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RESEARCH ARTICLE

Fetal Medicine

Predictive performance for placental dysfunction related stillbirth of the competing risks model for small-for-gestational-age fetuses

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Abstract

Objectives: To examine the predictive performance for placental dysfunction related stillbirths of the competing risks model for small-for-gestational-age (SGA) fetuses based on a combination of maternal risk factors, estimated fetal weight (EFW) and uterine artery pulsatility index (UtA-PI); and second, to compare the performance of this model with that of a stillbirth-specific model using the same biomarkers and with the Royal College of Obstetricians and Gynecologists (RCOG) guideline for the investigation and management of the SGA fetus.

Design: Prospective observational study.

Setting: Two UK maternity hospitals.

Population: A total of 131 514 women with singleton pregnancies attending for routine ultrasound examination at 19–24 weeks of gestation.

Methods: The predictive performance for stillbirth achieved by three models was compared.

Main Outcome Measure: Placental dysfunction related stillbirth.

Results: At 10% false-positive rate, the competing risks model predicted 59%, 66% and 71% of placental dysfunction related stillbirths, at any gestation, at <37 weeks and at <32 weeks, respectively, which were similar to the respective figures of 62%, 70% and 73% for the stillbirth-specific model. At a screen positive rate of 21.8%, as defined by the RCOG guideline, the competing risks model predicted 71%, 76% and 79% of placental dysfunction related stillbirths at any gestation, at <37 weeks and at <32 weeks, respectively, and the respective figures for the RCOG guideline were 40%, 44% and 42%.

Conclusion: The predictive performance for placental dysfunction related stillbirths by the competing risks model for SGA was similar to that of the stillbirth-specific model and superior to that of the RCOG guideline.

KEYWORDS

Bayes theorem, estimated fetal weight, fetal growth restriction, likelihood, pyramid of prenatal care, second-trimester screening, small for gestational age, stillbirth, survival model, uterine artery Doppler

Tweetable Abstract: The competing risks approach for SGA is superior to the RCOG guideline in the prediction of placental dysfunction related stillbirths.

This article includes Author Insights, a video abstract available at: https://vimeo.com/bjogabstracts/authorinsights17066

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1 | INTRODUCTION

Development of preventive strategies for stillbirth necessitates recognition that first, the aetiology is heterogeneous and often unknown, and second, the majority of stillbirths are related to placental dysfunction, reflected in the coexistence of small-for-gestational-age (SGA) fetuses and/or pre-eclampsia. In a prospective study on screening for adverse obstetric outcomes involving 131 514 women with singleton pregnancies attending for routine pregnancy care at 19–24 weeks of gestation, there were 477 (0.36%) stillbirths, 92.5% of which were antepartum and 7.5% intrapartum; placental dysfunction related stillbirths accounted for 59% of all antepartum stillbirths.[1] The data set was used to develop and validate a logistic regression model for the prediction of placental dysfunction related stillbirth; a combination of maternal risk factors, sonographic estimated fetal weight (EFW) and uterine artery pulsatility index (UtA-PI) predicted, at 10% false-positive rate (FPR), 62% of all cases of placental dysfunction related stillbirths, 70% of those at <37 weeks of gestation and 29% of those at ≥37 weeks of gestation.[1]

In 93% of the placental dysfunction related stillbirths, the birthweight was below the 10th centile of The Fetal Medicine Foundation population charts.[1,2] It may therefore be preferable to use one model for prediction of both SGA and stillbirth, rather than two separate models; the management of pregnancies at high risk for these conditions is essentially the same and involves serial ultrasound examinations for early diagnosis of SGA and then Doppler assessment of the fetal circulation to determine the best time and mode of delivery. The traditional approach to identify a group at high risk for SGA is the application of a scoring system. For example, in the UK, according to guidelines produced by the Royal College of Obstetricians and Gynaecologists (RCOG), a scoring system is applied to identify a group at high-risk for SGA in need of serial ultrasound scans from 26 weeks onwards.[3] An alternative method is provided by our novel two-dimensional continuous competing risks model in which SGA is considered as a spectrum disorder, the severity of which is continuously reflected in both the gestational age at delivery and Z score in birthweight for gestational age (Z).[4–8] The building block of this model is a patient-specific joint distribution of Z and gestational age at delivery that is obtained by combining a history model with multivariate likelihood of biomarkers according to Bayes theorem.[4–8] Risk computation is feasible for any chosen cut-off in gestational age at delivery and Z, at any stage of pregnancy by adding any desired biomarker in the same model. This competing risk model has also been internally validated.[7]

