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Mid-pregnancy fetal growth, uteroplacental Doppler indices and maternal demographic characteristics: role in prediction of stillbirth

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Second trimester screening, stillbirth, uterine artery Dopplers, fetal biometry, femur length

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Conflict of interest
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Abstract

Introduction. To evaluate the relative value of mid trimester fetal growth, uterine artery Doppler indices and maternal demographics in prediction of stillbirth. *Material and methods.* Retrospective cohort study; 23 894 singleton pregnancies routinely scanned between 19 and 24 weeks' gestation. Maternal characteristics included age, body mass index, ethnicity and medical history. Fetal biometry indices, birthweight and uterine artery pulsatility index values were converted to percentiles and multivariable logistic regression analysis was performed. The predictive accuracy was assessed using receiver operating characteristic curves analysis. The main outcome was prediction of preterm and term stillbirths. *Results.* Non-Caucasian ethnicity, femur length centile and uterine artery pulsatility index were significantly associated with the risk of stillbirth (all $p < 0.01$). The detection rate of screening by maternal factors alone was 19% for all stillbirths, and 12 and 14% for term and preterm stillbirth at a 10% false positive rate, respectively. Using femur length centile alone, the detection rates were 27 and 23%, respectively. Uterine artery pulsatility index alone was able to predict 24 and 31% of term and preterm stillbirths. Screening by combining maternal factors, femur length centile and uterine artery Doppler detected 27 and 35% of term and preterm stillbirths at a 10% false positive rate. *Conclusions.* Second trimester ultrasound assessment offers an opportunity to identify pregnancies at the highest risk of stillbirth occurring as a consequence of placental dysfunction. This information may be useful to improve pregnancy outcome by identifying women who may benefit from increased ultrasound surveillance and/or timely intervention.

Abbreviations: AC, abdominal circumference; AGA, appropriate birthweight for gestational age; AUC, area under the curve; BMI, body mass index; DR, detection rate; FL, femur length; FPR, false positive rate; IUD, intrauterine death; IUGR, intrauterine growth restriction; PI, pulsatility index; ROC, receiver operating characteristic; SGA, small for gestational age; UtA, uterine artery.

Introduction

The birth of a stillborn infant is a devastating outcome of pregnancy and unfortunately is still a relatively common occurrence (1,2). Although several maternal and obstetric characteristics are associated with the risk of stillbirth, they explain less than 20% of the variance in

Key Message

Our study provides evidence that a high resistance flow pattern in the uterine arteries is associated with an increased risk of stillbirth due to placental dysfunction.

the incidence of stillbirth, and the major risk factor recognized for intrauterine death (IUD) is placental insufficiency (3–5). While two-thirds of stillbirths are "unexplained" by conventional classification, fetal growth restriction resulting from placental insufficiency is present in over half of these cases, despite an apparently appropriate birthweight for gestational age (AGA) (6,7). Indeed, neonates defined as AGA may not have achieved their true growth potential, leading to an incorrect classification that is likely to account for the group of stillbirths classified as unexplained on the basis of fetal size rather than Doppler criteria. Uterine artery (UtA) Doppler assessment has a strong association with impaired placental function (8) and several publications have reported the association of abnormal uterine artery Doppler indices both in the first and second trimester to stillbirth, even when apparently unexplained (6,9–11). Several biophysical and biochemical tests performed during the first two trimesters of pregnancy have been proposed to predict stillbirth (5,9,11–13) but, to date, there is still no clinically useful first or second trimester test to predict IUD in unselected pregnant women. The aim of this study was to investigate the potential value of screening integrating mid-pregnancy maternal demographics, fetal biometry and UtA pulsatility index (PI) in the prediction of IUD and to examine the potential value of such assessment in identifying women who may benefit from increased antenatal surveillance. The ability to predict stillbirths early in pregnancy and to offer additional surveillance and intervention to high-risk mothers/fetuses is understandably an important part of antenatal care.

