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Development and validation of model for prediction of placental dysfunction-related stillbirth from maternal factors, fetal weight and uterine artery Doppler at mid-gestation

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

CONTRIBUTION

What are the novel findings of this work?
Screening at mid-gestation by a combination of maternal risk factors, estimated fetal weight (EFW) and uterine artery pulsatility index (UtA-PI) can predict a high proportion of placental dysfunction-related stillbirths and, in particular, those that occur preterm. Such screening provides poor prediction of unexplained stillbirth or stillbirth due to other causes. The predictive performance for placental dysfunction-related stillbirth in a validation dataset was consistent with that in the dataset used for development of the model.

What are the clinical implications of this work?
Combined screening at 22 weeks' gestation based on maternal risk factors, EFW and UtA-PI is effective in identifying pregnancies at risk of placental dysfunction-related stillbirth. The predictive models developed in this study can be used in clinical implementation studies to allow effective stratification of pregnancies that need close antenatal monitoring to prevent stillbirth related to placental dysfunction.

ABSTRACT

Objective *To examine the performance of a model combining maternal risk factors, uterine artery pulsatility index (UtA-PI) and estimated fetal weight (EFW) at 19–24 weeks' gestation, for predicting all antepartum stillbirths and those due to impaired placentation, in a training dataset used for development of the model and in a validation dataset.*

Methods *The data for this study were derived from prospective screening for adverse obstetric outcome in women with singleton pregnancy attending for routine pregnancy care at 19 + 0 to 24 + 6 weeks' gestation. The study population was divided into a training dataset used to develop prediction models for placental dysfunction-related antepartum stillbirth and a validation dataset to which the models were then applied. Multivariable logistic regression analysis was used to develop a model based on a combination of maternal risk factors, EFW Z-score and UtA-PI multiples of the normal median. We examined the predictive performance of the model by, first, the ability of the model to discriminate between the stillbirth and live-birth groups, using the area under the receiver-operating-characteristics curve (AUC) and the detection rate (DR) at a fixed false-positive rate (FPR) of 10%, and, second, calibration by measurements of calibration slope and intercept.*

Results *The study population of 131 514 pregnancies included 131 037 live births and 477 (0.36%) stillbirths. There are four main findings of this study. First, 92.5% (441/477) of stillbirths were antepartum and 7.5% (36/477) were intrapartum, and 59.2% (261/441) of antepartum stillbirths were observed in association with placental dysfunction and 40.8% (180/441) were unexplained or due to other causes. Second, placental dysfunction accounted for 80.1% (161/201) of antepartum stillbirths at < 32 weeks' gestation, 54.2% (52/96) at 32 + 0 to 36 + 6 weeks and 33.3% (48/144) at ≥ 37 weeks. Third, the risk of placental dysfunction-related antepartum stillbirth increased with increasing maternal weight and decreasing maternal height, was 3-fold higher in black than in white women, was 5.5-fold higher in parous*

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women with previous stillbirth than in those with previous live birth, and was increased in smokers, in women with chronic hypertension and in parous women with a previous pregnancy complicated by pre-eclampsia and/or birth of a small-for-gestational-age baby. Fourth, in screening for placental dysfunction-related antepartum stillbirth by a combination of maternal risk factors, EFW and UtA-PI in the validation dataset, the DR at a 10% FPR was 62.3% (95% CI, 57.2–67.4%) and the AUC was 0.838 (95% CI, 0.799–0.878); these results were consistent with those in the dataset used for developing the algorithm and demonstrate high discrimination between affected and unaffected pregnancies. Similarly, the calibration slope was 1.029 and the intercept was −0.009, demonstrating good agreement between the predicted risk and observed incidence of placental dysfunction-related antepartum stillbirth. The performance of screening was better for placental dysfunction-related antepartum stillbirth at < 37 weeks' gestation compared to at term (DR at a 10% FPR, 69.8% vs 29.2%).

Conclusions *Screening at mid-gestation by a combination of maternal risk factors, EFW and UtA-PI can predict a high proportion of placental dysfunction-related stillbirths and, in particular, those that occur preterm. Such screening provides poor prediction of unexplained stillbirth or stillbirth due to other causes. © 2021 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Stillbirths can be broadly classified as antepartum or intrapartum and the former group can be subdivided into those that are thought to be the consequence of impaired placentation and those that are due to other causes or unexplained. The rationale of categorizing stillbirths according to the likely underlying cause is that antenatal interventions and preventive strategies can be undertaken more effectively[1–3]. Impaired placentation-related stillbirths include those of small-for-gestational-age (SGA) fetuses and those that occur in pregnancies with pre-eclampsia. Such stillbirths could potentially be prevented by a two-stage strategy. The first stage involves screening for pre-eclampsia at 11–13 weeks' gestation, by a combination of maternal risk factors, mean arterial pressure, uterine artery pulsatility index (UtA-PI) and serum placental growth factor or pregnancy-associated plasma protein-A, and treatment of the high-risk group with aspirin[4–10]. The second stage, at 19–24 weeks, aims to identify a high-risk group that would benefit from close monitoring for early diagnosis of pre-eclampsia and a SGA fetus and prevention of stillbirth by defining the best approach to monitoring and timing of delivery[11–18].

The objective of this study was to examine the performance of a model combining maternal risk factors, UtA-PI and estimated fetal weight (EFW) at 19–24 weeks' gestation, for predicting all antepartum stillbirths and those due to impaired placentation, in a training dataset used for development of the model and in a validation dataset.