The objective of this study was to examine and compare the predictive performance for placental dysfunction-related stillbirths by three methods: first, the competing risks model for SGA based on a combination of maternal risk factors, EFW and UtA-PI;[7] second, our stillbirth-specific logistic regression model using the same biomarkers[1] and third, the RCOG guideline for the investigation and management of the SGA fetus.[3]

2 | METHODS

2.1 | Study population and design

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for routine pregnancy care at 19^{+0}–24^{+6} weeks of gestation at King's College Hospital and Medway Maritime Hospital, UK, between 2011 and 2020. In this visit we first recorded maternal demographic characteristics and medical history as self-reported by the patients, then carried out an ultrasound examination for fetal anatomy and measurement of fetal head circumference, abdominal circumference and femur length to calculate the EFW using the Hadlock formula,[9] because a systematic review identified this as being the most accurate model.[10] Third, we measured the left and right UtA-PI either by transvaginal or transabdominal colour Doppler ultrasound and calculated the mean value of the two arteries.[11,12] The majority of UtA-PI measurements were carried out transvaginally because at the same time we were measuring cervical length; the transabdominal approach was used when women declined transvaginal sonography. Gestational age was determined from measurement of fetal crown–rump length at 11–13 weeks or the fetal head circumference at 19–24 weeks of gestation.[13,14] The same study population was used for development and validation of the model based on multivariable logistic regression analysis for prediction of placental dysfunction related stillbirth.[1]

The inclusion criteria for this study were singleton pregnancies that delivered a phenotypically normal live birth or stillbirth at ≥24 weeks of gestation. We excluded pregnancies with known aneuploidies, major fetal abnormalities, and those ending in a miscarriage or termination of pregnancy. There was no patient involvement in the design of the study.

2.2 | Study funding

This study was supported by grants from the Fetal Medicine Foundation (UK Charity No. 1037116). This body had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

2.3 | Outcome measures

Data on pregnancy outcome were obtained from the maternity hospital records or the general practitioners of the women. Stillbirths were divided into those that occurred prenatally and those that occurred during labour (intrapartum stillbirths). Antepartum stillbirths were divided into those that were associated with placental dysfunction (pre-eclampsia or birthweight below the 10th centile) and those due to other causes or that were unexplained. Antepartum stillbirths were further divided based on gestational age at

stillbirth into those that occurred at any gestational age, at <37 weeks and at <32 weeks. The primary objective of the study was to compare the predictive performance of three models for placental dysfunction related stillbirths.

2.4 | Statistical analyses

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 chi-square test or Fisher's exact test for categorical variables or Mann–Whitney *U* test for continuous variables. The observed measurements of UtA-PI were expressed as a multiple of the normal median (MoM) after adjustment for maternal and pregnancy characteristics as previously described.[15] The values of EFW were expressed as *Z* scores using The Fetal Medicine Foundation population charts.[2] We used Bayes' theorem to combine the previous joint distribution of *Z* and gestational age according to the history model with the likelihoods of EFW *Z* score and UtA-PI MoM to obtain a pregnancy-specific posterior distribution; this was used to produce patient-specific risks according to the competing risks model for SGA. The distributions of patient-specific risks were used to estimate detection rates and FPR from analysis of receiver operating characteristic (ROC) curves. Similarly, patient-specific risks were estimated using our previously reported logistic regression model for placental dysfunction related stillbirth.[1] The predictive performance for stillbirth of the competing risks model for SGA[7] and the stillbirth-specific logistic regression model for placental dysfunction[1] was compared by the area under the ROC curve with 95% CI and by the detection rate with 95% CI at 10% FPR. McNemar's test was used to compare detection rates of stillbirth achieved from the application of the RCOG guideline and those resulting from the competing risks model for SGA, at the same screen positive rate as that determined from the use of the RCOG guideline. McNemar's test was also used to compare detection rates of stillbirth achieved from the application of the competing risks model for SGA, with and without the addition of UtA-PI.