Material and methods

This was a retrospective cohort study of data obtained in a single maternity center over a 14-year period from 2000 to 2014. Inclusion criteria were: morphologically normal singleton pregnancy women attending their routine, scheduled ultrasound examination between 19 and 24 weeks of gestation. As a retrospective study of routinely collected data, ethics approval was not required (as for NHS-REC). Secondly, the ethics committee approved the collection of pregnancy outcome data as part of the routine follow up of FMU patients. Pregnancies complicated by fetal abnormality, maternal medical disorders, previous adverse obstetric outcome, aneuploidy or infection were excluded from the analysis. In addition, all women who delivered elsewhere or were referred from other hospitals were excluded from the study as it was not possible to obtain the postnatal outcomes. Gestational age (GA) was determined according to crown–rump length (CRL) in the first trimester (13). All the patients underwent a nuchal scan and double test as for the first trimester NHS protocol and only those classified as low risk were included in the study. Data on ultrasound examinations were obtained from computerized records (VIEWPOINT software; General Electric, Wauwatosa, WI, USA) and only one (the anomaly scan) examination per fetus was included in the analysis. Ultrasound examinations were performed mainly with a Voluson GE (GE Medical Systems, Zipf Austria) ultrasound machine equipped with a 2–8 MHz convex probe. Qualified and experienced sonographers performed all scans. Maternal characteristics recorded included maternal age, body mass index, parity, ethnicity (Caucasian, Afro-Caribbean, Asian and mixed), medical history and obstetric history. Data on pregnancy outcomes were collected from the hospital maternity records. Ultrasound data, including head circumference, abdominal circumference and femur length (FL), were measured according to a standard protocol (15) and were converted to percentiles using reference values derived from low-risk pregnancies with documented normal outcome. Transabdominal color Doppler ultrasound was used to visualize the uterine arteries at the apparent crossover with the external iliac arteries (14). Measurements were taken with pulsed-wave Doppler at the lowest insonation angle achievable and when uniform waveforms with high signal-to-noise ratio were obtained, the PI was measured. Maternal characteristics, second trimester fetal biometry and Doppler measurements were compared between women who delivered stillborn and those who delivered live-born babies. Maternal age, body mass index and all the ultrasound parameters were included as continuous variables, and parity and ethnicity as nominal variables.

Stillbirth was defined as the death of a fetus with a birthweight $\geq$500 g or a gestational age $>23^{+6}$ weeks of gestation (1). We compared the potential value of maternal characteristics, fetal biometry and UtA Doppler at >37 weeks' gestation and preterm stillbirth occurring at <37 weeks' gestation.

Multivariate logistic regression analysis was used to estimate the association between second trimester ultrasound measurements and stillbirth, and to determine the independence and relative contribution of variables. All variables significantly associated with stillbirth were included in the model. The risk for each of the pregnancy outcomes was then calculated from the formula: odds/(1 + odds), where odds = eY, and Y was derived from the multivariate logistic regression analysis. The performance of screening was determined by receiver operating characteristic (ROC) curves. SPSS version 20 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis, and a *p*-value <0.05 was considered significant.

Results

The study included 23 894 pregnancies that were scanned between 19 and 24 weeks' gestation (Table 1). There were 90 stillbirths after 24 weeks' gestation: 38 stillbirths occurred at term and 52 were preterm. The results of the multivariate regression of the association between maternal characteristics and ultrasound parameters and the risk of stillbirth are shown in Table 2. Non-Caucasian ethnicity, FL centile and UtA PI were significantly associated with the risk of stillbirth (all $p < 0.01$). The ROC curves of second trimester maternal demographics, fetal biometry and UtA Doppler parameters for predicting all, term and preterm stillbirths are presented in Figures 1 and 2. The area under curve (AUC), the detection rates (DR) at a various false positive rates (FPR) of screening by maternal demographics, fetal biometry, UtA PI and their combination for stillbirth are given in Table 3.

Screening by maternal demographics alone – at a 10% FPR – had a DR of 12 and 14% for term and preterm stillbirths, respectively. Screening combining maternal demographic characteristics, FL centile and UtA Doppler indices at the same FPR had a DR of 31% for prediction for all stillbirths. In the term population, the DRs at 10% FPR were 27, 24 and 27% using the combined parameters, UtA Doppler indices alone and FL centile in isolation, respectively.

In addition, a sub-analysis was performed stratifying the results by Caucasian and non-Caucasian ethnicity (Table S1). No statistically significant differences were found comparing the AUCs and the DRs between these two groups (Table S1).