METHODS

Study population and design

The data for this study were derived from prospective screening for adverse obstetric outcome in women attending for routine pregnancy care at 19 + 0 to 24 + 6 weeks' gestation at King's College Hospital, London and Medway Maritime Hospital, Gillingham, UK, between 2011 and 2020. At this visit, we, first, recorded maternal demographic characteristics and medical history, second, carried out an ultrasound examination for assessment of fetal anatomy and measurement of fetal head circumference, abdominal circumference and femur length to calculate EFW, using the Hadlock formula[19] because a systematic review identified this as being the most accurate model[20], and, third, measured the left and right UtA-PI either by transvaginal or transabdominal color Doppler ultrasound and calculated the mean value of the two arteries[21,22]. The majority of UtA-PI measurements were carried out transvaginally because cervical length was also being measured at that time; the transabdominal approach was used when the woman declined transvaginal sonography. Gestational age was determined from measurement of fetal crown–rump length (CRL) at 11–13 weeks or fetal head circumference at 19–24 weeks[23,24]. The scans were carried out by sonographers who had received the Certificate of Competence in Doppler of The Fetal Medicine Foundation (http://www.fetalmedicine.com).

The inclusion criteria for this study were singleton pregnancy that delivered a phenotypically normal liveborn or stillborn neonate at ≥ 24 weeks' gestation. We excluded pregnancies with aneuploidy or major fetal abnormality and those ending in miscarriage or termination of pregnancy. Data on pregnancy outcome were obtained from the maternity hospital records or the general practitioners of the women. The hospital maternity records of all women with stillbirth were reviewed to determine if the death was associated with pre-eclampsia or birth weight < 10th percentile for gestational age[25] or was due to other causes or was unexplained.

Outcome measures

Stillbirths were divided into those that occurred prenatally and those that occurred during labor (intrapartum stillbirth). Antepartum stillbirths were divided into those that were associated with placental dysfunction (pre-eclampsia or birth weight < 10th percentile) and those that were due to other causes or were unexplained. Antepartum stillbirths were further divided, based on gestational age at stillbirth, into those that were early (< 32 weeks), preterm (< 37 weeks) or term (≥ 37 weeks).

Statistical analysis

Data from continuous variables were expressed as median and interquartile range, and data from categorical data were expressed as *n* (%). Comparison of maternal characteristics between the outcome groups was by the chi-square test or Fisher's exact test for categorical variables or the Mann–Whitney *U*-test for continuous variables. A *P*-value of < 0.05 was considered significant. EFW percentiles and *Z*-scores were calculated using The Fetal Medicine Foundation population charts[25]. The observed measurements of UtA-PI were expressed as multiples of the normal median (MoM) after adjustment for maternal and pregnancy characteristics, as described previously[26].

The study population was divided into a training dataset and a validation dataset by random allocation of stillbirths and live births into the two groups. The training dataset was used to develop prediction models which were then applied to the validation dataset. The following steps were undertaken to develop and validate the prediction models. First, multivariable logistic regression analysis with backwards stepwise elimination was used to determine which of the maternal and pregnancy characteristics provided a significant independent contribution to the prediction of antepartum stillbirth due to placental dysfunction in the training dataset and in the total study population. Prior to regression analysis, continuous variables, such as age, weight and height, were centered by subtracting the arithmetic mean from each value to avoid effects of multicollinearity. Multiple categorical variables were dummy coded as binary variables to estimate the independent effect of each category. Multivariable models were developed in both groups and the strength of the independent contribution of each variable was examined by comparing the coefficients and odds ratios. We chose the prediction model based on the total study population as it provided coefficients with a narrower 95% CI for the effect size. The predicted risks from the multivariable regression analysis for maternal factors were $\log_{10}$ transformed to derive the logit *a-priori* risks. Second, multivariable regression analysis with backwards stepwise elimination was carried out in the training dataset to examine the contribution of EFW *Z*-score and UtA-PI MoM in the prediction of stillbirth due to placental dysfunction. 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. Third, the predictive performance of the model was determined by its ability to discriminate between stillbirths and live births using the area under the receiver-operating-characteristics (ROC) curve (AUC) (a value of 1 indicates perfect discrimination and 0.5 indicates no discrimination beyond chance). The distributions of patient-specific risks were used to estimate detection rates (DR) and false-positive rates (FPR) from analysis of ROC curves. Fourth, the prediction models developed from the training dataset were applied to the validation dataset to estimate risk and assess the predictive performance from ROC-curve analysis. Fifth, the predictive accuracy of the models was assessed using a calibration study which compared the agreement between the predicted risk and outcome by comparison of the slope and intercepts of the models in the training and validation datasets. The statistical software package SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA) was used for data analyses.

