Prediction of small-for-gestational-age neonates: screening by uterine artery Doppler and mean arterial pressure at 19–24 weeks

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

ABSTRACT

Objective To investigate the potential value of uterine artery (UtA) pulsatility index (PI) and mean arterial pressure (MAP) at 19–24 weeks’ gestation, in combination with maternal characteristics and medical history and fetal biometry in the prediction of delivery of small-for-gestational-age (SGA) neonates in the absence of pre-eclampsia (PE) and to examine the potential value of such assessment in deciding whether the third-trimester scan should be performed at 32 and/or 36 weeks’ gestation.

Methods This was a screening study in 63 975 singleton pregnancies, including 3702 (5.8%) that delivered SGA neonates with birth weight < 5th percentile (SGA < 5th) in the absence of PE. Multivariable logistic regression analysis was used to determine if screening by a combination of maternal factors, fetal head circumference (HC), abdominal circumference (AC), femur length (FL), UtA-PI and MAP had significant contribution in predicting SGA neonates. A model was developed to select gestational age for the third-trimester assessment, at 32 and/or 36 weeks, based on the results of screening at 19–24 weeks.

Results The detection rates (DRs) of combined screening by maternal factors, fetal biometry and UtA-PI at 19–24 weeks were 90%, 68% and 44% for SGA < 5th delivering < 32, 32–36 and ≥ 37 weeks’ gestation, respectively, at a false-positive rate (FPR) of 10%. The performance of screening was not improved by the addition of MAP. The DR of SGA < 5th delivering at 32–36 weeks improved from 68% to 90% with screening at 32 rather than at 19–24 weeks. Similarly, the DR of SGA < 5th delivering ≥ 37 weeks improved from 44% with screening at 19–24 weeks to 59% and 76% when screening at 32 and 36 weeks, respectively. In a hypothetical model, it was estimated that if the desired objective of prenatal screening is to predict about 80% of the cases of SGA < 5th, it would be necessary to select 17% of the population at the 19–24-week assessment to be reassessed at 32 weeks and 38% to be reassessed at 36 weeks; 62% would not require a third-trimester scan.

Conclusion Prenatal prediction of a high proportion of SGA neonates necessitates the undertaking of screening in the third trimester of pregnancy in addition to assessment in the second trimester, and the timing of such screening, at 32 and/or 36 weeks, should be contingent on the results of the assessment at 19–24 weeks. Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.

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 and timely delivery and prompt neonatal care4. The traditional approach of identifying pregnancies at high risk of delivering SGA neonates is maternal abdominal palpation or measurement of the symphysis–fundus height, but the performance of such screening is poor, with a detection rate (DR) of less than 30%2,3. A routine third-trimester scan is, by far, superior in identifying pregnancies at high risk of delivering SGA neonates than maternal abdominal palpation or measurement of the symphysis–fundus height, but the performance of such screening is poor, with a detection rate (DR) of less than 30%2,3. A routine third-trimester scan is, by far, superior in identifying pregnancies at high risk of delivering SGA neonates than abdominal palpation4–7. However, the timing of such a scan is uncertain. About 90% of SGA neonates with birth weight < 5th percentile (SGA < 5th) are born ≥ 37 weeks’ gestation and 10% are born < 37 weeks7. In the prediction of SGA delivering ≥ 37 weeks,
screening at 36 weeks is superior to screening at 32 weeks but at the inevitable expense of missing most cases delivering < 37 weeks. We have proposed that the decision on whether a third-trimester scan is necessary and, if so, whether this is carried out at 32 and/or 36 weeks should be contingent on the results of the assessment at 19–24 weeks. It was estimated that if the method of screening at 19–24 weeks is a combination of maternal characteristics and medical history (maternal factors) with fetal biometry and the desired objective of prenatal screening is to predict about 80% of the cases of SGA < 5th, it would be necessary to select about 28% of the population at the 19–24-week scan to be reassessed at 32 weeks and 41% to be reassessed at 36 weeks.

