Ultrasound Obstet Gynecol 2016; **48**: 624–630
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17295

Prediction of stillbirth from maternal factors, fetal biometry and uterine artery Doppler at 19–24 weeks

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KEYWORDS: fetal biometry; impaired placentation; pyramid of pregnancy care; stillbirth; uterine artery Doppler

ABSTRACT

Objectives *To evaluate the performance of screening for all stillbirths and those due to impaired placentation and unexplained or other causes using a combination of maternal factors, fetal biometry and uterine artery pulsatility index (UtA-PI) at 19–24 weeks' gestation and to compare this performance with that of screening by UtA-PI alone.*

Methods *This was a prospective screening study of 70 003 singleton pregnancies including 69 735 live births and 268 (0.38%) antepartum stillbirths; 159 (59%) were secondary to impaired placentation and 109 (41%) were due to other or unexplained causes. Multivariable logistic regression analysis was used to develop a model for prediction of stillbirth based on a combination of maternal factors, fetal biometry and UtA-PI.*

Results *Combined screening predicted 55% of all stillbirths, including 75% of those due to impaired placentation and 23% of those that were unexplained or due to other causes, at a false-positive rate of 10%. Within the impaired placentation group, the detection rate of stillbirth < 32 weeks' gestation was higher than that of stillbirth ≥ 37 weeks (88% vs 46%; P < 0.001). The performance of screening by the combined test was superior to that of selecting the high-risk group on the basis of UtA-PI > 90th percentile for gestational age, which predicted 48% of all stillbirths, 70% of those due to impaired placentation and 15% of those that were unexplained or due to other causes.*

Conclusions *Second-trimester screening by a combination of UtA-PI with maternal factors and fetal biometry can predict a high proportion of stillbirths and, in particular, those that are due to impaired placentation.* *Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Antepartum stillbirths can be classified broadly into those thought to be the consequence of impaired placentation and those that are unexplained or due to other causes; the rationale for categorizing stillbirths according to the likely underlying cause is that antenatal interventions and preventive strategies could potentially be undertaken more effectively[1–3]. In the case of stillbirth due to impaired placentation, a two-stage preventative strategy could be adopted. The first stage, at 11–13 weeks, is aimed at improving placentation through pharmacological interventions such as low-dose aspirin and pravastatin in those at high risk[4,5]; first-trimester screening by a combination of maternal factors, uterine artery pulsatility index (UtA-PI), fetal ductus venosus pulsatility index for veins (DV-PIV) and maternal serum placental growth factor could potentially detect 61% of stillbirths due to impaired placentation, at a false-positive rate (FPR) of 10%[6]. The second stage, at 19–24 weeks, aims to identify a high-risk group that would benefit from close monitoring for early diagnosis of pre-eclampsia (PE) and small-for-gestational-age (SGA) fetuses and prevention of stillbirth by defining the best time for delivery. There is evidence that effective identification of pregnancies at high risk of stillbirth can be achieved by measurement of UtA-PI in the second trimester; a screening study of 66 026 singleton pregnancies, including 306 that resulted in stillbirth, reported that, in 64% of antenatal stillbirths due to PE and/or SGA, the UtA-PI was > 90th percentile[7].

The objective of this study was to evaluate the performance of screening for all stillbirths and those due to impaired placentation or were unexplained or due to other causes by a combination of maternal factors, fetal biometry and UtA-PI at 19–24 weeks' gestation and compare this performance to that of screening by UtA-PI alone.

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Accepted: 31 August 2016

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METHODS

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for routine pregnancy care at 19 + 0 to 24 + 6 weeks' gestation at King's College Hospital and Medway Maritime Hospital, UK, between March 2006 and October 2015. We recorded maternal characteristics and medical history and performed ultrasound examinations for measurement of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL)[8]. Gestational age was determined from measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[8,9]. Transvaginal color Doppler ultrasound was used to visualize the left and right uterine arteries at the level of the internal os[10]. Pulsed-wave Doppler was then used to obtain waveforms and when three similar waveforms were obtained consecutively, the PI was measured and the mean of the two vessels was calculated. The ultrasound examinations 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 uterine artery Doppler received routine antenatal care.

Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the ethics committee of both participating hospitals. The inclusion criteria were women with a singleton pregnancy who delivered a phenotypically normal live birth or stillbirth ≥ 24 weeks' gestation. Pregnancies with aneuploidy, major fetal abnormality, and those ending in a miscarriage, termination of pregnancy or stillbirth due to intrapartum causes were excluded.