RESULTS

Study population

The total study population included 131 514 singleton pregnancies fulfilling the inclusion criteria; we recorded prospectively maternal history, EFW and UtA-PI, either transabdominally or transvaginally, in all cases. There were 131 037 live births and 477 (0.36%) stillbirths, including 441 (0.34%) antepartum and 36 (0.03%) intrapartum stillbirths. The gestational age at antepartum stillbirth was < 32 weeks in 45.6% (201/441) of cases, $32 + 0$ to $36 + 6$ weeks in 21.8% (96/441) of cases and ≥ 37 weeks in 32.7% (144/441) of cases. The gestational age and birth-weight distribution of antepartum stillbirths is shown in Figure 1. Placental dysfunction was associated with 59.2% (261/441) of all antepartum stillbirths, 80.1% (161/201) of those at < 32 weeks' gestation, 71.7% (213/297) of those at < 37 weeks, 54.2% (52/96) of those at $32 + 0$ to $36 + 6$ weeks and 33.3% (48/144) of those at ≥ 37 weeks, while 40.8% (180/441) of all antepartum stillbirths were unexplained or due to other causes. The maternal and pregnancy characteristics of stillbirths

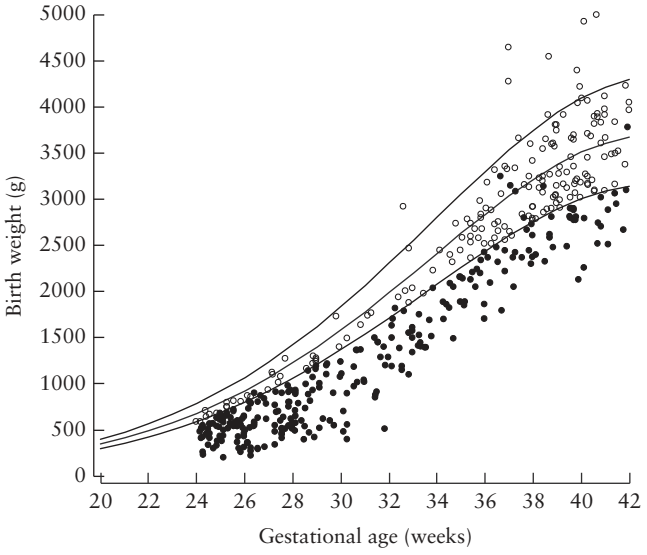

Figure 1 Gestational-age and birth-weight distribution of antepartum stillbirths, plotted on the reference range demonstrating the median and 90th and 10th percentiles[25]. ●, stillbirth classified as being placental dysfunction-related because the baby was small-for-gestational age or the pregnancy was complicated by pre-eclampsia; ○, stillbirth classified as being due to other causes or unexplained.

Table 1 Characteristics of 131 514 pregnancies, according to stillbirth or live birth

Characteristic	Live birth (n = 131 037)	Stillbirth		
		All (n = 477)	Placental dysfunction-related (n = 261)	Unexplained or other cause (n = 216)
Age (years)	31.1 (26.7–34.9)	31.0 (26.4–35.5)	30.7 (26.1–35.7)	31.1 (26.7–35.1)
Weight (kg)	67.2 (59.7–78.1)	72.6 (63.2–85.0)	74.6 (62.6–85.6)	70.8 (63.7–84.0)
Height (cm)	165 (160–169)	165 (160–168)	164 (160–168)	165 (161–169)
Racial origin				
White	95 575 (72.9)	270 (56.6)	131 (50.2)	139 (64.4)
Black	23 397 (17.9)	170 (35.6)	107 (41.0)	63 (29.2)
South Asian	6045 (4.6)	18 (3.8)	13 (5.0)	5 (2.3)
East Asian	2496 (1.9)	7 (1.5)	5 (1.9)	2 (0.9)
Mixed	3524 (2.7)	12 (2.5)	5 (1.9)	7 (3.2)
Method of conception				
Spontaneous	126 500 (96.5)	457 (95.8)	252 (96.6)	205 (94.9)
Assisted	4537 (3.5)	20 (4.2)	9 (3.4)	11 (5.1)
Cigarette smoker	12 178 (9.3)	64 (13.4)	32 (12.3)	32 (14.8)
Chronic hypertension	1650 (1.3)	21 (4.4)	18 (6.9)	3 (1.4)
SLE/APS	281 (0.2)	2 (0.4)	2 (0.8)	0 (0)
Diabetes mellitus	1362 (1.0)	13 (2.7)	7 (2.7)	6 (2.8)
Parity				
Nulliparous	62 084 (47.4)	236 (49.5)	128 (49.0)	108 (50.0)
Parous, previous stillbirth	975 (0.7)	21 (4.4)	16 (6.1)	5 (2.3)
Parous, previous SGA	9573 (7.3)	57 (11.9)	37 (14.2)	20 (9.3)
Parous, previous pre-eclampsia	3713 (2.8)	41 (8.6)	30 (11.5)	11 (5.1)
Interpregnancy interval (years)*	2.9 (1.8–4.8)	3.6 (2.1–6.6)	4.2 (2.4–7.3)	3.1 (1.9–6.0)

Data are given as median (interquartile range) or *n* (%). *Interpregnancy interval is reported for parous women. APS, antiphospholipid syndrome; SGA, small-for-gestational age; SLE, systemic lupus erythematosus.

and live births in the study population are summarized in Table 1. The training and validation datasets had similar characteristics (Table S1).

Prediction of stillbirth due to placental dysfunction

The results of multivariable logistic regression analysis to determine which of the maternal and pregnancy characteristics provided a significant independent contribution to the prediction of placental dysfunction-related antepartum stillbirth in the study population are given in Table 2. The risk for stillbirth increased with increasing maternal weight and decreasing maternal height and was higher in black than in white women, in cigarette smokers, in women with chronic hypertension, in parous women with a previous pregnancy complicated by pre-eclampsia and/or birth of a SGA baby and in parous women with previous stillbirth.

Multivariable logistic regression analysis for the prediction of placental dysfunction-related antepartum stillbirth by maternal risk factors and a combination of EFW *Z*-score and UtA-PI MoM at 19–24 weeks' gestation is shown in Table S2.

