Competing-risks model for prediction of small-for-gestational-age neonates from biophysical and biochemical markers at 11–13 weeks' gestation

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Running Head: A new model in screening for small for gestational age neonates.

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CONTRIBUTION

What are the novel findings of this work?

The study presents a new competing risk model for the prediction of small for gestational age (SGA) neonates by maternal factors and biomarkers at 11-13 weeks' gestation. This approach involves a joint prior distribution of gestational age at delivery (GA) and birth weight Z – scores (Z), updated by the biomarkers' likelihood according to Bayes' theorem. The pattern of change, conditional to GA and Z, is similar for all biomarkers and it is captured by the same folded plane regression modelling. The best biophysical predictor of preterm SGA was uterine artery pulsatility index and the best biochemical marker was placental growth factor. The prediction of SGA was consistently better for increasing degree of prematurity, higher severity of smallness, co-existence of preeclampsia and increasing number of biomarkers.

What are the clinical implications of this work?

A single continuous two-dimensional model provides early risk stratification, for any desired cut-offs, laying the ground for a personalized antenatal plan for predicting and managing SGA, in the milieu of a new inverted pyramid of prenatal care.

ABSTRACT

Objectives: To develop a new competing risks model for the prediction of small for gestational age (SGA) neonates, based on maternal factors and biophysical and biochemical markers at 11 - 13 weeks' gestation.

Methods: This is a prospective observational study in 60,875 women with singleton pregnancies undergoing routine ultrasound examination at 11^{+0} - 13^{+6} weeks' gestation. All pregnancies had PAPP-A and PlGF measurements, 59,001 had uterine artery pulsatility index (UtA-PI) measurements and 58,479 had mean arterial pressure (MAP) measurements; 57,131 cases had complete data for all biomarkers. We used a previously developed competing risks model for the joint distribution of gestational age at delivery (GA) and birth weight Z score (Z), according to maternal demographic characteristics and medical history. The likelihoods of the biophysical markers were developed by fitting folded plane regression models, a technique that has already been used in previous studies for the likelihoods of biochemical markers. The next step was to modify the prior distribution by the likelihood, according to Bayes theorem, to obtain individualized distributions for GA and Z. We used the 57,131 cases with complete data, to assess the discrimination and the calibration of the model for predicting SGA with, without or independently of preeclampsia (PE), by different combinations of maternal factors and biomarkers.

Results: The distribution of biomarkers, conditional to both GA and Z, was best described by folded plane regression models. These continuous two-dimensional likelihoods update the joint distribution of Z and GA that has resulted from a competing risks approach; this method allows application of user-defined cut-offs. The best biophysical predictor of preterm SGA was UtA-PI and the best biochemical marker was PlGF. The prediction of SGA was consistently better for increasing degree of prematurity, higher severity of smallness, co-existence of PE and increasing number of biomarkers. The combination of maternal factors with all biomarkers predicted 34.3%, 48.6% and 59.1% of all cases of SGA neonates with birth weight <10th percentile delivered at ≥37, <37 and <32 weeks' gestation, at 10% false positive rate. The respective values for birth weight <3rd percentile were 39.9%,

53.2% and 64.4% and for birth weight <3rd percentile with PE were 46.3%, 66.8% and 80.4%. The new model was well calibrated.

Conclusions: The study has presented a single continuous two-dimensional model for prediction of SGA for any desired cut-offs in smallness and gestational age, laying the ground for a personalized antenatal plan for predicting and managing SGA, in the milieu of a new inverted pyramid of prenatal care.

INTRODUCTION

Small for gestational age (SGA) fetuses / neonates are at increased risk of adverse perinatal outcome and such adverse outcomes are more common for higher degrees of smallness and prematurity.[1-8] First trimester prediction of preterm SGA, with delivery at <37 weeks' gestation, is beneficial because many of such cases can be prevented by the prophylactic use of aspirin; in the ASPRE trial, use of aspirin reduced the overall incidence of SGA <10th percentile by about 40% in babies born at <37 weeks' gestation and by about 75% in babies born at <32 weeks.[9,10] In the cases of SGA fetuses / neonates not prevented by aspirin prenatal identification can substantially reduce the risks of adverse perinatal outcome through close monitoring, appropriate timing of delivery and prompt neonatal care.[11,12]

The traditional approach of identifying a group of women at high-risk of delivering SGA neonates is use of risk scoring systems; for example, in the UK, according to guidelines by the National Institute for Health and Clinical Excellence (NICE) women should be considered to be at high-risk based on certain maternal demographic characteristics and medical history and low first-trimester serum pregnancy associated plasma protein-A (PAPP-A).[13] Although this approach is relatively simple to perform, it does not provide patient-specific risks and has a poor performance of predicting SGA.[14] Another approach to predict delivery of SGA neonates is to use logistic regression models that combine maternal factors with biomarkers.[15-18] These models provide patient-specific risks for different pre-specified cut-offs of birth weight percentile and gestational age at delivery, which has led to an arbitrary dichotomization of the disease; different models for different SGA definitions are required and adding new biomarkers requires re-fitting the whole model. We have recently proposed a new approach for prediction of SGA neonates which considers SGA as a spectrum disorder whose severity is continuously reflected in both the gestational age at delivery and z-score in birth weight for gestational age.[14,19,20] The concept of this approach is similar to that of the competing risks model in the assessment of risks for preeclampsia (PE).[21-25] The initial step was a patient-specific joint distribution of z scores of birth weight (Z) and gestational age at delivery (GA),

by a model driven by maternal demographic characteristics and medical history.[19] Subsequently we developed a continuous likelihood, according to a folded plane regression model, that best described the distribution of PAPP-A in relation to Z and GA.[14] We then combined PAPP-A and placental growth factor (PlGF) by using a multivariate continuous likelihood, presenting a benchmark on how to combine more than one biomarkers.[20]

The objectives of this study are first, to incorporate the biophysical markers of uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) into the new competing risks model, and second, to evaluate all possible combinations of maternal history, UtA-PI, MAP, PAPP-A and PlGF in first-trimester prediction of SGA.

