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

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Abstract

Objectives: To evaluate the performance of screening for all stillbirths and those due to impaired placentation and unexplained or other causes by a combination of maternal factors, fetal biometry and uterine artery pulsatility index (UT-PI) at 19-24 weeks' gestation and compare this performance to that of screening by UT-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. Multivariate logistic regression analysis was used to develop a model for prediction of stillbirth based on a combination of maternal factors, fetal biometry and UT-PI.

Results: Combined screening predicted 55% of all stillbirths, including 75% of those due to impaired placentation and 23% of those that were due to other causes or unexplained, at false positive rate of 10%; within the impaired placentation group the detection rate of stillbirth at <32 weeks' gestation was higher than that of stillbirth at ≥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 UT-PI being above the 90th percentile for gestational age, which predicted 48% of all stillbirths, 70% of those due to impaired placentation and 15% of those that were due to other causes or unexplained.

Conclusions: Second-trimester screening by a combination of UT-PI with maternal factors and fetal biometry can predict a high proportion of stillbirths and in particular those due to impaired placentation.

Introduction

Antepartum stillbirths can be broadly classified into those thought to be the consequence of impaired placentation and those due to other causes or being unexplained; the rationale of 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 impaired placentation related stillbirth a two stage preventative strategy could be adopted. The first stage, at 11-13 weeks, is aimed at improving placentation through such pharmacological interventions as low-dose aspirin and pravastatin in the high-risk group;[4,5] first-trimester screening by a combination of maternal factors, uterine artery pulsatility index (UT-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 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 preeclampsia (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 UT-PI in the second-trimester; a screening study of 66,026 singleton pregnancies, including 306 stillbirths, reported that in 64% of antenatal stillbirths due to PE and/or SGA the UT-PI was above the 90th percentile.[7]

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

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}-24^{+6} weeks' gestation at King's College Hospital and Medway Maritime Hospital, United Kingdom. We recorded maternal characteristics and medical history and performed ultrasound examination 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 (CRL) at 11-13 weeks or fetal head circumference at 19-24 weeks.[8,9] Transvaginal colour 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 consecutive waveforms are obtained the PI is measured, and the mean PI of the two vessels is calculated. The scans are 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 uterine artery PI greater than 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 each participating hospital. The inclusion criteria for this study were singleton pregnancies that delivered a phenotypically normal live birth or stillbirth at ≥24 weeks' gestation. We excluded pregnancies with aneuploidies, major fetal abnormalities, those ending in a miscarriage, termination of pregnancy or stillbirths due to intrapartum causes. Data on pregnancy outcome were obtained from the maternity hospital records or the general practitioners of women. The hospital maternity records of all women with antepartum stillbirths were reviewed to determine

if the death was associated with preeclampsia, abruption or the birthweight was <10th percentile for gestational age [11] or it was due to other causes or was unexplained.

Statistical analysis

Data from continuous variables were expressed as medians and interquartile ranges and from categorical data as n (%). Comparison of the maternal characteristics between the outcome groups was by the χ2-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 UT-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 those characteristics found to provide a substantial contribution to the $\log_{10}$ transformed value.[12]

The *a priori* risk for stillbirths was estimated from the algorithm derived from multivariate logistic regression analysis of maternal characteristics and history as previously described.[13] Univariate and multivariate logistic regression analysis was then used to determine if the maternal factor-derived logit (*a priori* risk), Z-scores of HC, AC, FL and UT-PI MoM had a significant contribution in the prediction of stillbirth. The variables which provided a significant contribution in the multivariate 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 characteristic (ROC) curves analysis and the DR and FPR were estimated.

Regression analysis of $\log_{10}$ UT-PI on 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 UT-PI was estimated.

The statistical software package SPSS 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp, 2013) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for the data analyses.

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. The maternal and pregnancy characteristics of the outcome groups are compared in Table 1. In total x of the 70,003 pregnancies in this study were included in a previous one on prediction of stillbirth.[14]

Fetal biometry and uterine artery PI in outcome groups

In the stillbirth group, compared to live births, the Z-scores of HC, AC and FL were lower (-0.26 vs 0.0, p<0.0001; -0.37 vs. 0.0, p<0.0001; -0.21 vs -0.01, p<0.0001, respectively), and UT-PI MoM was higher (1.38 vs 1.00, p<0.0001) (sTable 1, Figure 1). Similarly, in the stillbirths due to impaired placentation, compared to live births, the Z-scores of HC, AC and FL were significantly lower (-0.45 vs 0.0, p<0.0001; -0.70 vs. 0.0, p<0.0001; -0.48 vs -0.01, p<0.0001,

respectively), and UT-PI MoM was higher (1.69 vs 1.00, p<0.0001); in the stillbirths due to unexplained causes there were no significant differences from live births in any of the biomarkers (sTable 1).