Extensive studies at 19–24 weeks’ gestation have reported that screening by measurement of uterine artery (UtA) pulsatility index (PI) can identify a high proportion of pregnancies that develop pre-eclampsia (PE), especially those with severe early-onset disease that is commonly associated with fetal growth restriction. These studies have also reported that increased UtA-PI is observed in pregnancies with SGA fetuses/neonates in the absence of PE. A screening study investigating 3347 pregnancies at 22–24 weeks’ gestation reported that the performance of screening for PE was improved by the addition of mean arterial pressure (MAP) to UtA-PI, but MAP was not significantly altered in pregnancies that deliver SGA without PE.

The objectives of this study, in women with a singleton pregnancy undergoing routine antenatal care, were first, to investigate the potential value of combined screening by maternal factors, fetal biometry, UtA-PI and MAP at 19–24 weeks’ gestation in the prediction of delivery of SGA neonates in the absence of PE and second, to examine the potential value of such assessment in deciding whether the third-trimester scan should be at 32 and/or 36 weeks’ gestation.

**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 second trimester of pregnancy at King’s College Hospital, London, between April 2006 and June 2014, Medway Maritime Hospital, Kent, between February 2007 and June 2014 and at University College London Hospital, London, between May 2009 and September 2013.

This visit, which is attended at 19 + 0 to 24 + 6 weeks’ gestation, included the recording of maternal factors and estimation of fetal size from transabdominal ultrasound measurement of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL)17. Gestational age was calculated by measurement of the fetal crown–rump length at 11–13 weeks or the fetal HC at this visit17,18. Transvaginal color Doppler ultrasound was used to visualize the left and right UtAs at the level of the internal os19. Pulsed-wave Doppler was then used to obtain waveforms and, when three similar waveforms were 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). Women with a mean UtA-PI > 1.6 were followed up with growth scans at 28, 32 and 36 weeks’ gestation. Women with normal UtA Doppler received routine antenatal care.

In the second part of the study, we measured the MAP in addition to the measurement of 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 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.

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 second-trimester prediction of PE and/or SGA. In this paper, we present the results on combined screening with maternal factors and biophysical markers in the prediction of SGA neonates in the absence of PE. All patients included in the study had pregnancies resulting in a live birth or stillbirth of phenotypically normal babies ≥ 24 weeks’ gestation.

**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 (SLE) or antiphospholipid syndrome (APS), family history of PE in the mother of the patient (yes/no) and obstetric history including parity (parous/nulliparous if no previous pregnancies ≥ 24 weeks’ gestation), previous pregnancy with PE (yes/no), maternal age at delivery and conception of the current pregnancy in years. The maternal weight and height were also measured.

**Outcome measures**

Data on pregnancy outcome 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)\(^{21}\). The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy\(^ {22}\). The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to confirm if the condition was chronic hypertension, PE or GH.

**Statistical analysis**

The observed measurements of fetal HC, AC and FL were expressed as the respective Z-score, corrected for gestational age\(^ {17}\). The observed 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\(^ {23,24}\). 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 association between log\(_{10}\) MoM of UtA-PI and MAP with gestational age at delivery and birth-weight Z-score.

The a-priori risk for SGA < 5th delivering < 37 weeks’ gestation was determined using the algorithm derived from the multivariable logistic regression analysis of maternal factors for the prediction of SGA < 5th delivering < 37 weeks’ gestation\(^ {7}\). Multivariable logistic regression analysis was used to determine if the maternal factor-derived logit (a-priori risk), the Z-scores for HC, AC and FL and log\(_{10}\) MoM values of UtA-PI and MAP had significant contributions in predicting SGA < 5th delivering < 37 weeks’ gestation. 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 < 5th delivering < 32, at 32–36 and ≥ 37 weeks’ gestation and SGA defined by birth weight < 10th percentile (SGA < 10th) and < 3rd percentile (SGA < 3rd).