METHODS

Study population and design

The dataset for this study was derived from prospective screening for adverse obstetric outcomes in women attending for their routine first-trimester hospital visit in pregnancy at King's College Hospital and Medway Maritime Hospital, UK. In this visit, at 11^{+0} - 13^{+6} weeks' gestation, we recorded maternal characteristics and medical history, we performed combined screening for aneuploidies[26], we measured the left and the right UtA-PI by color Doppler transabdominal ultrasound and we calculated the mean PI,[27] we measured MAP by validated automated devices and standardized protocol,[28] and we measured serum concentration of PlGF and PAPP-A. Serum PAPP-A was measured by DELFIA Xpress system (PerkinElmer Life and Analytical Sciences, Waltham, USA) during the whole study period in both hospitals. Serum PlGF was measured by DELFIA Xpress system (PerkinElmer Life and Analytical Sciences, Waltham, USA) between March 2006 and July 2012 and between August 2013 and March 2017 at King's College Hospital and between April 2010 and July 2012 and between August 2013 and March 2017 at Medway Maritime Hospital, it was also measured by Cobas e411 (Roche Diagnostics, Penzberg, Germany) between August 2012 and July 2012 in both hospitals. Gestational age was determined from the fetal crown-rump length.[29] Participants gave written informed consent to take part in the study, which was approved by the NHS Research Ethics Committee. Singleton pregnancies undergoing first-trimester combined screening for aneuploidy and subsequently delivering a phenotypically normal live birth or stillbirth at ≥24 weeks' gestation were included in the study. Pregnancies with aneuploidies and major fetal abnormalities and those ending in termination, miscarriage or fetal death before 24 weeks' gestation were excluded from the analyses.

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 birth of a neonate at or below different thresholds of birth weight percentile for different cut-offs of gestational age at delivery; with, without or independently of PE occurrence. The obstetric records of all women with pre-existing or pregnancy associated hypertension were reviewed, to determine if the condition was PE, as defined by the American College of Obstetricians and Gynecologists (ACOG).[30] According to this definition, diagnosis of PE requires the presence of new onset hypertension (blood pressure ≥140 mmHg systolic and / or ≥90 mmHg diastolic) at ≥ 20 weeks' gestation and either proteinuria (≥300 mg/24h or protein to creatinine ratio >30 mg/mmol or ≥2 + on dipstick testing) or evidence of renal dysfunction (serum creatinine >97 μmol/L), hepatic dysfunction (transaminases ≥65 IU/L) or hematological dysfunction (platelet count <100,000/μL).[30] The Fetal Medicine Foundation fetal and neonatal population weight charts were used to convert birth weight to percentiles and Z scores.[31]

Statistical analyses

The new model uses a personalized joint distribution of birth weight Z scores and gestational age at delivery obtained in two steps. The first step is a *prior* distribution by the model based on maternal characteristics and medical history. In the second step, this *prior* distribution is updated according to Bayes' theorem, by a multivariable Gaussian distribution that was fitted to the $\log_{10}$ MoM values of the biomarkers. We assumed a constant covariance matrix. We used likelihood functions for each biomarker, conditional to Z and GA according to a folded plane regression model. The resultant pregnancy specific *posterior* distribution was used to compute risks for different cut-offs. The *prior* model and the likelihood functions for the biochemical markers are given in previous studies,[14,19,20] whereas the likelihood models for the biophysical markers are presented in this study.

The likelihood models for the biomarkers were developed in a population of 60,875 pregnancies, in which all pregnancies had available data on biochemical markers, 59,001 cases had UtA-PI measurements, 58,479 cases had MAP measurements and 57,131 pregnancies had complete data on UtA-PI, MAP, PlGF, and PAPP-A. We used all the available data to develop the likelihood functions and the new model was evaluated in the 57,131 cases with complete data. We assessed the performance of the new model by means of detection rate (DR) of SGA neonates of different severities (<10th and <3rd percentiles) at different gestational age cut-offs (≥37, <37 and <32 weeks) with, without or independently of PE occurrence, at fixed false positive rates (FPR) of 5%, 10% and 20%. Calibration intercepts and slopes, using logistic regression analysis of outcome incidence against the logit of the respective risks, were obtained.

Model fitting was carried out within a Bayesian framework using Markov chain Monte Carlo (MCMC).[32] The statistical software package R was used for data analyses.[33]

RESULTS

The whole study population included 60,875 singleton pregnancies. The maternal and pregnancy characteristics are given in Table 1. In the SGA group, compared to the non-SGA group, there was a lower median maternal age, weight, height and body mass index, lower prevalence of White women and 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 PE or delivered SGA neonates. For the parous women, in the SGA group, compared with the non-SGA group, there was a higher inter-pregnancy interval.

The new model was evaluated in the 57,131 cases with complete data; the birth weight was <10th and <3rd percentiles in 274 (46.8%) and 219 (37.4%), respectively, of the 586 pregnancies delivering at <32 weeks' gestation, in 1210 (33.9%) and 803 (22.5%) of the 3,566 pregnancies delivering at <37 weeks and in 6,299 (11.8%) and 2,417 (4.5%) of the 53,565 pregnancies delivering at ≥37 weeks.

Likelihoods of biomarkers

We developed likelihoods for UtA-PI and MAP conditional to Z and GA, according to a folded plane regression model. The inferences for the parameters are presented in Table 2. The correlation coefficients that we used for the covariance matrices are given in Table 3. The structure of the likelihood is illustrated in Figure 1. This approach overcomes the issue of the conventional regression analysis, where parameters are driven mainly by pregnancies at term with normal birth weight and normal biomarker values. The biomarkers gradually deviate for earlier gestations and lower birth weights and this association holds true until the mean predicted by the model reaches one MoM (Figure 1). The outcome is now unified in a single two dimensional continuous model with a structure that emphasizes the clinically relevant domain of the distributions of biomarkers. Figure 2 shows the joint distribution of Z

and GA after the addition of biomarkers, for a high-risk and low-risk case. For the high-risk case the contour lines descend to earlier gestational ages and lower birth weights, because of the effect of the likelihoods. A larger part of the joint distribution falls within the area defined by the chosen cut-offs resulting in a higher risk for SGA.