Table 2 Prediction of placental dysfunction-related stillbirth from maternal and pregnancy characteristics in the study population

Characteristic	Odds ratio (95% CI)	P
Age (in years) – 30	1.01 (0.99–1.04)	0.278
Weight (in kg) – 74	1.02 (1.01–1.02)	< 0.0001
Height (in cm) – 164	0.97 (0.95–0.99)	0.001
Racial origin		< 0.0001
White	1.00 (reference)	—
Black	2.97 (2.26–3.89)	< 0.0001
South Asian	1.51 (0.84–2.71)	0.170
East Asian	1.59 (0.64–3.92)	0.319
Mixed	1.02 (0.42–2.49)	0.970
Assisted conception	1.08 (0.54–2.14)	0.826
Cigarette smoker	1.84 (1.25–2.71)	0.002
Diabetes mellitus	1.50 (0.69–3.24)	0.307
Chronic hypertension	2.30 (1.34–3.87)	0.002
Parity		< 0.0001
Nulliparous	1.00 (reference)	—
Parous, no previous PE/SGA	0.57 (0.43–0.75)	< 0.0001
Parous, previous PE/SGA	1.87 (1.19–2.92)	0.006
Previous fetal loss		< 0.0001
Live birth	1.00 (reference)	—
Fetal death < 24 weeks	1.03 (0.75–1.40)	0.872
Fetal death ≥ 24 weeks	5.50 (3.17–9.55)	< 0.0001

PE, pre-eclampsia; SGA, small-for-gestational age.

Predictive performance of model

The predictive performance of the model for antepartum stillbirth due to placental dysfunction is summarized in Tables 3 and 4. The AUC and DRs at a FPR of 10% for stillbirth in screening by maternal risk factors and combinations of biomarkers in the validation dataset were consistent with those in the development dataset (Table 3). In the validation dataset, the DR for all stillbirths, at a FPR of 10%, increased from 27.7% for maternal risk factors only to 41.6% with the addition of EFW and

Table 3 Prediction of stillbirth in 131 514 pregnancies, in the training and validation datasets

Outcome measure/ screening method	*Training dataset*		*Validation dataset*	
	AUC	*DR (%) at 10% FPR*	*AUC*	*DR (%) at 10% FPR*
All stillbirths (n = *477)*				
MF	0.652 (0.615–0.688)	27.2 (22.5–31.9)	0.680 (0.646–0.715)	27.7 (23.0–32.4)
MF + EFW	0.662 (0.622–0.702)	34.7 (29.7–39.7)	0.682 (0.644–0.721)	35.7 (30.7–40.7)
MF + UtA-PI	0.738 (0.701–0.774)	43.5 (38.3–48.7)	0.706 (0.668–0.745)	42.9 (37.7–48.1)
MF + EFW + UtA-PI	0.720 (0.682–0.758)	42.8 (37.6–48.0)	0.701 (0.662–0.740)	41.6 (36.4–46.8)
Antepartum stillbirths				
All ($n = 441$)				
MF	0.656 (0.618–0.694)	28.1 (23.4–38.2)	0.683 (0.647–0.718)	28.2 (28.5–32.9)
MF + EFW	0.674 (0.633–0.716)	36.2 (31.2–41.2)	0.691 (0.651–0.730)	36.8 (31.8–41.8)
MF + UtA-PI	0.740 (0.702–0.779)	45.2 (40.0–50.4)	0.713 (0.672–0.753)	43.6 (38.4–48.8)
MF + EFW + UtA-PI	0.729 (0.690–0.768)	44.9 (36.7–50.1)	0.708 (0.668–0.749)	43.6 (38.4–48.8)
All placental dysfunction-related ($n = 261$)				
MF	0.699 (0.654–0.743)	30.5 (25.7–35.3)	0.736 (0.692–0.780)	34.6 (29.6–39.6)
MF + EFW	0.782 (0.735–0.828)	51.9 (46.7–57.1)	0.810 (0.769–0.852)	52.3 (47.1–57.5)
MF + UtA-PI	0.827 (0.783–0.870)	61.8 (56.7–66.9)	0.805 (0.759–0.852)	60.0 (54.9–65.1)
MF + EFW + UtA-PI	0.852 (0.814–0.889)	62.1 (57.0–67.2)	0.838 (0.799–0.878)	62.3 (57.2–67.4)
Placental dysfunction-related < 37 weeks ($n = 213$)				
MF	0.714 (0.666–0.763)	31.8 (26.9–36.7)	0.743 (0.694–0.793)	35.8 (30.8–40.8)
MF + EFW	0.818 (0.769–0.867)	58.9 (53.8–64.1)	0.835 (0.790–0.880)	57.5 (52.3–62.7)
MF + UtA-PI	0.848 (0.802–0.894)	67.3 (62.4–72.2)	0.815 (0.763–0.866)	64.2 (59.1–69.2)
MF + EFW + UtA-PI	0.875 (0.834–0.916)	68.2 (63.3–73.1)	0.856 (0.813–0.900)	69.8 (65.0–74.6)
Placental dysfunction-related < 32 weeks ($n = 161$)				
MF	0.706 (0.648–0.765)	33.3 (28.4–38.2)	0.759 (0.705–0.812)	37.8 (32.7–42.9)
MF + EFW	0.857 (0.807–0.907)	65.4 (60.4–70.4)	0.808 (0.747–0.870)	62.5 (57.4–67.6)
MF + UtA-PI	0.834 (0.775–0.893)	70.4 (65.6–75.2)	0.879 (0.834–0.924)	67.5 (62.6–72.4)
MF + EFW + UtA-PI	0.886 (0.838–0.933)	74.1 (69.5–78.7)	0.864 (0.813–0.916)	72.5 (67.8–77.2)

Values in parentheses are 95% CI. AUC, area under the receiver-operating-characteristics curve; DR, detection rate; EFW, estimated fetal weight; FPR, false-positive rate; MF, maternal risk factors; UtA-PI, uterine artery pulsatility index.

