (97.5)	0.790 (0.665–0.990)†	1.101 (0.915–1.378)†	0.056 ± 0.134†	224 (13.3, 11.8–15.0)†	402 (23.9, 21.9–26.0)†
SGA delivering < 5 weeks* ($n = 277$)	268 (96.8)	0.925 (0.715–1.225)‡	1.281 (0.994–1.690)‡	0.116 ± 0.160‡	89 (33.2, 27.8–39.0)‡	118 (44.0, 38.2–50.0)‡
SGA delivering ≥ 5 weeks* ($n = 1450$)	1415 (97.6)	0.775 (0.655–0.960)‡	1.077 (0.909–1.328)‡	0.045 ± 0.126‡	155 (11.0, 9.4–12.7)‡	284 (20.1, 18.1–22.2)‡
MAP						
Normal ($n = 29\,122$)	26 921 (92.4)	87.0 (82.1–92.2)	0.999 (0.948–1.054)	0.000 ± 0.034	1346 (5.0, 4.7–5.3)	2692 (10.0, 9.6–10.4)
All SGA ($n = 1727$)	1548 (89.6)	87.3 (82.3–93.1)†	1.020 (0.962–1.079)†	0.009 ± 0.038†	166 (10.7, 9.3–12.4)†	274 (17.7, 15.9–19.7)†
SGA delivering < 5 weeks* ($n = 277$)	227 (81.9)	91.5 (84.8–97.1)‡	1.054 (0.987–1.126)‡	0.024 ± 0.045‡	51 (22.5, 17.5–28.3)‡	68 (30.0, 24.4–36.2)‡
SGA delivering ≥ 5 weeks* ($n = 1450$)	1321 (91.1)	87.0 (82.0–92.0)	1.013 (0.960–1.072)‡	0.006 ± 0.036‡	115 (8.7, 7.3–10.3)‡	206 (15.6, 13.7–17.7)‡

n is number of cases for which UtA-PI or MAP were recorded. *Following assessment. †Comparison between normal and total SGA pregnancies: chi-square test or Fisher's exact test for categorical variables and Mann–Whitney *U*-test or Student's *t*-test for continuous variables ($P < 0.05$). ‡Comparison between normal and SGA pregnancies delivering < 5 weeks and ≥ 5 weeks following assessment: chi-square test or Fisher's exact test for categorical variables and Mann–Whitney *U*-test or Student's *t*-test for continuous variables ($P < 0.025$). IQR, interquartile range; MoM, multiples of the unaffected median.

$\log_{10}$MoM UtA-PI and birth-weight *Z*-score ($r = -0.138$; $P < 0.0001$; Figure 1b), and between $\log_{10}$MoM MAP and the assessment-to-delivery interval ($r = -0.198$; $P < 0.0001$; Figure 1c) and birth-weight *Z*-score ($r = -0.084$; $P = 0.001$; Figure 1d).

Multivariable logistic regression analysis demonstrated that in the prediction of SGA < 5th delivering < 5 weeks and ≥ 5 weeks following assessment, there were significant contributions from maternal characteristics, EFW *Z*-score, UtA-PI and MAP (Tables S1 and S2). The