Model evaluation

The discrimination of the model improved by the addition of biomarkers. The detection rates for several SGA definitions for all cases, SGA with PE and SGA with no PE at fixed FPRs are given in Tables 4 and 5. The best biophysical predictor of preterm SGA was UtA-PI and the best biochemical marker was PlGF. The prediction of SGA was consistently better for increasing degree of prematurity, higher severity of smallness, co-existence of PE and increasing number of biomarkers (Tables 4 and 5). The combination of maternal factors with all biomarkers predicted 34.3%, 48.6% and 59.1% of all cases of SGA neonates with birth weight <10th percentile delivered at ≥37, <37 and <32 weeks' gestation, at 10% FPR. The respective values for birth weight <3rd percentile were 39.9%, 53.2% and 64.4% and for birth weight <3rd percentile with PE were 46.3%, 66.8% and 80.4%. The new model was well calibrated and realistic risks would be anticipated in the actual clinical use (Table 6).

DISCUSSION

Main findings of the study

This prospective observational study involving more than 60,000 singleton pregnancies at 11-13 weeks' gestation presents a new competing risk model for the prediction of SGA neonates by maternal demographic characteristics, medical history and biomarkers. This approach involves a joint prior distribution of gestational age at delivery and birth weight Z-scores, updated by the likelihood of UtA-PI, MAP, PAPP-A and PlGF according to Bayes' theorem. The pattern of change, conditional to gestational age at delivery and birth weight Z-scores, is similar for all biomarkers and it is captured by the same folded plane regression modelling. The best biophysical predictor of preterm SGA was UtA-PI and the best biochemical marker was PlGF. The prediction of SGA was consistently better for increasing degree of prematurity, higher severity of smallness, co-existence of PE and increasing number of biomarkers.

In this study, the traditional cut-offs were used in evaluating the new model. However, we fundamentally challenge the rationale for these cut-offs. We consider birth weight deviation expressed in Z-scores and gestational age at delivery as a joint outcome, described by a single continuous model. Instead of having predictors that affect the risk for a subjectively defined fixed categorical outcome, the new model shifts a whole joint probability distribution for birth weight and gestational age at delivery according to maternal factors and biomarker measurements. Ultimately arbitrary and vague categorizations have been eliminated and adjustments to the needs of each pregnancy and to the health care system distinctiveness, are now possible.

Comparison with results of previous studies

Previous first trimester studies using logistic regression models that combine maternal factors with biomarkers reported similar sensitivities in the prediction of SGA neonates as the ones achieved by our new model.[15-18] However, the predictive performance of the new approach is actually higher than that of previous models because our definition of SGA was based on the new Fetal Medicine Foundation birth weight charts[31]; these charts modeled the overrepresentation of preterm SGA pregnancies and this has led to an increasing percentage of SGA for lower gestational age cut-offs.[20] Thus, we are predicting an outcome that is less extreme, compared to the previous definitions, and consequently more difficult to predict. Additionally, the logistic regression models suffer from over fitting to the rare preterm SGA cases and therefore the reported performance of these models is overestimated compared to the true one when the model is applied to new cases.

Implications for clinical practice

The new model for SGA can be incorporated as a module in the already widely installed infrastructure for first trimester assessment of a wide range of pregnancy complications. This is particularly important after publication of the results from the ASPRE study that prophylactic use of aspirin is effective in the prevention of preterm PE and early onset SGA.[9,10] We present all possible combinations of biomarkers to assist the implementation of any desired protocol. Recording maternal characteristics, medical history, and measuring the blood pressure at 12 weeks is part of the routine antenatal care in many countries. Measurement of UtA-PI can be done by the same sonographers and ultrasound machines as part of the 11–13-week scan, with the precondition that sonographers have received adequate training and being aware that the measurement would add only a couple of minutes scanning time. Measurement of serum PAPP-A and quality control for such measurement is already in place in centers providing routine first-trimester combined screening for trisomies. Serum PlGF can be measured on the same sample and by the same

platforms used for PAPP-A, but at a slightly increased cost. We have previously demonstrated that cost effective policies of substituting PAPP-A with PlGF in screening for trisomies, PE and SGA are also feasible.[20,34,35]

Strengths and limitations

The strengths of this study are: first, large study population with prospectively collected biomarkers; second, use of a continuous folded surface model that best describes the distribution of biomarkers; third, use of a joint model that allows estimation of patient-specific risks for any desired definition of SGA; and fourth, use of Bayes rule that allows the application of the model repeatedly during the course of pregnancy. Internal validation demonstrated that the new model is stable and better than other screening methods.[14,19] Ultimately, external validation is needed to show the applicability of our results in other populations.

Conclusion

The study has presented a single continuous two-dimensional model for prediction of SGA for any desired cut-offs in degree of smallness and gestational age at birth, laying the ground for a personalized antenatal plan for predicting and managing SGA, in the milieu of a new inverted pyramid of prenatal care.

Conflict of interest statement: The authors report no conflict of interest.

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Data availability statement: Research data are not shared

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FIGURE LEGENDS

Figure 1. Three dimensional demonstration of the folded regression plane for the UtA-PI likelihood model from two different angles.

Figure 2. Contour plots of the joint distribution of birth weight Z scores and gestational age at delivery according to maternal factors and biomarkers for a high risk and a low risk case. The shaded area corresponds to the risk of delivery before 32 weeks' gestation with SGA below the 10^{th} percentile.

Table 1. Maternal and pregnancy characteristics in the study population.