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 that required the use of ovulation drugs), cigarette smoking during pregnancy (yes/no), history of chronic hypertension (yes/no), history of systemic lupus erythematosus or antiphospholipid syndrome (SLE/APS), history of pre-existing diabetes mellitus (yes/no), and obstetric history that included parity (parous/nulliparous if no previous pregnancy ≥ 24 weeks' gestation), previous pregnancy with miscarriage between 16 and 23 weeks, previous pregnancy with stillbirth, previous pregnancy with a SGA neonate, gestational age at delivery and birth weight of the neonate in the last pregnancy, interval in years between birth of the last child and estimated date of conception of the current pregnancy. Maternal weight and height were measured.

Outcome measures

Data on pregnancy outcome were obtained from the maternity hospital records or the general practitioners of the women. The hospital maternity records of all women with antepartum stillbirths were reviewed to determine whether the death was associated with PE, placental abruption or a birth weight < 10th percentile for gestational age[11] or was due to other or unexplained reasons.

Statistical analysis

Data from continuous variables were expressed as median (interquartile range) and from categorical variables as *n* (%). Comparison of the maternal characteristics between the outcome groups was by the chi-square test or Fisher's exact test for categorical variables and Kruskal-Wallis or Mann–Whitney *U*-test for continuous variables, respectively. A *P*-value of < 0.05 was considered significant. *Post-hoc* Bonferroni correction was used for multiple comparisons.

The observed measurements of fetal HC, AC and FL were expressed as the respective *Z*-score corrected for gestational age[8]. The observed measurements of UtA-PI were $\log_{10}$ transformed to ensure homogeneity of variance and make the distribution Gaussian and each measured value was expressed as a multiple of the normal median (MoM) after adjustment for characteristics that were found to provide a substantial contribution to the $\log_{10}$ transformed value[12].

The *a-priori* risk for stillbirth was estimated from the algorithm derived from multivariable logistic regression analysis of maternal characteristics and history, as described previously[13]. Univariable and multivariable logistic regression analyses were then used to determine if the maternal factor-derived logit (*a-priori* risk), *Z*-scores of HC, AC, FL and UtA-PI MoM had a significant contribution to the prediction of stillbirth. The variables which provided a significant contribution in the multivariable analysis were used to determine the patient-specific risk of stillbirth using the equation odds/(1 + odds), where odds = e^Y and Y was estimated from the coefficients of variables in the logistic regression analysis. The distribution of patient-specific risks was used to determine the performance of screening by receiver–operating characteristics (ROC) curve analysis and the detection rate (DR) and FPR were estimated.

Regression analysis of $\log_{10}$ UtA-PI according to gestational age at the time of measurement was used to construct a reference range. The performance of screening for stillbirth using the 90th and 95th percentiles of UtA-PI was estimated.

The statistical software package SPSS 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for the data analyses.

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Table 1 Maternal and pregnancy characteristics in pregnancies that resulted in stillbirth, stratified according to whether this was unexplained or due to impaired placentation, compared with pregnancies that resulted in live birth

		Stillbirth		
Characteristic	*Live birth* (n = 69 735)	*All* (n = 268)	*Unexplained* (n = 109)	*Impaired placentation* (n = 159)
Age (years)	30.5 (25.8–34.5)	30.5 (25.8–35.4)	30.9 (26.1–35.5)	30.4 (25.5–35.4)
Weight (kg)	67.0 (59.2–78.0)	73.4 (63.7–85.2)†	71.6 (64.2–84.0)†	74.0 (63.5–85.8)†
Height (m)	1.64 (1.60–1.69)	1.65 (1.60–1.68)	1.65 (1.62–1.68)	1.63 (1.60–1.68)
Racial origin				
Caucasian	48 794 (70.0)	144 (53.7)	65 (59.6)	79 (49.7)
Afro-Caribbean	15 053 (21.6)	103 (38.4)	39 (35.8)†	64 (40.3)†
South Asian	2775 (4.0)	9 (3.4)	1 (0.9)	8 (5.0)
East Asian	1363 (2.0)	5 (1.9)	1 (0.9)	4 (2.5)
Mixed	1750 (2.5)	7 (2.6)	3 (2.8)	4 (2.5)
Mode of conception				
Spontaneous	67 777 (97.2)	255 (95.1)	105 (96.3)	150 (94.3)
Assisted	1958 (2.8)	13 (4.9)	4 (3.7)	9 (5.7)
Cigarette smoker	7478 (10.7)	35 (13.1)	14 (12.8)	21 (13.2)
Chronic hypertension	1031 (1.5)	17 (6.3)†	2 (1.8)	15 (9.4)†
APS/SLE	132 (0.2)	4 (1.5)†	0 (0)	4 (2.5)†
Pre-existing diabetes mellitus	638 (0.9)	7 (2.6)*	3 (2.8)	4 (2.5)
Nulliparous	34 279 (49.2)	132 (49.3)	56 (51.4)	76 (47.8)
Previous miscarriage	883 (1.3)	4 (1.5)	2 (1.8)	2 (1.3)
Previous stillbirth	604 (0.9)	15 (5.6)†	3 (2.8)	12 (7.5)†
Previous SGA	2315 (3.3)	12 (4.5)	2 (1.8)	10 (6.3)
Interpregnancy interval (years)	3.0 (2.0–5.1)	4.2 (2.2–7.1)†	3.9 (2.2–7.0)	4.3 (2.2–8.0)*