In the impaired placentation group, there was a significant association between UT-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 univariate and multivariate regression analysis are shown in sTable 2. In the multivariate regression analysis, there was a significant contribution to the prediction of stillbirths due to impaired placentation from maternal factor derived *a priori* risk, Z-scores of HC, AC, FL and UT-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 FPR of 10%, increased from 30% for maternal factors to 55% with addition of fetal biometry and UT-PI (p<0.0001). Within the impaired placentation group, the DR increased from 34% for maternal factors to 75% with addition of fetal biometry and UT-PI MoM (p<0.0001); the DR of stillbirth based on maternal factors, biometry and UT-PI was higher for stillbirths at <32 weeks' gestation than those at ≥37 weeks (88% vs 46%; p<0.001).

Performance of screening by UT-PI above the 90th and 95th percentiles for gestational age

Log_{10} UT-PI decreased linearly with gestational age at 19-24 weeks' gestation (intercept 0.26593 [95%CI 0.24554 to 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 (sTable 3).

The performance of screening for stillbirth by UT-PI above the 90th and 95th percentiles for gestational age is shown in Table 3, sTable 4 and Figure 3. In general, the performance of screening by this approach was inferior to that achieved by combined screening; in screening by UT-PI above the 90th percentile, compared to combined screening at 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 (Table 2 and 3).

Discussion

Main findings of the study

The findings of the 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, UT-PI and fetal biometry at 19-24 weeks' gestation can potentially predict about 75% of stillbirths due to impaired placentation, at 10% FPR; the performance of screening is better for stillbirths at <32 weeks' gestation (88%) compared to those at term (46%).

The performance of screening for stillbirth is superior by a model combining UT-PI with maternal factors and fetal biometry than UT-PI alone. Additionally, the approach utilizing Bayes theorem is that in addition to UT-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 UT-PI, fourth, expression of the values of UT-PI as MoMs after adjustment for factors that affect the measurements, and fifth, use of multivariate 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 UT-PI were monitored more intensively and this would have inevitably 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 UT-PI at 22-24 weeks' gestation was a better predictor of stillbirth due to impaired placentation, especially at <33 weeks, than 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 7-fold higher in the group with high impedance to flow in the uterine arteries above the 90th percentile at 19-24 weeks' gestation, compared to those with values $\leq$ 90th percentile. [16] The DR of all stillbirth 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 uterine artery PI at 20–24 weeks' gestation, was observed in antepartum stillbirths associated with impaired placentation but not in intrapartum stillbirths or in antepartum stillbirths without PE, SGA or abruption. In the impaired placentation group uterine artery PI was inversely associated with gestational age at birth. The UT-PI was > 90th percentile in 81% of stillbirths due to impaired placentation at <32 weeks, in 42% at 33–36 weeks and in 34% at $\geq$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 at <37 weeks' gestation, but poor in the prediction of these complications occurring at $\geq$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.

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Table 1. Maternal and pregnancy characteristics in pregnancies that had a stillbirth, stratified according to sub-groups, compared with pregnancies that had live births.

Maternal characteristics	Live births (n=69,735)	All stillbirths (n=268)	Unexplained (n=109)	Impaired placentation (n=159)
Age, median (IQR)	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, median (IQR)	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, median (IQR)	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, n (%)	48,794 (70.0)	144 (53.7)	65 (59.6)	79 (49.7)
Afro-Caribbean, n (%)	15,053 (21.6)	103 (38.4)	39 (35.8)*	64 (40.3)*
South Asian, n (%)	2,775 (4.0)	9 (3.4)	1 (0.9)	8 (5.0)
East Asian, n (%)	1,363 (2.0)	5 (1.9)	1 (0.9)	4 (2.5)
Mixed, n (%)	1,750 (2.5)	7 (2.6)	3 (2.8)	4 (2.5)
Method of conception				
Spontaneous, n (%)	67,777 (97.2)	255 (95.1)	105 (96.3)	150 (94.3)
Assisted conception, n (%)	1,958 (2.8)	13 (4.9)	4 (3.7)	9 (5.7)
Cigarette smoking, n (%)	7,478 (10.7)	35 (13.1)	14 (12.8)	21 (13.2)
Chronic hypertension, n (%)	1,031 (1.5)	17 (6.3)*	2 (1.8)	15 (9.4)*
SLE / APS, n (%)	132 (0.2)	4 (1.5)*	0	4 (2.5)*
Diabetes mellitus, n (%)	638 (0.9)	7 (2.6) †	3 (2.8)	4 (2.5)
Parity				
Nulliparous, n (%)	34,279 (49.2)	132 (49.3)	56 (51.4)	76 (47.8)
Previous miscarriage, n (%)	883 (1.3)	4 (1.5)	2 (1.8)	2 (1.3)
Previous stillbirth, n (%)	604 (0.9)	15 (5.6)*	3 (2.8)	12 (7.5)*
Previous SGA, n (%)	2,315 (3.3)	12 (4.5)	2 (1.8)	10 (6.3)
Inter-pregnancy interval, median (IQR)[a]	3.0 (2.0-5.1)	4.2 (2.2-7.1)*	3.9 (2.2-7.0)	4.3 (2.2-8.0)†

