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Research Article
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Evaluation of the RCOG guideline for the prediction of neonates that are small for gestational age and comparison with the competing risks model

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Objective To examine the predictive performance of the relevant guideline by the Royal College of Obstetricians and Gynaecologists (RCOG) for neonates that are small for gestational age (SGA), and to compare the performance of the RCOG guideline with that of our competing risks model for SGA.

Design Prospective observational study.

Setting Obstetric ultrasound departments in two UK maternity hospitals.

Population A total of 96 678 women with singleton pregnancies attending for routine ultrasound examination at 19–24 weeks of gestation.

Methods Risks for SGA for different thresholds were computed, according to the competing risks model using maternal history, second-trimester estimated fetal weight, uterine artery pulsatility index and mean arterial pressure. The detection rates by the RCOG guideline scoring system and the competing risks model for SGA were compared, at the screen positive rate (SPR) derived from the RCOG guideline.

Main outcome measures Small for gestational age (SGA), <10th or <3rd percentile, for different gestational age thresholds.

Results At an SPR of 22.5%, as defined by the RCOG guideline, the competing risks model predicted 56, 72 and 81% of cases of neonates that are SGA, with birthweights of <10th percentile, delivered at ≥37, <37 and <32 weeks of gestation, respectively, which were significantly higher than the respective figures of 36, 44 and 45% achieved by the application of the RCOG guideline. The respective figures for neonates that were SGA with birthweights of <3rd percentile were 66, 79, 85 and 41, 45, 44%.

Conclusion The detection rate for neonates that were SGA with the competing risk approach is almost double than that obtained with the RCOG guideline.

Keywords Bayes' theorem, estimated fetal weight, fetal growth restriction, likelihood, mean arterial pressure, pyramid of prenatal care, second-trimester screening, small for gestational age, survival model, uterine artery doppler.

Tweetable abstract The competing risks approach for the prediction of SGA performs better than the existing RCOG guideline.

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Introduction

Neonates that are small for gestational age (SGA) neonates are at an increased risk of adverse perinatal outcomes and the development of metabolic and cardiovascular diseases in adult life.[1–5] National societies have issued guidelines for SGA screening, antenatal monitoring and the timing for the delivery of pregnancies suspected to be SGA.[6] However, the best policy for identifying fetuses that are SGA remains under debate.[7] The traditional approach is to identify a high-risk group for SGA by the application of a scoring system. For example, in the UK, according to guidelines

published by the Royal College of Obstetricians and Gynaecologists (RCOG), a scoring system is applied to identify a high-risk group for SGA in need of serial ultrasound scans from 26 weeks of gestation onwards.[8] The high-risk group consists of two subgroups: the first subgroup is made up of pregnancies with any one major risk factor (Table S1); and the second subgroup involves women with any three or more minor risk factors (Table S1) who also have abnormal uterine artery Doppler at 20–24 weeks of gestation.[8] Abnormal uterine artery Doppler is defined as a uterine artery pulsatility index (UtA-PI) of >95th percentile and/or the presence of notching in the waveform. In the cases with three or more minor risk factors and normal uterine artery Doppler at 20–24 weeks of gestation, it is recommended that a scan is offered at some stage during the third trimester of pregnancy.

An alternative method for the prediction of neonates that are SGA is to consider SGA as a spectrum disorder, the severity of which is continuously reflected in both the gestational age at delivery (GA) and the *Z*-score of birthweight for gestational age.[9–13] Conceptually, this approach is similar to the competing risks model for the prediction of pre-eclampsia.[14] The building block of the competing risks model for SGA is a patient-specific joint distribution of Z and GA, which is obtained by combining a history model with the multivariate likelihood of biomarkers according to Bayes theorem.[9–13] Risk computation is feasible for any chosen cut-off in GA and Z, at any stage of pregnancy, by adding any desired biomarker in the same model.

The objectives of this study were first to examine the predictive performance for neonates that were diagnosed as SGA by the policy suggested by RCOG, and second to compare the performance of the RCOG guideline with that of the competing risks model for SGA.

