Ultrasound Obstet Gynecol 2016; **48**: 607–612
Published online 5 October 2016 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17290

Prediction of stillbirth from maternal demographic and pregnancy characteristics

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KEYWORDS: maternal factors; pyramid of pregnancy care; stillbirth

ABSTRACT

Objectives *To develop a model for prediction of stillbirth based on maternal characteristics and components of medical history and to evaluate the performance of screening with this model for all stillbirths and those due to impaired placentation and to unexplained causes.*

Methods *This was a prospective screening study of 113 415 singleton pregnancies at 11 + 0 to 13 + 6 weeks' gestation and at 19 + 0 to 24 + 6 weeks. The study population included 113 019 live births and 396 (0.35%) antepartum stillbirths; 230 (58%) were secondary to impaired placentation and 166 (42%) were due to other or unexplained causes. Multivariable logistic regression analysis was used to determine the factors from maternal characteristics and medical history which provided a significant contribution to the prediction of stillbirth.*

Results *The risk for stillbirth increased with maternal weight (odds ratio (OR), 1.01 per kg above 69 kg), was higher in women of Afro-Caribbean racial origin (OR, 2.01), those with assisted conception (OR, 1.79), cigarette smokers (OR, 1.71), and in those with a history of chronic hypertension (OR, 2.62), systemic lupus erythematosus/antiphospholipid syndrome (OR, 3.61) or diabetes mellitus (OR, 2.55) and was increased in women with a history of previous stillbirth (OR, 4.81). Screening with the model predicted 26% of unexplained stillbirths and 31% of those due to impaired placentation, 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 (38% vs 28%).*

Conclusions *A model based on maternal characteristics and medical history recorded in early pregnancy can potentially predict one-third of subsequent stillbirths. The extent to which such stillbirths could be prevented remains to be determined. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Risk factors for antepartum stillbirth include increasing maternal age and weight, Afro-Caribbean racial origin, chronic hypertension and cigarette smoking. In a prospectively screened population of 33 856 singleton pregnancies, including 142 stillbirths, we used multiple regression analysis to combine these risk factors into a model and reported that about 30% of stillbirths could be predicted in the first trimester of pregnancy at a false-positive rate (FPR) of 10%[1].

The objectives of this study were first, to examine the accuracy of our previously published model in a population of 79 559 pregnancies screened after the development of the model, second, to derive an updated model using the total screened population of 113 415 pregnancies and third, to evaluate the performance of the new model in screening for all stillbirths and for subgroups of stillbirths that occurred due to impaired placentation and to unexplained or other causes. Antepartum stillbirths attributed to impaired placentation are those associated with pre-eclampsia, birth of small-for-gestational-age neonates or placental abruption. The rationale for categorizing stillbirths according to the likely underlying cause is that antenatal interventions and preventive strategies could potentially be undertaken more effectively[2–4]. A systematic review and meta-analysis of 96 population-based studies reported that, in developed countries, impaired placentation is a major contributor to stillbirth[5].

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 11 + 0 to 13 + 6 and at 19 + 0 to 24 + 6 weeks' gestation at King's College

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Accepted: 9 August 2016

Hospital and Medway Maritime Hospital, UK, between March 2006 and October 2015. We recorded maternal characteristics and medical history and performed combined screening for fetal aneuploidy at the first visit and assessed fetal growth and anatomy at the second visit[6]. Gestational age was determined from measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[7,8]. The study was approved by the ethics committee and written informed consent was obtained from all women participating in the study.

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, those ending in a miscarriage or termination of pregnancy or stillbirths 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 small-for-gestational-age 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 and body mass index (BMI) was calculated.

Outcome measures

Data on pregnancy outcome were obtained from the maternity hospital records or the general practitioners of the participating women. Pregnancies resulting in a pregnancy loss prior to 24 weeks were classified as miscarriages and those occurring ≥ 24 weeks as stillbirths. The hospital maternity records of all women with antepartum stillbirths were reviewed to determine whether the death was associated with pre-eclampsia, placental abruption, a birth weight < 10th percentile for gestational age[9] or it 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 the Mann–Whitney *U*-test for continuous variables. A *P*-value < 0.05 was considered statistically significant. *Post-hoc* Bonferroni correction was used for multiple comparisons.