Variables	Total (n=60,875)	No-SGA (n=52,854)	SGA (n=8,021)	p value
Maternal age (years)	31 (26.6 -34.8)	31.1 (26.7-34.8)	30.3 (25.5-34.6)	<0.0001
Maternal weight (kg)	67.1 (59.4-78.2)	67.9 (60.0-79.0)	63.6 (56.0-74.0)	<0.0001
Maternal height (cm)	165 (160-169)	165 (160-169)	163 (158-167)	<0.0001
Body mass index (kg/m^2)	24.8 (22.1-28.7)	24.9 (22.2-28.9)	24.0 (21.4-27.9)	<0.0001
Gestational age (weeks)	12.7 (12.3 - 13.1)	12.7 (12.3-13.1)	12.7 (12.3-13.0)	0.1682
Racial origin				
White	44956 (73.9)	40045 (75.8)	4911 (61.2)	<0.0001
Black	10389 (17.1)	8401 (15.9)	1988 (24.8)	<0.0001
South Asian	2724 (4.5)	2044 (3.9)	680 (8.5)	<0.0001
East Asian	1254 (2.1)	1074 (2.0)	180 (2.4)	0.2286
Mixed	1552 (2.6)	1290 (2.4)	262 (3.3)	<0.0001
Conception				
Natural	58902 (96.8)	51163 (96.8)	7739 (96.5)	0.1451
Ovulation induction	493 (0.8)	420 (0.8)	73 (0.9)	0.3133
In-vitro fertilization	1480 (2.4)	1271 (2.4)	209 (2.6)	0.2938
Medical history				
Chronic hypertension	845 (1.4)	633 (1.2)	212 (2.6)	<0.0001
Diabetes mellitus	560 (0.9)	487 (0.9)	73 (0.9)	0.9713
SLE/APS	122 (0.2)	98 (0.2)	24 (0.3)	0.04665
Cigarette smokers	5768 (9.5)	4464 (8.5)	1304 (16.3)	<0.0001
Family history of preeclampsia	2393 (3.9)	2054 (3.9)	339 (4.2)	0.1527
Parity				
Nulliparous	28311 (46.5)	23790 (45.0)	4521 (56.4)	<0.0001
Parous without previous preeclampsia or SGA	5526 (9.1)	4243 (8.0)	1283 (16.0)	<0.0001
Parous with previous SGA	4666 (7.7)	3366 (6.4)	1300 (16.2)	<0.0001
Parous with previous preeclampsia and (or) SGA	6005 (9.9)	4568 (8.6)	1437 (17.9)	<0.0001
Interpregnancy interval (years)	3.0 (2.0 - 4.9)	3.0 (2.0 - 4.8)	3.3 (2.1 - 5.8)	<0.0001
Gestational age of last birth (weeks)	40 (39 - 40)	40 (39 - 40)	40 (38 - 40)	<0.0001
Preeclampsia	1736 (2.8)	1092 (2.1)	644 (8.0)	<0.0001
Pregnancy induced hypertension	1741 (2.8)	1419 (2.7)	322 (4.0)	<0.0001

Values are given as median (interquartile range) or number (%).

Comparisons between outcome groups were performed by chi-square test or Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables.

SGA = small for gestational age with birth weight <10th percentile; SLE = Systemic lupus erythematosus; APS = Antiphospholipid syndrome.

Table 2. Fitted regression model for the mean log_{10} MoM UtA-PI and mean log_{10} MoM MAP conditional to birthweight Z score and gestational age at delivery.

Term	Estimate (upper and lower credibility limits)	SD
log_{10} MoM UtA-PI		
Intercept	-0.056310714 (-0.069730 to -0.04447000)	0.0060606534
Birth weight Z score	-0.039447609 (-0.044240 to -0.03496000)	0.0023191192
GA - 40	-0.015560167 (-0.018730 to -0.01247000)	0.0016012759
(GA – 40)^2	-0.000833378 (-0.001089 to -0.00057529)	0.0001288877
SD for log_{10} MoM UtA-PI	0.1286880760 (0.128000 to 0.129400000)	0.0003767300
log_{10} MoM MAP		
Intercept	-0.000239856 (-0.0017850 to 0.00057960)	0.0006151287
Birth weight Z score	-0.001752502 (-0.0023960 to -0.00123900)	0.0002949314
GA - 40	-0.001512578 (-0.0021650 to -0.00110800)	0.0002717200
(GA – 40)^2	-0.000076992 (-0.0001372 to -0.00003548)	0.0000248370
SD for log_{10} MoM MAP	0.035903306 (0.0357000 to 0.03611000)	0.0001047405

UtA-PI =Uterine artery pulsatility index; MAP=Mean arterial pressure; GA = gestational age at delivery; SD = standard deviation.

Table 3. Correlations for the $\log_{10}$ MoM values of the examined biomarkers.

Correlation	Correlation coefficient (95% confidence interval)
UtA-PI with MAP	-0.03833283 (-0.04654932 to -0.03011115)
UtA-PI with PAPP-A	-0.1604627 (-0.1683439 to -0.1525609)
UtA-PI with PlGF	-0.1605271 (-0.1684081 to -0.1526255)
MAP with PAPP-A	-0.008953812 (-0.0170575132 to -0.0008489346)
MAP with PlGF	-0.04538137 -0.05346664 to -0.03729014)
PAPP-A with PlGF	0.3279437 (0.3208357 to 0.3350148)

UtA-PI = Uterine artery pulsatility index; MAP = Mean arterial pressure; PAPP-A = Pregnancy associated plasma protein A; PlGF = Placental growth factor

Table 4. Performance of screening based on maternal factors and combinations of biomarkers, for all cases of small for gestational age (SGA) with birthweight <10th percentile, SGA with preeclampsia and SGA without preeclampsia.

