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Uterine artery pulsatility index at 30–34 weeks' gestation in the prediction of adverse perinatal outcome

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ABSTRACT

Objective *To investigate the potential value of uterine artery (UtA) Doppler at 30–34 weeks' gestation in the prediction of adverse perinatal outcome.*

Methods *This was a screening study in 30 780 singleton pregnancies at 30–34 weeks. UtA pulsatility index (UtA-PI) was measured and the values were converted to multiples of the median (MoM) after adjustment for variables relating to maternal characteristics and medical history that affect the measurements. Multivariable logistic regression analysis was used to determine if measuring UtA-PI improved the prediction of adverse perinatal outcome provided by screening with maternal characteristics, medical history and obstetric factors. The detection rate (DR) and false-positive rate (FPR) of screening by UtA-PI were estimated for stillbirth, Cesarean section for fetal distress, umbilical arterial cord blood pH ≤ 7.0 or umbilical venous cord blood pH ≤ 7.1 and 5-min Apgar score < 7.*

Results *The incidence of adverse perinatal outcome was higher in small-for-gestational-age (SGA) fetuses than in non-SGA fetuses, but the majority of cases with each adverse outcome were in the non-SGA group, including about 70% of stillbirths and more than 80% with Cesarean section for fetal distress, low cord blood pH and low Apgar score. The performance of UtA-PI > 95th percentile in screening for each adverse outcome was poor with DR of 6–16% and a FPR of 5–6%. The DR of adverse outcome when screening by high UtA-PI was greater in pregnancies complicated by SGA than in non-SGA pregnancies; 24%* vs *13% for stillbirth, 15%* vs *5% for Cesarean section for fetal distress, 30%* vs *9% for low cord blood pH and 20%* vs *3% for low 5-min Apgar score, respectively.*

Conclusion *High UtA-PI at 30–34 weeks' gestation may be useful in the prediction of adverse perinatal outcome in pregnancies with a SGA fetus, however, in the absence of SGA, UtA-PI is a poor predictor of adverse outcome.*

INTRODUCTION

Impaired placentation, reflected in an increased impedance to flow in the uterine arteries (UtAs) during the first, second and third trimesters of pregnancy, is associated with subsequent development of pre-eclampsia (PE) and delivery of small-for-gestational-age (SGA) neonates[1–7]. There is also evidence that, in pregnancies with an SGA fetus or PE, persistence of high impedance to flow in the UtAs during the third trimester is associated with an increased risk of adverse perinatal events, including stillbirth, Cesarean section for fetal distress and low cord blood pH[8–13].

A screening study at 30–34 weeks' gestation, involving more than 30 000 singleton pregnancies, reported that the incidence of adverse perinatal outcome is higher in SGA than in non-SGA fetuses, but the majority of cases with each adverse event were in the non-SGA group, including about 70% of stillbirths and more than 80% of cases of Cesarean section for fetal distress, low cord blood pH and low 5-min Apgar score[14]. This is analogous to screening for Down syndrome for which the risk in women aged ≥ 35 years is substantially higher than in younger women, but the overall contribution of the younger group is more than twice that of the older group. On the assumption that adverse outcome is the consequence of impaired placentation reflected in high UtA pulsatility index (UtA-PI) rather than just small fetal size, it could be argued that prenatal care should focus not only on

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pregnancies with SGA fetuses but also on those with high UtA-PI.

The objective of this screening study was to investigate the potential value of UtA-PI at 30–34 weeks' gestation in the prediction of adverse perinatal outcome, by examining the relationship between UtA-PI and the rates of PE, delivery of a SGA neonate, stillbirth, Cesarean section for fetal distress, umbilical arterial cord blood pH ≤ 7.0 or umbilical venous cord blood pH ≤ 7.1 and 5-min Apgar score < 7.

METHODS

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

This visit, which is attended at 30 + 0 to 34 + 6 weeks' gestation, included the recording of maternal characteristics and medical history, estimation of fetal size from transabdominal ultrasound measurement of fetal head circumference, abdominal circumference and femur length. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or the fetal head circumference at 19–24 weeks[15,16]. Transabdominal color Doppler ultrasound was used to visualize the left and right UtAs at their apparent crossover with the external iliac arteries[17]. Pulsed-wave Doppler was then used to assess impedance to flow; when three similar waveforms were obtained consecutively the PI was measured, and the mean PI of the two vessels was calculated.

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.