The datasets from our previous studies of fetal biometry, UtA-PI and MAP at 30–34 weeks’ gestation\(^ {25}\) and fetal biometry at 35–37 weeks\(^ {26}\) were used to combine the maternal factor-derived logit (a-priori risk), using the algorithm derived from the previously reported multivariable logistic regression analysis\(^ {7}\), with fetal biometry, UtA-PI and MAP at 30–34 weeks\(^ {7,25}\) and fetal biometry at 35–37 weeks\(^ {6,26}\) to determine the performance of screening for SGA < 5th delivering at 32–36 weeks and ≥ 37 weeks, respectively. At 35–37 weeks, the performance of screening by maternal factors and fetal biometry is not improved by the addition of UtA-PI and MAP\(^ {6,26}\).

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

**RESULTS**

The study population, in which maternal factors and UtA-PI were recorded, comprised of 63,975 pregnancies, including 60,273 (94.2%) cases that were unaffected by SGA, PE or GH, and 447 and 3255 that delivered SGA < 5th neonates, in the absence of PE, < 37 and ≥ 37 weeks’ gestation, respectively. In 29,404 of the pregnancies, including 195 and 1529 that delivered SGA < 5th neonates, in the absence of PE, < 37 and ≥ 37 weeks’ gestation, respectively, MAP was also recorded. In 27,817 of the pregnancies, including 185 and 1438 that delivered SGA < 5th neonates, in the absence of PE, < 37 and ≥ 37 weeks’ gestation, respectively, both UtA-PI and MAP were recorded. The characteristics of the study population are given in Table 1.

**Normal pregnancy outcome**

The mean ± SD and 90th and 95th percentiles of log\(_{10}\) MoM UtA-PI were 0.001 ± 0.111, 0.141 and 0.181, respectively. The mean ± SD and 90th and 95th percentiles of log\(_{10}\) MoM MAP were –0.003 ± 0.036, 0.043 and 0.057, respectively.

There was a negative linear significant association between log\(_{10}\) MoM values of UtA-PI and MAP (r = −0.050, P < 0.0001). There was a significant inverse association between log\(_{10}\) MoM UtA-PI with gestational age at delivery (r = −0.036, P < 0.0001) and birth-weight Z-score (r = −0.111, P < 0.0001), and between log\(_{10}\) MoM MAP with gestational age at delivery (r = −0.038, P < 0.0001), but not with birth-weight Z-score (r = 0.004, P = 0.461).

**Small-for-gestational age**

The median MoM values of UtA-PI and MAP at 19–24 weeks’ gestation were significantly higher in the SGA < 5th group than in the normal group (Table S1). There was no significant association between log\(_{10}\) MoM values of UtA-PI and MAP (r = 0.020, P = 0.410). There was a significant inverse association between log\(_{10}\) MoM UtA-PI with gestational age at delivery (r = −0.254, P < 0.0001; Figure S1a) and birth-weight Z-score (r = −0.176, P < 0.0001; Figure S1b), and between log\(_{10}\) MoM MAP with gestational age at delivery (r = −0.148, P < 0.0001; Figure S2a) and birth-weight Z-score (r = −0.066, P = 0.006; Figure S2b).

**Performance of screening at 19–24 weeks**

Multivariable logistic regression analysis demonstrated that in the prediction of SGA < 5th delivering < 37 weeks’ gestation, there were significant contributions from maternal factors\(^ {7}\), Z-scores for HC, AC and FL and log\(_{10}\) MoM values of UtA-PI and MAP (Table S2). However, the performance of combined screening in the detection of SGA < 10th, SGA < 5th and SGA < 3rd delivering < 32, 32–36 and ≥ 37 weeks’ gestation by maternal factors, fetal biometry and UtA-PI was not...
Table 1 Characteristics of the study population of women with singleton pregnancy that underwent uterine artery pulsatility index (UaA-PI) and mean arterial pressure (MAP) measurements at 19–24 weeks' gestation for the prediction of small-for-gestational age (SGA), according to timing of delivery

