Prediction of stillbirth from maternal demographic and pregnancy characteristics

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Abstract

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

Methods: This was a prospective screening study of 113,415 singleton pregnancies at 11^{+0}-13^{+6} and 19^{+0}-24^{+6} weeks' gestation. The 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. Multivariate 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 (OR 1.01 per kg after 69 kg), was higher in women of Afro-Caribbean race (OR 2.01), assisted conception (OR 1.79), cigarette smokers (OR 1.71), those with a history of chronic hypertension (OR 2.62), SLE/APS (OR 3.61) or diabetes mellitus (OR 2.55) and was increased in parous women with a history of previous stillbirth (OR 4.81). The model predicted 26% of unexplained stillbirths and 31% of those due to impaired placentation at FPR of 10%; within the impaired placentation group the DR of stillbirth at <32 weeks' gestation was higher than that of stillbirth at ≥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.

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 35% 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 are firstly, to examine the accuracy of our previously published model in a population of 79,559 pregnancies screened after the development of the model, secondly, to derive an updated model using the total screened population of 113,415 pregnancies and thirdly, to evaluate the performance of the new model in screening for all stillbirths and in the sub-groups of stillbirths due impaired placentation and unexplained causes. The rationale of 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}-13^{+6} and 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 combined screening for fetal aneuploidies 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 (CRL) at 11-13 weeks or fetal head circumference at 19-24 weeks.[7,8] The women were screened between March 2006 and October 2015 and gave written informed consent to participate in the study, which was approved by the Ethics Committee.

The inclusion criteria for this study were singleton pregnancies who delivered a phenotypically normal live birth or stillbirth at or after 24 weeks' gestation. We excluded pregnancies with aneuploidies, major fetal abnormalities, those ending in a miscarriage or termination of pregnancy or those stillbirths due to intrapartum causes.

Patient characteristics

Patient characteristics included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian, and Mixed), method of conception (spontaneous or assisted conception that required the use of ovulation drugs), cigarette smoking during pregnancy (yes or no), history of chronic hypertension (yes or no), history of systemic lupus erythematosus or antiphospholipid syndrome (SLE/APS), history of pre-existing diabetes mellitus (yes or no), and obstetric history that included parity (parous or nulliparous if no previous pregnancies at or after 24 weeks' gestation), previous pregnancy with miscarriage between 16 and 23 weeks' (yes or no), previous pregnancy with stillbirth, gestational age at delivery and birthweight 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 the body mass index (BMI) was calculated.

Outcome measures

Data on pregnancy outcome were obtained from the maternity hospital records or the general practitioners of women. The pregnancies resulting in a pregnancy loss prior to 24 weeks were classified as miscarriages and those at ≥24 weeks as stillbirths. 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 [9] or it 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 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 accuracy of our previously reported model for prediction of stillbirth, which was derived from the first 33,856 pregnancies in this cohort (Akolekar *et al.,* 2011), 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. Univariate and multivariate 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 stillbirths. 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 detection rates (DR) and false positive rates (FPR) were estimated.

The statistical software package SPSS 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp, 2013) was used for the data analyses.

Results

Study population

During the study period, we prospectively screened 119,622 pregnancies. We excluded 6,207 cases because they had missing outcome data (n = 3,517), the pregnancies resulted in miscarriage, termination, major chromosomal abnormalities, the birth of babies with major fetal defects (n = 2,649) or they had stillbirth due to intrapartum factors (n=41). The 113,415 singleton pregnancies fulfilling the 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 ended in stillbirth compared to livebirths, the median maternal weight was higher, there were more women of Afro-Caribbean racial origin, cigarette smokers, women with chronic hypertension, SLE/APS or diabetes mellitus and a higher prevalence of parous women with a previous history of stillbirth.

Accuracy of previous model

Our previous prediction model for stillbirth detected 28.9% (95%CI: 20.7 to 37.1) of stillbirths at 10% FPR (AUROC of 0.658, 95% CI 0.611-0.706) in the original cohort of 33,856 pregnancies; in the subsequent 79,559 pregnancies the DR was 23.6% (95%CI: 18.6-28.6) with an AUROC of 0.608 (0.572-0.644); there was no significant difference between the two AUROC curves (z=-1.512; p=0.131).