The statistical software package R was used for data analyses.[16]

3 | RESULTS

3.1 | Study population

The entry criteria were fulfilled by 131 514 singleton pregnancies; there were 131 037 livebirths and 477 (0.36%) stillbirths, including 441 (0.34%) antepartum and 36 (0.03%) intrapartum stillbirths. The maternal and pregnancy characteristics in stillbirths and live births in the study population are summarised in Table 1.

The gestational age distribution of antepartum stillbirths was <32 weeks in 45.6% (201/441) of cases, <37 weeks in 67.3% (297/441) of cases and ≥37 weeks in 32.7% (144/441) of cases. The gestational age and birthweight distribution of the antepartum stillbirths is shown in Figure 1. The birthweight was below the 10th centile in 55.1% (243/441) of all antepartum stillbirths, including 78.6% (158/201) of those at <32 weeks of gestation, 69.4% (206/297) at <37 weeks of gestation and 25.7% (37/144) at ≥37 weeks of gestation. The birthweight was below the 10th centile in 93.1% (243/261) of all placental dysfunction related stillbirths, including 98.1% (158/161) of those at <32 weeks of gestation, 96.7% (206/213) at <37 weeks of gestation and 78.7% (37/47) at ≥37 weeks of gestation.

3.2 | Comparison of the competing risks model for SGA with the stillbirth-specific logistic regression model

Prediction of stillbirth, expressed as area under the ROC curve and detection rate at 10% FPR, in screening by maternal risk factors and combinations with EFW and UtA-PI for all stillbirths and the subgroups of antepartum stillbirths and those that were related to placental dysfunction by the two models of screening are summarised in Table 2. At 10% FPR, the competing risks model predicted 58.6% (52.6–64.6%), 66.2% (59.9–72.6%) and 70.8% (63.8–77.8%) of placental dysfunction related stillbirths at any gestation, at <37 weeks of gestation and at <32 weeks of gestation, respectively, which were similar to the respective figures of 62.3% (57.2–67.4%), 69.8% (65.0–74.6%) and 72.5% (67.8–77.2%) achieved by the application of the stillbirth-specific logistic regression model.

The ROC curves for prediction of all antepartum stillbirths and placental dysfunction related stillbirths at any gestation, at <37 weeks of gestation and at <32 weeks of gestation, by the competing risks model for SGA fetuses, are shown in Figure 2. The detection rates at 1%, 3%, 5% and 10% FPR in screening by the competing risks model using maternal risk factors and combinations with EFW and UtA-PI are shown in Table S1. Reducing the FPR from 10% to 3% resulted in a relatively mild reduction in the detection rate, an observation that might be useful in balancing effective prediction and availability of resources.

3.3 | Comparison of the competing risks model for SGA with the RCOG guideline for the prediction of SGA

The variables used for the comparison are given in Table S2. The ROC curves for the prediction of stillbirth by the competing risks model combining maternal risk factors, EFW and UtA-PI are presented in Figure 2. Prediction of stillbirth by the competing risks model was superior to that of the RCOG guideline (Table 3, Figure 2). At a screen positive rate of 21.8%, as defined by the RCOG guideline, the competing risks model predicted 79%, 76% and 71% of placental dysfunction related