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/use of ovulation drugs/*in-vitro* fertilization), 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) (yes/no) and parity (parous/nulliparous if no previous pregnancy ≥ 24 weeks' gestation). 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 outcome measures of the study were stillbirth, Cesarean section for fetal distress in labor, umbilical arterial cord blood pH ≤ 7.0 or umbilical venous cord blood pH ≤ 7.1 and a 5-min Apgar score < 7. The newborn was considered to be SGA if the birth weight was less than the 10th percentile after correcting for gestational age at delivery[18]. The birth weight *Z*-score was also derived from the normal range for gestational age[18]. The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy[19].

Statistical analysis

Comparison between the outcome groups was performed by chi-square test or Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. Categorical data are presented as *n* (%) and continuous data as median (interquartile range (IQR)).

The measured UtA-PI value was expressed as multiples of the median (MoM) after adjustment for variables relating to maternal characteristics and medical history that affect this measurement[20]. The association between $\log_{10}$ MoM UtA-PI and birth-weight *Z*-score in each of the adverse perinatal-outcome groups and those without an adverse outcome was examined in scatterplots. Univariable and multivariable logistic regression analysis was used to determine if $\log_{10}$ MoM UtA-PI had a significant additional contribution to that of maternal characteristics, medical history and obstetric factors in predicting adverse outcome. The detection rate (DR) and false-positive rate (FPR) of screening by UtA-PI were estimated for each adverse outcome.

The statistical software package SPSS 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA) was used for all data analyses.

RESULTS

Study population

During the study period, we prospectively examined and measured UtA-PI in 31 804 singleton pregnancies. We excluded 206 (0.6%) for major fetal abnormalities or genetic syndromes diagnosed prenatally or postnatally and 1337 (4.2%) for no follow-up. The final study population comprised 30 261 pregnancies and included 30 181 with live births and 80 stillbirths. The characteristics of the study population and the various subgroups according to adverse perinatal outcome are given in Table 1.

UtA-PI in pregnancies with PE or SGA

PE developed in 661 (2.2%) of the 30 261 pregnancies, including 152 (0.5%) that delivered < 37 weeks' gestation (preterm) and 509 (1.7%) ≥ 37 weeks (term). The median UtA-PI MoM was significantly higher in both the preterm-PE and term-PE groups than in those without PE (Table 2). Delivery of SGA neonates in the absence of PE occurred in 3213 (10.6%) pregnancies, including 249 (0.8%) that delivered < 37 weeks and 2964 (9.8%)

Table 1 Maternal and pregnancy characteristics of total study population of singleton pregnancies and those subgroups with an adverse perinatal outcome of stillbirth, fetal distress in labor leading to Cesarean section, low umbilical arterial or venous cord blood pH or 5-min Apgar score < 7