Data are given as median (interquartile range) or *n* (%). Comparison of stillbirth groups with live-birth group by chi-square test and Mann–Whitney *U*-test with *post-hoc* Bonferroni correction for multiple comparisons: *$P < 0.01$; †$P < 0.001$. APS, antiphospholipid syndrome; SGA, small-for-gestational age; SLE, systemic lupus erythematosus.

RESULTS

Study population

In total, 70 003 singleton pregnancies fulfilled the entry criteria; there were 69 735 live births and 268 (0.38%) antepartum stillbirths including 159 (59%) secondary to impaired placentation and 109 (41%) due to other or unexplained causes. In total, 29 832 of the 70 003 pregnancies in this study were included in a previous study on prediction of stillbirth[14]. The maternal and pregnancy characteristics of the outcome groups are compared in Table 1.

Fetal biometry and UtA-PI in outcome groups

In pregnancies with stillbirth, compared to live births, the *Z*-scores of HC, AC and FL were lower (−0.26 *vs* 0.00, $P < 0.0001$; −0.37 *vs* 0.00, $P < 0.0001$; −0.21 *vs* −0.01, $P < 0.0001$, respectively) and UtA-PI MoM was higher (1.38 *vs* 1.00, $P < 0.0001$) (Table S1 and Figure 1). Similarly, in stillbirths due to impaired placentation, compared to live births, the *Z*-scores of HC, AC and FL were significantly lower (−0.45 *vs* 0.00, $P < 0.0001$; −0.70 *vs* 0.00, $P < 0.0001$; −0.48 *vs* −0.01, $P < 0.0001$, respectively), and UtA-PI MoM was higher (1.69 *vs* 1.00, $P < 0.0001$); in stillbirths due to unexplained causes there were no significant differences in any of the biomarkers when compared to live births (Table S1).

In the impaired-placentation group, there was a significant association between UtA-PI MoM and gestational age at delivery ($r = -0.412$, $P < 0.0001$); in the unexplained stillbirths the association was not significant ($P = 0.604$).

Prediction of stillbirth and performance of combined screening

The results of univariable and multivariable regression analyses are shown in Table S2. In the multivariable regression analysis, there were significant contributions to the prediction of stillbirth due to impaired placentation from maternal factor-derived *a-priori* risk, and *Z*-scores of HC, AC, FL and UtA-PI MoM ($R^2 = 0.341$; $P < 0.0001$).

The performance of screening for stillbirth is shown in Table 2 and Figure 2. The DR for all stillbirths, at a 10% FPR, increased from 30% when screening by maternal factors alone to 55% with the addition of fetal biometry and UtA-PI ($P < 0.0001$). Within the impaired-placentation group, the DR increased from 34% when using maternal factors alone to 75% with the addition of fetal biometry and UtA-PI MoM ($P < 0.0001$); the DR of stillbirth based on maternal factors, biometry and UtA-PI was higher for stillbirths < 32 weeks' gestation than those ≥ 37 weeks (88% *vs* 46%; $P < 0.001$).