Method of screening	All SGA				SGA with preeclampsia				SGA without preeclampsia			
	AUC	False positive rate			AUC	False positive rate			AUC	False positive rate		
		5%	10%	20%		5%	10%	20%		5%	10%	20%
≥ 37 weeks												
H	0.7240	19.0	31.1	48.5	0.7512	23.0	34.8	54.7	0.7248	19.2	31.3	48.5
H+MAP	0.7614	24.7	37.0	55.1	0.7606	24.7	35.6	55.5	0.7250	19.6	31.1	48.5
H+UtA-PI	0.7304	19.8	31.8	49.9	0.7738	28.3	39.7	57.1	0.7307	19.9	31.9	50.0
H+PAPP-A	0.7377	20.7	33.3	51.0	0.7677	27.5	39.3	56.7	0.7384	20.7	33.4	51.1
H+PlGF	0.7309	19.7	32.5	50.4	0.7786	25.9	39.3	57.9	0.7311	19.8	32.8	50.5
H+MAP+UtA-PI	0.7309	19.7	31.9	49.9	0.7838	28.8	39.8	57.5	0.7311	19.8	31.8	50.1
H+MAP+PAPP-A	0.7379	20.6	33.3	51.1	0.7754	28.3	38.5	56.7	0.7385	20.8	33.5	51.2
H+MAP+PlGF	0.7312	19.9	32.5	50.0	0.7862	25.1	40.5	61.1	0.7312	20.0	32.6	50.0
H+UtA-PI+PAPP-A	0.7412	21.1	33.8	51.6	0.7831	30.8	43.3	60.3	0.7416	21.2	33.7	51.6
H+UtA-PI+PlGF	0.7352	20.4	33.2	51.2	0.7927	29.6	44.2	60.7	0.7352	20.4	33.2	51.2
H+PlGF+PAPP-A	0.7397	21.4	33.7	51.8	0.7800	28.3	41.3	60.3	0.7402	21.5	33.8	51.7
H+MAP+UtA-PI+PAPP-A	0.7417	21.1	33.9	51.7	0.7914	32.0	44.5	60.3	0.7419	21.0	34.0	51.7
H+MAP+PAPP-A+PlGF	0.7400	21.2	33.6	51.4	0.7867	29.2	41.7	60.7	0.7403	21.1	33.8	51.4
H+MAP+UtA-PI+PlGF	0.7356	20.5	33.0	51.3	0.8007	30.4	44.5	63.6	0.7354	20.4	33.0	51.3
H+UtA-PI+PAPP-A+PlGF	0.7427	21.2	34.5	51.8	0.7917	31.6	45.3	62.4	0.7429	21.2	34.3	51.9
H+MAP+UtA-PI+PAPP-A+PlGF	0.7431	21.4	34.3	52.2	0.7990	32.0	46.6	63.2	0.7432	21.3	34.2	52.2
<37 weeks												
H	0.7187	21.6	32.2	48.0	0.7122	22.3	31.4	47.5	0.7249	22.1	32.8	48.9
H+MAP	0.7295	21.9	33.5	49.4	0.7585	26.5	38.1	56.7	0.7236	21.3	32.3	47.7
H+UtA-PI	0.7512	27.0	39.8	57.4	0.8139	36.0	51.2	69.2	0.7324	24.7	36.2	53.9
H+PAPP-A	0.7576	25.2	37.9	56.0	0.7493	27.7	37.2	53.4	0.7645	25.6	39.1	57.8
H+PlGF	0.7767	29.3	41.8	60.5	0.8292	38.4	50.6	70.1	0.7618	27.1	39.3	57.3
H+MAP+UtA-PI	0.7596	28.4	41.4	58.4	0.8448	43.9	56.4	74.1	0.7332	24.2	37.0	53.7
H+MAP+PAPP-A	0.7654	26.9	39.1	57.3	0.7874	31.4	44.8	58.5	0.7620	26.2	38.4	57.8
H+MAP+PlGF	0.7809	29.2	43.1	60.6	0.8518	43.0	54.9	72.3	0.7599	25.4	39.7	57.5
H+UtA-PI+PAPP-A	0.7724	30.4	43.7	60.8	0.8233	37.8	52.1	68.3	0.7579	28.8	41.4	59.2
H+UtA-PI+PlGF	0.7832	32.2	46.6	63.0	0.8654	47.3	62.5	76.5	0.7576	28.1	41.7	58.6
H+PlGF+PAPP-A	0.7859	30.0	44.2	62.0	0.8261	39.0	50.3	68.6	0.7755	28.6	43.3	60.1
H+MAP+UtA-PI+PAPP-A	0.7794	31.7	45.4	61.4	0.8527	44.8	59.2	75.0	0.7572	28.8	42.0	57.8
H+MAP+PAPP-A+PlGF	0.7901	31.1	44.5	64.4	0.8485	43.3	54.9	73.2	0.7735	28.0	41.0	62.6
H+MAP+UtA-PI+PlGF	0.7883	33.2	47.3	63.2	0.8860	51.5	66.5	80.5	0.7574	27.7	41.6	58.4
H+UtA-PI+PAPP-A+PlGF	0.7903	33.8	48.3	63.4	0.8629	48.2	61.6	76.2	0.7680	29.6	44.6	60.2
H+MAP+UtA-PI+PAPP-A+PlGF	0.7950	35.0	48.6	65.2	0.8838	53.1	65.9	80.2	0.7674	29.6	44.4	60.1
<32 weeks												
H	0.7259	23.0	32.1	45.6	0.7398	23.0	35.3	48.0	0.7236	23.0	31.0	46.0
H+MAP	0.7449	21.9	35.4	50.4	0.7949	24.0	42.0	61.0	0.7233	21.3	31.6	44.8
H+UtA-PI	0.7852	32.1	46.7	62.8	0.8683	42.0	62.0	80.0	0.7439	29.3	40.2	54.0
H+PAPP-A	0.7520	25.6	37.2	55.1	0.7686	26.0	37.0	57.0	0.7483	27.6	37.9	55.8
H+PlGF	0.8005	37.2	49.3	63.1	0.8670	48.0	57.0	76.0	0.7690	32.2	46.0	56.3
H+MAP+UtA-PI	0.7960	35.8	48.9	66.8	0.8972	52.0	66.0	86.0	0.7455	31.0	42.0	56.3
H+MAP+PAPP-A	0.7679	25.2	38.0	58.4	0.8189	25.0	42.0	66.0	0.7458	26.4	37.4	55.2
H+MAP+PlGF	0.8068	35.0	51.1	65.7	0.8875	49.0	64.0	78.0	0.7680	28.7	44.8	59.8
H+UtA-PI+PAPP-A	0.7967	33.9	51.5	64.6	0.8715	46.0	62.0	77.0	0.7602	32.2	46.0	59.8
H+UtA-PI+PlGF	0.8190	43.1	56.2	70.4	0.9106	60.0	77.0	84.0	0.7731	35.1	46.6	62.6
H+PlGF+PAPP-A	0.8019	35.0	49.3	65.7	0.8633	48.0	58.0	74.0	0.7732	29.3	47.7	62.1

H+MAP+UtA-PI+PAPP-A	0.8075	37.6	52.9	70.5	0.9020	49.0	70.0	87.0	0.7607	31.0	46.6	61.5
H+MAP+PAPP-A+PlGF	0.8085	35.8	52.2	68.3	0.8858	48.0	63.0	80.0	0.7715	29.3	48.9	63.2
H+MAP+UtA-PI+PlGF	0.8242	44.5	59.1	71.9	0.9277	62.0	79.0	89.0	0.7723	35.6	50.0	62.1
H+UtA-PI+PAPP-A+PlGF	0.820	42.7	56.2	70.4	0.9078	60.0	74.0	85.0	0.7763	35.6	47.7	62.6
H+MAP+UtA-PI+PAPP-A+PlGF	0.8257	45.3	59.1	71.5	0.9266	63.0	78.0	90.0	0.7751	37.4	51.2	62.1

AUC = Area under the curve; H = maternal demographic characteristics and medical history; UtA-PI = Uterine artery pulsatility index; MAP = Mean arterial pressure; PAPP-A = Pregnancy associated plasma protein A; PlGF = Placental growth factor.