Variable	*Total population (n = 30 261)*	*Stillbirth (n = 80)*	*Fetal distress (n = 1881)*	*Low cord blood pH (n = 253)*	*5-min Apgar score < 7 (n = 251)*
GA at assessment (weeks)	32.3 (32.0–32.9)	32.3 (32.0–32.9)	32.3 (32.0–32.9)	32.3 (32.0–32.8)†	32.3 (32.0–32.9)
Assessment-to-delivery interval (weeks)	7.4 (6.3–8.4)	6.3 (4.3–8.3)†	8.0 (6.6–9.0)†	7.3 (5.9–8.6)	7.6 (5.9–8.6)
Maternal characteristics					
Age (years)	31.3 (26.8–35.0)	30.0 (25.2–35.9)	31.1 (26.7–35.4)†	30.4 (26.4–34.6)	30.7 (26.1–34.3)
Weight (kg)	75.5 (67.8–85.6)	82.5 (70.0–94.5)†	78.2 (69.5–89.9)†	78.0 (71.0–85.9)	76.0 (68.0–87.0)
Height (m)	1.65 (1.60–1.69)	1.65 (1.62–1.68)	1.63 (1.58–1.68)†	1.63 (1.58–1.68)†	1.63 (1.59–1.67)†
Cigarette smoker	2741 (9.1)	11 (13.8)	159 (8.5)	28 (11.1)	22 (8.8)
Racial origin					
Caucasian	21 281 (70.3)	47 (58.8)	1175 (62.5)†	169 (66.8)	145 (57.8)†
Afro-Caribbean	5582 (18.4)	26 (32.5)†	489 (26.0)†	52 (20.6)	84 (33.5)†
South Asian	1754 (5.8)	5 (6.3)	126 (6.7)	23 (9.1)*	15 (6.0)
East Asian	943 (3.1)	2 (2.5)	56 (3.0)	2 (0.8)*	2 (0.8)*
Mixed	701 (2.3)	0 (0.0)	35 (1.9)	7 (2.8)	5 (2.0)
Mode of conception					
Spontaneous	29 117 (96.2)	76 (95.0)	1798 (95.6)	247 (97.6)	244 (97.2)
Assisted	1144 (3.8)	4 (5.0)	83 (4.4)†	6 (2.4)	7 (2.8)
Medical disorder					
Chronic hypertension	404 (1.3)	2 (2.5)	29 (1.5)*	4 (1.6)	4 (1.6)
SLE/APS	58 (0.2)	0 (0.0)	7 (0.4)	0 (0.0)	3 (1.2)†
Diabetes mellitus	281 (0.9)	0 (0.0)	24 (1.3)†	2 (0.8)	4 (1.6)
Obstetric history					
Parous	15 076 (49.8)	38 (47.5)	504 (26.8)	108 (42.7)	103 (41.0)
Nulliparous	15 185 (50.2)	42 (52.5)	1377 (73.2)†	145 (57.3)	148 (59.0)
Pregnancy complication					
Pre-eclampsia	661 (2.2)	3 (3.8)	90 (4.8)†	10 (4.0)	11 (4.4)*
Gestational diabetes	739 (2.4)	2 (2.5)	57 (3.0)†	16 (6.3)	10 (4.0)
Obstetric cholestasis	146 (0.5)	0 (0.0)	14 (0.7)	1 (0.4)	0 (0.0)
SROM	1580 (5.2)	1 (1.3)	209 (11.1)†	10 (4.0)*	11 (4.4)
Onset of labor and mode of delivery					
Spontaneous labor					
Vaginal delivery	19 374 (64.0)	24 (30.0)	—	124 (49.0)	111 (44.2)†
Cesarean section	2909 (9.6)	0 (0.0)	1242 (66.0)	57 (22.5)†	50 (19.9)†
Induced labor					
Vaginal delivery	3143 (10.4)	51 (63.8)	—	26 (10.3)	31 (12.4)
Cesarean section	1218 (4.0)	0 (0.0)	639 (34.0)†	24 (9.5)	32 (12.7)†
Elective Cesarean section	3617 (12.0)	5 (6.3)	—	22 (8.7)*	27 (10.8)
Outcome					
GA at delivery (weeks)	40.0 (39.0–40.9)	38.9 (37.1–40.8)†	40.5 (39.3–41.4)†	40.0 (38.7–41.0)	40.0 (38.6–41.1)
Birth weight (g)	3390 (3064–3710)	3000 (2637–3554)†	3352 (3016–3704)†	3434 (2952–3757)	3370 (2935–3370)
Birth-weight percentile	46.5 (22.3–72.7)	28.0 (7.0–74.6)†	37.9 (14.5–68.6)†	48.8 (16.7–75.0)	46.7 (14.7–73.9)

Data are given as median (interquartile range) for continuous variables and *n* (%) for categorical variables. Significant difference from cohort without adverse outcome: *$P < 0.05$; †$P < 0.01$. APS, antiphospholipid syndrome; GA, gestational age; SLE, systemic lupus erythematosus; SROM, spontaneous rupture of membranes.

≥ 37 weeks. The median UtA-PI MoM was significantly higher in both the preterm-SGA and term-SGA groups than in the non-SGA group (Table 2).

UtA-PI in SGA and non-SGA pregnancies resulting in stillbirth

In the total study population there were 80 stillbirths, including 73 antepartum and seven intrapartum. The birth weight was < 10th percentile in 25 (31.3%) of the cases. UtA-PI was > 95th percentile in six (24.0%) of the 25 stillbirths with a birth weight < 10th percentile and in seven (12.7%) of the 55 with a birth weight ≥ 10th percentile. For both SGA and non-SGA pregnancies, the median UtA-PI MoM was significantly higher in those with a stillbirth compared to those with a live birth (Table 2).