UtA-PI. In screening by a combination of maternal risk factors, EFW and UtA-PI, the DR at a FPR of 10% for placental dysfunction-related antepartum stillbirth was 62.3% (81/130) for all cases, 69.8% (74/106) for those at < 37 weeks' gestation, 72.5% (58/80) for those at < 32 weeks and 29.2% (7/24) for those at ≥ 37 weeks.

The calibration study demonstrated very good agreement between the risk predicted by the model and the observed incidence of placental dysfunction-related antepartum stillbirth (Table 4, Figure 2). The calibration of the model was optimal for the binary outcome for which the model was fitted, but, as expected, it deteriorated for different subcategories of stillbirth. Overall, the calibration was similar in the training and validation datasets.

DISCUSSION

Principal findings

There are four main findings of this large prospective screening study for adverse pregnancy outcome. First, in our population, 92.5% of stillbirths were antepartum and 7.5% were intrapartum, and 59.2% of antepartum stillbirths were observed in association with placental dysfunction and 40.8% were unexplained or due to other causes. Second, placental dysfunction accounted for 80.1% of antepartum stillbirths at < 32 weeks' gestation, 54.2% at 32 + 0 to 36 + 6 weeks and 33.3% at ≥ 37 weeks. Third, the risk of placental dysfunction-related antepartum stillbirth increased with increasing maternal weight and decreasing height, was 3-fold higher in black than in white women, was 5.5-fold higher in parous women with previous stillbirth than in those with previous live birth, and was increased in smokers, in women with chronic hypertension and in parous women with a previous pregnancy complicated by pre-eclampsia and/or birth of a SGA baby. Fourth, in screening for placental dysfunction-related antepartum stillbirth by a combination of maternal risk factors, EFW and UtA-PI, the DR at a 10% FPR was 62.3% (95% CI, 57.2–67.4%) and the AUC was 0.838 (95% CI, 0.799–0.878); these results were consistent with those in the data used for developing the algorithm and demonstrate high discrimination between affected and unaffected pregnancies. Similarly, the calibration slope was 1.029 and the intercept was −0.009, demonstrating good agreement between the predicted risk and observed incidence of placental dysfunction-related antepartum stillbirth. The performance of screening was better for placental dysfunction-related antepartum stillbirth at < 37 weeks' gestation compared to at term (DR at a 10% FPR, 69.8% *vs* 29.2%).

Table 4 Calibration study for the model for prediction of stillbirth, in the training and validation datasets

Outcome measure/ Screening method	*Training dataset*		*Validation dataset*	
	Slope	*Intercept*	*Slope*	*Intercept*
All stillbirths				
MF	0.790 (0.647–0.934)	0.613 (0.486 to 0.741)	0.859 (0.719–0.993)	0.603 (0.472 to 0.728)
MF + EFW	0.738 (0.656–0.821)	0.657 (0.524 to 0.789)	0.810 (0.724–0.897)	0.667 (0.532 to 0.797)
MF + UtA-PI	0.796 (0.715–0.876)	0.628 (0.495 to 0.756)	0.777 (0.695–0.856)	0.610 (0.476 to 0.738)
MF + EFW + UtA-PI	0.772 (0.704–0.839)	0.684 (0.549 to 0.819)	0.780 (0.712–0.849)	0.681 (0.542 to 0.814)
Antepartum stillbirths				
All				
MF	0.814 (0.667–0.962)	0.535 (0.402 to 0.667)	0.873 (0.729–1.01)	0.524 (0.388 to 0.654)
MF + EFW	0.770 (0.685–0.855)	0.572 (0.434 to 0.709)	0.837 (0.748–0.927)	0.583 (0.442 to 0.717)
MF + UtA-PI	0.810 (0.725–0.891)	0.547 (0.408 to 0.679)	0.792 (0.708–0.874)	0.529 (0.390 to 0.662)
MF + EFW + UtA-PI	0.792 (0.723–0.861)	0.597 (0.455 to 0.737)	0.801 (0.731–0.872)	0.594 (0.450 to 0.733)
All placental dysfunction-related				
MF	0.935 (0.756–1.114)	0.010 (−0.162 to 0.182)	1.061 (0.892–1.222)	−0.005 (−0.183 to 0.163)
MF + EFW	0.999 (0.819–1.181)	0.000 (−0.181 to 0.181)	1.126 (1.015–1.238)	0.006 (−0.180 to 0.182)
MF + UtA-PI	0.999 (0.902–1.097)	0.000 (−0.180 to 0.170)	0.994 (0.896–1.091)	−0.022 (−0.202 to 0.149)
MF + EFW + UtA-PI	1.000 (0.916–1.083)	0.000 (−0.183 to 0.183)	1.029 (0.944–1.117)	−0.009 (−0.199 to 0.172)
Placental dysfunction-related < 37 weeks				
MF	0.992 (0.800–1.184)	−0.193 (−0.383 to −0.003)	1.112 (0.930–1.284)	−0.210 (−0.407 to −0.025)
MF + EFW	1.075 (0.962–1.188)	−0.225 (−0.426 to −0.024)	1.207 (1.087–1.330)	−0.221 (−0.429 to −0.025)
MF + UtA-PI	1.058 (0.952–1.163)	−0.211 (−0.410 to −0.023)	1.050 (0.945–1.155)	−0.234 (−0.435 to −0.045)
MF + EFW + UtA-PI	1.064 (0.972–1.154)	−0.233 (−0.436 to −0.028)	1.095 (1.002–1.190)	−0.245 (−0.457 to −0.046)
Placental dysfunction-related < 32 weeks				
MF	1.018 (0.801–1.234)	−0.472 (−0.690 to −0.254)	1.156 (0.951–1.348)	−0.491 (−0.719 to −0.279)
MF + EFW	1.180 (1.056–1.309)	−0.539 (−0.781 to −0.315)	1.316 (1.181–1.457)	−0.537 (−0.779 to −0.311)
MF + UtA-PI	1.074 (0.956–1.192)	−0.498 (−0.728 to −0.283)	1.053 (0.935–1.171)	−0.523 (−0.755 to −0.307)
MF + EFW + UtA-PI	1.125 (1.023–1.226)	−0.554 (−0.789 to −0.319)	1.143 (1.040–1.251)	−0.569 (−0.816 to −0.339)