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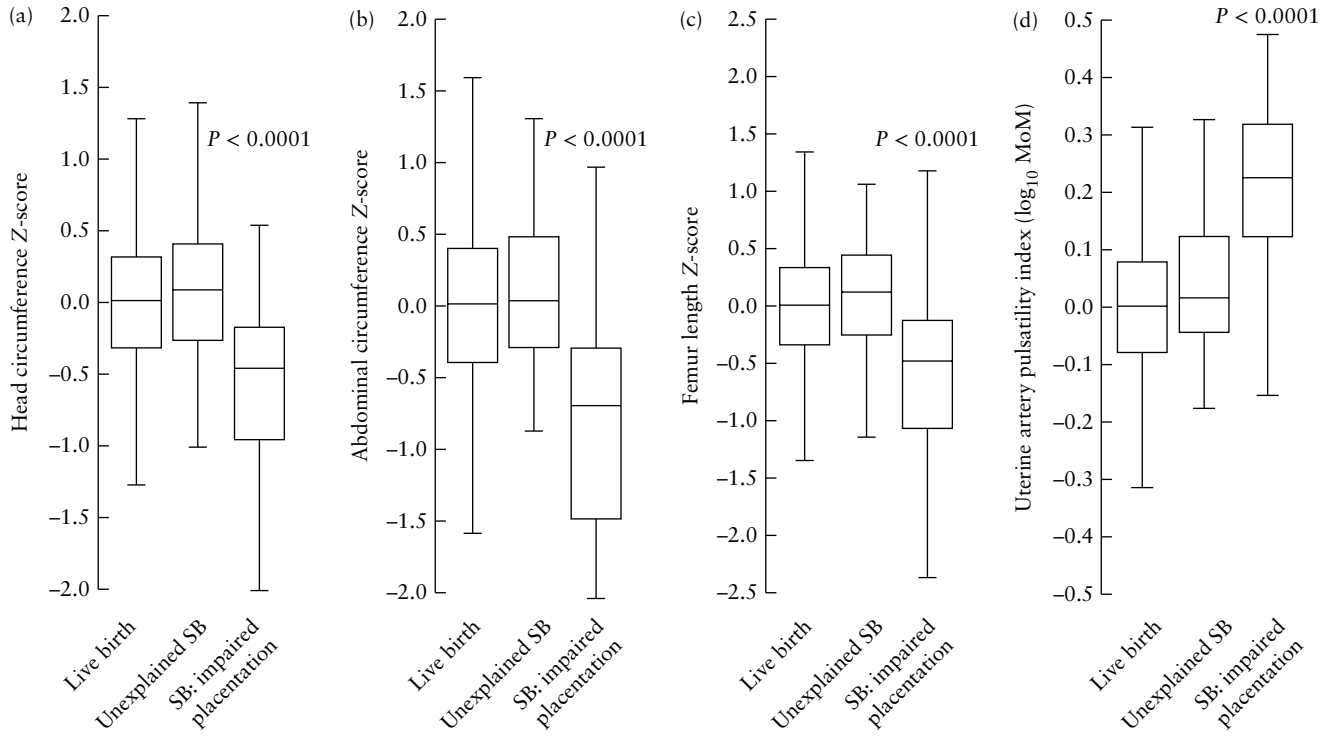

Figure 1 Box-and-whisker plots of *Z*- scores for fetal head circumference (a), abdominal circumference (b) and femur length (c) and uterine artery pulsatility index multiples of the median (MoM) (d) in live births, unexplained stillbirths (SB) and SB due to impaired placentation. Boxes with internal lines represent median and interquartile range and whiskers are range.

Performance of screening by UtA-PI > 90th and 95th percentiles for gestational age

Log_{10} UtA-PI decreased linearly with gestational age between 19 and 24 weeks (intercept, 0.26593 (95% CI, 0.24554–0.28633); slope, −0.01137 (95% CI, −0.01230 to −0.01045); $P < 0.0001$). The relationship with gestational age was used to construct a reference range with median, 5th, 10th, 90th and 95th percentiles (Table S3).

The performance of screening for stillbirth by UtA-PI > 90th and 95th percentiles for gestational age is shown in Tables 3 and S4 and Figure 3. In general, the performance of screening by this approach was inferior to that achieved by combined screening; when screening by UtA-PI > 90th percentile, compared to combined screening at a fixed FPR of 10%, the DR for all stillbirths, unexplained stillbirths and those due to impaired placentation were 48% *vs* 55%, 15% *vs* 23% and 70% *vs* 75%, respectively (Tables 2 and 3).