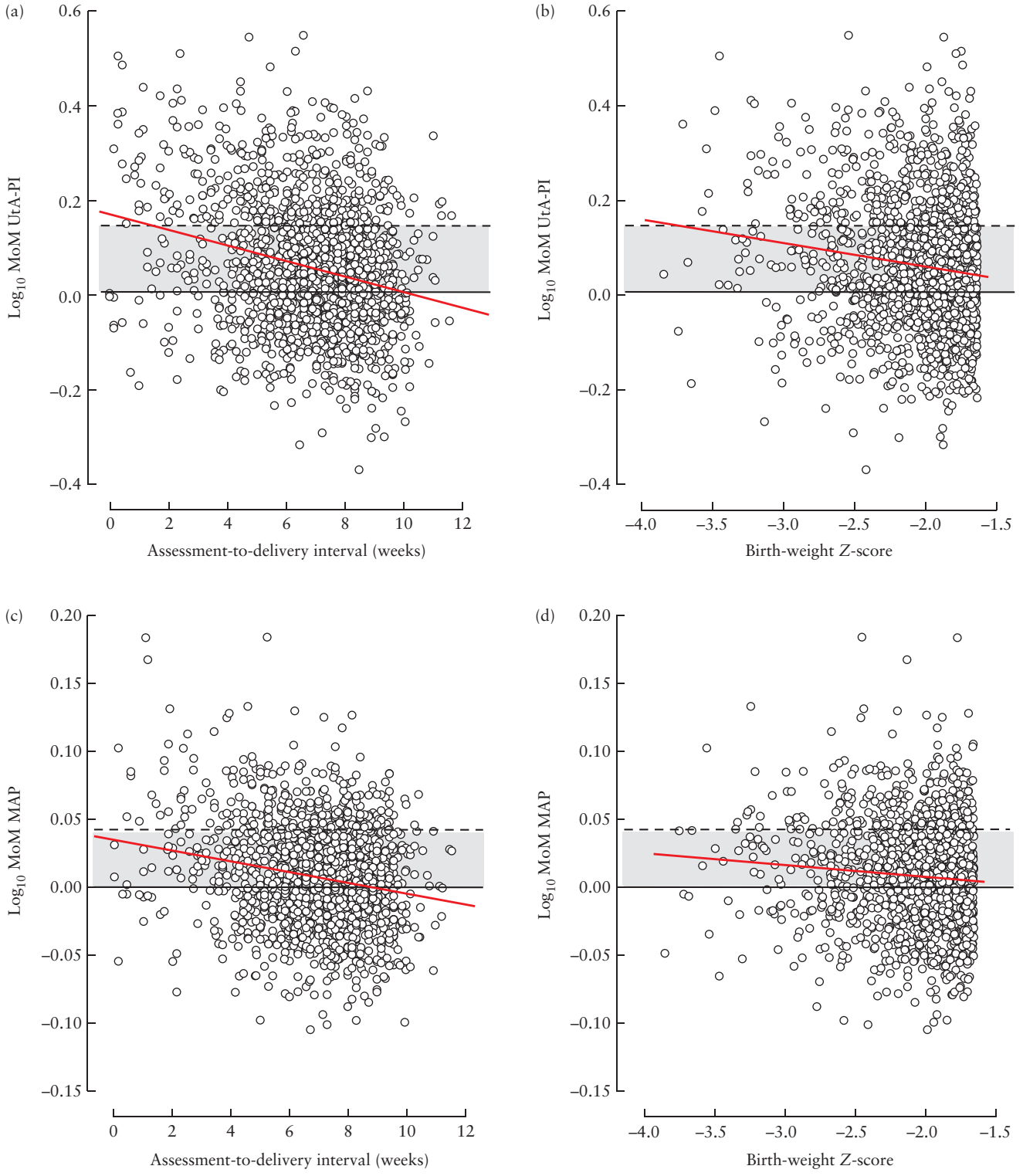

Figure 1 Relationship of uterine artery pulsatility index (UtA-PI) $\log_{10}$multiples of the median (MoM) at 30–34 weeks' gestation with assessment-to-delivery interval (a) and birth-weight *Z*-score (b) and mean arterial pressure (MAP) $\log_{10}$MoM at 30–34 weeks' gestation with assessment-to-delivery interval (c) and birth-weight *Z*-score (d) in pregnancies delivering small-for-gestational-age neonates with birth weight < 5th percentile, plotted on the range (gray box) between the 50th (——) and 90th (– – –) percentiles of the normal range.

areas under the ROC curves and the detection rates of SGA < 10th, SGA < 5th and SGA < 3rd delivering < 5 and ≥ 5 weeks after assessment, with an FPR of 5% and 10%, when screening by maternal characteristics, EFW *Z*-score, UtA-PI, MAP and their combination are given in Tables 2 and S3 and Figure 2.