UtA-PI in SGA and non-SGA pregnancies with Cesarean section for fetal distress

Of the 30 181 pregnancies with a live birth, there were 22 442 with vaginal delivery following spontaneous or induced labor, 3612 with elective Cesarean section for a variety of indications and 4127 with Cesarean section following spontaneous or induced labor; in the latter

Table 2 Uterine artery pulsatility index (UtA-PI) and adverse perinatal outcome

Perinatal outcome	n	*UtA-PI (median (IQR))*	*UtA-PI > 95th centile (n (%))*
Pre-eclampsia			
Pre-eclampsia with delivery < 37 weeks	152	1.60 (1.19–2.00)‡	77 (50.7)‡
Pre-eclampsia with delivery ≥ 37 weeks	509	1.06 (0.87–1.35)‡	64 (12.6)‡
No pre-eclampsia (reference)	29 600	0.99 (0.85–1.17)	1517 (5.1)
SGA			
SGA without pre-eclampsia and with delivery < 37 weeks	249	1.27 (0.98–1.70)‡	81 (32.5)‡
SGA without pre-eclampsia and with delivery ≥ 37 weeks	2964	1.05 (0.89–1.28)‡	275 (9.3)‡
Non-SGA without pre-eclampsia (reference)	26 387	0.98 (0.84–1.16)	1161 (4.4)
Stillbirth			
SGA and stillbirth	25	1.30 (1.06–1.58)‡	6 (24.0)†
SGA and live birth	3379	1.07 (0.90–1.34)‡	428 (12.7)‡
Non-SGA and stillbirth	55	1.09 (0.91–1.31)†	7 (12.7)*
Non-SGA and live birth (reference)	26 802	0.99 (0.84–1.16)	1217 (4.5)
Mode of delivery			
SGA and Cesarean section for fetal distress	348	1.10 (0.91–1.41)‡	53 (15.2)‡
SGA and vaginal delivery	2466	1.05 (0.89–1.28)‡	236 (9.6)‡
Non-SGA and Cesarean section for fetal distress	1533	0.98 (0.84–1.15)	76 (5.0)
Non-SGA and vaginal delivery (reference)	19 976	0.98 (0.84–1.15)	860 (4.3)
Umbilical arterial cord blood pH			
SGA and arterial blood pH ≤ 7.0	25	1.11 (0.99–1.54)†	6 (24.0)†
SGA and arterial blood pH > 7.0	1108	1.11 (0.91–1.38)‡	174 (15.7)‡
Non-SGA and arterial blood pH ≤ 7.0	176	1.01 (0.84–1.19)	15 (8.5)
Non-SGA and arterial blood pH > 7.0 (reference)	7913	0.99 (0.85–1.16)	396 (5.0)
Umbilical venous cord blood pH			
SGA and venous blood pH ≤ 7.1	37	1.18 (0.94–1.63)†	10 (27.0)‡
SGA and venous blood pH > 7.1	1471	1.10 (0.90–1.37)‡	220 (15.0)‡
Non-SGA and venous blood pH ≤ 7.1	157	1.02 (0.85–1.21)	14 (8.9)*
Non-SGA and venous blood pH > 7.1 (reference)	10 894	0.98 (0.85–1.16)	514 (4.7)
5-min Apgar score			
SGA and Apgar score < 7	45	1.09 (0.89–1.46)†	9 (20.0)‡
SGA and Apgar score ≥ 7	2743	1.08 (0.90–1.34)‡	354 (12.9)‡
Non-SGA and Apgar score < 7	206	0.96 (0.82–1.12)	7 (3.4)
Non-SGA and Apgar score ≥ 7 (reference)	21 558	0.98 (0.84–1.16)	998 (4.6)

Significant difference from cohort without adverse outcome (reference): *$P < 0.05$; †$P < 0.01$; ‡$P < 0.0001$. IQR, interquartile range; SGA, small-for-gestational age with birth weight < 10th percentile.

group, the indication for Cesarean section was fetal distress in 1881 cases. In the elective Cesarean section group ($n = 3612$) there were a variety of indications, including breech or transverse lie ($n = 806$), placenta previa ($n = 171$), previous Cesarean section, traumatic birth or maternal request ($n = 2268$), maternal medical disorder ($n = 214$) and fetal compromise diagnosed by abnormal Doppler findings or fetal heart-rate patterns ($n = 153$).