Table 5. Performance of screening based on maternal factors and combinations of biomarkers, for all cases of small for gestational age (SGA) with birthweight <3rd percentile, SGA with preeclampsia and SGA without preeclampsia.

Method of screening	All SGA				SGA with preeclampsia				SGA without preeclampsia			
	AUC	False positive rate			AUC	False positive rate			AUC	False positive rate		
		5%	10%	20%		5%	10%	20%		5%	10%	20%
≥ 37 weeks												
H	0.7098	17.0	28.4	46.0	0.7537	19.8	31.6	51.0	0.7107	17.2	28.5	46.0
H+MAP	0.7477	22.2	34.6	52.3	0.7637	21.3	33.8	55.2	0.7488	22.6	34.8	52.5
H+UtA-PI	0.7569	22.9	36.8	54.3	0.7901	27.9	40.4	62.5	0.757	23.0	37.3	54.5
H+PAPP-A	0.7670	24.5	38.3	55.8	0.7769	25.7	41.2	58.1	0.7682	24.9	38.2	55.9
H+PlGF	0.7598	22.7	37.0	55.6	0.7936	27.9	39.7	60.3	0.7599	23.0	37.1	55.8
H+MAP+UtA-PI	0.7572	23.1	36.6	54.5	0.7980	29.4	41.2	62.5	0.7572	23.2	36.7	54.5
H+MAP+PAPP-A	0.7670	24.4	37.9	55.8	0.7825	28.7	41.2	55.9	0.7681	24.6	38.2	56.3
H+MAP+PlGF	0.7598	22.9	36.7	55.1	0.7992	26.5	39.0	64.0	0.7598	23.1	37.1	55.4
H+UtA-PI+PAPP-A	0.7716	25.2	39.7	57.1	0.7993	32.4	44.1	61.8	0.7720	25.3	40.0	57.3
H+UtA-PI+PlGF	0.7654	24.0	37.9	56.6	0.8151	30.9	42.7	66.2	0.7648	24.1	38.2	56.4
H+PlGF+PAPP-A	0.7711	25.3	38.6	57.3	0.7958	30.9	43.4	62.5	0.7717	25.6	39.0	57.3
H+MAP+UtA-PI+PAPP-A	0.7717	25.5	39.1	57.5	0.8055	34.6	44.9	65.4	0.7720	25.3	39.5	57.5
H+MAP+PAPP-A+PlGF	0.7711	25.3	39.0	57.4	0.8003	30.9	43.4	64.0	0.7716	25.4	39.3	57.5
H+MAP+UtA-PI+PlGF	0.7655	23.8	37.8	56.7	0.8208	30.9	46.3	67.6	0.7647	23.9	38.0	56.6
H+UtA-PI+PAPP-A+PlGF	0.7746	25.9	40.3	57.8	0.8129	33.1	47.1	64.7	0.7746	26.0	40.3	57.8
H+MAP+UtA-PI+PAPP-A+PlGF	0.7747	25.7	39.9	58.3	0.8178	33.8	46.3	69.1	0.7746	25.6	40.0	58.1
<37 weeks												
H	0.7326	23.0	32.8	50.2	0.7185	22.3	32.5	47.9	0.7437	24.0	34.2	51.5
H+MAP	0.7446	23.8	36.0	52.6	0.7601	26.4	39.6	58.1	0.7423	23.6	35.1	51.3
H+UtA-PI	0.7731	30.4	43.5	61.8	0.8236	36.6	52.8	71.3	0.7531	28.4	40.0	57.8
H+PAPP-A	0.7771	28.3	42.0	60.0	0.7579	29.1	39.6	54.7	0.7908	29.2	44.4	63.2
H+PlGF	0.8029	34.3	45.8	65.0	0.8368	41.5	52.1	70.9	0.7913	32.7	43.9	62.8
H+MAP+UtA-PI	0.7829	32.5	44.6	63.0	0.8503	46.4	57.4	76.2	0.7555	27.9	39.8	57.6
H+MAP+PAPP-A	0.7869	29.4	43.0	60.9	0.7924	32.5	45.3	59.6	0.7892	28.8	42.9	62.8
H+MAP+PlGF	0.8081	34.4	48.8	65.6	0.8554	46.0	57.4	72.5	0.7905	30.1	45.5	63.0
H+UtA-PI+PAPP-A	0.7953	34.5	49.2	65.4	0.8346	37.7	54.3	70.6	0.7807	33.6	47.2	63.2
H+UtA-PI+PlGF	0.8088	38.1	52.7	67.4	0.8744	50.2	65.7	77.4	0.7819	33.6	47.8	63.4
H+PlGF+PAPP-A	0.8118	35.1	48.9	67.9	0.8346	42.3	52.5	70.6	0.8054	34.4	48.1	66.9
H+MAP+UtA-PI+PAPP-A	0.8041	36.5	51.1	66.3	0.8601	47.6	61.1	75.9	0.7820	33.5	46.8	62.6
H+MAP+PAPP-A+PlGF	0.8172	36.1	50.3	69.6	0.8535	46.4	58.5	74.0	0.8047	33.3	47.0	68.2
H+MAP+UtA-PI+PlGF	0.8152	38.0	52.9	67.6	0.8909	53.6	68.3	81.5	0.7839	32.7	46.5	62.1
H+UtA-PI+PAPP-A+PlGF	0.8158	39.7	53.8	68.7	0.8730	52.1	63.8	78.1	0.7928	35.7	50.0	64.5
H+MAP+UtA-PI+PAPP-A+PlGF	0.8220	41.1	53.2	70.1	0.8899	55.5	66.8	82.3	0.7944	35.9	48.3	64.9
<32 weeks												
H	0.7178	22.4	30.1	45.2	0.7406	25.0	35.9	48.9	0.7074	20.5	28.4	42.5
H+MAP	0.7389	21.4	34.7	51.1	0.7951	28.3	44.6	62.0	0.7059	17.3	29.1	44.1
H+UtA-PI	0.7923	34.3	47.0	65.0	0.8691	42.4	63.0	80.4	0.7437	30.0	38.6	55.1
H+PAPP-A	0.7547	26.0	36.5	55.7	0.7745	26.1	38.0	58.7	0.7466	26.0	37.0	55.1
H+PlGF	0.8194	40.6	52.1	66.7	0.8728	53.3	58.7	78.3	0.7877	32.3	48.0	59.8
H+MAP+UtA-PI	0.8042	37.9	50.2	67.1	0.8969	51.1	66.3	84.8	0.7451	29.9	41.0	56.7
H+MAP+PAPP-A	0.7721	24.2	37.4	60.7	0.8233	29.4	44.6	66.3	0.7426	24.4	34.7	56.7
H+MAP+PlGF	0.8255	39.3	54.8	69.0	0.8919	54.4	67.4	77.2	0.7852	29.9	47.2	64.6
H+UtA-PI+PAPP-A	0.8075	37.4	53.4	67.6	0.8746	45.7	64.1	79.4	0.7658	33.9	46.5	62.2
H+UtA-PI+PlGF	0.8362	48.0	61.2	74.0	0.9133	62.0	77.2	85.9	0.7872	40.2	52.8	66.1
H+PlGF+PAPP-A	0.8195	38.8	52.1	69.9	0.8707	50.0	60.9	76.1	0.7894	32.3	48.8	66.1
H+MAP+UtA-PI+PAPP-A	0.8193	38.4	55.7	72.6	0.9037	53.3	69.6	88.0	0.7660	30.7	46.5	62.2
H+MAP+PAPP-A+PlGF	0.8264	38.4	54.3	72.2	0.8917	52.2	65.2	82.6	0.7867	29.9	48.0	67.7
H+MAP+UtA-PI+PlGF	0.8420	48.9	63.9	74.0	0.9291	65.2	81.5	88.0	0.7866	38.6	53.5	64.6
H+UtA-PI+PAPP-A+PlGF	0.8376	50.2	60.7	73.5	0.9155	63.0	73.9	85.9	0.7909	44.1	52.8	65.4
H+MAP+UtA-PI+PAPP-A+PlGF	0.8439	50.7	64.4	73.5	0.9288	65.2	80.4	89.1	0.7901	43.3	55.9	63.0