Post hoc Bonferroni correction for multiple comparisons; † = p< 0.01; * = p< 0.001

IQR=interquartile range; SLE=systemic lupus erythematosus; APS=anti-phospholipid syndrome; SGA= small for gestational age

[a] Inter-pregnancy interval median (IQR) reported for parous women

Table 2. Performance of screening for stillbirths by maternal factors and combination of maternal factors with fetal biometry and uterine artery pulsatility index at 19-24 weeks' gestation at fixed false positive rates of 5% and 10%.

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

AUROC = area under receiver operating characteristic curves; CI = confidence interval; UT-PI = uterine artery pulsatility index; FPR = false positive rate

Table 3. Detection rate with 95% confidence interval of stillbirth in screening by uterine artery pulsatility index adjusted for gestational age.

Outcome	N	Uterine artery pulsatility index cut-off	
		95th percentile	**90th percentile**
All stillbirths	268	100 (37.3; 31.5-43.1)	128 (47.8; 41.8-53.7)
Unexplained	109	5 (4.6; 0.8-8.5)	16 (14.7; 8.1-21.4)
Abnormal placentation	159	95 (59.7; 52.1-67.3)	112 (70.4; 63.3-77.5)
< 32 weeks	90	68 (75.6; 66.7-84.5)	76 (84.4; 76.9-91.9)
< 37 weeks	126	88 (69.8; 61.8-77.8)	101 (80.2; 73.2-87.1)
≥ 37 weeks	33	7 (21.2; 7.3-35.2)	11 (33.3; 17.2-43.4)

Supplementary Table 1. Median and interquartile range of uterine artery pulsatility index (PI) and fetal biometry at 19-24 week's gestation in pregnancies with livebirths compared to those that had a stillbirth

Biomarker	Live births (n=69,735)	All stillbirths (n=268)	Unexplained (n=109)	Impaired placentation (n=159)
Uterine artery pulsatility index (MoM)	1.00 (0.84-1.20)	1.38 (0.99-1.76)**	1.03 (0.83-1.26)	1.69 (1.33-2.01)**
Head circumference z-score	0.00 (-0.31-0.33)	-0.26 (-0.62-0.08)**	0.07 (-0.26-0.41)	-0.45 (-0.96- -0.16)**
Abdominal circumference z-score	0.00 (-0.39-0.40)	-0.37 (-0.87-0.02)**	0.04 (-0.30-0.49)	-0.70 (-1.52- -0.29)**
Femur length z-score	-0.01 (-0.33-0.34)	-0.21 (-0.71-0.18)**	0.12 (-0.25-0.44)	-0.48 (-1.07- -0.12)**

MoM = multiple of the median; Significance value (p): *Post hoc* Bonferroni correction for multiple comparisons; * = p< 0.01; ** = p< 0.001

Supplementary Table 2. Univariate and multivariate logistic regression analysis for the prediction of stillbirths due to impaired placentation by maternal factors and combination of uterine artery pulsatility index and fetal biometry at 19-24 week's gestation

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Maternal factor derived logit (*a priori* risk)	14.52 (9.29-22.69)	<0.0001	7.56 (4.46-12.81)	<0.0001
Log_{10} uterine artery PI MoM	$22.75e^4$ ($73.20e^3$-$70.72e^4$)	<0.0001	$8.25e^3$ ($2.39e^3$-$28.47e^3$)	<0.0001
Head circumference z-score	0.07 (0.05-0.09)	<0.0001	0.49 (0.33-0.72)	<0.0001
Abdominal circumference z-score	0.09 (0.07-0.12)	<0.0001	0.32 (0.23-0.44)	<0.0001
Femur length z-score	0.15 (0.12-0.18)	<0.0001	0.67 (0.50-0.89)	0.005

PI = pulsatility index; MoM = multiple of the median; OR = odds ratio; CI = confidence interval

Supplementary Table 3. Reference range for uterine artery pulsatlility index, with 95% confidence interval, at 19-24 weeks' gestation.