DISCUSSION

Main findings of the study

The findings of this study demonstrate that in women who deliver SGA neonates in the absence of PE, UtA-PI and MAP at 30–34 weeks' gestation are increased and the increase is inversely related to the severity of the disease, reflected in the gestational age at delivery and the birth-weight *Z*-score. The selected intervals of < 5 and ≥ 5 weeks after assessment correspond to < 37 and ≥ 37 weeks' gestation.

Screening for SGA with birth weight < 10th, < 5th and < 3rd percentiles by maternal factors predicted 30%, 31% and 32% of those that delivered < 5 weeks following assessment, at a FPR of 10%. The respective detection rates for the prediction of SGA neonate delivered ≥ 5 weeks following assessment were 28%, 32% and 34%. Screening by a combination of maternal factors

Table 2 Detection rate in screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th and < 3rd percentile in the absence of pre-eclampsia, delivering < 5 weeks or ≥ 5 weeks following assessment, by maternal characteristics and history, estimated fetal weight (EFW), uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) and their combination at 30–34 weeks' gestation

	Detection rate (%, 95% CI) for fixed false-positive rate (FPR)			
	Delivery < 5 weeks		*Delivery ≥ 5 weeks*	
Screening test	*FPR = 5%*	*FPR = 10%*	*FPR = 5%*	*FPR = 10%*
SGA < 10th percentile				
Maternal characteristics and history	19.5 (15.9–23.4)	30.4 (26.2–34.9)	17.0 (15.7–18.4)	27.6 (26.0–29.3)
UtA-PI	26.5 (22.4–31.0)	36.5 (32.0–41.3)	10.1 (9.1–11.3)	18.3 (16.9–19.8)
MAP	16.8 (13.1–20.9)	24.5 (20.2–29.1)	7.6 (6.6–8.6)	13.9 (12.6–15.2)
UtA-PI and MAP	30.4 (25.7–35.4)	39.0 (33.9–44.2)	10.3 (9.2–11.5)	18.1 (16.7–19.6)
EFW	66.2 (61.6–70.6)	76.1 (71.8–79.9)	32.3 (30.7–34.0)	47.0 (45.2–48.8)
Maternal characteristics and history plus:				
UtA-PI	33.3 (28.8–37.9)	44.4 (39.7–49.3)	18.0 (16.6–19.4)	30.5 (28.8–32.2)
MAP	25.8 (21.4–30.5)	39.9 (34.9–45.0)	17.0 (15.6–18.4)	27.8 (26.1–29.5)
UtA-PI and MAP	36.7 (31.8–41.9)	47.2 (42.0–52.5)	19.5 (18.0–21.0)	29.8 (28.0–31.5)
EFW	67.6 (63.0–71.9)	79.2 (75.1–82.9)	36.2 (34.5–38.0)	52.7 (50.9–54.5)
Maternal characteristics and history, EFW plus:				
UtA-PI	70.0 (65.4–74.3)	81.6 (77.6–85.2)	37.4 (35.7–39.2)	52.4 (50.6–54.2)