DISCUSSION

Main findings of the study

The findings of this study demonstrate that, in our population, about 60% of antepartum stillbirths are due to impaired placentation and 40% are unexplained or due to other causes. A model which combines maternal factors, UtA-PI and fetal biometry at 19–24 weeks' gestation can potentially predict about 75% of stillbirths due to impaired placentation, at a 10% FPR; the performance of screening is better for stillbirth < 32 weeks' gestation (88%) compared to those at term (46%).

The performance of screening for stillbirth is superior by a model combining UtA-PI with maternal factors and fetal biometry than by UtA-PI alone. Additionally, the approach utilizing Bayes' theorem is that, in addition to UtA-PI, maternal factors and other potentially useful biomarkers can be combined to improve the performance of screening.

Strengths and limitations

The strengths of this screening study are first, examination of a large population of pregnant women attending for routine assessment at 19–24 weeks' gestation, second, systematic recording of data on maternal characteristics and medical history to identify known risk factors associated with stillbirth, third, use of a specific methodology and appropriately trained doctors to measure UtA-PI, fourth, expression of the values of UtA-PI as MoMs after adjustment for factors that affect the measurements, and fifth, use of multivariable regression analysis to take into account possible interrelations between the different variables to define the relative predictive value of each factor.

A potential limitation of the study is that the performance of screening by a model derived and tested using the same dataset is overestimated. An additional limitation is that pregnancies with high UtA-PI were monitored more intensively and this would have inevitably

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Table 2 Performance of screening for stillbirths by maternal factors and a combination of maternal factors with fetal biometry and uterine artery pulsatility index (UtA-PI) at 19–24 weeks' gestation, at a fixed false-positive rate (FPR)

Screening test	n	*AUC (95% CI)*	*Detection rate (% (95% CI))*	
			5% FPR	*10% FPR*
All stillbirth	268			
Maternal factors		0.652 (0.617–0.688)	19.0 (14.3–23.7)	29.5 (24.0–34.9)
Maternal factors plus:				
Fetal biometry		0.718 (0.683–0.754)	32.2 (26.6–37.8)	42.5 (36.6–48.4)
UtA-PI		0.748 (0.712–0.783)	41.8 (35.9–47.7)	52.6 (46.6–58.6)
Fetal biometry + UtA-PI		0.748 (0.711–0.785)	45.1 (39.1–51.0)	54.7 (48.7–60.6)
Unexplained stilbirth	109			
Maternal factors		0.618 (0.565–0.672)	13.8 (7.3–20.3)	22.9 (15.0–30.8)
Stillbirth from impaired placentation	159			
Maternal factors		0.675 (0.628–0.723)	22.6 (16.1–29.1)	34.0 (26.6–41.4)
Maternal factors plus:				
Fetal biometry		0.861 (0.830–0.893)	52.8 (45.0–60.6)	63.5 (56.0–70.9)
UtA-PI		0.874 (0.840–0.907)	62.3 (54.8–69.8)	73.6 (66.8–80.5)
Fetal biometry + UtA-PI		0.904 (0.875–0.933)	69.8 (62.7–76.9)	74.8 (68.1–81.6)
Stillbirth < 32 weeks	90			
Maternal factors		0.706 (0.641–0.770)	33.3 (23.6–43.0)	42.2 (32.0–52.4)
Maternal factors plus:				
Fetal biometry		0.941 (0.912–0.969)	76.3 (67.5–85.1)	83.4 (75.7–91.1)
UtA-PI		0.925 (0.890–0.961)	76.7 (68.0–85.4)	85.6 (78.4–92.9)
Fetal biometry + UtA-PI		0.952 (0.921–0.982)	85.6 (78.4–92.9)	87.8 (81.0–94.6)
Stillbirth < 37 weeks	126			
Maternal factors		0.699 (0.648–0.751)	26.2 (18.5–33.9)	35.7 (27.3–44.1)
Maternal factors plus:				
Fetal biometry		0.891 (0.859–0.924)	61.1 (52.6–69.6)	70.6 (62.6–78.5)
UtA-PI		0.909 (0.875–0.942)	73.0 (65.3–80.8)	81.7 (75.0–88.5)
Fetal biometry + UtA-PI		0.929 (0.899–0.959)	79.4 (72.3–86.5)	82.5 (75.9–89.1)
Stillbirth ≥ 37 weeks	33			
Maternal factors		0.584 (0.476–0.693)	9.1 (1.7–18.8)	27.3 (12.1–42.5)
Maternal factors plus:				
Fetal biometry		0.736 (0.669–0.823)	20.2 (6.5–33.9)	36.4 (20.0–52.8)
UtA-PI		0.740 (0.654–0.825)	21.2 (7.1–34.9)	42.4 (25.5–59.3)
Fetal biometry + UtA-PI		0.810 (0.743–0.877)	33.3 (17.2–49.4)	45.5 (28.4–62.4)

AUC, area under receiver–operating characteristics curve; UtA-PI, uterine artery pulsatility index.