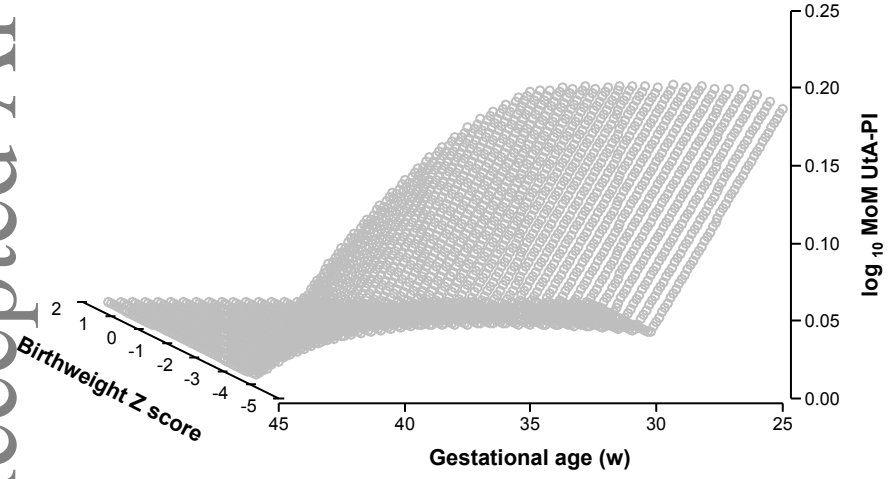
AUC = Area under the curve; H = maternal demographic characteristics and medical history; UtA-PI = Uterine artery pulsatility index; MAP = Mean arterial pressure; PAPP-A = Pregnancy associated plasma protein A; PlGF = Placental growth factor.

Table 6. Calibration study for the new model for prediction of small for gestational age neonates by maternal history, MAP, UtA-PI, PAPP-A, PlGF and their combination.

Method of screening	Birth weight <10th percentile		Birth weight <3rd percentile	
	Calibration		Calibration	
	Slope	Intercept	Slope	Intercept
Birth ≥ 37 weeks				
H	1.16262	1.01515	1.10188	0.6438
H+MAP	1.16080	1.01331	1.09808	0.6412
H+UtA-PI	1.17505	1.01964	1.10324	0.65174
H+PAPP-A	1.20020	1.02553	1.13936	0.65547
H+PlGF	1.18897	1.02097	1.13162	0.65202
H+MAP+UtA-PI	1.17372	1.01894	1.10022	0.65044
H+MAP+PAPP-A	1.19790	1.02483	1.13549	0.65411
H+MAP+PlGF	1.18737	1.02022	1.12857	0.65076
H+UtA-PI+PAPP-A	1.21003	1.02901	1.14248	0.66229
H+UtA-PI+PlGF	1.19685	1.02473	1.13015	0.65854
H+PlGF+PAPP-A	1.20879	1.02775	1.15010	0.65877
H+MAP+UtA-PI+PAPP-A	1.20842	1.02840	1.13901	0.66117
H+MAP+PAPP-A+PlGF	1.20685	1.02707	1.14659	0.65756
H+MAP+UtA-PI+PlGF	1.19560	1.02403	1.12740	0.65740
H+UtA-PI+PAPP-A+PlGF	1.21700	1.03068	1.15208	0.66465
H+MAP+UtA-PI+PAPP-A+PlGF	1.21550	1.03000	1.14890	0.66356
Birth <37 weeks				
H	0.87953	0.09038	0.85030	0.17426
H+MAP	0.87726	0.07617	0.85801	0.15806
H+UtA-PI	0.85761	0.10562	0.83568	0.19937
H+PAPP-A	0.90880	0.08943	0.88230	0.17183
H+PlGF	0.90756	0.07428	0.89973	0.15005
H+MAP+UtA-PI	0.86437	0.09543	0.84897	0.18811
H+MAP+PAPP-A	0.90828	0.07818	0.88901	0.15883
H+MAP+PlGF	0.90859	0.03004	0.90542	0.13997
H+UtA-PI+PAPP-A	0.89513	0.11056	0.87425	0.20543
H+UtA-PI+PlGF	0.88719	0.08986	0.87738	0.17542
H+PlGF+PAPP-A	0.92097	0.07730	0.91046	0.15380
H+MAP+UtA-PI+PAPP-A	0.89902	0.10079	0.88438	0.19465
H+MAP+PAPP-A+PlGF	0.92129	0.06812	0.91546	0.14354
H+MAP+UtA-PI+PlGF	0.89039	0.08166	0.88494	0.16671
H+UtA-PI+PAPP-A+PlGF	0.90247	0.09484	0.89156	0.18224
H+MAP+UtA-PI+PAPP-A+PlGF	0.90532	0.08670	0.89896	0.17360
Birth <32 weeks				
H	0.76633	0.13880	0.71452	0.31526
H+MAP	0.77097	0.11914	0.72279	0.29366
H+UtA-PI	0.83877	0.15920	0.79774	0.34706
H+PAPP-A	0.78332	0.13722	0.74273	0.31300
H+PlGF	0.87270	0.10768	0.86693	0.27420
H+MAP+UtA-PI	0.84570	0.14645	0.80578	0.33341
H+MAP+PAPP-A	0.78942	0.12259	0.75005	0.29670
H+MAP+PlGF	0.87363	0.09638	0.86741	0.26209
H+UtA-PI+PAPP-A	0.84890	0.1659	0.81287	0.35562
H+UtA-PI+PlGF	0.89741	0.13218	0.88417	0.31058