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

Maternal characteristics	Live births (*n* = 131 037)	Stillbirths	
		All (*n* = 477)	Placental dysfunction (*n* = 261)
Age in years, median (IQR)	31.1 (26.7–34.9)	31.0 (26.4–35.5)	30.7 (26.1–35.7)
Weight in kg, median (IQR)	67.2 (59.7–78.1)	72.6 (63.2–85.0)	74.6 (62.6–85.6)
Height in cm, median (IQR)	165 (160–169)	165 (160–168)	164 (160–168)
Racial origin, *n* (%)			
White	95 575 (72.9)	270 (56.6)	131 (50.2)
Black	23 397 (17.9)	170 (35.6)	107 (41.0)
South Asian	6045 (4.6)	18 (3.8)	13 (5.0)
East Asian	2496 (1.9)	7 (1.5)	5 (1.9)
Mixed	3524 (2.7)	12 (2.5)	5 (1.9)
Method of conception, *n* (%)			
Spontaneous	126 500 (96.5)	457 (95.8)	150 (96.6)
Assisted conception	4537 (3.5)	20 (4.2)	9 (3.5)
Cigarette smoking, *n* (%)	12 178 (9.3)	64 (13.4)	32 (12.3)
Chronic hypertension, *n* (%)	1650 (1.3)	21 (4.4)	18 (6.9)
SLE/APS, *n* (%)	281 (0.2)	2 (0.4)	2 (0.8)
Diabetes mellitus, *n* (%)	1362 (1.0)	13 (2.7)	7 (2.7)
Parity, *n* (%)			
Nulliparous	62 084 (47.4)	236 (49.5)	128 (49.0)
Previous stillbirth	975 (0.7)	21 (4.4)	16 (6.1)
Previous SGA	9573 (7.3)	57 (12.0)	37 (14.2)
Previous pre-eclampsia	3713 (2.8)	41 (8.6)	30 (11.5)
Inter-pregnancy interval in years, median (IQR)[a]	2.9 (1.8–4.8)	3.6 (2.1–6.6)	4.2 (2.4–7.3)

Abbreviations: APS, antiphospholipid syndrome; IQR, interquartile range; SLE, systemic lupus erythematosus.

[a]Inter-pregnancy interval reported for parous women.

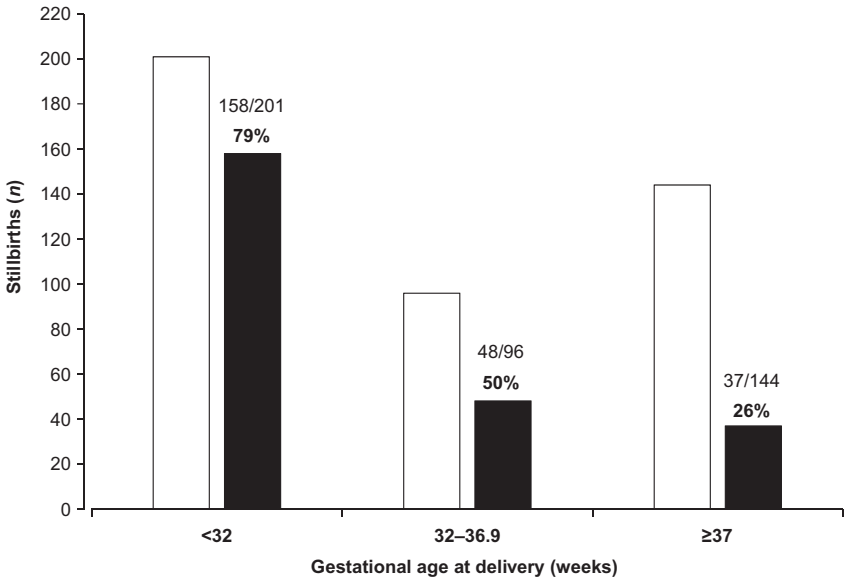

FIGURE 1 Gestational age distribution of antepartum stillbirths (white histograms) and proportion with birthweight below the 10th centile (black histograms)

TABLE 2 Prediction of stillbirth by the two models of screening, expressed as areas under the ROC curve and detection rate at 10% FPR, in screening by maternal risk factors and combinations with EFW and UtA-PI for all stillbirths and the subgroups of antepartum stillbirths and those that were related to placental dysfunction