Methods

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 between 19^{+0} and 24^{+6} weeks of gestation at King's College Hospital and Medway Maritime Hospital, UK, between 2011 and 2020. At this visit we: (i) record maternal demographic characteristics and medical history; (ii) carry out an ultrasound examination for fetal anatomy and growth; (iii) measure the left and right UtA-PI, either by transvaginal or transabdominal colour Doppler ultrasound, and calculate the mean value of the two arteries;[15,16] and (iv) measured the mean arterial pressure (MAP) by validated automated devices and a standardised protocol.[17] 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. The fetal head circumference, abdominal circumference and femur length were measured and the estimated fetal weight (EFW) was calculated with the Hadlock formula,[18] because a systematic review identified this as being the most accurate model.[19]

Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks of gestation or fetal head circumference at 19–24 weeks of gestation.[20,21] The inclusion criteria for this study were singleton pregnancies delivering a non-malformed live birth or stillbirth at >24 weeks of gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities. Women gave written informed consent to take part in the study. Details of ethical approval are given in the relative section.

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.

Outcome measures

Data on pregnancy outcome were collected from hospital maternity records or the general medical practitioners of the women. The outcome measures of the study were the birth of a neonate that was SGA, with a birthweight of <10th or <3rd percentiles for different cut-offs of gestational age at delivery. The fetal and neonatal population weight charts from the Fetal Medicine Foundation were used to convert birthweight and EFW to percentiles and *Z*-scores.[22]

Statistical analyses

The competing risks approach for SGA is a model for the personalised joint distribution of Z and GA. We used Bayes' theorem to combine the *prior* joint distribution of Z and GA according to the history model with the likelihoods of biophysical markers to obtain a pregnancy-specific *posterior* distribution that was used to compute risks for different cut-off values.[9,13] The likelihood of the *Z*-score of EFW was modelled in relation to *Z* and GA by fitting a regression model with an interaction term between *Z* and GA, as previously described.[13] Essentially, the intercept of the linear model that links *Z* and EFW–*Z* was constant and practically zero, whereas the slope of this linear model was a function of GA: the earlier the gestation the steeper the slope (Figure S1). The development and the parameters of the likelihood for EFW were presented in detail in a previous study.[13] We found significant gestational age-dependent effects on EFW for some maternal factors;

however, these effects were <0.1 standard deviations and therefore we assumed independency between EFW and maternal factors. We converted UtA-PI and MAP to multiples of the median (MoM) values, as previously described.[23] Recently published reference ranges for transabdominal and transvaginal UtA-PI were used to convert UtA-PI to percentiles.[23] A folded-plane regression model was fitted to describe the distribution of log MoM UtA-PI and MAP conditional to *Z* and GA according to a published methodology (Figure S1).[10–12] The combination of different biomarkers was achieved by a multivariable Gaussian distribution. We assumed a constant covariance matrix. The multivariate Gaussian likelihood of the biophysical markers updates the *prior* history-driven distribution of *Z* and GA to obtain the *posterior* joint distribution of *Z* and GA. In the high-risk cases this patient-specific distribution is shifted towards earlier gestational ages and lower birthweights, resulting in a higher risk for SGA, as we have previously demonstrated (Figure S2).[9–13]

We used maternal factors, EFW, UtA-PI and MAP to produce patient-specific risks according to the competing risks model. McNemar's test was used to compare the detection rates achieved from the application of the RCOG guideline with those resulting from the competing risks model, at the same screen-positive rate (SPR) as that determined from the use of the RCOG guideline. Model fitting was carried out within a Bayesian framework using Markov chain Monte Carlo (MCMC).[24] The statistical software package R was used for data analyses.[25]

Results

The maternal and pregnancy characteristics of the study population of 96 678 singleton pregnancies are given in Table S2, and are the same as those in our previous publication.[13] Compared with the non-SGA group, in the group with SGA <10th percentile there was a lower median maternal age, weight, height and body mass index, a lower prevalence of white women, and a higher prevalence of women of black, South Asian and mixed racial origin, women with a history of chronic hypertension, systemic lupus erythematosus or anti-phospholipid syndrome, smokers, nulliparous women and parous women that had previously developed pre-eclampsia or had delivered neonates that were SGA. For parous women in the SGA group, compared with the non-SGA group, there was a higher interpregnancy interval.