Table 1. Baseline demographics of the study population. Data are given as mean ± SD or *n* (%). For uterine artery pulsatility index, data are given as mean of the right and left uterine artery pulsatility index. Small-for-gestational age is defined as a birthweight <10th centile. The most significant values are given in bold.

Characteristic	Live birth pregnancies (n = 23 804)	Stillbirths (n = 90)	p-value
Maternal age (years)	29.99 ± 5.6	30.6 ± 6.6	**0.021**
Body mass index (kg/m^2)	24.55 ± 4.8	25.24 ± 5.1	0.062
Ethnicity			
Caucasian	13 401 (56.3%)	51 (56.8%)	0.940
Asian	4942 (20.8%)	13 (14.4%)	**0.039**
Afro-Caribbean	3501 (14.7%)	13 (14.4%)	0.078
Mixed-others	1960 (8.2%)	13 (14.4%)	**0.033**
Gestation age at scan (weeks)	21.8 ± 0.6	21.9 ± 0.6	0.630
Gestational age at delivery (weeks)	39.7 ± 2	35.4 ± 4	**0.000**
Head circumference centile	58.81 ± 22.6	55.74 ± 24.1	0.146
Abdominal circumference centile	59.42 ± 21.09	53.75 ± 25.37	**0.003**
Femur length centile	59.83 ± 22.70	50.12 ± 27.46	**0.001**
Uterine artery Doppler pulsatility index	0.875 ± 0.55	1.09 ± 0.72	**0.000**
Birthweight (g)	3295.6 ± 578	2508 ± 824	**0.000**
Term delivery	22,241 (93.4%)	38 (42.2%)	**0.000**
Preterm delivery <37 weeks	1,563 (6.6%)	52 (57.8%)	**0.000**
Small-for-gestational age	2908 (12.2%)	35 (38.9%)	**0.000**

Table 2. Results of the multivariate logistic regression analysis of factors associated with stillbirth. All the variables listed above were included in the regression model. The most significant values are given in bold.

Maternal demographics, fetal biometry and Doppler	Unadjusted odds ratio	Adjusted odds ratio	95% Confidence Interval	p-value
Body mass Index	1.0	1.0	0.9–1.1	0.189
Age	1.0	1.0	0.9–1.1	0.776
Ethnicity				
Caucasian	0.7	0.7	0.4–1.1	0.063
Asian	1.4	1.3	1.2–1.5	**0.015**
Afro-caribbean	1.2	1.1	0.9–1.3	0.079
Mixed-others	2.3	2.6	1.1–5.6	**0.017**
Abdominal circumference centile	0.9	0.9	0.9–1.0	0.184
Femur length centile	0.9	0.9	0.9–0.9	**0.003**
Head circumference centile	1.0	0.9	0.9–1.0	0.615
Uterine artery Doppler pulsatility index	2.1	2.2	1.7–2.6	**0.000**

Discussion

This screening study evaluated the role of mid-pregnancy maternal demographics, fetal biometry and UtA Doppler indices, alone or in combination, in prediction of stillbirth in a large population of low-risk women attending for routine care at 19–24 weeks' gestation. The findings of the study demonstrate that the second trimester assessment does not have a high sensitivity in detecting term stillbirths and this is consistent with the current available literature (9–16). On the other hand, the performance improved to a sensitivity of 35% for a 10% FPR when examining the rate of preterm stillbirths. Preterm stillbirths show a strong association with severe intrauterine growth restriction (IUGR), explaining why the UtA