Values in parentheses are 95% CI. EFW, estimated fetal weight; MF, maternal risk factors; UtA-PI, uterine artery pulsatility index.

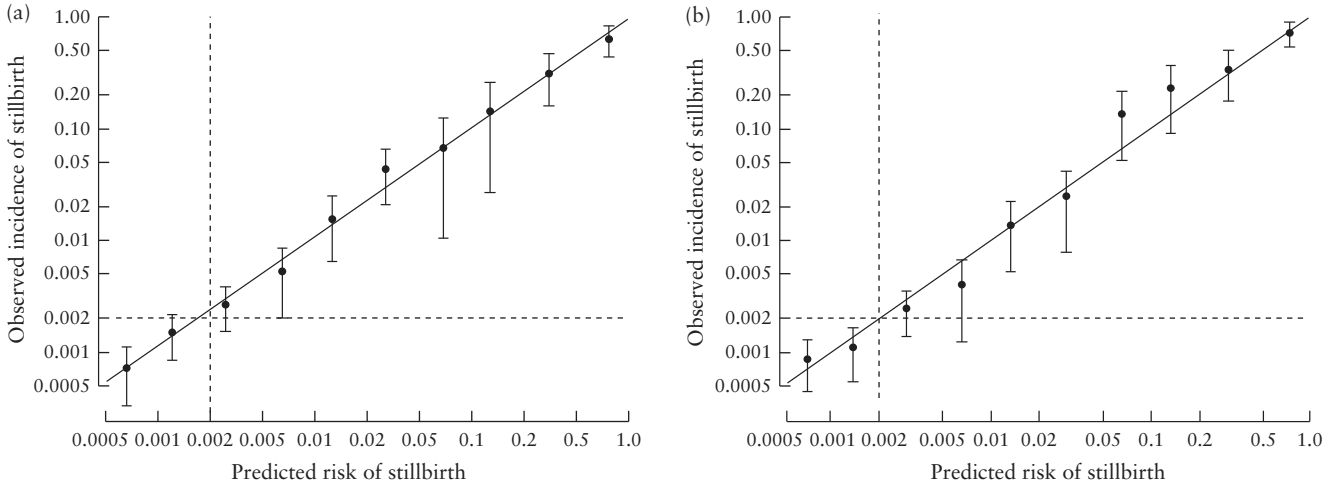

Figure 2 Calibration plots for screening for placental dysfunction-related antepartum stillbirth by maternal risk factors, estimated fetal weight and uterine artery pulsatility index in the training dataset (a) and validation dataset (b). The observed incidence is given as median with 95% CI. The overall mean risk is shown by the vertical dashed line and the overall incidence by the horizontal dashed line.

Comparison with previous studies

In a series of previous first- and second-trimester studies on the prediction of stillbirth, we highlighted that the causes of this adverse event are heterogeneous and that the objective of screening should be prediction of placental dysfunction-related stillbirth rather than all antepartum and intrapartum fetal deaths[27–32]. The finding of our current study that maternal risk factors and high UtA-PI at mid-gestation are predictors of placental dysfunction-related stillbirth, especially of those that occur preterm, are consistent with the results of previous studies[27,29,32]. Stillbirth is not only a heterogeneous condition but also a rare adverse event, and criticisms of our previous prediction models are the introduction of bias due to lack of internal validation and overfitting due to a low number of events per predictor variable. In our current study, we overcame these biases by examining a

large study population that included many stillbirths and could be divided into training and validation datasets.