The accuracy of our previously reported model for prediction of stillbirth, which was derived from the first 33 856 pregnancies in this cohort[1], was examined in the 79 559 pregnancies screened after the development of the model. We then used the total population of 113 415 pregnancies to derive a new model. Univariable and multivariable logistic regression analysis was used to determine which of the factors from maternal characteristics and medical history provided 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) curves analysis and the detection rates (DR) and FPR were estimated.

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

RESULTS

Study population

During the study period, we prospectively screened 119 622 pregnancies. We excluded 6207 cases because they had missing outcome data (*n* = 3517), the pregnancies resulted in miscarriage or termination, there were major fetal chromosomal abnormalities, babies with major fetal defects were born (*n* = 2649) or stillbirth occurred due to intrapartum factors (*n* = 41). The 113 415 singleton pregnancies that fulfilled the study entry criteria included 113 019 livebirths and 396 (0.35%) antepartum stillbirths; 230 (58%) were secondary to impaired placentation and 166 (42%) were due to other or unexplained causes.

The maternal and pregnancy characteristics of the outcome groups are compared in Table 1. In pregnancies that resulted in stillbirth, the median maternal weight was higher, there was a greater proportion of women of Afro-Caribbean racial origin, cigarette smokers, women with chronic hypertension, SLE/APS or pre-existing diabetes mellitus and there was a higher prevalence of parous women with a previous history of stillbirth compared to livebirths.

Accuracy of previous model for prediction of stillbirth

Our previous prediction model for stillbirth detected 28.9% (95% CI, 20.7–37.1%) of stillbirths at a 10% FPR (area under the ROC curve (AUC), 0.658 (95% CI, 0.611–0.706)) in the original cohort of 33 856 pregnancies from which it was developed. In the subsequent 79 559 pregnancies that were screened using this original

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 = *113 019*)	*All* (n = *396*)	*Unexplained* (n = *166*)	*Impaired placentation* (n = *230*)
Age (years)	30.9 (26.3–34.5)	30.4 (25.5–35.5)	30.8 (25.5–36.1)	30.4 (25.4–35.5)
Weight (kg)	66.7 (59.0–77.0)	71.0 (62.6–83.4)*	70.5 (62.9–83.6)*	72.7 (62.0–82.9)†
Height (m)	1.64 (1.60–1.69)	1.65 (1.60–1.68)	1.65 (1.61–1.68)	1.63 (1.60–1.68)
Racial origin				
Caucasian	84 007 (74.3)	236 (59.6)	104 (62.7)	132 (57.4)
Afro-Caribbean	19 435 (17.2)	125 (31.6)†	50 (30.1)†	75 (32.6)†
South Asian	4686 (4.1)	16 (4.0)	4 (2.4)	12 (5.2)
East Asian	2213 (2.0)	7 (1.8)	2 (1.2)	5 (2.2)
Mixed	2678 (2.4)	12 (3.0)	6 (3.6)	6 (2.6)
Mode of conception				
Spontaneous	109 577 (97.0)	377 (95.2)	158 (95.2)	219 (95.2)
Assisted	3442 (3.0)	19 (4.8)	8 (4.8)	11 (4.8)
Cigarette smoker	12 089 (10.7)	60 (15.2)*	25 (15.1)	35 (15.2)
Chronic hypertension	1438 (1.3)	22 (5.6)†	2 (1.2)	20 (8.7)†
APS/SLE	209 (0.2)	4 (1.0)*	0 (0)	4 (1.7)†
Pre-existing diabetes mellitus	996 (0.9)	13 (3.3)†	8 (4.8)†	5 (2.2)
Nulliparous	54 206 (48.0)	200 (50.5)	86 (51.8)	114 (49.6)
Previous miscarriage	1306 (1.2)	5 (1.3)	3 (1.8)	2 (0.9)
Previous stillbirth	882 (0.8)	20 (5.1)†	8 (4.8)†	12 (5.2)†
Previous SGA	3620 (3.2)	16 (4.0)	4 (2.4)	12 (5.2)
Interpregnancy interval	3.0 (2.0–5.0)	3.9 (2.2–7.0)†	3.9 (2.0–7.3)	3.9 (2.3–6.8)*