In the non-SGA group that delivered vaginally, the median UtA-PI MoM was 0.98 and the values were above the 95th percentile in 4.3% (860/19 976) of cases. In the 3612 pregnancies with elective Cesarean section, the median UtA-PI MoM (0.98) was not significantly different from the non-SGA group with vaginal delivery. However, in the subgroup of 153 cases with elective Cesarean section for abnormal fetal-heart rate patterns or Doppler indices in SGA fetuses, the median UtA-PI MoM (1.48) was increased and the values were above the 95th percentile in 71 (46.4%) cases.

We compared the outcomes of the 22 442 pregnancies with vaginal delivery to the 1881 with Cesarean section for fetal distress during labor. The birth weight was < 10th percentile in 348 (18.5%) cases with Cesarean section for fetal distress. In the cases requiring Cesarean section for fetal distress, the UtA-PI was > 95th percentile in 53/348 (15.2%) cases with SGA and in 76/1533 (5.0%) cases without SGA. The median UtA-PI MoM was significantly higher in those with Cesarean section compared to those with vaginal delivery in the SGA group ($P = 0.004$), but the difference was not significant in the non-SGA group ($P = 0.796$) (Table 2).

UtA-PI in SGA and non-SGA pregnancies with low cord blood pH

Of the 30 181 pregnancies with a live birth, the umbilical arterial and venous cord blood pH was recorded in 9222 and 12 559 cases, respectively. The umbilical arterial cord blood pH was ≤ 7.0 in 201 (2.2%) cases and the umbilical venous blood pH was ≤ 7.1 in 194 (1.5%) cases; low blood pH in either vessel was observed in 253 (2.0%) cases.

Birth weight was < 10th percentile in 37 (14.6%) cases with low cord blood pH. UtA-PI was > 95th percentile in 11/37 (29.7%) cases with low cord blood pH and a birth

weight $<10^{th}$ percentile, and in 19/216 (8.8%) cases with low cord blood pH and a birth weight $\geq 10^{th}$ percentile. There was no significant difference in median UtA-PI MoM between SGA and non-SGA groups in either those with low cord blood pH or those with normal pH (Table 2).

UtA-PI in SGA and non-SGA pregnancies with low Apgar score

Of the 30 181 pregnancies with a live birth, the 5-min Apgar score was recorded in 24 552 cases and was < 7 in 251 (1.0%) cases. Birth weight was $< 10^{th}$ percentile in 45 (17.9%) cases with an Apgar score < 7. The UtA-PI was $> 95^{th}$ percentile in 9/45 (20.0%) cases with 5-min Apgar score < 7 and birth weight $< 10^{th}$ percentile and in 7/206 (3.4%) with 5-min Apgar score < 7 and birth weight $\geq 10^{th}$ percentile. There was no significant difference in median UtA-PI MoM between SGA and non-SGA groups in either those with an Apgar score < 7 or those with a score ≥ 7 (Table 2).

Prediction of stillbirth

The results of univariable and multivariable regression analyses for the prediction of stillbirth are given in Table S1. Multivariable regression analysis demonstrated that a significant contribution to the prediction of stillbirth was provided by maternal weight, Afro-Caribbean racial origin, birth-weight *Z*-score and $\log_{10}$ MoM UtA-PI ($R^2 = 0.122$, $P < 0.0001$).

The relationship between $\log_{10}$ MoM UtA-PI and birth-weight *Z*-score in stillbirths and live births is shown in Figure 1a. The performance of screening for high UtA-PI in the prediction of stillbirth is shown in Table 3. The DR and FPR were 24.0% and 12.7%, respectively, for the SGA group and 12.7% and 4.5%, respectively, for the non-SGA group.

Prediction of Cesarean section for fetal distress in labor

The results of univariable and multivariable regression analyses for the prediction of fetal distress during labor leading to Cesarean section are given in Table S2. Multivariable regression analysis demonstrated that a significant contribution to the prediction of fetal distress was provided by maternal age, weight, height, Afro-Caribbean racial origin, nulliparity, gestational diabetes in the current pregnancy, prelabor spontaneous rupture of membranes, induction of labor and $\log_{10}$ MoM UtA-PI ($R^2 = 0.148$, $P < 0.0001$).

The relationship between $\log_{10}$ MoM UtA-PI and birth-weight *Z*-score in those that underwent Cesarean section for fetal distress in labor and those with a vaginal delivery is shown in Figure 1b. The performance of screening for high UtA-PI in the prediction of fetal distress in labor leading to Cesarean section is shown in Table 3. The DR and FPR were 15.2% and 9.6%, respectively, for the SGA group and 5.0% and 4.3%, respectively, for the non-SGA group.