A recent study attempted to externally validate previously published prediction models for stillbirth using individual participant data (IPD) meta-analysis in a heterogeneous group of 19 datasets[33]. A systematic search identified 40 stillbirth models published between 2007 and 2020, but only three of these models could be validated due to a lack of availability of the necessary predictors in their dataset or the model equations in the previous publications; there was no attempt to contact the authors of the studies to request details of the equations. It was reported that the three models showed poor and uncertain predictive performance in their data and had limited clinical utility and that further research is needed to identify stronger prognostic factors and develop more robust prediction models[33]. However, these conclusions are misleading and can have a potential adverse impact on clinical practice and future research, because, first, two of the three models they evaluated were based on maternal risk factors only and they overlooked many prediction models based on a combination of maternal risk factors and first- or second-trimester biomarkers, second, the heterogeneous datasets used for their IPD meta-analysis were not derived from prospective screening for stillbirth, and, third, the authors examined the value of the reported models for prediction of all stillbirths and overlooked the fact that the original publications highlighted that the models provided good prediction of placental dysfunction-related stillbirth, particularly those occurring preterm, rather than prediction of all stillbirths. It is also surprising that, since the authors of the IPD meta-analysis had access to data from 491 201 pregnant women, they did not develop and validate their own models[33].

Clinical implications

The most common cause of antepartum stillbirth is placental dysfunction, and models for prediction of placental dysfunction-related stillbirth provide useful prediction of this condition but not of all stillbirths. A high proportion of placental dysfunction-related stillbirths can potentially be prevented by a strategy of screening for pre-eclampsia at 11–13 weeks' gestation and treatment of the high-risk group by aspirin[4–10]. Screening during the routine mid-trimester scan by a combination of maternal risk factors, EFW and UtA-PI identifies a high-risk group that contains a high proportion of placental dysfunction-related stillbirths that occur at 24–37 weeks' gestation; close monitoring of these pregnancies for early diagnosis of pre-eclampsia and a SGA fetus could prevent at least some of these stillbirths by defining the best timing of delivery[11–18]. The detection rate of stillbirth is about 10% higher when UtA-PI is included in the model in addition to maternal risk factors and EFW. Such incremental benefit of UtA-PI highlights the necessity of including this measurement in the routine mid-trimester scan because it is easy for competent sonographers to learn this technique and it adds only about 2 min to the examination. Screening at mid-gestation provides poor prediction of stillbirth at term. More effective screening for late pre-eclampsia and SGA can be achieved by screening at 36 weeks' gestation[34–38].

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 and systematic recording of data on maternal characteristics and medical history to identify known risk factors associated with stillbirth, second, use of a specific methodology for measurement of UtA-PI by appropriately trained doctors and expression of the values of UtA-PI as MoMs after adjustment for factors that affect the measurements, and, third, development and internal validation of a model for prediction of placental dysfunction-related stillbirth.

A potential limitation of this study is that pregnancies with high UtA-PI were monitored more intensively and this would have inevitably prevented some stillbirths, thereby reducing the potential performance of this biomarker. Furthermore, the model requires external validation.

Conclusions

Screening at mid-gestation by a combination of maternal risk factors, EFW and UtA-PI can predict a high proportion of placental dysfunction-related stillbirths and, in particular, those that occur preterm. Such screening provides poor prediction of unexplained stillbirth or stillbirth due to other causes.

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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 Comparison of maternal and pregnancy characteristics in the training and validation datasets

Table S2 Multivariable logistic regression analysis for the prediction of placental dysfunction-related antepartum stillbirth by maternal risk factors and combination of estimated fetal weight and uterine artery pulsatility index at 19–24 weeks' gestation

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Desarrollo y validación de un modelo de predicción del éxitus fetal relacionado con la disfunción placentaria a partir de factores maternos, el peso fetal y el Doppler de la arteria uterina a mitad de la gestación

RESUMEN

Objetivo. Examinar la eficacia de un modelo que combina los factores de riesgo maternos, el índice de pulsatilidad de la arteria uterina (UtA-PI) y el peso estimado del feto (PEF) a las 19–24 semanas de gestación, para predecir todos los casos de éxitus fetal prenatal y los debidos a una alteración de la placentación, en un conjunto de datos de entrenamiento utilizado para el desarrollo del modelo y en un conjunto de datos de validación.

Métodos. Los datos de este estudio proceden del cribado prospectivo de resultados obstétricos adversos en mujeres embarazadas con feto único que acudieron a exámenes de atención rutinaria del embarazo entre las 19+0 y las 24+6 semanas de gestación. La población del estudio se dividió en un conjunto de datos de entrenamiento utilizados para desarrollar modelos de predicción del éxitus fetal prenatal relacionado con la disfunción placentaria y un conjunto de datos de validación al que se aplicaron los modelos. Se utilizó un análisis de regresión logística multivariable para desarrollar un modelo basado en una combinación de factores de riesgo maternos, la puntuación Z del PEF y múltiplos de la mediana normal del UtA-PI. Se examinó la bondad de predicción del modelo mediante, en primer lugar, la capacidad del modelo para distinguir entre los grupos de éxitus fetal y de nacidos vivos, para lo cual se utilizó el área bajo la curva (ABC) de la característica operativa del receptor y la tasa de detección (TD) con una tasa fija de falsos positivos (TFP) del 10%, y, en segundo lugar, la calibración mediante mediciones de la pendiente y la intersección de la calibración.