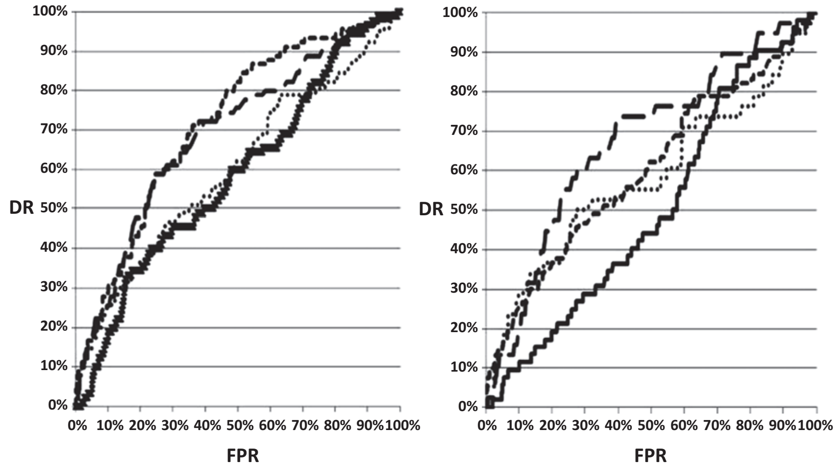

Figure 1. Receiver operating characteristic curves for screening by maternal demographics (smooth black line), femur length centile (round dot line), uterine artery Doppler pulsatility index (dash line) and maternal factors, femur length centile and uterine artery Doppler pulsatility index (square dot line) in the prediction of all stillbirths (left) and term stillbirths (right). DR, detection rate; FPR, false positive rate.

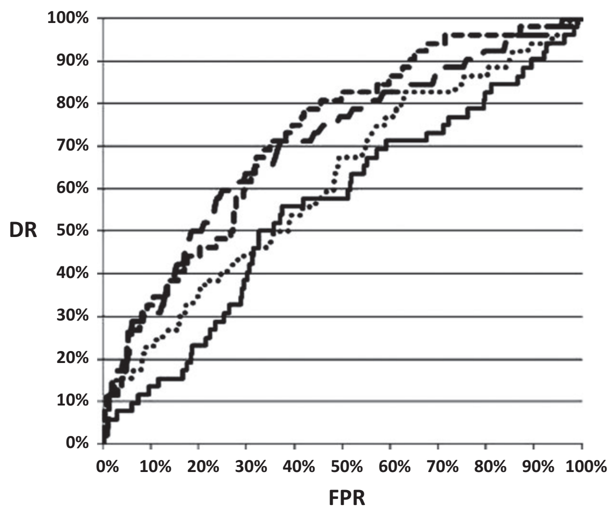

Figure 2. Receiver operating characteristic curves for screening by maternal demographics (smooth black line), femur length centile (round dot line), uterine artery Doppler pulsatility index (dash line) and maternal factors, femur length centile and uterine artery Doppler pulsatility index (square dot line) in the prediction of preterm (<37 weeks' gestation). DR, detection rate; FPR, false positive rate.

Table 3. Performance of screening for all, term and preterm stillbirths with maternal demographics, FL centile, and UtA Doppler PI.

Screening test	AUC	Detection rate at 10% FPR
All stillbirths		
Maternal demographics	0.568	19%
Femur length centile	0.601	26%
UtA Dopplers	0.693	28%
Mat demographics + FL+ UtA PI	0.717	31%
Term stillbirths		
Maternal demographics	0.574	12%
Femur length centile	0.595	27%
UtA Dopplers	0.682	24%
Mat demographics + FL+ UtA PI	0.714	27%
Preterm stillbirths		
Maternal demographics	0.556	14%
Femur length centile	0.615	23%
UtA Dopplers	0.705	31%
Mat demographics + FL+ UtA PI	0.722	35%

FL, femur length; UtA, uterine artery; PI, pulsatility index; AUC, area under the curve; FPR, false positive rate.

Doppler indices are the best single predictor (9). Moreover, this study shows that, of the fetal biometry parameters, only the FL centile was an independent predictor of IUD in our population of low-risk woman. The performance of the screening for detection of stillbirth was only marginally improved by the addition of FL to the UtA Doppler assessment, as shown by ROC curves (Figures 1 and 2). In contrast, second trimester assessment performed better than the use of maternal demographic characteristics and risk factors, as is conventional in clinical practice currently. These discordant findings for gestation of stillbirth could be explained either because term stillbirth has a different etiology or because the interval between the assessment and the time of the stillbirth affects the performance of the screening. The major strengths of our study include the large number of pregnancies attending for routine assessment at 19–24 weeks' gestation, adjusting for possible confounding variables and ascertainment of the outcome data. The retrospective design is a limitation and the data could be biased by selective assessment of a high-risk population based on the availability of results of UtA Doppler indices to the obstetricians.