Prediction of low cord blood pH

The results of univariable and multivariable regression analyses for the prediction of low cord blood pH are given in Table S3. Multivariable regression analysis demonstrated that a significant contribution to the prediction of umbilical arterial cord blood pH ≤ 7.0 or umbilical venous cord blood pH ≤ 7.1 was provided by maternal weight, height, East Asian racial origin, gestational diabetes mellitus during the current pregnancy, prelabor spontaneous rupture of membranes, onset of labor and method of delivery, however $\log_{10}$ MoM UtA-PI did not contribute to the prediction (adjusted $R^2 = 0.027$, $P < 0.0001$).

The relationship between $\log_{10}$ MoM UtA-PI and birth-weight *Z*-score in those with low and normal cord blood pH are shown in Figure 1c. The performance of screening for high UtA-PI in the prediction of low cord blood pH is shown in Table 3. The DR and FPR were 29.7% and 15.1%, respectively, for the SGA group and 8.8% and 4.7%, respectively, for the non-SGA group.

Prediction of low Apgar score

The results of univariable and multivariable regression analyses for the prediction of 5-min Apgar score < 7 are given in Table S4. Multivariable regression analysis demonstrated that a significant contribution to the prediction of a 5-min Apgar score < 7 was provided by maternal height, Afro-Caribbean racial origin, history of SLE or APS and onset of labor and method of delivery, however $\log_{10}$ MoM UtA-PI did not contribute significantly to the prediction (adjusted $R^2 = 0.040$, $P < 0.0001$).

The relationship between UtA-PI MoM and birth-weight *Z*-score in those with a 5-min Apgar score < 7 and those with a score ≥ 7 is shown in Figure 1d. The performance of screening for high UtA-PI in the prediction of a 5-min Apgar score < 7 is shown in Table 3. The DR and FPR were 20.0% and 12.9%, respectively, for the SGA group and 3.4% and 4.6%, respectively, for the non-SGA group.

DISCUSSION

Main findings of the study

The findings of this study demonstrate that high UtA-PI at 30–34 weeks' gestation is associated with subsequent development of PE, delivery of SGA neonates and stillbirth. In pregnancies with SGA, high UtA-PI is also associated with fetal distress in labor leading to Cesarean section, low cord blood pH and a low 5-min Apgar score.

The rationale for the study was that, if adverse outcome is the consequence of impaired placentation, prenatal care should be directed at identifying and monitoring