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UtA-PI</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>SGA delivering &lt; 37 weeks</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>30.8 (26.2–34.7)</td>
<td>30.7 (25.5–35.7)</td>
</tr>
<tr>
<td>Maternal weight (kg)</td>
<td>70.0 (63.0–80.3)</td>
<td>68.0 (61.0–81.0)*</td>
</tr>
<tr>
<td>GA at examination (weeks)</td>
<td>22.2 (21.6–22.7)</td>
<td>22.1 (21.4–22.7)</td>
</tr>
<tr>
<td>Racial origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>42 960 (71.3)</td>
<td>253 (56.6)*</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>11 626 (19.3)</td>
<td>122 (27.3)*</td>
</tr>
<tr>
<td>South Asian</td>
<td>2766 (4.6)</td>
<td>36 (8.1)*</td>
</tr>
<tr>
<td>East Asian</td>
<td>1463 (2.4)</td>
<td>16 (3.6)</td>
</tr>
<tr>
<td>Mixed</td>
<td>1458 (2.4)</td>
<td>20 (4.5)*</td>
</tr>
<tr>
<td>Obstetric history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>29 831 (49.5)</td>
<td>251 (56.2)*</td>
</tr>
<tr>
<td>Parous with no prior PE or SGA</td>
<td>27 193 (45.1)</td>
<td>134 (30.0)*</td>
</tr>
<tr>
<td>Parous with prior PE, no SGA</td>
<td>1527 (2.5)</td>
<td>17 (3.8)</td>
</tr>
<tr>
<td>Parous with prior SGA, no PE</td>
<td>1531 (2.5)</td>
<td>33 (7.4)*</td>
</tr>
<tr>
<td>Parous with prior SGA and PE</td>
<td>191 (0.3)</td>
<td>12 (2.7)*</td>
</tr>
<tr>
<td>Interpregnancy interval (years)</td>
<td>2.9 (1.9–4.9)</td>
<td>4.4 (2.4–7.1)*</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>5719 (9.5)</td>
<td>111 (24.8)*</td>
</tr>
<tr>
<td>Mode of conception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>58 346 (96.8)</td>
<td>424 (94.9)</td>
</tr>
<tr>
<td>Ovulation drugs</td>
<td>609 (1.0)</td>
<td>12 (2.7)*</td>
</tr>
<tr>
<td>In-vitro fertilization</td>
<td>1318 (2.2)</td>
<td>11 (2.5)</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>674 (1.1)</td>
<td>23 (5.1)*</td>
</tr>
<tr>
<td>Pre-existing diabetes mellitus</td>
<td>482 (0.8)</td>
<td>8 (1.8)</td>
</tr>
<tr>
<td>Type 1</td>
<td>215 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Type 2</td>
<td>267 (0.4)</td>
<td>8 (1.8)*</td>
</tr>
<tr>
<td>SLE or APS</td>
<td>99 (0.2)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>GA at delivery (weeks)</td>
<td>40.0 (39.0–40.9)</td>
<td>34.9 (32.1–36.3)*</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3426 (3128–3740)</td>
<td>1674 (1160–1930)*</td>
</tr>
<tr>
<td>Birth-weight percentile</td>
<td>49.5 (26.6–74.7)</td>
<td>1.2 (0.3–2.8)*</td>
</tr>
</tbody>
</table>

Data are given as median (interquartile range) or n (%). Comparisons between outcome groups: chi-square test or Fisher’s exact test for categorical variables and Mann–Whitney U-test or Student’s t-test for continuous variables, with Bonferroni correction; *P < 0.025. APS, antiphospholipid syndrome; GA, gestational age; PE, pre-eclampsia; SLE, systemic lupus erythematosus.
The performance of combined screening with maternal factors, fetal biometry and uterine artery pulsatility index at 19–24 weeks' gestation improved by the addition by MAP (Table S3). The performance of combined screening with maternal factors, fetal biometry and UtA-PI is provided in Table 2. The performance of screening for SGA < 5th delivering at 32, 32–36 and ≥ 37 weeks' gestation is illustrated in Figures S3 and S4.