MAP	69.7 (64.8–74.3)	79.5 (75.1–83.5)	36.8 (35.0–38.6)	52.0 (50.1–53.8)
All markers	70.2 (65.2–74.8)	82.6 (78.3–86.4)	37.3 (35.5–39.2)	52.8 (50.9–54.7)
SGA < 5th percentile				
Maternal characteristics and history	22.4 (17.6–27.8)	31.1 (25.6–36.9)	19.7 (17.6–21.8)	31.9 (30.8–35.9)
UtA-PI	33.2 (27.6–39.2)	44.0 (38.0–50.2)	11.0 (9.4–12.7)	20.1 (18.0–22.3)
MAP	22.5 (17.2–28.5)	30.0 (24.1–36.4)	8.7 (7.2–10.4)	15.6 (13.7–17.7)
UtA-PI and MAP	38.9 (32.4–45.7)	46.6 (39.9–53.4)	13.0 (11.2–15.0)	20.9 (18.7–23.2)
EFW	74.4 (68.8–79.4)	83.8 (78.5–87.9)	38.8 (36.2–41.3)	54.0 (51.3–56.5)
Maternal characteristics and history plus:				
UtA-PI	40.7 (34.7–46.8)	51.5 (45.3–57.6)	21.1 (19.0–23.3)	35.7 (33.2–38.2)
MAP	33.9 (27.8–40.5)	46.7 (40.1–53.4)	19.5 (17.4–21.8)	31.6 (29.1–34.2)
UtA-PI and MAP	44.8 (38.1–51.6)	54.8 (47.9–61.4)	23.0 (20.7–25.4)	35.0 (32.4–37.7)
EFW	79.8 (74.6–84.4)	87.4 (82.9–91.0)	42.1 (39.5–44.7)	58.4 (55.8–61.0)
Maternal characteristics and history, EFW plus:				
UtA-PI	84.0 (79.0–88.1)	88.8 (84.4–92.3)	44.6 (42.0–47.2)	59.4 (56.8–61.9)
MAP	79.3 (73.4–84.4)	88.6 (83.2–92.0)	43.2 (40.5–45.9)	58.1 (55.4–60.8)
All markers	83.7 (78.2–88.3)	90.5 (85.8–94.0)	45.1 (42.3–47.8)	60.2 (57.4–63.0)
SGA < 3rd percentile				
Maternal characteristics and history	22.2 (16.5–28.8)	31.8 (25.2–38.9)	21.6 (18.9–24.5)	33.9 (30.8–37.2)
UtA-PI	34.1 (27.2–41.4)	47.3 (39.8–54.8)	12.2 (10.1–14.6)	22.2 (19.4–25.1)
MAP	23.3 (16.7–31.0)	30.1 (22.8–38.3)	9.7 (7.7–12.0)	17.3 (14.7–20.2)
UtA-PI and MAP	38.7 (30.7–47.3)	48.6 (40.1–57.1)	14.5 (12.0–17.1)	23.3 (20.4–26.5)
EFW	82.0 (75.8–87.2)	88.4 (82.9–92.6)	42.2 (38.9–45.5)	57.4 (54.0–60.7)
Maternal characteristics and history plus:				
UtA-PI	41.2 (34.0–48.7)	53.3 (45.8–60.7)	23.4 (20.6–26.3)	39.0 (35.7–42.3)
MAP	33.6 (26.0–41.8)	46.6 (38.3–55.0)	21.3 (18.5–24.3)	35.9 (32.6–39.4)
UtA-PI and MAP	46.5 (38.1–55.0)	55.6 (47.1–64.0)	25.5 (22.5–28.8)	40.2 (36.7–43.8)
EFW	86.2 (80.5–90.8)	92.1 (87.2–95.5)	45.2 (41.8–48.5)	61.0 (57.7–64.3)
Maternal characteristics and history, EFW plus:				
UtA-PI	90.1 (84.8–94.0)	92.3 (87.4–95.7)	47.9 (44.5–51.3)	62.2 (58.9–65.5)
MAP	85.6 (78.9–90.9)	91.8 (86.1–95.7)	47.1 (43.6–50.7)	61.3 (57.8–64.7)
All markers	89.4 (83.2–94.0)	93.0 (87.4–96.6)	49.0 (45.4–52.6)	63.3 (59.8–66.7)