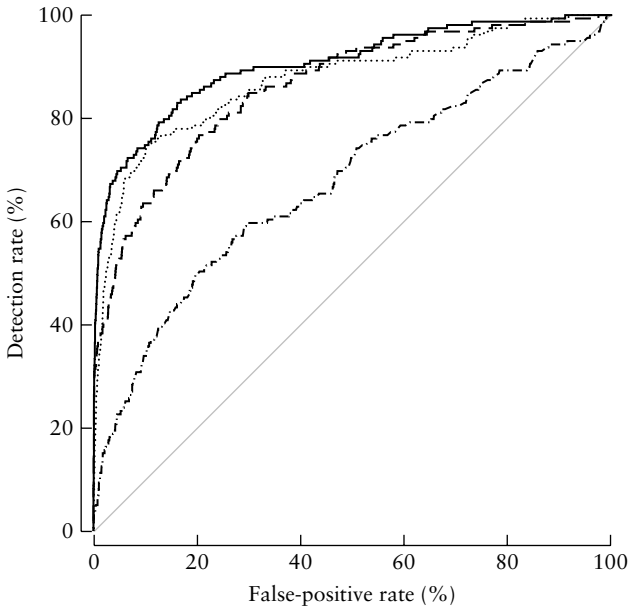

Figure 2 Receiver–operating characteristics curves for prediction of stillbirth due to impaired placentation by maternal factors (–·–·–) and by a combination of maternal factors and fetal biometry (— —), maternal factors and uterine artery pulsatility index (UtA-PI)(·····) and maternal factors, fetal biometry and UtA-PI (——).

prevented some stillbirths, thereby reducing the potential performance of this biomarker.

Comparison with other studies

A previous study of 30 519 singleton pregnancies highlighted that increased UtA-PI at 22–24 weeks' gestation was a better predictor of stillbirth due to impaired placentation, especially < 33 weeks, than of unexplained stillbirth[15].

A screening study in 15 835 nulliparous and high-risk parous women with an obstetric history of placental syndromes, which included 144 (0.9%) stillbirths, reported that the risk of stillbirth was seven-fold higher in the group with high impedance to flow in the uterine arteries > 90th percentile at 19–24 weeks' gestation, compared to those with values ≤ 90th percentile[16]. The DR of all stillbirths for Doppler indices > 90th percentile was 46%, which is similar to the 48% observed in our study.

A screening study of 65 819 singleton pregnancies included 306 (0.46%) stillbirths, and in 159 (52.0%) of these there was impaired placentation[14]. The study reported that high UtA-PI at 20–24 weeks' gestation was observed in antepartum stillbirths associated with impaired placentation but not in intrapartum stillbirths

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Table 3 Detection rate of stillbirths when screening by uterine artery pulsatility index (UtA-PI) adjusted for gestational age, with cut-offs of 90th and 95th percentiles

	Detection rate (% (95% CI)) [n/N]	
Stillbirth	*UtA-PI > 95th percentile*	*UtA-PI > 90th percentile*
All	37.3 (31.5–43.1) [100/268]	47.8 (41.8–53.7) [128/268]
Unexplained	4.6 (0.8–8.5) [5/109]	14.7 (8.1–21.4) [16/109]
Due to impaired placentation		
At any gestational age	59.7 (52.1–67.3) [95/159]	70.4 (63.3–77.5) [112/159]
< 32 weeks	75.6 (66.7–84.5) [68/90]	84.4 (76.9–91.9) [76/90]
< 37 weeks	69.8 (61.8–77.8) [88/126]	80.2 (73.2–87.1) [101/126]
≥ 37 weeks	21.2 (7.3–35.2) [7/33]	33.3 (17.2–43.4) [11/33]