Several biophysical and biochemical tests performed during the first two trimesters of pregnancy have been proposed to predict stillbirth (5,9,11) but to date there is no clinically useful first or second trimester test to predict IUD as a sole category in unselected pregnant women. Studies over the past two decades have confirmed UtA Doppler as potentially useful in predicting pregnancies at high risk of developing complications related to utero-placental insufficiency (9,11,16). Smith et al. (9) showed that UtA Doppler at 20–24 weeks' gestation in a population of low-risk unselected women is associated with increased risk of all causes of stillbirth up to 32 weeks (sensitivity 58% for an FPR of 5%). Conversely, the prediction at later gestational age was poor, with a sensitivity of 7% at the same FPR. However, fetal biometry was not included in the analysis and, interestingly, the results of our study show an independent contribution of FL measurement in prediction of stillbirth. In high-risk women, the use of UtA Doppler indices had a better sensitivity in predicting stillbirth at term (6). The explanation of this difference can be identified in the increased prevalence of stillbirth in the high-risk population and the influence of intervention bias, as abnormal results were revealed to clinicians who may have modified the management of the pregnancy (6).

A recent systematic review and meta-analysis (11) showed that serum levels of pregnancy-associated plasma protein A (PAPP-A) in the first trimester and UtA PI in the second trimester have a high predictive accuracy for stillbirth related to placental dysfunction and pointed out the impact that the introduction of such tests could have, in reducing the risk of placental dysfunction-related stillbirth. Evidence suggests that the detection of an FL below the expected value (<5th centile) at mid trimester ultrasound examination is a feature of IUGR (17–19). Weisz et al. (19) showed in a large cohort that 20% of cases of isolated short femur in the second trimester were associated with subsequently diagnosed IUGR and lower levels of PAPP-A. However, this study did not incorporate Doppler analysis. The etiology of femur shortening in IUGR fetuses is unclear. A study of body proportionality of small-for-gestational-age fetuses found that in most cases of small for gestational age due to abnormal placentation, the reduced FL was concordant with the small abdominal circumference (20). Another study (21) speculated that abnormal placentation altered the level of fibroblast growth factor receptor-2, resulting in growth restriction of the fetal long bones and this can account for the finding of isolated short femur in pregnancies with impaired placental function.

The well-accepted hypothesis that stillbirth is related to multiple etiologies and not to a single disorder makes it unlikely that any single test will be able to predict all-cause stillbirth. The most avoidable cause of stillbirth is certainly the one related to an impaired placental function defined as IUGR, rather than the one based on birthweight criteria. The results of our study show that a high resistance pattern of flow in the UtA in the second trimester is associated with an increased risk of stillbirth and that this association is strongest for stillbirths due to placental dysfunction. Although consistent with other studies, the current comprehensive evaluation of mid-pregnancy maternal demographics, fetal biometry and UtA Doppler provides evidence that other factors have a relative importance for prediction of placental stillbirths such as the finding of shortening of FL. The clinical custom of using fetal size as an indicator of adverse outcome makes it difficult to identify placental insufficiency near term in a fetus of normal weight. Indeed, placental insufficiency can result from an abnormal placental development, leading to the early onset fetal growth restriction. Alternatively, placental dysfunction may occur because a normally formed placenta is unable to cope with the higher fetal metabolic demands, as may occur at term with a normal or increased fetal size (22,23). This could explain why the second trimester screening using UtA Doppler indices is not as sensitive in identifying this subset of patients as "high-risk" of term stillbirth and suggests that a third trimester assessment might be required. In this scenario it becomes a priority to recognize criteria directly related to placental function rather than fetal weight population definitions in order to reduce the rate of "unexplained" stillbirth by correctly classifying the placental stillbirths. This information may be useful to improve pregnancy outcome by increased surveillance and timely intervention. Future studies will be needed to investigate the potential benefit of scheduling further scans and Doppler evaluation for the selected "high-risk" pregnancies to improve performance in the prediction of pregnancy outcomes.

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References

1. Confidential Enquiry into Maternal and Child Health (CEMACH). Perinatal mortality 2007: United Kingdom. London: CEMACH, 2009. RCOG Guidelines. Available online at: http://www.cmace.org.uk/getattachment/1d2c0ebc-d2aa-4131-98ed56bf8269e529/PerinatalMortality-2007.aspx (accessed October, 2010).