Updated algorithm for prediction of stillbirth

The results of univariate and multivariate regression analysis in the total of 113,415 pregnancies are shown in Table 2 and Supplementary Table 1. The risk of stillbirth increased with maternal weight, was higher in women of Afro-Caribbean race, cases of assisted conception, cigarette smokers, those with a history of chronic hypertension, SLE/APS or 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 due to impaired placentation than in the unexplained group, but the difference was not significant. Within the impaired placentation group the DR of stillbirth at <32 weeks' gestation was higher than that of stillbirth at ≥37 weeks.

Conclusions

Main findings of the study

The findings of the 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 secondary to impaired placentation compared to those that are unexplained 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 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 multivariate 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 is overestimated.

Comparison with other studies

The performance of screening for stillbirths in this study of 113,415 pregnancies is similar to our previous study in 33,452 pregnancies; the DR of stillbirths for FPR of 10% was 29.0% in this study and 28.9% in the 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 1% increase in risk of stillbirth for every 1 kg increase in

maternal weight. This is compatible with other studies which have demonstrated increased risk of stillbirth with increasing maternal weight and body mass index (BMI).[10-12] A large population study of 2,868,482 singleton births including 9,030 stillbirths reported that compared to women with a normal BMI, the hazard ratio for stillbirth increased linearly with BMI categories with HR of 1.36, 1.71, 2.04 and 2.50 for BMI groups 25-29.9, 30-34.9, 35-39.9 and 40-40.0 respectively.[12] These results are similar to our previous screening study involving 41,577 women in which we reported that the odds ratio for still birth for BMI groups 25-29.9, 30-34.9 and $\geq$35 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 the United States in 5,138,122 singleton pregnancies 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 lack of appropriate antenatal care and lower socio-economic status [14] but as all women in our study booked 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 PE and FGR.

We found that the odds of stillbirth in assisted conception pregnancies are increased by a factor 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 odds ratio of 1.81.[15] A large population based study including 305,225 spontaneous and 1,770 assisted conceptions reported that the odds ratio 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 PE.[15]

We found that in cigarette smokers the risk of stillbirth is 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 odds of a stillbirth at $\geq$24 weeks' gestation.[17] Although the exact mechanism for this association is not known there is evidence that factors in cigarette smoke lead to constriction of placental vessels and increased placental vascular resistance.[18,19]

We found that the odds ratio of stillbirth in women with chronic hypertension was 2.62. A population-based study examining 532,088 singleton pregnancies including 5,560 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 odds ratio of stillbirth in women with diabetes mellitus was 2.55. A UK national population based cohort study of 2,359 pregnancies in women with diabetes mellitus reported that the rate of stillbirth was 4.7 times higher than in non-diabetics but after exclusion of congenital defects the increased rate was reduced to 2.1.[21] We found that the odds ratio 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% but there was no control group for comparison.[22]

We found that the odds ratio of stillbirth in parous women with a previous stillbirth was 4.81. A systematic review and meta-analysis of 16 studies on a combined total of 3,412,079 pregnancies including 24,541 stillbirths reported that the pooled unadjusted odds ratio for stillbirth in women with a previous stillbirth was 4.83; in studies reporting risk for stillbirth after adjusting for confounding factors, the pooled odds ratio was 3.38.[23] It is uncertain what 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 in the impaired placentation group and 40% were in the unexplained group.

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.