			Competing risk model for SGA		Logistic regression model	
Outcome measure	*n*	Method of screening	AUROC	DR for FPR 10%	AUROC	DR for FPR 10%
All stillbirths	477	MF	0.639 (0.596–0.682)	23.5 (19.7–27.3)	0.680 (0.646–0.715)	27.7 (23.0–32.4)
		MF + EFW	0.659 (0.617–0.702)	34.2 (29.9–38.5)	0.682 (0.644–0.721)	35.7 (30.7–40.7)
		MF + UtA-PI	0.707 (0.667–0.748)	40.7 (36.3–45.1)	0.706 (0.668–0.745)	42.9 (37.7–48.1)
		MF + EFW + UtA-PI	0.698 (0.657–0.739)	39.4 (35.0–43.8)	0.701 (0.662–0.740)	41.6 (36.4–46.8)
Antepartum stillbirths	441	MF	0.643 (0.598–0.688)	23.4 (19.5–27.4)	0.683 (0.647–0.718)	28.2 (28.5–32.9)
		MF + EFW	0.670 (0.626–0.714)	35.6 (31.1–40.1)	0.691 (0.651–0.730)	36.8 (31.8–41.8)
		MF + UtA-PI	0.712 (0.670–0.754)	42.0 (37.4–46.6)	0.713 (0.672–0.753)	43.6 (38.4–48.8)
		MF + EFW + UtA-PI	0.708 (0.665–0.750)	41.5 (36.9–46.1)	0.708 (0.668–0.749)	43.6 (38.4–48.8)
Placental dysfunction all	261	MF	0.689 (0.633–0.745)	28.4 (22.9–33.9)	0.736 (0.692–0.780)	34.6 (29.6–39.6)
		MF + EFW	0.779 (0.729–0.829)	51.3 (45.2–57.4)	0.810 (0.769–0.852)	52.3 (47.1–57.5)
		MF + UtA-PI	0.804 (0.756–0.852)	58.2 (52.2–64.2)	0.805 (0.759–0.852)	60.0 (54.9–65.1)
		MF + EFW + UtA-PI	0.829 (0.783–0.875)	58.6 (52.6–64.6)	0.838 (0.799–0.878)	62.3 (57.2–67.4)
Placental dysfunction <37 weeks	213	MF	0.715 (0.654–0.776)	32.4 (26.1–38.7)	0.743 (0.694–0.793)	35.8 (30.8–40.8)
		MF + EFW	0.817 (0.765–0.869)	58.2 (51.6–64.8)	0.835 (0.790–0.880)	57.5 (52.3–62.7)
		MF + UtA-PI	0.825 (0.774–0.876)	63.4 (56.9–69.9)	0.815 (0.763–0.866)	64.2 (59.1–69.2)
		MF + EFW + UtA-PI	0.857 (0.810–0.904)	66.2 (59.9–72.6)	0.856 (0.813–0.900)	69.8 (65.0–74.6)
Placental dysfunction <32 weeks	161	MF	0.722 (0.653–0.791)	33.5 (26.2–40.8)	0.759 (0.705–0.812)	37.8 (32.7–42.9)
		MF + EFW	0.859 (0.805–0.913)	64.6 (57.2–72.0)	0.808 (0.747–0.870)	62.5 (57.4–67.6)
		MF + UtA-PI	0.819 (0.760–0.879)	68.3 (61.1–75.5)	0.879 (0.834–0.924)	67.5 (62.6–72.4)
		MF + EFW + UtA-PI	0.871 (0.819–0.923)	70.8 (63.8–77.8)	0.864 (0.813–0.916)	72.5 (67.8–77.2)

Abbreviations: DR, detection rate; MF, maternal risk factors.

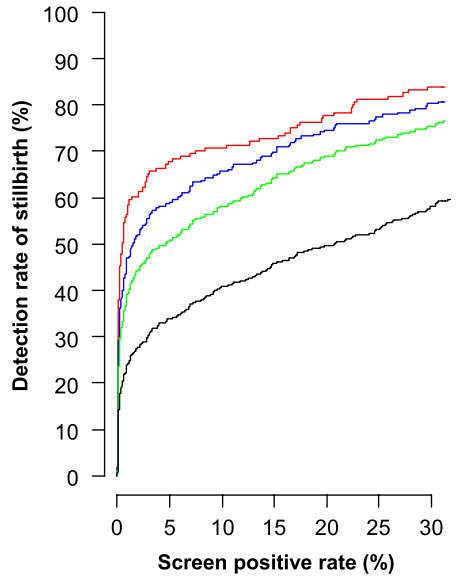

FIGURE 2 Detection rates and screen positive rates by the competing risks model for SGA combining maternal risk factors, *Z* score of EFW, and UtA-PI MoM for placental dysfunction related stillbirth at <32 weeks of gestation (red curve), <37 weeks of gestation (blue curve), any gestation (green curve) and all antepartum stillbirths (black curve). The circles demonstrate the respective detection rates according to the RCOG guideline

stillbirths at <32 weeks of gestation, <37 weeks of gestation and any gestational age and the respective figures for the RCOG guideline were 42%, 44% and 40%.[3]

3.4 | Impact of UtA-PI in the prediction of stillbirth

Table S3 reports the comparisons of detection rates of stillbirths in both the competing risks model for SGA and the logistic regression model for placental dysfunction related stillbirths, with and without the addition of UtA-PI. In both models, addition of UtA-PI improved significantly the detection rate of all stillbirths and those related to placental dysfunction.