Three hundred pregnancies (0.31% of the study population) resulted in a stillbirth. A total of 117 stillbirth cases (39.0% of the stillbirths) occurred in pregnancies with SGA <10th percentile delivered before 37 weeks of gestation. Twenty-six stillbirth cases (8.67% of the stillbirths) occurred in pregnancies with SGA <10th percentile delivered after 37 weeks of gestation.

Comparison of performance of the new model with the RCOG guideline

The variables used for the comparison are given in Table S1. The receiver operating characteristic (ROC) curves for the overall prediction of the competing risks model by the combination of maternal factors, EFW, UtA-PI and MAP are presented in Figure 1. The predictive performance of the competing risks model was superior to that of the RCOG guideline (Figure 1; Table 1). At an SPR of 22.5%, as defined by the RCOG guideline, the new model predicted 56, 72 and 81% of cases of neonates that were SGA with a birthweight <10th percentile delivered at ≥37, <37 and <32 weeks of gestation, respectively, which were significantly higher than the respective figures of 36, 44 and 45% achieved by the application of the RCOG guideline. At an SPR of about 22.5%, as defined by the RCOG guideline, the new model predicted 66, 79 and 85% of cases of neonates that were SGA with a birthweight <3rd percentile delivered at ≥37, <37 and <32 weeks of gestation, respectively, which were significantly higher than the respective figures of 41, 45 and 44% achieved by the application of the RCOG guideline.

Discussion

Main findings

This study examined for the first time the predictive performance of the RCOG green-top guideline for SGA, in a large unselected low-risk population. We have demonstrated that the performance of screening for SGA by the RCOG guideline is low, at an SPR of about 22.5%. In contrast the competing risk approach using readily available information after ultrasound examination at 22 weeks of gestation almost doubles this detection rate for the same SPR.

Strengths and limitations

The strengths of the study are: (i) the large sample size with prospectively collected data; and (ii) the use of a two-dimensional continuous competing risks model as an alternative to the RCOG recommendations. Even though internal validation has been carried out in previous studies,[9,10] we acknowledge the prerequisite for external validation to support the generalisation of our results and wide implementation of our model.

We acknowledge that the women who screened positive according to the RCOG guideline had increased surveillance that often led to an elective birth. This intervention may have reduced the incidence of SGA <3rd percentile in our data set and caused an increase in the performance of the screening. However, this process would probably affect both screening methods equally without afflicting our comparisons.