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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 a live births

Maternal characteristics	Live births (n=113,019)	All stillbirths (n=396)	Unexplained (n=166)	Impaired placentation (n=230)
Age, median (IQR)	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, median (IQR)	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, median (IQR)	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, n (%)	84,007 (74.3)	236 (59.6)	104 (62.7)	132 (57.4)
Afro-Caribbean, n (%)	19,435 (17.2)	125 (31.6) *	50 (30.1) *	75 (32.6) *
South Asian, n (%)	4,686 (4.1)	16 (4.0)	4 (2.4)	12 (5.2)
East Asian, n (%)	2,213 (2.0)	7 (1.8)	2 (1.2)	5 (2.2)
Mixed, n (%)	2,678 (2.4)	12 (3.0)	6 (3.6)	6 (2.6)
Method of conception				
Spontaneous, n (%)	109,577 (97.0)	377 (95.2)	158 (95.2)	219 (95.2)
Assisted conception, n (%)	3442 (3.0)	19 (4.8)	8 (4.8)	11 (4.8)
Cigarette smoking, n (%)	12,089 (10.7)	60 (15.2)†	25 (15.1)	35 (15.2)
Chronic hypertension, n (%)	1,438 (1.3)	22 (5.6) *	2 (1.2)	20 (8.7) *
SLE / APS, n (%)	209 (0.2)	4 (1.0) †	0	4 (1.7) *
Pre-existing diabetes mellitus	996 (0.9)	13 (3.3) *	8 (4.8) *	5 (2.2)
Parity				
Nulliparity, n (%)	54,206 (48.0)	200 (50.5)	86 (51.8)	114 (49.6)
Previous miscarriage, n (%)	1,306 (1.2)	5 (1.3)	3 (1.8)	2 (0.9)
Previous stillbirth, n (%)	882 (0.8)	20 (5.1) *	8 (4.8) *	12 (5.2) *
Previous SGA, n (%)	3,620 (3.2)	16 (4.0)	4 (2.4)	12 (5.2)
Inter-pregnancy interval, median (IQR)[a]	3.0 (2.0-5.0)	3.9 (2.2-7.0) *	3.9 (2.0-7.3)	3.9 (2.3-6.8) †

Post hoc Bonferroni correction for multiple comparisons; † = p< 0.01; * = p< 0.001; IQR = interquartile range; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; SGA = small for gestational age; [a] Inter-pregnancy interval median (IQR) reported for parous women

Table 2. Univariate and multivariate logistic regression analysis for the prediction of stillbirth by maternal characteristics and compenents medical history

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
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		
Method of conception				
Spontaneous	1.00			
Assisted	1.60 (1.01-2.55)	0.045	1.79 (1.12-2.85)	0.015
Cigarette smoking	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
SLE / APS	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		
Inter-pregnancy interval	1.04 (1.01-1.07)	0.004		

OR = odds ratio; CI = confidence interval; SLE = systemic lupus erythematosus; APS = anti-phospholipid syndrome; SGA = small for gestational age

Table 3. Performance of screening for stillbirth by an algorithm based on maternal factors.

Outcome	N	AUROC (95% CI)	Detection rates (95% CI)	
			5% FPR	10% FPR
All stillbirths	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)
Abnormal placentation				
Any gestation	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)
$\geq$ 37 weeks	50	0.581 (0.495-0.666)	12.0 (3.0-21.1)	28.0 (15.6-40.5)

Supplementary table 1. Multivariate logistic regression analysis for the prediction of stillbirth by maternal characteristics and compenents medical history

Variables	Coefficient (95% CI)	P value
Constant	-6.02615	<0.0001
Weight (per kg) – 69	0.01037 (0.00463 to 0.01612)	<0.0001
Afro-Caribbean racial origin	0.70027 (0.47856 to 0.92198)	<0.0001
Assisted conception	0.57994 (0.11351 to 1.04637)	0.015
Cigarette smoking	0.53367 (0.25410 to 0.81325)	<0.0001
Chronic hypertension	0.96253 (0.50533 to 1.41973)	<0.0001
SLE / APS	1.28416 (0.26898 to 2.29934)	0.013
Diabetes mellitus	0.93628 (0.36329 to 1.50926)	0.001
Parous with previous history of stillbirth	1.57086 (1.10633 to 2.03539)	<0.0001

CI = confidence interval; SLE = systemic lupus erythematosus; APS = anti-phospholipid syndrome

Figure 1. Forest plot demonstrating odds ratio (95% confidence intervals) for risk of stillbirth from maternal demographic characteristics and medical history.