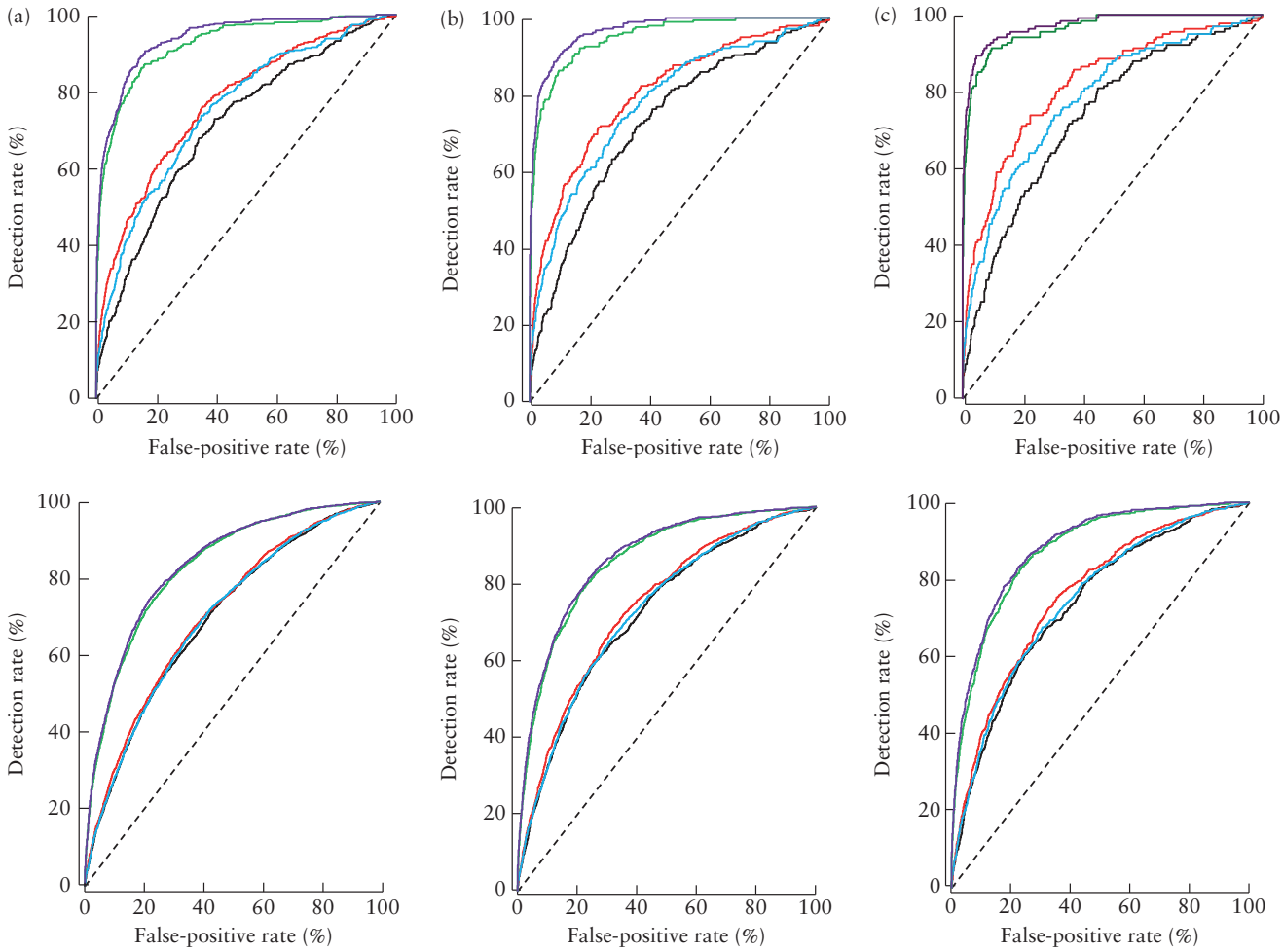

Figure 2 Receiver–operating characteristics curves of maternal factors (——) and maternal factors with uterine artery pulsatility index (——), mean arterial pressure (——), estimated fetal weight *Z*-score (——) and their combination (——), at 30–34 weeks' gestation, in the prediction of small-for-gestational-age neonates with birth weight < 10th (a), < 5th (b) or < 3rd (c) percentile, delivering < 5 (top) or ≥ 5 (bottom) weeks following assessment.