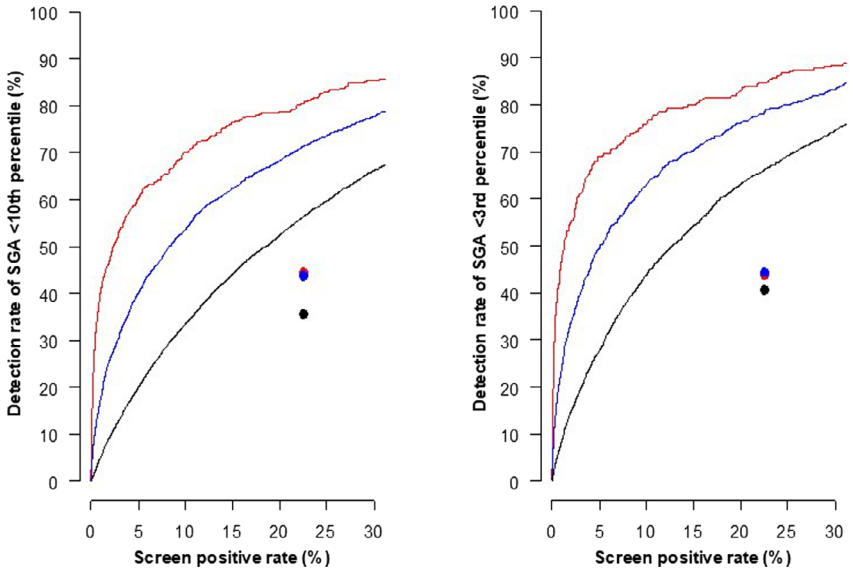

Figure 1. Detection rate and screen-positive rates of SGA <3rd percentile or <10th percentile by a combination of maternal factors, *Z*-score of EFW, UtA-PI MoM and MAP MoM for delivery <32 weeks of gestation (red curve), <37 weeks of gestation (blue curve) and >37 weeks of gestation (black curve). The detection rates for the screen-positive rate for delivery <32 weeks of gestation (red circle), <37 weeks of gestation (blue circle) and >37 weeks of gestation (black circle) according to the RCOG guideline are superimposed.

Table 1. Comparison between the competing risks model and the RCOG guideline for the detection of neonates that were SGA

Method of screening	Outcome measure	SGA*n*	SPR%	Comparison of detection rates*n* (%) vs *n* (%)	Difference in detection rates*n* (%; 95% CI)	*P*
	≥37 weeks					
RCOG vs competing risks model	<10th percentile	10 052	22.5	3590 (35.7) vs 5669 (56.4)	2079 (20.7; 19.9–21.5)	<0.0001
RCOG vs competing risks model	<3rd percentile	3755	22.5	1530 (40.8) vs 2490 (66.3)	960 (25.5; 24.1–26.9)	<0.0001
	<37 weeks					
RCOG vs competing risks model	<10th percentile	1971	22.5	866 (43.9) vs 1409 (71.5)	543 (27.6; 25.6–29.6)	<0.0001
RCOG vs competing risks model	<3rd percentile	1283	22.5	572 (44.6) vs 1008 (78.6)	436 (34.0; 31.4–36.6)	<0.0001
	<32 weeks					
RCOG vs competing risks model	<10th percentile	390	22.5	174 (44.6) vs 314 (80.5)	140 (35.9; 31.1–40.7)	<0.0001
RCOG vs competing risks model	<3rd percentile	315	22.5	138 (43.8) vs 267 (84.8)	129 (41.0; 35.6–46.4)	<0.0001

RCOG, Royal College of Obstetricians and Gynaecologists; SGA, small for gestational age; *n*, number; SPR, screen-positive rate.
The competing risks model uses maternal and pregnancy characteristics and medical history, estimated fetal weight by ultrasound scan, uterine artery Doppler pulsatility index and mean arterial pressure. The SPR was that derived from the RCOG guideline. McNemar's test was used to compare the detection rate of the competing risks model with that of the RCOG guideline.

The RCOG guideline defines abnormal uterine artery Doppler as UtA-PI >95th centile and/or notching in the waveform.[8] We have not included notching in our data set because a previous study demonstrated that in screening for SGA <10th percentile, the inclusion of bilateral notches in the definition of the screen-positive group introduces a technical element of subjectivity and nearly doubles the SPR, with only a minor improvement in sensitivity.[15] We did not have data available on pregnancy-associated plasma protein A (PAPP-A) for all of our patients and did not use the criterion of <0.4 MoM for the assessment of risk. In a previous study we have shown that the inclusion of PAPP-A as a major factor in the form of a binary variable (<0.4 MoMs) increases the SPR without any significant increase in the detection rate.[10] Therefore, adding PAPP-A to the RCOG method would probably have no impact in the differences reported, or would increase them because of the increase in the SPR (Figure 1). Also the simultaneous addition of PAPP-A in the form of a continuous likelihood in the competing risks model will significantly improve the prediction by the new model, increasing the divergence between the two methods.[10]

Some of the factors proposed by the RCOG guideline, such as low fruit intake pre-pregnancy, paternal SGA, maternal SGA, cocaine use, daily vigorous exercise and heavy bleeding, similar to menses, were not available and therefore were not included in the comparisons (Table S1). However, these factors may well suffer from subjectivity or information bias.