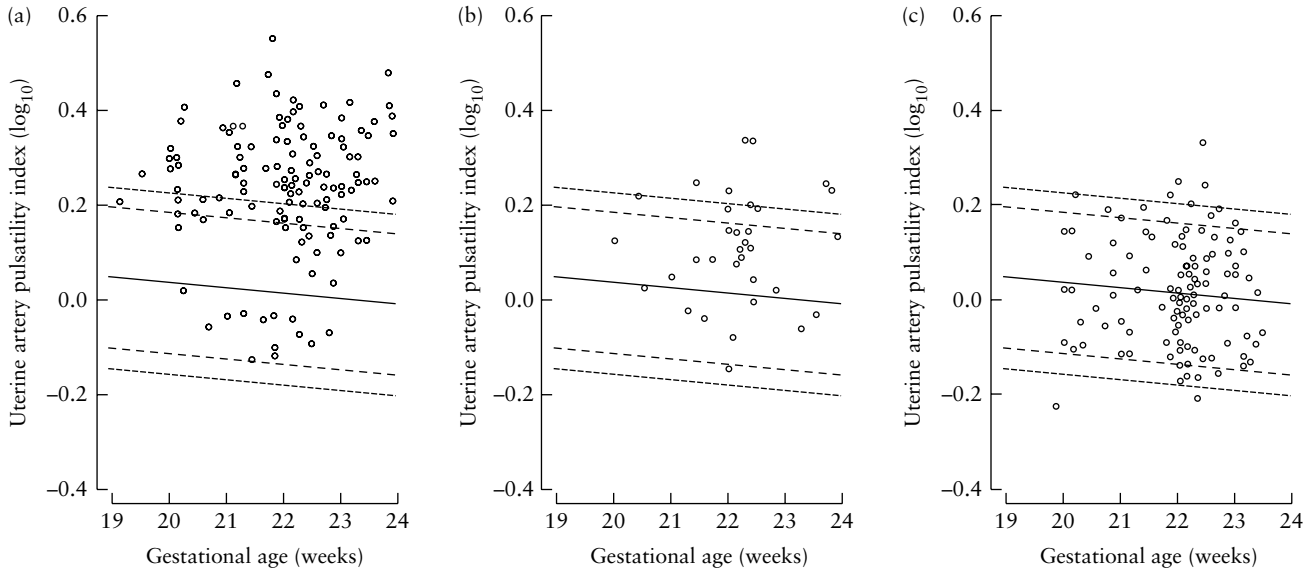

Figure 3 Uterine artery pulsatility index in pregnancies with stillbirth: (a) < 37 weeks due to impaired placentation; (b) ≥ 37 weeks due to impaired placentation; and (c) due to other causes or unexplained causes, plotted on reference range for gestational age. Median and 5th, 10th, 90th and 95th percentiles are shown.

or in antepartum stillbirths without PE, SGA or placental abruption. In the impaired-placentation group, UtA-PI was inversely associated with gestational age at birth. The UtA-PI was > 90th percentile in 81% of stillbirths due to impaired placentation < 32 weeks, in 42% at 33–36 weeks and in 34% ≥ 37 weeks; the respective percentages for stillbirths without impaired placentation were 16%, 25% and 12%.

Clinical implications of the study

Combined screening at 22 weeks' gestation is effective in identifying pregnancies at high risk of stillbirth, PE and SGA < 37 weeks' gestation, but poor in the prediction of these complications occurring ≥ 37 weeks[17,18]. More effective screening for late PE and SGA can be achieved by screening at 36 weeks[19,20]. Pharmacological intervention by prophylactic use of low-dose aspirin at 22 weeks is not useful in reducing the risk of PE, SGA or stillbirth[4,21]. Future studies will determine whether the prophylactic use of pravastatin[5] and/or close monitoring and timely delivery in the high-risk group can reduce the rate of these complications.

ACKNOWLEDGMENT

This study was supported by a grant from The Fetal Medicine Foundation (Charity No: 1037116).

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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 fetal biometry at 19–24 weeks' gestation in pregnancies with live birth compared to those with a stillbirth

Table S2 Univariable and multivariable logistic regression analyses for prediction of stillbirth due to impaired placentation by maternal factors and a combination of uterine artery pulsatility index and fetal biometry at 19–24 weeks' gestation

Table S3 Reference range for uterine artery pulsatility index at 19–24 weeks' gestation

Table S4 Performance of screening for stillbirth and stillbirth due to impaired placentation or unexplained causes by uterine artery pulsatility index > 90^{th} or 95^{th} percentile for gestational age

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