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.

model, the DR was 23.6% (95% CI, 18.6–28.6%) with an AUC of 0.608 (95% CI, 0.572–0.644); there was no significant difference between the two AUCs ($z = -1.512$; $P = 0.131$).

Updated algorithm for prediction of stillbirth

The results of univariable and multivariable regression analyses in the total cohort of 113 415 pregnancies are shown in Table 2 and Table S1. The risk of stillbirth was higher with increased maternal weight, in women of Afro-Caribbean racial origin, cases of assisted conception, cigarette smokers, those with a history of chronic hypertension, SLE/APS or pre-existing diabetes mellitus and was increased in parous women with a history of previous stillbirth (Figure 1).

The performance of screening for stillbirth is shown in Table 3. The DR, for a given FPR, was higher for stillbirths that occurred due to impaired placentation than for unexplained stillbirths, however the difference did not reach statistical significance. Within the impaired-placentation group, the DR was higher for stillbirth < 32 weeks' gestation than for stillbirth ≥ 37 weeks.

DISCUSSION

Main findings of the study

The findings of this study demonstrate that about one-third of all stillbirths can be predicted in the first trimester of pregnancy by assessment of maternal characteristics and medical history. The performance of screening may be better for stillbirths that are secondary to impaired placentation compared to those that are unexplained or due to other causes and, in the impaired-placentation group, the DR is higher for stillbirths that occur preterm than at term.

The risk for stillbirth increases with maternal weight, is higher in women of Afro-Caribbean racial origin than in Caucasians, pregnancies conceived by assisted conception, women who are cigarette smokers, those who have medical disorders such as chronic hypertension, diabetes mellitus and SLE/APS and in parous women with a previous history of stillbirth.

Strengths and limitations

The strengths of this screening study are first, examination of a large population of pregnant women attending for routine assessment at 11–13 and 19–24 weeks' gestation, second, recording of data on maternal characteristics and medical history to identify known risk factors for impaired placentation and stillbirth and third, use of multivariable regression analysis to take into account possible interrelations between the risk factors and 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 may be overestimated.

Table 2 Univariable and multivariable logistic regression analyses for prediction of stillbirth by maternal characteristics and medical history

	Univariable		*Multivariable*	
Variable	*OR (95% CI)*	P	*OR (95% CI)*	P
Age (per year) (−30*)	1.00 (0.98–1.02)	0.991		
Weight (per kg) (−69†)	1.02 (1.01–1.02)	< 0.0001	1.01 (1.01–1.02)	< 0.0001
Height (per cm) (−164‡)	0.99 (0.98–1.01)	0.372		
Racial origin				
Caucasian (reference)	1.00			
Afro-Caribbean	2.29 (1.84–2.85)	< 0.0001	2.01 (1.61–2.51)	< 0.0001
South Asian	1.22 (0.73–2.02)	0.451		
East Asian	1.13 (0.53–2.39)	0.757		
Mixed	1.60 (0.89–2.85)	0.115		
Mode of conception				
Spontaneous	1.00			
Assisted	1.60 (1.01–2.55)	0.045	1.79 (1.12–2.85)	0.015
Cigarette smoker	1.49 (1.13–1.96)	0.004	1.71 (1.29–2.26)	< 0.0001
Chronic hypertension	4.56 (2.96–7.04)	< 0.0001	2.62 (1.66–4.14)	< 0.0001
APS/SLE	5.51 (2.04–14.89)	0.001	3.61 (1.31–9.97)	0.013
Diabetes mellitus	3.82 (2.19–6.66)	< 0.0001	2.55 (1.44–4.52)	0.001
Parity				
Nulliparous (reference)	1.00			
Parous with previous miscarriage	1.09 (0.45–2.65)	0.842		
Parous with previous stillbirth	6.76 (4.29–10.66)	< 0.0001	4.81 (3.02–7.66)	< 0.0001
Parous with previous SGA	1.27 (0.77–2.10)	0.346		
Interpregnancy interval	1.04 (1.01–1.07)	0.004		