2. Child mortality statistics: childhood, infant and perinatal. Office for National Statistics (ONS), 2012.
3. The Stillbirth Collaborative Research Network Writing Group. Association between stillbirth and risk factors known at pregnancy confirmation. JAMA. 2011;306:2469–79.
4. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet. 2011;377:1331–40.
5. Smith GC. Predicting antepartum stillbirth. Clin Obstet Gynecol. 2010;53:597–606.
6. Singh T, Leslie K, Bhide A, D'Antonio F, Thilaganathan B. Role of second trimester uterine artery Doppler in assessing stillbirth risk. Obstet Gynecol. 2012;119:256–61.
7. Gardosi J, Kadi SM, McGeown P. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. BMJ. 2005;331:1113–7.
8. Prefumo F, Sebire NJ, Thilaganathan B. Decreased endovascular trophoblast invasion in first trimester pregnancies with high-resistance uterine artery Doppler indices. Hum Reprod. 2004;19:206–9.
9. Smith GC, Yu CK, Papageorghiou AT, Cacho AM, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Maternal uterine artery Doppler flow velocimetry and the risk of stillbirth. Obstet Gynecol. 2007;109:144–51.
10. Iacovella C, Franchi M, Egbor M, Bhide A, Thilaganathan B. Relationship of first-trimester uterine artery Doppler to late stillbirth. Prenat Diagn. 2012;32:557–61.
11. Conde-Agudelo A, Bird S, Kennedy SH, Villar J, Papageorghiou AT. First- and second trimester tests to predict stillbirth in unselected pregnant women: a systematic review and meta-analysis. BJOG. 2015;122:41–56.
12. Khalil A, Rezende J, Akolekar R, Syngelaki A, Nicolaides KH. Maternal racial origin and adverse pregnancy outcome: a cohort study. Ultrasound Obstet Gynecol. 2013;41:278–85.
13. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurement. BJOG. 1975;82:702–10.
14. Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. Obstet Gynecol. 2000;96:559–64.
15. Salomon LJ, Alfirevic Z, Berghella V, Bilardo C, Hernandez-Andrade E, Johnsen SL, et al. ISUOG Clinical Standards Committee. Practice guidelines for performance of the routine mid trimester fetal ultrasound scan. Ultrasound Obstet Gynecol. 2011;37:116–26.
16. Papageorghiou AT, Leslie K. Uterine artery Doppler in the prediction of adverse pregnancy outcome. Curr Opin Obstet Gynecol. 2007;19:103–9.
17. Todros T, Massarenti I, Gaglioti P, Biolcati M, Botta G, De Felice C. Fetal short femur length in the second trimester and the outcome of pregnancy. BJOG. 2004;111:83–5.
18. Papageorghiou AT, Fratelli N, Leslie K, Bhide A, Thilaganathan B. Outcome of fetuses with antenatally diagnosed short femur. Ultrasound Obstet Gynecol. 2008;31:507–11.
19. Weisz B, David AL, Chitty L, Peebles D, Pandya P, Patel P, et al. Association of isolated short femur in the mid trimester fetus with perinatal outcome. Ultrasound Obstet Gynecol. 2008;31:512–6.
20. Todros T, Plazzotta C, Pastorin L. Body proportionality of the small-for-date fetus: is it related to aetiological factors? Early Hum Dev. 1996;45:1–9.
21. Sheldon RE, Peeters LL, Jones MD Jr, Makowski EL, Meschia G. Redistribution of cardiac output and oxygen delivery in the hypoxemic fetal lamb. Am J Obstet Gynecol. 1979;135:1071–8.
22. Zalel Y, Lehavi O, Schiff E, Shalmon B, Cohen S, Schulman A, et al. Shortened fetal long bones: a possible in utero manifestation of placental function. Prenat Diagn. 2002;22:553–7.
23. Morales-Roselló J, Khalil A, Morlando M, Papageorghiou A, Bhide A, Thilaganathan B. Changes in fetal Doppler indices as a marker of failure to reach growth potential at term. Ultrasound Obstet Gynecol. 2014;43:303–10.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Subanalysis of the performance of screening for all, term and preterm stillbirths with maternal demographics, femur length centile and uterine artery Dopplers dividing the studied population into Caucasian and non-Caucasian groups.