with UtA-PI and MAP predicted 47%, 55% and 56% of those delivered < 5 weeks following assessment and 30%, 35% and 40% of those delivering ≥ 5 weeks following assessment. The prediction of SGA neonates provided by UtA-PI was superior to that of MAP, but for delivery within 5 weeks following assessment, combined screening was superior to that achieved by either biophysical marker alone.

The best performance of screening for SGA with birth weight < 10th, < 5th and < 3rd percentile was achieved by a combination of maternal factors and EFW *Z*-score, with detection rates of 79%, 87% and 92%, at an FPR of 10%, for delivery < 5 weeks after assessment and 53%, 58% and 61% for delivery ≥ 5 weeks[2]. The performance of screening was improved by the addition of UtA-PI and MAP, with an increase in detection rates to 83%, 91% and 93% for delivery < 5 weeks after assessment and 53%, 60% and 63% for delivery ≥ 5 weeks.

Strengths and limitations of the study

The strengths of this third-trimester screening study for SGA in the absence of PE include, first, the examination of a large population of pregnant women attending for routine care in a gestational-age range that is widely used for the assessment of fetal growth and wellbeing; second, use of a specific methodology and appropriately-trained doctors to measure UtA-PI and MAP; third, expression of the values of UtA-PI and MAP as MoMs, after adjustment for factors that affect the measurements; and fourth, use of Bayes' theorem to combine the prior risk from maternal factors with biomarkers to estimate the patient-specific risks and the performance of screening for SGA of different severities, delivering at selected intervals from the time of assessment.

There are two major limitations to the study. First, the results of the 30–34 weeks' scan were made available to the patients' obstetricians, who would have taken specific actions to further monitor cases of suspected SGA and, as a consequence, the performance of screening, especially for severe SGA delivering < 5 weeks from assessment, would be positively biased. Second, this was a cross-sectional study and for most cases of SGA, especially those delivering ≥ 5 weeks after screening, the diagnosis was made after birth. Consequently, we do not have complete data on prenatal markers of fetal

hypoxia, such as abnormal fetal Doppler, that would help distinguish between fetal growth restriction (FGR) due to impaired placentation and constitutionally-small fetuses. However, the proportion of FGR to constitutional SGA is likely to be higher in the SGA < 5th and SGA < 3rd groups than in the SGA < 10th group and in those delivering < 5 weeks following assessment than in those delivering ≥ 5 weeks, and this is reflected in the better performance of screening for the earlier and more severe forms of SGA.

Comparison with findings from previous studies

Previous studies that examined pregnancies with SGA fetuses in the third trimester reported that the outcome was worse in cases with Doppler evidence of increased, rather than normal, impedance to flow in the UtAs[26,27].

Previous screening studies in women attending for routine pregnancy care at 30–34 weeks' gestation have examined the prediction of PE by a combination of maternal factors, UtA-PI and MAP[10,11,14]. In the largest study, which included 350 cases of PE and 13 878 normal pregnancies, about 90% of cases developing PE and requiring delivery within the subsequent 4 weeks, but less than half of those with PE developing after this interval, were detected, at an FPR of 5%[11]. Consequently, the performance of such screening for PE is superior to that of screening for SGA in the absence of PE.