4 | DISCUSSION

4.1 | Main findings

There are three main findings of this large prospective screening study for adverse pregnancy outcome. First, about 60% of antepartum stillbirths are related to placental dysfunction as defined by birth of SGA neonates or

TABLE 3 Comparisons of detection rates of stillbirths between the competing risks model for SGA and the RCOG guideline

Outcome measure	Stillbirths	SPR%	Comparison of detection rates, Competing risks *n* (%) versus RCOG *n* (%)	*p* value
All stillbirths	477	21.8	240 (50.3) versus 171 (35.8)	<0.0001
Antepartum stillbirths	441	21.8	230 (52.2) versus 157 (35.6)	<0.0001
Placental dysfunction all				
Any gestation	261	21.8	185 (70.9) versus 104 (39.9)	<0.0001
<37 weeks	213	21.8	162 (76.1) versus 93 (43.7)	<0.0001
<32 weeks	161	21.8	127 (78.9) versus 68 (42.2)	<0.0001

Note: Competing risks model uses maternal and pregnancy characteristics and medical history, sonographic EFW and UtA-PI. The screen positive rate (SPR) was the one that was derived from the RCOG guideline. McNemar's test was used to compare detection rates of the competing risks model and that of the RCOG guideline.

pre-eclampsia. Second, in screening for placental dysfunction related stillbirth by a combination of maternal risk factors, EFW and UtA-PI using the competing risks model for SGA,[7] the predictive performance is similar to that achieved in screening by a specific logistic regression model for placental dysfunction related stillbirth[1]; this is not surprising as SGA below the 10th centile was a prerequisite for defining a placental dysfunction related stillbirth. Third, the performance of screening by the competing risks model for SGA was by far superior to the RCOG guideline[3] not only for the prediction of placental dysfunction related stillbirths, but for all stillbirths.

4.2 | Strengths and limitations

The strengths of the study are: first, large sample size with prospectively collected data, second, focus on placental dysfunction related stillbirths, rather than treating all stillbirths as a homogeneous condition, and third, comparison of the predictive performance of two of our models that were previously internally validated.[1,7] We acknowledge the prerequisite for external validation to support generalisation of our results and wide implementation of our model. Such external validation would require a large prospective multicenter study.

It is possible that in some cases the birthweight of the stillborn babies is lower than the weight at the time of death because there is a relationship between intrauterine retention interval and reduction in birthweight.[17] In our cases we did not have information on this interval and therefore the incidence of placental dysfunction related stillbirths may be overestimated. It is also possible that stillborn babies with birthweight above the 10th centile may have been growth restricted as the result of placental dysfunction and a model predicting SGA below the 10th centile would have inevitably underestimated such stillbirths; however, all three models in this study were compared against the same end point.

This study has provided external validation for a simplified version of the RCOG guideline for the prediction of SGA. Some of the risk factors included in the RCOG guideline were not included in the competing risks model for SGA because we did not have such risk factors for any or some of our patients. For example, we did not have data on low fruit intake before pregnancy, paternal SGA, daily vigorous exercise, heavy bleeding similar to menses, or notching of the uterine artery Doppler waveforms, but these factors may well suffer from subjectivity or information bias. Similarly, we did not have available data on pregnancy-associated plasma protein-A (PAPP-A) for all of our patients and did not use the criterion of <0.4 MoM for assessment of risk; in a previous study we reported that inclusion of PAPP-A as a binary variable (<0.4 MoMs) increases the screen positive rate without any significant improvement in the detection rate.[18]

4.3 | Comparison with results of previous studies

In a series of previous first- and second-trimester studies for the prediction of stillbirth we highlighted that the causes of this adverse event are heterogeneous and that the focus of research should be placental dysfunction related stillbirths because they are relatively common and, to a great extent, potentially preventable.[19–24] However, a systematic review of 69 previous systematic reviews that aimed to identify variables that could be relevant to the development of a clinical prediction model for stillbirth treated this adverse event as a homogeneous condition.[25] The study reported that no marker had useful screening performance, but maternal age, body mass index and history of previous adverse pregnancy outcomes had a more convincing association than the best performing tests, which were PAPP-A, placental growth factor and UtA-PI.[25] Such types of publications that do not recognise the fact that the causes of stillbirth are heterogeneous could not advance the development of strategies for prediction and prevention of stillbirth.