Gestational age	N	Uterine artery pulsatility index				
		5th centile	10th centile	50th centile	90th centile	95th centile
19 weeks	1048	0.72 (0.66-0.78)	0.80 (0.73-0.87)	1.12 (1.04-1.20)	1.58 (1.49-1.67)	1.74 (1.64-1.84)
20 weeks	7633	0.70 (0.64-0.76)	0.77 (0.71-0.83)	1.09 (1.01-1.17)	1.54 (1.45-1.63)	1.70 (1.60-1.80)
21 weeks	15,269	0.68 (0.62-0.74)	0.75 (0.69-0.81)	1.06 (0.98-1.14)	1.50 (1.41-1.59)	1.65 (1.56-1.74)
22 weeks	34,134	0.67 (0.61-0.73)	0.74 (0.68-0.80)	1.04 (0.96-1.12)	1.46 (1.37-1.55)	1.61 (1.52-1.70)
23 weeks	11,135	0.65 (0.59-0.71	0.72 (0.66-0.78)	1.01 (0.94-1.08)	1.42 (1.33-1.51)	1.57 (1.48-1.66)
24 weeks	813	0.63 (0.57-0.69)	0.70 (0.64-0.76)	0.98 (0.91-1.05)	1.39 (1.30-1.48)	1.53 (1.44-1.62)

Supplementary Table 4. Performance of screening for stillbirths and subgroups of stillbirths by uterine artery pulsatility index above the 90th or 95th percentile for gestational age.

Stillbirth subgroups	Gestation at stillbirth			
	Any gestation	**<32 weeks**	**<37 weeks**	**≥37 weeks**
	Uterine artery pulsatility index (> 90th percentile)			
All stillbirths	128/268 (47.8)	81/113 (71.1)	110/171 (64.3)	18/97 (18.6)
Impaired placentation group	112/159 (70.4)	76/90 (84.4)	101/126 (80.2)	11/33 (33.3)
Small for gestation	53/88 (60.2)	36/48 (75.0)	47/67 (70.1)	6/21 (28.6)
Preeclampsia	45/51 (88.2)	34/36 (94.4)	42/44 (95.5)	3/7 (42.9)
Small for gestation and / or preeclampsia	98/139 (70.5)	70/84 (83.3)	89/111 (80.2)	9/28 (32.1)
Placental abruption	14/20 (70.0)	6/6 (100.0)	12/15 (80.0)	2/5 (40.0)
Unexplained group	16/109 (14.7)	5/23 (21.7)	9/45 (20.0)	7/64 (10.9)
	Uterine artery pulsatility index (95th percentile)			
All stillbirths	100/268 (37.3)	69/113 (61.1)	90/171 (52.6)	10/97 (10.3)
Impaired placentation group	95/159 (59.7)	68/90 (75.6)	88/126 (69.8)	7/33 (21.2)
Small for gestation	45/88 (51.1)	32/48 (66.7)	40/67 (59.7)	5/21 (23.8)
Preeclampsia	39/51 (76.5)	30/36 (83.3)	38/44 (86.4)	1/7 (42.3)
Small for gestation and / or preeclampsia	84/139 (60.4)	62/84 (73.8)	78/111 (70.3)	6/28 (21.4)
Placental abruption	11/20 (55.0)	6/6 (100.0)	10/15 (66.7)	1/5 (20.0)
Unexplained group	5/109 (4.6)	1/23 (4.3)	2/45 (4.4)	3/64 (4.7)

Figure 1. Box and whiskers plot of head circumference, abdominal circumference, femur length Z-score and uterine artery pulsatility index multiple of the median (MoM) in live births (a), unexplained stillbirths (b) and stillbirths due to impaired placentation (c). The bottom and top edges of each box represent the first and third quartiles, respectively; the band within the box represents the median value.

Figure 2. Receiver–operating characteristics curves for prediction of stillbirth due to impaired placentation from maternal factors and maternal factors with biomarkers.

Figure 3. Uterine artery pulsatility index in pregnancies with stillbirths at <37 weeks due to impaired placentation (left), stillbirths at ≥37 weeks due to impaired placentation (middle) and stillbirths due to other causes or unexplained (right) plotted on the reference ranges with gestation (___ median, - - - 10^{th} and 90^{th} percentiles, ….5^{th} and 95^{th} percentiles).