**Performance of screening at 32 and 36 weeks**

The fitted regression models of maternal factors, fetal biometry, UtA-PI and MAP at 30–34 weeks' gestation for the prediction of SGA < 5th in the absence of PE are shown in Table S4. The fitted regression model of maternal factors and fetal biometry at 35–37 weeks' gestation for the prediction of SGA < 5th delivering at 32 weeks has been published previously16,26.

The ROC curves for prediction of SGA < 5th delivering at 32–36 weeks by combined screening with maternal factors, fetal biometry and UtA-PI in this study at 19–24 weeks and our previous study at 30–34 weeks25 are shown in Figure S5a. Similarly, the ROC curves for prediction of SGA < 5th delivering ≥ 37 weeks by combined screening from this study at 19–24 weeks and our previous studies at 30–34 weeks25 and at 35–37 weeks6 are shown in Figure S5b.

**Selection of gestational age for third-trimester screening**

In this section we develop a hypothetical model for the follow-up of pregnancies after the assessment at 22 weeks, with the aim of detecting prenatally a high proportion of cases of SGA < 5th. The concept is illustrated in Figure 1. All pregnancies are assessed at 22 weeks and stratified into one of four groups: low risk, moderate risk, high risk and very high risk.

- The low-risk group would not require any further assessment.
- The moderate-risk group would be assessed at 36 weeks for risk of SGA < 5th delivering ≥ 37 weeks. On the basis of such assessment, they would be further stratified into a high-risk group in need of close monitoring or a low-risk group that would not have further assessment.
- The very high-risk group would require further assessment at around 26 weeks to distinguish between the SGA < 5th that would deliver < 32 weeks and the unaffected pregnancies; on the basis of such assessment, they would be further stratified into a high-risk group in need of close monitoring or a low-risk group that would be reassessed at 32 weeks. The management after the assessment at 36 weeks would be the same as in the moderate-risk group above.
- The very high-risk group would require further assessment at around 26 weeks to distinguish between the SGA < 5th that would deliver < 32 weeks and the unaffected pregnancies; on the basis of such assessment, they would be further stratified into a high-risk group in need of close monitoring or a low-risk group that would be reassessed at 32 weeks. The management after the assessment at 36 weeks would be the same as in the high-risk group above.

For the model, we assumed that, if 100 000 pregnancies are examined, there will be 5000 cases of SGA < 5th, including 135, 465 and 4400 that would deliver < 32, 32–36 and ≥ 37 weeks' gestation, respectively7. The model is also based on the findings of this study, that the performance of screening for SGA < 5th that will deliver < 32 weeks and the unaffected pregnancies; on the basis of such assessment, they would be further stratified into a high-risk group in need of close monitoring or a low-risk group that would be reassessed at 32 weeks. The management after the assessment at 36 weeks would be the same as in the high-risk group above.

**Prediction of SGA delivering < 32 weeks**

In a population of 100 000 pregnancies, there are 135 cases of SGA < 5th delivering < 32 weeks. The estimated FPR to detect between 50% and 100% of these fetuses...
Second-trimester biophysical markers of SGA

High risk (13.8%) Moderate risk (21.1%) Low risk (62.4%)

Assessment at 22 weeks (100%)

High risk (79.6%) Moderate risk (43.0%) Low risk (20.4%)

Follow-up at 38 weeks

Assessment at 36 weeks (37.6%)

Follow-up at 34 weeks

Assessment at 32 weeks (16.5%)

Follow-up at 26 weeks

No further scan

Figure 1 Flowchart demonstrating potential value of the 19–24-week assessment in identifying pregnancies delivering small-for-gestational-age (SGA) neonates with birth weight < 5th percentile.