The same group of authors attempted to externally validate previously published prediction models for stillbirth using individual participant data meta-analysis from a heterogeneous group of 19 data sets.[26] A literature search identified 40 stillbirth models, but they could only validate three of these models because of a lack of availability of the necessary predictors in their data set or the model equations in the previous publications; surprisingly for such a study there was no attempt to contact the authors of the models

to request details on the equations. The authors reported that the three models showed poor and uncertain predictive performance in their data and had limited clinical utility; they also reported that further research is needed to identify stronger prognostic factors and develop more robust prediction models.[18] 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 data sets used for their individual participant data meta-analysis were not derived from prospective screening for stillbirth and were therefore inadequate for assessing models derived from prospective examination of patients, 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.

In our study we have focused on placental dysfunction related stillbirth, prospectively recorded data from the maternal history and biomarkers shown over the last few decades to be associated with the birth of SGA neonates, developed and validated a model for prediction of SGA and demonstrated that such a model can effectively predict a high proportion of stillbirths, especially those that occur preterm. We have previously reported that increased risk for SGA fetuses/neonates is provided by lower maternal weight and height; black, south and east Asian racial origin; medical history of chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome; conception by in vitro fertilisation or ovulation induction and smoking.[4] For parous women, variables from the last pregnancy that increased the risk for SGA were history of pre-eclampsia or stillbirth, decreasing birthweight *Z* score and decreasing gestational age at delivery of the last pregnancy and inter-pregnancy interval <0.5 years.[4]

4.4 | Clinical implications of the study

A high proportion of placental dysfunction related stillbirths can potentially be prevented by a three-stage strategy. First, screening for pre-eclampsia at 11–13 weeks of gestation and treatment of the high-risk group by aspirin; this is effective not only in the prevention of preterm pre-eclampsia but also in the prevention of early SGA in the absence of pre-eclampsia.[27–32] Second, screening during the routine mid-trimester scan by a combination of maternal risk factors, EFW and UtA-PI, which identifies a high-risk group that contains a high proportion of placental dysfunction related stillbirths that occur at 24–37 weeks of gestation; close monitoring of these pregnancies for early diagnosis of SGA fetuses could prevent at least some of such stillbirths by defining the best approach to monitoring and best timing of delivery. The detection rate of stillbirths is higher when UtA-PI is included in the model in addition to maternal risk factors and EFW, highlighting the necessity of including this measurement in the routine mid-trimester scan; it is easy for competent sonographers to learn this technique and it only adds about 2 minutes to the examination. Third, routine ultrasound examination at 36 weeks of gestation, because screening at mid-gestation provides poor prediction of stillbirth at term; more effective screening for late SGA can be achieved by screening at 36 weeks; the detection rate for term SGA by assessment at 36 weeks of gestation is twice as high as with screening at mid-gestation.[33,34]

5 | CONCLUSION

Placental dysfunction related stillbirth is to a great extent predictable and potentially preventable. In more than 90% of such stillbirths the fetuses are SGA and many of these can be predicted at a routine mid-pregnancy assessment using a combination of maternal risk factors, ultrasonographic EFW and UtA-PI.

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CONFLICT OF INTERESTS

None declared. Completed disclosure of interests form available to view online as supporting information.

AUTHOR CONTRIBUTIONS

KHN and IP conceptualised and designed the study. AS searched the databases and provided the necessary files for analysis. KHN and RA oversaw the study. IP conducted the statistical analysis. KHN, IP and GA wrote the paper. All authors revised and contributed to the intellectual content of the manuscript.

ETHICS APPROVAL

Women gave written informed consent to take part in the study, which was carried out in compliance with the 1975 Declaration of Helsinki Guidelines. The study was approved by the NHS Research Ethics Committee (REC reference 02-03-033, date of approval 11 March 2003).

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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