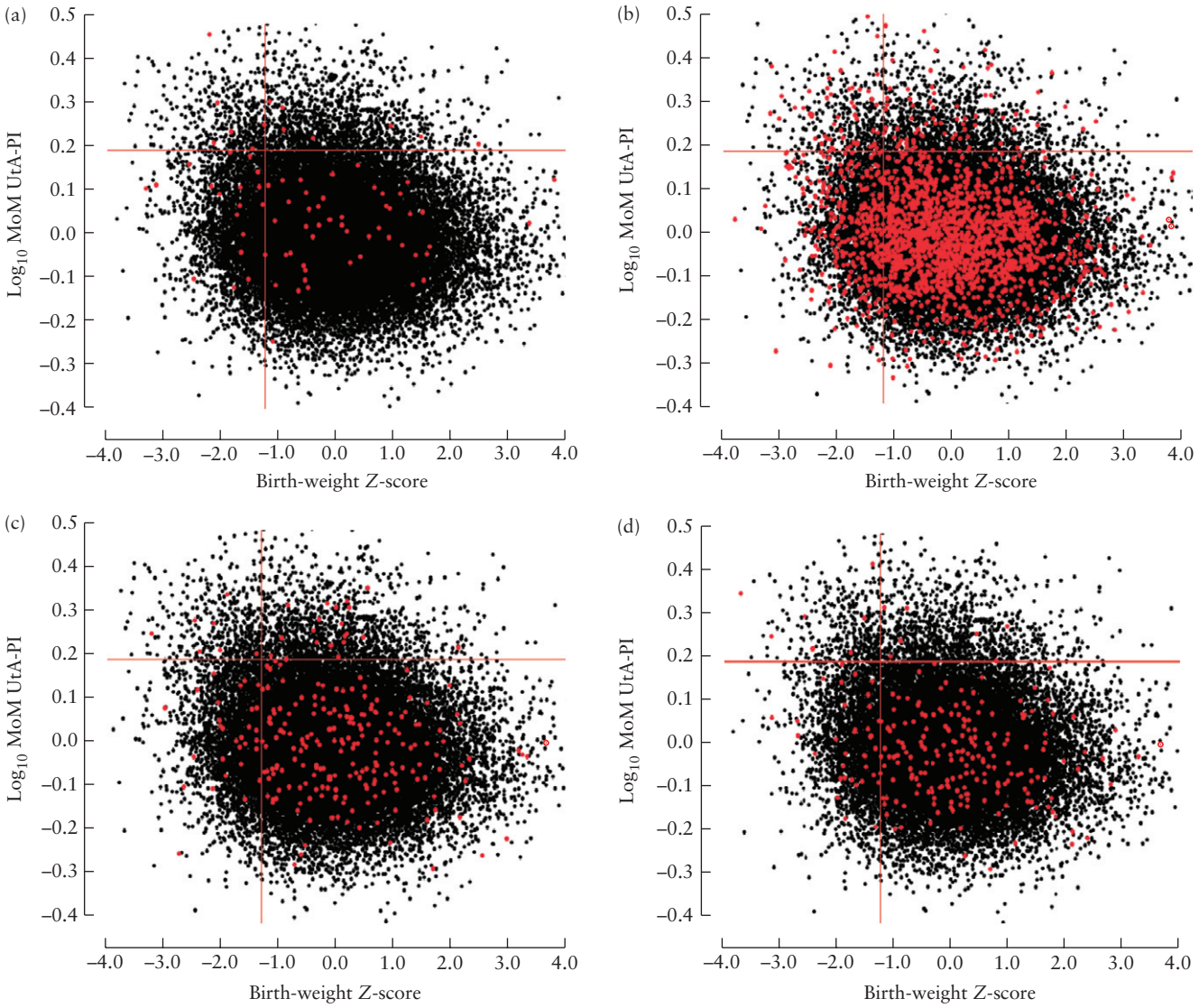

Figure 1 Relationship between $\log_{10}$ uterine artery pulsatility index (UtA-PI) multiples of the median (MoM) and birth-weight *Z*-score in: (a) stillbirths (●) and live births (●); (b) pregnancies delivering by Cesarean section for fetal distress (●) and those delivering vaginally (●); (c) pregnancies with umbilical arterial cord blood pH ≤ 7.0 or venous cord blood pH ≤ 7.1 (●) and those with umbilical cord pH > 7.0 (●); and (d) pregnancies with a 5-min Apgar score < 7 (●) and those with a score ≥ 7 (●). Vertical red line corresponds to 10th percentile for birth weight and horizontal red line corresponds to 95th percentile for UtA-PI.

pregnancies with high UtA-PI rather than only those with small fetuses. The findings confirm that, although the incidence of adverse perinatal outcome was higher in SGA than in non-SGA fetuses, the majority of cases for each adverse outcome were in the appropriately-grown group, including about 70% of stillbirths and more than 80% of cases that underwent Cesarean section for fetal distress in labor, low cord blood pH and low 5-min Apgar score.

Assessment by UtA-PI contributed significantly, in addition to maternal characteristics, medical history and obstetric factors, to the prediction of stillbirth and fetal distress in labor leading to Cesarean section. However, the performance of high UtA-PI in screening for each adverse outcome was poor, with DR of 6–16% and a FPR of 5–6%. The performance of screening for adverse outcome using high UtA-PI was superior in SGA than non-SGA pregnancies; the DR was 24% *vs* 13% for stillbirth, 15% *vs* 5% for Cesarean section for fetal distress, 30% *vs* 9% for low cord blood pH and 20% *vs* 3% for low Apgar score.

Strengths and limitations of the study

The strengths of this third-trimester screening study are first, examination of a large population of pregnant women attending for routine care at a gestational-age range which 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 estimate the MoM value after adjustment for factors that affect the measurements, and third, use of a wide range of well accepted indicators for adverse perinatal outcome.