*Subtracted from age in years. †Subtracted from weight in kg. ‡Subtracted from height in cm. APS, antiphospholipid syndrome; OR, odds ratio; SGA, small-for-gestational age; SLE, systemic lupus erythematosus.

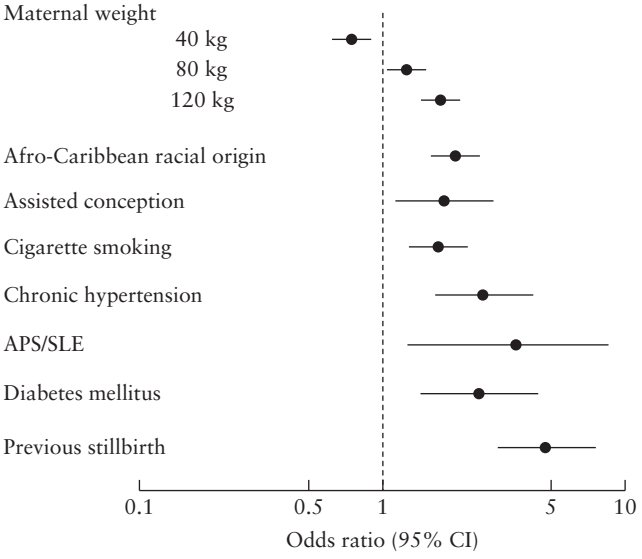

Figure 1 Forest plot demonstrating odds ratios (95% CI) for risk of stillbirth from maternal demographic characteristics and medical history. APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

Comparison with other studies

The performance of screening for stillbirths in this study of 113 415 pregnancies is similar to that in our previous study in 33 452 pregnancies; the DR of stillbirths at a FPR of 10% was 29.0% in this study and 28.9% in our previous one.

Our findings on the risk for stillbirth in association with maternal factors are compatible with those of previous studies. We found that the there was a linear relationship between maternal weight and stillbirth, with a 1% increase in risk for every 1-kg increase in maternal weight. This is similar to the findings of other studies that have demonstrated an increased risk of stillbirth with increasing maternal weight and BMI[10–12]. A large population study of 2 868 482 singleton births including 9030 stillbirths reported that, compared to women with a normal BMI, the hazard ratio (HR) for stillbirth increased linearly with the BMI category with a HR of 1.36, 1.71, 2.04 and 2.50 for BMI groups 25–29.9 kg/m^2, 30–34.9 kg/m^2, 35–39.9 kg/m^2 and 40–44.9 kg/m^2, respectively[12]. These results are similar to those of our previous screening study involving 41 577 women in which we reported that the OR for stillbirth for BMI groups 25–29.9 kg/m^2, 30–34.9 kg/m^2 and ≥ 35 kg/m^2 were 1.92, 2.23 and 2.28, respectively[11].

In women of Afro-Caribbean racial origin the risk of stillbirth was twice as high as in Caucasians. A population-based study in 5 138 122 singleton pregnancies in the USA reported that black women have 2.2-fold increased risk of stillbirth compared to white women[13]. The increase in risk for stillbirth in Afro-Caribbean women may be attributed to a lack of appropriate antenatal care and lower socioeconomic status[14], however, as all women in our study underwent routine assessment at 11–13 weeks and had equal access to antenatal care, it is likely that the increased risk may be secondary to a higher prevalence of impaired placentation reflected in a higher incidence of pre-eclampsia and fetal growth restriction.