Implications for clinical practice

In the proposed new pyramid of pregnancy care[28], an integrated clinical assessment at 11–13 weeks' gestation, in which biophysical and biochemical markers are combined with maternal characteristics and medical history, aims to identify pregnancies at high risk of developing PE and/or SGA and, through pharmacological intervention with medications such as low-dose aspirin, reduce the prevalence of these complications[29,30]. In pregnancies with impaired placentation, the use of low-dose aspirin beyond 16 weeks' gestation does not prevent the subsequent development of PE and/or SGA[29–32]. Consequently, the objective of screening at around 32 weeks' gestation is not to prevent SGA, but rather to identify the high-risk group and, through close monitoring of such pregnancies, to minimize adverse perinatal events by determining the appropriate time and place for iatrogenic delivery.

Assessment at 30–34 weeks by a combination of maternal factors, fetal biometry, UtA-PI and MAP identifies a high proportion of SGA neonates. Although the apparent additional benefit from UtA-PI and MAP in the prediction of SGA is small, these measurements are included in the integrated third-trimester assessment because of the great benefit in detecting PE[11]. Future studies will investigate the potential improvement in performance of screening for SGA by the inclusion of biochemical markers.

ACKNOWLEDGMENTS

This study was supported by a grant from The Fetal Medicine Foundation (Charity No: 1037116) and by the European Union 7th Framework Programme - FP7-HEALTH-2013-INNOVATION-2 (ASPRE Project # 601852).

REFERENCES

1. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? *Ultrasound Obstet Gynecol* 2005; **25**: 258–264.
2. Bakalis S, Silva M, Akolekar R, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by fetal biometry at 30–34 weeks. *Ultrasound Obstet Gynecol* 2015; **45**; 551–558.
3. Sheppard BL, Bonnar J. An ultrastructural study of utero-placental spiral arteries in hypertensive and normotensive pregnancy and fetal growth retardation. *Br J Obstet Gynaecol* 1981; **88**: 695–705.
4. Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. *Br J Obstet Gynaecol* 1986; **93**: 1049–1059.
5. Poon LC, Kametas NA, Maiz N, Akolekar R, Nicolaides KH. First-trimester prediction of hypertensive disorders in pregnancy. *Hypertension* 2009; **53**: 812–818.
6. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther* 2013; **33**: 8–15.
7. Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol* 2000; **96**: 559–564.
8. Yu CK, Smith GC, Papageorghiou AT, Cacho AM, Nicolaides KH. An integrated model for the prediction of preeclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women. *Am J Obstet Gynecol* 2005; **193**: 429–436.
9. Gallo DM, Poon LC, Akolekar R, Syngelaki A, Nicolaides KH. Prediction of preeclampsia by uterine artery Doppler at 20–24 weeks' gestation. *Fetal Diagn Ther* 2013; **34**: 241–247.
10. Lai J, Poon LC, Pinas A, Bakalis S, Nicolaides KH. Uterine artery Doppler at 30–33 weeks' gestation in the prediction of preeclampsia. *Fetal Diagn Ther* 2013; **33**: 156–163.
11. Tayyar A, Garcia-Tizon Larroca S, Poon LC, Wright D, Nicolaides KH. Competing risk model in screening for preeclampsia by mean arterial pressure and uterine artery pulsatility index at 30–33 weeks' gestation. *Fetal Diagn Ther* 2014; **36**: 18–27.
12. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11–13 weeks' gestation. *Fetal Diagn Ther* 2012; **31**: 42–48.
13. Gallo D, Poon LC, Fernandez M, Wright D, Nicolaides KH. Prediction of preeclampsia by mean arterial pressure at 11–13 and 20–24 weeks' gestation. *Fetal Diagn Ther* 2014; **36**: 28–37.
14. Lai J, Poon LC, Bakalis S, Chiriac R, Nicolaides KH. Systolic, diastolic and mean arterial pressure at 30–33 weeks in the prediction of preeclampsia. *Fetal Diagn Ther* 2013; **33**: 173–181.
15. Karagiannis G, Akolekar R, Sarquis R, Wright D, Nicolaides KH. Prediction of small-for-gestation neonates from biophysical and biochemical markers at 11–13 weeks. *Fetal Diagn Ther* 2011; **29**: 148–154.
16. Khalil A, Sodre D, Syngelaki A, Akolekar R, Nicolaides KH. Maternal hemodynamics at 11–13 weeks of gestation in pregnancies delivering small for gestational age neonates. *Fetal Diagn Ther* 2012; **32**: 231–238.
17. Bakker R, Steegers EA, Hofman A, Jaddoe VW. Blood pressure in different gestational trimesters, fetal growth, and the risk of adverse birth outcomes: the generation R study. *Am J Epidemiol* 2011; **174**: 797–806.
18. Churchill D, Perry IJ, Beevers DG. Ambulatory blood pressure in pregnancy and fetal growth. *Lancet* 1997; **349**: 7–10.
19. Robinson HP, Fleming JE. A critical evaluation of sonar "crown–rump length" measurements. *Br J Obstet Gynaecol* 1975; **82**: 702–710.
20. Snijders RJ, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34–48.
21. Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol* 2000; **96**: 559–564.
22. Poon LCY, Volpe N, Muto B, Syngelaki A, Nicolaides KH. Birthweight with gestation and maternal characteristics in live births and stillbirths. *Fetal Diagn Ther* 2012; **32**: 156–165.
23. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001; **20**: IX–XIV.
24. Tayyar A, Guerra L, Wright A, Wright D, Nicolaides KH. Uterine artery pulsatility index in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 689–697.
25. Wright A, Wright D, Ispas CA, Poon LC, Nicolaides KH. Mean arterial pressure in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 698–706.
26. Severi FM, Bocchi C, Visentin A, Falco P, Cobellis L, Florio P, Zagonari S, Pilu G. Uterine and fetal cerebral Doppler predict the outcome of third-trimester