Table 3 Performance of screening for uterine artery pulsatility index > 95th percentile in the prediction of adverse perinatal outcomes

Adverse event	*Birth-weight centile*	*DR*	*FPR*
Stillbirth ($n = 80$)	< 10th centile	6/25 (24.0)	428/3379 (12.7)
	≥ 10th centile	7/55 (12.7)	1217/26 802 (4.5)
	All	13/80 (16.3)	1645/30 181 (5.5)
Fetal distress ($n = 1881$)	< 10th centile	53/348 (15.2)	236/2466 (9.6)
	≥ 10th centile	76/1533 (5.0)	860/19 976 (4.3)
	All	129/1881 (6.9)	1096/22 442 (4.9)
Arterial pH ≤ 7.0 or venous pH ≤ 7.1 ($n = 253$)	< 10th centile	11/37 (29.7)	222/1471 (15.1)
	≥ 10th centile	19/216 (8.8)	509/10 835 (4.7)
	Total	30/253 (11.9)	731/12 306 (5.9)
5-min Apgar < 7 ($n = 251$)	< 10th centile	9/45 (20.0)	354/2743 (12.9)
	≥ 10th centile	7/206 (3.4)	998/21 558 (4.6)
	Total	16/251 (6.4)	1352/24 301 (5.6)

Data are given as *n*/*N* (%). DR, detection rate; FPR, false-positive rate.

The main limitation of the study is that the results of the 30–34 weeks' scan were made available to the patients' obstetricians who would have taken specific actions of further monitoring and delivery of the cases with suspected SGA and those with abnormal Doppler findings. Consequently, the performance of screening by UtA-PI would have been negatively biased. For example, SGA fetuses with abnormal fetal heart-rate patterns or fetal Doppler indices were delivered by elective Cesarean section and therefore the performance of UtA-PI in the prediction of Cesarean section for fetal distress in labor would have been underestimated. Similarly, some stillbirths and cases of asphyxia at birth, reflected in low cord blood pH and low Apgar score, could have been avoided. In our study there were 71 pregnancies with SGA fetuses and high UtA-PI that were delivered by elective Cesarean section because of abnormal fetal heart-rate patterns or fetal Doppler indices and this number is not negligible in comparison with the number of pregnancies with SGA fetuses and high UtA-PI that resulted in stillbirth ($n = 6$), Cesarean section for fetal distress ($n = 53$), low arterial blood pH ($n = 6$), low venous blood pH ($n = 10$) or low Apgar score ($n = 9$).

Comparison with findings from previous studies

Previous studies in a small number of pregnancies with SGA fetuses reported that high impedance to flow in the UtAs during the third trimester is associated with increased risk of adverse perinatal events, including stillbirth, Cesarean section for fetal distress and low cord blood pH[8,9,11–13]. Our study evaluated UtA-PI as part of routine screening for adverse perinatal outcome in all pregnant women at 30–34 weeks' gestation. Our results confirm those of the previous studies concerning SGA fetuses and, in addition, they demonstrate that, in general, high UtA-PI is not useful in the prediction of adverse perinatal outcome in pregnancies with non-SGA fetuses.

This study has shown that high UtA-PI at 30–34 weeks predicts about 50% of cases that subsequently deliver with preterm-PE and 33% that deliver preterm SGA in the absence of PE; the DR for term PE and term SGA in the absence of PE was 13% and 9%, respectively. In previous third-trimester screening studies, we combined maternal characteristics and medical history with UtA-PI, mean arterial pressure, serum placental growth factor and serum soluble fms-like tyrosine kinase-1 and such combined screening predicted 99% of those with preterm PE and 75% of those with term PE[21]. Similarly, combined screening with maternal characteristics and medical history with estimated fetal weight, UtA-PI, mean arterial pressure and serum placental growth factor, predicted 89% of preterm SGA and 57% of term SGA[22].

Implications for clinical practice

Measurement of UtA-PI at 30–34 weeks' gestation should be an integral part of combined screening with maternal factors and biomarkers which predicts most cases of SGA and/or PE[21,22]. Such screening will identify the high-risk group in need of close monitoring for fetal growth and wellbeing to define the best timing and mode of delivery. Within the SGA group, high UtA-PI identifies a subgroup at increased risk of adverse perinatal events. In the absence of SGA, UtA-PI is not useful in predicting fetal distress in labor leading to Cesarean section, low cord blood pH or low Apgar score.

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SUPPORTING INFORMATION ON THE INTERNET

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

Tables S1–S4 Univariable and multivariable regression analysis in prediction, based on maternal and pregnancy characteristics, of: stillbirth (Table S1); Cesarean section for fetal distress (Table S2); arterial cord blood pH $\leq$ 7.0 or venous cord blood pH $\leq$ 7.1 (Table S3); 5-min Apgar score < 7 (Table S4).