Increases from 0.05% to 95.93% and the total number of pregnancies classified at 22 weeks as being very high risk, requiring follow-up scans at around 26 weeks, would vary from 116 to 91 269, respectively (Table S5).

Prediction of SGA delivering at 32–36 weeks

In a population of 100 000 pregnancies, there are 465 cases of SGA < 5th delivering at 32–36 weeks. The estimated FPR to detect between 50% and 100% of these fetuses increases from 3.57% to 96.52% and the total number of pregnancies classified at 22 weeks as being very high risk or high risk requiring assessment at 32 weeks would vary from 3625 to 92 159, respectively (Tables S5 and S6).

On the basis of the data from combined screening at 30–34 weeks, the estimated FPR to detect between 50% and 100% of the cases of SGA < 5th that deliver between 32–36 weeks would vary from 0.30% to 56.05% (Table S6). Consequently, the number of pregnancies requiring follow-up scans at around 34 weeks would vary from 508 to 51 859, respectively.

In Table S6, we provide the necessary data to estimate the number of assessments required at 22 and 32 weeks to achieve a desired DR of SGA < 5th neonates delivering at 32–36 weeks. There are several approaches that can be used to achieve a desired prenatal DR. For example, one option for a DR of about 50% of SGA < 5th that deliver at 32–36 weeks, is to identify, at 22 weeks, the pregnancies that contain 100% of this SGA group, reassess these pregnancies at 32 weeks and then define the FPR necessary to detect 50% of the affected cases. Another option is to identify, at 22 weeks, the pregnancies that contain 50% of the SGA group, reassess these pregnancies at 32 weeks and then define the FPR necessary to detect 100% of the affected cases. Since the performance of screening at 32 weeks is superior to that at 22 weeks, the second option would be preferable because the same overall DR can be achieved with the need for a considerably lower number of assessments at 32 weeks.

Prediction of SGA delivering ≥ 37 weeks

In a population of 100 000 pregnancies, there are 4400 cases of SGA < 5th delivering ≥ 37 weeks. The estimated FPR to detect between 50% and 100% of these fetuses increases from 12.62% to 99.08% and the total number of pregnancies classified at 22 weeks as being very high risk, high risk or moderate risk requiring assessment at 36 weeks would vary from 14 189 to 98 526, respectively (Tables S5 and S7).

On the basis of the data from combined screening at 35–37 weeks by maternal factors and fetal biometry, the estimated FPR to detect between 50% and 100% of the cases of SGA < 5th that deliver ≥ 37 weeks would vary from 3.37% to 77.48% (Table S7). Consequently, the number of pregnancies requiring follow-up scans or early delivery at around 38 weeks would vary from 5372 to 77 329, respectively.

There are several approaches that can be used to achieve a desired prenatal DR of SGA < 5th delivering ≥ 37 weeks’ gestation. As in the case of prediction of SGA delivering at 32–36 weeks described above, the preferred strategy would be to select, at 22 weeks, the group for assessment at 36 weeks and then define the FPR necessary to detect 100% of the affected cases. In Table S7 we provide all
the necessary data to estimate the number of assessments required at 22 and 36 weeks to achieve a desired DR of SGA $<5^{th}$ delivering $\geq 37$ weeks.

**Prenatal prediction of 80% of SGA delivering at any gestational age**

On the basis of the data provided in Tables S5–S7, it was estimated that if the desired objective of prenatal screening is to predict about 80% of the cases of SGA $<5^{th}$ in a population of 100,000 pregnancies, the following steps would be necessary (Figure 1). First, at 22 weeks, identify a very high-risk group of 2683 pregnancies that would contain 80% of cases of SGA delivering $<32$ weeks’ gestation; these pregnancies would require monitoring which would include at least one scan at around 26 weeks. Second, at 22 weeks, identify a group of 16,465 pregnancies that would contain 80% of cases of SGA delivering at 32–36 weeks’ gestation and provide combined screening at 32 weeks; such screening will identify 9,392 of pregnancies that would require monitoring, including at least one scan at around 34 weeks. Third, at 22 weeks, identify a group of 37,625 pregnancies that would contain 80% of cases of SGA delivering $\geq 37$ weeks’ gestation and provide combined screening at 36 weeks; such screening will identify 29,945 pregnancies that would require monitoring, including at least one scan at around 38 weeks. Fourth, at 22 weeks, identify a low-risk group of 62,375 pregnancies that would not require any further scans.