We found that the OR of stillbirth in pregnancies achieved by assisted conception are increased by a factor

Table 3 Performance of screening for all stillbirths, unexplained stillbirths and those due to abnormal placentation, by an algorithm based on maternal factors

			Detection rate (% (95% CI))	
Stillbirth	n	*AUC (95% CI)*	*5% FPR*	*10% FPR*
All	396	0.642 (0.612–0.672)	18.4 (14.6–22.2)	29.0 (24.5–33.4)
Unexplained	166	0.635 (0.591–0.679)	16.3 (10.7–21.9)	25.9 (19.2–32.6)
Due to impaired placentation				
At any gestational age	230	0.647 (0.607–0.687)	20.0 (14.8–25.2)	31.3 (25.3–37.2)
< 32 weeks	125	0.667 (0.610–0.724)	28.0 (20.1–35.9)	38.4 (29.9–46.9)
< 37 weeks	180	0.666 (0.621–0.711)	22.2 (16.1–28.3)	32.2 (24.4–39.0)
≥ 37 weeks	50	0.581 (0.495–0.666)	12.0 (3.0–21.1)	28.0 (15.6–40.5)

AUC, area under receiver–operating characteristics curve; FPR, false-positive rate.

of 1.79, compared to those conceived spontaneously. A previous systematic review reported that the risk of stillbirth was increased following assisted conception with an OR of 1.81[15]. A large population-based study including 295 227 singleton pregnancies conceived spontaneously and 4350 assisted conceptions reported that the OR of stillbirth in the assisted-conception group was 1.82[16]. The increased risk in such pregnancies may be mediated by impaired placentation because there is also increased risk for pre-eclampsia[15].

In cigarette smokers, the risk of stillbirth was about 70% higher than in non-smokers. A systematic review and meta-analysis of studies involving a total of more than 10 000 000 pregnancies reported that smoking during pregnancy was associated with a 58% increase in the OR of stillbirth ≥ 24 weeks' gestation[17]. Although the exact mechanism for this association is not known, there is evidence that components in cigarette smoke lead to constriction of placental vessels and increased placental vascular resistance[18,19].

The OR of stillbirth in women with chronic hypertension was 2.62 in our study. A population-based study examining 532 088 singleton pregnancies including 5560 women with chronic hypertension reported that the rate of stillbirths was 2.5-times higher in the group with chronic hypertension compared to controls[20]. We found that the OR of stillbirth in women with diabetes mellitus was 2.55. A UK national population-based cohort study of 2359 pregnancies of women with diabetes mellitus reported that the rate of stillbirth was 4.7-times higher than in non-diabetics, however after exclusion of congenital defects the increased rate was reduced to 2.1[21]. We found that the OR of stillbirth in women with SLE or APS was 3.61. A systematic review of 37 studies with 1842 patients with SLE and a total of 2751 pregnancies reported that the rate of stillbirth was 3.6%, however there was no control group for comparison[22].

We found that the OR of stillbirth in parous women with a previous stillbirth was 4.81. A systematic review and meta-analysis of 16 studies with a combined total of 3 412 079 pregnancies, including 24 541 stillbirths, reported that the pooled unadjusted OR for stillbirth in women with a previous stillbirth was 4.83; in studies reporting the risk for stillbirth after adjusting for confounding factors, the pooled OR was 3.38[23]. It is uncertain which mechanism contributes to the high risk of recurrence in pregnancies with a previous stillbirth. In some cases it may be impairment in placentation but in many others it is unexplained. In our study, 60% of previous stillbirths were due to impaired placentation and 40% were unexplained.

Clinical implications of the study

The proposed model allows estimation of the patient-specific *a-priori* risk for stillbirth, which is an essential first step in the use of Bayes' theorem to combine maternal factors with biomarkers for the continuing development of more effective methods of screening for this adverse pregnancy outcome. In the case of stillbirth due to impaired placentation, identification of a high-risk group and prophylactic therapeutic interventions starting from the first trimester could potentially improve placentation and reduce stillbirth.

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 Multivariable logistic regression analysis for prediction of stillbirth by maternal characteristics and medical history