small-for-gestational age fetuses with normal umbilical artery Doppler. *Ultrasound Obstet Gynecol* 2002; **19**: 225–228.
27. Ghosh G, Gudmundsson S. Uterine and umbilical artery Doppler are comparable in predicting perinatal outcome of growth-restricted fetuses. *BJOG* 2009; **116**: 424–430.
28. Nicolaides KH. Turning the pyramid of prenatal care. *Fetal Diagn Ther* 2011; **29**: 183–196.
29. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, Forest JC, Giguère Y. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010; **116**: 402–414.
30. Roberge S, Villa P, Nicolaides K, Giguère Y, Vainio M, Bakthi A, Ebrashy A, Bujold E. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. *Fetal Diagn Ther* 2012; **31**: 141–146.
31. Yu CK, Papageorghiou AT, Parra M, Palma DR, Nicolaides KH. Randomized controlled trial using low-dose aspirin in the prevention of pre-eclampsia in women with abnormal uterine artery Doppler at 23 weeks' gestation. *Ultrasound Obstet Gynecol* 2003; **22**: 233–239.
32. Roberge S, Nicolaides KH, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. *Ultrasound Obstet Gynecol* 2013; **41**: 491–499.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Fitted regression models with maternal characteristics and history, uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP) and estimated fetal weight (EFW) at 30–34 weeks' gestation for prediction of small-for-gestational-age neonates with birth weight < 5th percentile, delivering < 5 weeks following assessment, in the absence of pre-eclampsia

Table S2 Fitted regression models with maternal characteristics and history, uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP) and estimated fetal weight (EFW) at 30–34 weeks' gestation for prediction of small-for-gestational-age neonates with birth weight < 5th percentile, delivering ≥ 5 weeks following assessment, in the absence of pre-eclampsia

Table S3 Areas under the receiver–operating characteristics curve (AUC) in screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th or < 3rd percentile, in the absence of pre-eclampsia, delivering < 5 weeks or ≥ 5 weeks following assessment, using maternal characteristics and history, estimated fetal weight (EFW), uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP) and their combination at 30–34 weeks' gestation