**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 19–24 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. Screening by a combination of maternal factors, fetal biometry and UtA-PI at 19–24 weeks, predicted 90%, 68% and 44% of SGA $<5^{th}$ neonates delivering $<32$, 32–36 and $\geq 37$ weeks’ gestation, at a 10% FPR. The performance of screening was not improved by the addition of MAP.

The performance of combined screening for SGA by maternal factors, fetal biometry and UtA-PI was poorer in the second than in the third trimester. Thus, the DR of SGA $<5^{th}$ delivering at 32–36 weeks improved from 68% with screening at 19–24 weeks to 90% with screening at 30–34 weeks, at a 10% FPR. Similarly, the DR of SGA $<5^{th}$ delivering $\geq 37$ weeks improved from 44% with screening at 19–24 weeks to 59% with screening at 30–34 weeks and 76% with screening at 35–37 weeks.

Prenatal detection of a high proportion of SGA neonates necessitates assessment in the third trimester and the timing of such assessment, at 32 and/or 36 weeks, could be determined from the findings of combined screening at 22 weeks.

**Strengths and limitations of the study**

The major strengths of the study are first, prospective examination of a large number of pregnancies attending for routine care in a gestational-age range which is widely used for the assessment of fetal anatomy and growth; second, use of appropriately-trained doctors and a specific protocol 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 patient-specific risks and the performance of screening for SGA of different severities delivering at selected gestational-age cut-offs.

The main limitation of the study is that the UtA-PI results of the 19–24 weeks’ scan were made available to the obstetricians of the patients who would have taken specific actions to further monitor cases of high PI and, as a consequence, the performance of screening, especially for SGA delivering $<32$ and $<37$ weeks’ gestation, would be positively biased.

**Comparison with previous studies**

Our finding that, in pregnancies delivering SGA neonates in the absence of PE, UtA-PI at 19–24 weeks’ gestation was increased, is compatible with the results of previous smaller screening studies. In our study, MAP was significantly increased in pregnancies that delivered SGA neonates in the absence of PE, but in a previous small study of 3347 pregnancies at 22–24 weeks’ gestation, the MAP was not significantly altered.

**Implications for clinical practice**

Extensive studies have established that screening by a combination of maternal factors and UtA-PI, at the time of the routine second-trimester ultrasound examination at 19–24 weeks’ gestation, can identify a high proportion of pregnancies that subsequently develop PE. This study demonstrates that second-trimester combined screening can also be used for detection of pregnancies that deliver SGA neonates in the absence of PE.

In the proposed new pyramid of pregnancy care, combined screening at 11–13 weeks’ gestation aims to identify pregnancies at high risk of developing PE and/or SGA and, through pharmacological intervention, reduce the prevalence of these complications. In contrast to the evidence of a beneficial effect of low-dose aspirin when started $<16$ weeks’ gestation, a major randomized study in pregnancies with impaired placentation demonstrated that the daily administration of 150 mg of aspirin after 23 weeks does not prevent the subsequent development of PE and/or SGA. Consequently, the objective of screening at around 22 weeks and in the third trimester is not prevention of PE and/or 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, place and method for iatrogenic delivery.
The best approach for identifying the high-risk group for SGA is to carry out screening in the whole population by combining biophysical and fetal Doppler features significantly improve their outcome? Ultrasound Obstet Gynecol 2003; 25: 258–264.


SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Uterine artery pulsatility index and mean arterial pressure at 19–24 weeks’ gestation in pregnancies with normal and those with small-for-gestational-age (SGA) neonate with birth weight < 5th percentile in the absence of pre-eclampsia

Table S2 Fitted regression models with maternal factors, fetal biometry, uterine artery pulsatility index and mean arterial pressure at 19–24 weeks’ gestation for the prediction of small-for-gestational-age neonates with birth weight < 5th percentile delivering < 37 weeks’ gestation in the absence of pre-eclampsia

Table S3 Performance of screening for small-for-gestational-age (SGA) neonates with birth weight < 10th, < 5th and < 3rd percentile in the absence of pre-eclampsia, delivering < 32, 32–36 and ≥ 37 weeks’ gestation by maternal factors, fetal biometry, uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP) and their combination at 19–24 weeks’ gestation

Table S4 Fitted regression models with maternal characteristics and history, Z-scores for fetal biometric measurements, uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) at 30–34 weeks’ gestation for the prediction of small-for-gestational-age with birth weight < 5th percentile, in the absence of pre-eclampsia

Table S5 Estimated number of follow-up scans required in 100 000 pregnancies screened for small-for-gestational-age with birth weight < 5th percentile, in the absence of pre-eclampsia, delivering < 32, 32–36 and ≥ 37 weeks’ gestation by a combination of maternal factors, fetal biometry and uterine artery pulsatility index at 19–24 weeks’ gestation

Table S6 Estimated number of follow-up scans required in 100 000 pregnancies screened for small-for-gestational-age with birth weight < 5th percentile, in the absence of pre-eclampsia, delivering at 32–36 weeks’ gestation with a combination of maternal factors, fetal biometry and uterine artery pulsatility index at 19–24 weeks’ gestation and subsequent combined screening at 30–34 weeks

Table S7 Estimated number of follow up scans required in 100 000 pregnancies screened for small-for-gestational-age with birth weight < 5th percentile, in the absence of pre-eclampsia, delivering at 32–36 weeks’ gestation by a combination of maternal factors, fetal biometry and uterine artery pulsatility index at 19–24 weeks’ gestation and subsequent combined screening at 30–34 weeks

Figure S1 Uterine artery pulsatility index (UtA-PI) log10 multiples of median (MoM) according to gestational age at delivery (a) and birth-weight Z-score (b) in pregnancies complicated by delivery of small-for-gestational-age neonates, plotted on the 50th (solid line) and 90th (dashed line) percentile of the normal range.

Figure S2 Mean arterial pressure (MAP) log10 multiples of median (MoM) according to gestational age at delivery (a) and birth-weight Z-score (b) in pregnancies complicated by delivery of small-for-gestational-age neonates, plotted on the 50th (solid line) and 90th (dashed line) percentile of the normal range.

Figure S3 Receiver–operating characteristics curves of maternal factors (black line), maternal factors with fetal biometry (green line), maternal factors with uterine artery pulsatility index (blue line) and the combination of all (red line) at 19–24 weeks, in the prediction of small-for-gestational-age neonates with birth weight < 5th percentile, delivering < 32 (a), 32–36 (b) and ≥ 37 (c) weeks’ gestation.

Figure S4 Receiver–operating characteristics curves of combined screening with maternal factors, fetal biometry and uterine artery pulsatility index at 19–24 weeks, in the prediction of small-for-gestational-age neonates with birth weight < 10th (black line), < 5th (blue line) and < 3rd (red line) percentile, delivering < 32 (a), 32–36 (b) and ≥ 37 (c) weeks’ gestation.

Figure S5 Receiver–operating characteristics curves of combined screening at: (a) 19–24 weeks (black line) and 30–34 weeks (blue line) in the prediction of small-for-gestational-age neonates with birth weight < 5th percentile (SGA < 5th) delivering at 32–36 weeks’ gestation; and at (b) 19–24 weeks (black), 30–34 weeks (blue line) and 35–37 weeks (red line) in the prediction of SGA < 5th delivering ≥ 37 weeks’ gestation.