H+PlGF+PAPP-A	0.86658	0.11354	0.85786	0.28189
H+MAP+UtA-PI+PAPP-A	0.85483	0.15346	0.81966	0.34236
H+MAP+PAPP-A+PlGF	0.86746	0.10207	0.85834	0.26955
H+MAP+UtA-PI+PlGF	0.89909	0.12214	0.88536	0.30022
H+UtA-PI+PAPP-A+PlGF	0.89494	0.13805	0.88093	0.31867
H+MAP+UtA-PI+PAPP-A+PlGF	0.89683	0.12800	0.88243	0.30831

H = maternal demographic characteristics and medical history; UtA-PI = Uterine artery pulsatility index; MAP = Mean arterial pressure; PAPP-A = Pregnancy associated plasma protein A; PlGF = Placental growth factor.



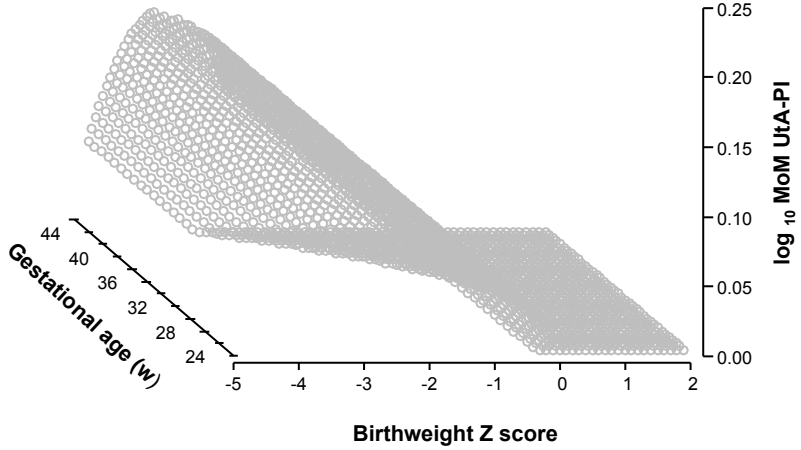


Figure 1

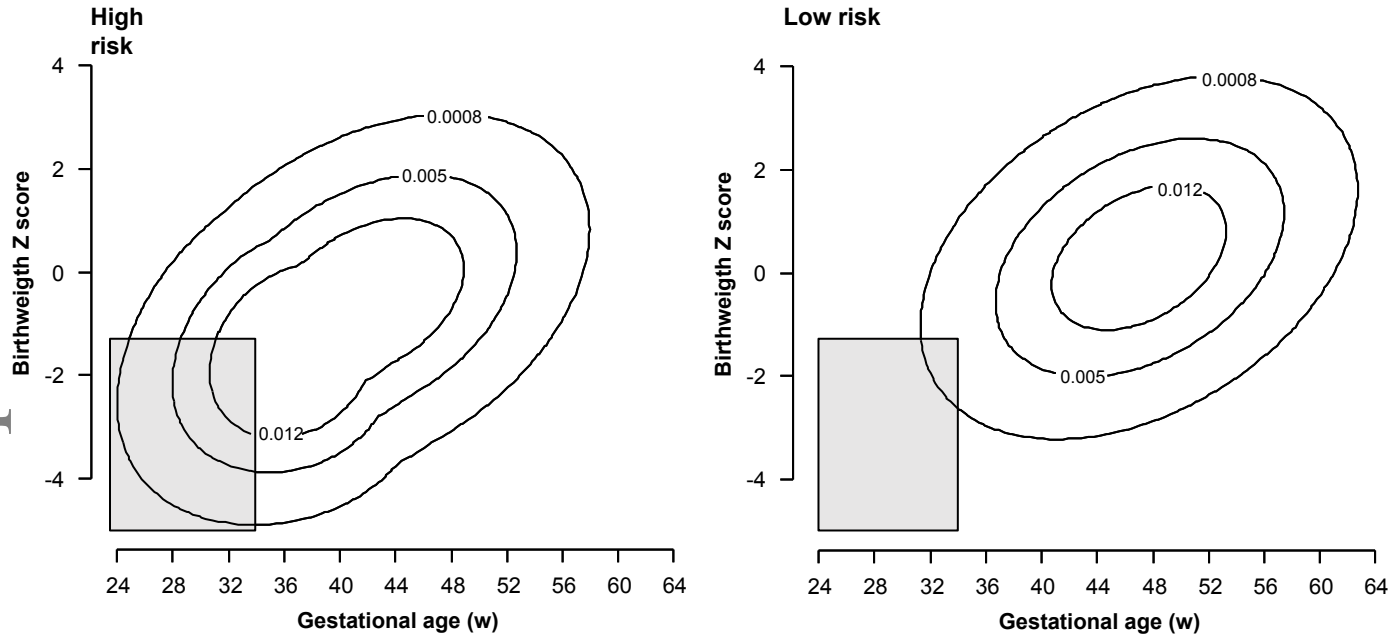


Figure 2