Resultados. La población del estudio de 131.514 embarazos incluyó 131.037 nacimientos vivos y 477 (0,36%) casos de éxitus fetal. Las conclusiones principales de este estudio son cuatro. En primer lugar, el 92,5% (441/477) de los casos de éxitus fetal fueron prenatales y el 7,5% (36/477) fueron durante el parto, y se observó que el 59,2% (261/441) de los casos de éxitus fetal prenatales estaban asociados con una disfunción placentaria y el 40,8% (180/441) fueron sin causa aparente o se debieron a otras causas. En segundo lugar, la disfunción placentaria representó el 80,1% (161/201) de los casos de éxitus fetal prenatal a < 32 semanas de gestación, el 54,2% (52/96) entre 32+0 a 36+6 semanas y el 33,3% (48/144) a ≥37 semanas. En tercer lugar, el riesgo de éxitus fetal prenatal relacionado con la disfunción placentaria aumentó con el aumento del peso y la disminución de la altura de la madre, fue 3 veces mayor en las mujeres de raza negra que en las de raza blanca, fue 5,5 veces mayor en las mujeres no nulíparas con un éxitus fetal previo que en aquellas con un nacimiento vivo previo, y aumentó en las fumadoras, en las mujeres con hipertensión crónica y en las mujeres no nulíparas con un embarazo anterior complicado por preeclampsia y/o el nacimiento de un bebé pequeño para la edad gestacional. En cuarto lugar, en el cribado del éxitus fetal prenatal relacionado con la disfunción placentaria a partir de una combinación de factores de riesgo maternos, PEF y UtA-PI en el conjunto de datos de validación, la TD con una TFP del 10% fue del 62,3% (IC 95%, 57,2–67,4%) y el ABC fue de 0,838 (IC 95%, 0,799–0,878); estos resultados fueron coherentes con los del conjunto de datos utilizado para desarrollar el algoritmo y demuestran una alta capacidad de discriminación entre embarazos afectados y no afectados. Asimismo, la pendiente de la calibración fue de 1,029 y la intersección fue de -0,009, lo que demuestra una buena concordancia entre el riesgo previsto y la incidencia observada de casos de éxitus fetal prenatal relacionados con la disfunción placentaria. La eficacia del cribado fue mejor para el éxitus fetal prenatal relacionado con la disfunción placentaria a < 37 semanas de gestación en comparación con las embarazadas a término (TD con una TFP de 10%, 69,8% frente a 29,2%).

Conclusiones. El cribado a mitad de la gestación mediante una combinación de factores de riesgo materno, PEF y UtA-PI puede predecir una elevada proporción de los casos de éxitus fetal relacionados con la disfunción placentaria y, en particular, los que se producen pretérmino. Este tipo de cribado proporciona una predicción deficiente del éxitus fetal sin causa aparente o debido a otras causas.

根据产妇因素、胎儿体重和孕中期子宫动脉多普勒，开发并验证预测胎盘功能异常相关死产的模型

摘要

目的在一个用于开发模型的培训数据集中和一个验证数据集中，检验一个结合了产妇风险因素、子宫动脉搏动指数（UtA-PI）和在孕 19-24 周估计胎儿重量（EFW）的模型，来预测所有产前死产和由于受损胎盘造成的死产。

方法本研究的数据取自在孕 19+0 周至 24+6 周参加常规妊娠检查的单胎孕妇中不利分娩结局的前瞻性筛查。研究人群被分为一个培训数据集（用于开发预测胎盘功能异常相关死产的模型）和一个验证集（将模型在其中应用）。根据结合了产妇风险因素、EFW Z 评分和 UtA-PI 乘以正常中位值，采用多元逻辑斯蒂回归分析法开发了一个模型。我们检验了该模型的预测表现：首先，是检验模型分辨死产和活产群体的能力，使用接受者操作特性曲线（AUC）下的区域和检出率（DR），以及一个固定的 10%假阳性率；其次，通过测量标定斜率和截点来校准。

结果研究人群为 131514 个妊娠，含 131037 个活产和 477 个死产（占 0.36%）。本研究有四个主要发现。首先，92.5%的死产（441/477）是在产前，而 7.5%（36/477）是在分娩期，且观察到 59.2%（261/441）的产前死产与胎盘功能异常相关，而 40.8%（180/441）的产前死产无法解释或由于其他原因造成。第二，胎盘功能异常占孕 32 周前产前死产的 80.1%（161/201），占 32+0 至 36+6 周产前死产的 54.2%（52/96），占孕 37 周及以上产前死产的 33.3%（48/144）。第三，胎盘功能异常相关产前死产的风险随产妇体重增加而增加，并随产妇身高变矮而增加，在黑人孕妇中的风险比在白人孕妇中高三倍，在曾有过死产的经产妇女中的风险比之前活产的经产妇女中高 5.5 倍，风险在吸烟人群中增加，在有慢性高血压的孕妇中增加，并且在之前妊娠中曾有先兆子痫和/或小于胎龄儿的经产妇女中增加。第四，在验证集中结合产妇风险因素、EFW 和 UtA-PI 来筛查胎盘功能异常相关的产前死产，FPR 在 10%时的 DR 为 62.3%（95% CI，57.2 – 67.4%）且 AUC 为 0.838（95% CI，0.799 – 0.878）；这些结果与在数据集中用于开发算法的结果一致，并在受影响和不受影响的妊娠之间显示出高度辨别力。同样地，标定斜率为 1.029，截点为-0.009，说明预测风险与观察到的胎盘功能异常相关产前死产的发病率之间有良好的一致性。与足月分娩相比，对孕 37 周前胎盘功能异常相关产前死产的筛查表现更好（FPR 在 10%时，DR 分别为 69.8%和 29.2%）。

结论在孕中期通过结合产妇风险因素、EFW 和 UtA-PI，筛查能够预测出高比例的胎盘功能异常相关死产，尤其是发生在产前的。此类筛查对于原因不明的死产或因其他原因造成的死产的预测差。