Interpretation

The RCOG essentially recommends the use of a scoring system based on maternal characteristics and medical history and the conditional, to this scoring system, use of UtA-PI, to identify the cases in need of serial third-trimester scans. Our study has demonstrated a new approach for predicting SGA by using readily available information at 19–24 weeks of gestation in the framework of a competing risks model. This method is superior to the RCOG guideline (Figure 1; Table 1). The routine anomaly scan in the second trimester has been adopted worldwide and EFW calculation is an integral part of this scan. The measurement of UtA-PI can be carried out by the same sonographers and ultrasound machines as used in the scan at 19–24 weeks of gestation, and such an examination would add only a couple of minutes to the scanning time. It is also feasible to measure MAP in the same visit. UtA-PI and MAP are also useful in the prediction of pre-eclampsia.[14] The higher sensitivity of the proposed method will reduce the number of third-trimester scans. Additionally, the new model will stratify pregnancies for an appropriate timing of the third-trimester scan instead of carrying out serial scans in about one-fifth of the population.

We have previously shown that the competing risks model performs better than the RCOG guideline when using maternal pregnancy characteristics and medical history.[10] Moreover, our method handles more efficiently the information that is contained in the values of biomarkers. This is explicable by realizing that a pregnancy with increased UtA-PI that lies below the 95th percentile may still have a substantial risk for SGA. Conversely screen positivity by the RCOG method disregards the magnitude of UtA-PI increase. On the contrary, the continuous likelihood in the new model allows for a quantifiable effect in the computation of risk, according to the exact UtA-PI measurement (Figure S1). This measurement-specific effect can be also effectively combined with other measurements routinely gathered, such as fetal biometry or MAP, and is also conditioned for both the degree of smallness and GA.

Conclusion

The method proposed by RCOG will cause more than one-fifth of the population to be considered as high risk and in need of serial ultrasound scans, and this approach would identify <45% of neonates that were SGA. The screen-positive group will be handled as such until term without any capability to transition from the high- to the low-risk group, and vice versa. As a result, the number of scans increases significantly, because of these consecutive scans in the screen-positive group, whereas the sensitivity of the method remains low. In contrast, the proposed new method nearly doubles the detection rate and has the capability of using the same model at the third-trimester reassessment. The individualised nature of the new model will enhance the customisation of antenatal care in the emerging era of precision medicine. The distribution of biomarkers in the context of the competing risks approach proves that SGA is a single continuous two-dimensional outcome that can be attached in the new pyramid of prenatal care.[26] There is a need to tailor the timing of the third-trimester assessment for each pregnancy on the basis of the visit at 22 weeks of gestation.

Disclosure of interests

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

Contribution to authorship

KHN, IP and DW conceptualised and designed the study. KHN oversaw the study. KHN and IP wrote the article. UN, OB and RA were involved in sample collection. IP and DW conducted the statistical analysis. All authors revised and contributed to the intellectual content of the article.

Details of ethical 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 ref. 02-03-033, approved 11 March 2003).

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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 the data, in the writing of the article and in the decision to submit the article for publication.

Data Availability Statement

Research data are not shared.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Three-dimensional demonstration of the folded regression plane for the $\log_{10}$ MoM UtA-PI MoM likelihood, conditionally to birthweight *Z*-scores and gestational age at delivery. The predicted mean $\log_{10}$ MoM UtA-PI MoM depended on both *Z* and GA, until it reaches zero, and beyond the break line the mean was presumed to be constant and equal to zero. Three-dimensional demonstration of the regression plane for the EFW *Z*-score likelihood, conditionally to birthweight *Z*-score and gestational age at delivery. This model uses an interaction term that assumes the coefficient for birthweight *Z*-scores is a function of gestational age at delivery.

Figure S2. Contour plots of the joint distribution of birthweight *Z*-scores and gestational age at delivery according to maternal factors and biomarkers for a high-risk case and a low-risk case. The shaded area corresponds to the risk of delivery before 32 weeks of gestation with SGA below the 10th percentile.

Table S1. Variables used in the RCOG guideline and the competing risks model for the prediction of neonates that are SGA.

Table S2. Maternal and pregnancy characteristics in the study population. Descriptive measures are reported within each group. ■

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