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Competing-risks model for prediction of small-for-gestational-age neonates from estimated fetal weight at 19–24 weeks' gestation

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CONTRIBUTION

What are the novel findings of this work?

The study expands a new competing risk model for the prediction of small for gestational age (SGA) neonates using maternal demographic characteristics and medical history and second trimester fetal biometry. 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. Estimated fetal weight (EFW) was expressed conditionally to GA and Z. The association between EFW and birth weight was steeper for earlier gestations. The prediction of SGA was better for increasing degree of prematurity and higher severity of smallness.

What are the clinical implications of this work?

A competing risks model using maternal demographic characteristics and medical history and second trimester fetal biometry provides effective risk stratification for SGA neonates.

ABSTRACT

Objectives: To develop further a new competing risks model for the prediction of small for gestational age (SGA) neonates, by including second trimester ultrasonographic estimated fetal weight (EFW).

Methods: This is a prospective observational study in 96,678 women with singleton pregnancies undergoing routine ultrasound examination at 19 - 24 weeks' gestation. All pregnancies had ultrasound biometry assessment and EFW was calculated according to the Hadlock formula. We refitted in this large dataset a previously described 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, to obtain the prior distribution. The continuous likelihood of the EFW was fitted conditionally to GA and Z and modified the prior distribution, according to Bayes theorem, to obtain individualized distribution for GA and Z and therefore patient specific risks for any cut-offs for Z and GA. We assessed the discrimination ability of the model for predicting SGA with, without or independently of preeclampsia (PE) occurrence. A calibration study was carried out. Performance of screening was evaluated for SGA defined according to the Fetal Medicine Foundation (FMF) birth weight charts.

Results: The distribution of EFW, conditional to both GA and Z, was best described by a regression model. For earlier gestations the association between EFW and birth weight was steeper. The prediction of SGA by maternal factors and EFW improved for increasing degree of prematurity and higher severity of smallness but not for co-existence of PE. Screening by maternal factors predicted 31%, 34% and 39% of SGA neonates with birth weight <10th percentile delivered at ≥37, <37 and <30 weeks' gestation, at 10% false positive rate, and after addition of EFW these rates increased to 38%, 43% and 59%, respectively; the respective rates for birth weight <3rd percentile were 43%, 50% and 64%. The addition of EFW improved the calibration of the model.

Conclusion: In the competing risks model for prediction of SGA the performance of screening by maternal characteristics and medical history is improved by the addition of second trimester EFW.

INTRODUCTION

The antenatal identification of small for gestational age (SGA) fetuses / neonates reduces the incidence of stillbirth and neonatal morbidities, in these high risk pregnancies.[1] Abdominal palpation and measurement of symphysis–fundal height are the traditional but ineffective methods to prenatally identify SGA fetuses.[2,3] There is good evidence that a third trimester scan is substantially better than the traditional methods and ultrasonography at around 36 weeks' gestation identifies most pregnancies resulting in the birth of SGA neonates.[4,5] However, many SGA-related stillbirths occur before 36 weeks and an ultrasound scan at mid-gestation can help identify the pregnancies at increased risk of preterm stillbirth and in need of additional scans before 36 weeks' gestation.[6-10]

We have recently proposed a new competing risks model for the prediction of SGA.[11-14] This new approach is based on the concept that SGA is a two dimensional spectrum disorder whose severity is continuously reflected in both the gestational age at delivery and z-score in birth weight for gestational age. The first step was a history model that defined a patient-specific joint distribution of z scores of birth weight (Z) and gestational age at delivery (GA).[11] The second step was the addition of the first trimester biomarkers' multivariate likelihood according to Bayes theorem.[12-14] The model enable us to compute risks for any chosen cut-off. We have demonstrated through a process of internal validation that the new model is superior to logistic regression models and to the scoring system proposed by the RCOG. [11,12,15]

The objective of this study was to develop further the new competing risks model for the prediction of SGA neonates, by including second trimester ultrasonographic estimated fetal weight (EFW).

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 at 19 + 0 to 24 + 6 weeks' gestation at King's College Hospital and Medway Maritime Hospital, UK, between 2011 and 2020. We recorded maternal characteristics and medical history and performed ultrasound examinations for measurement of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL).[16] Gestational age was determined from measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks.[16,17] The ultrasound examinations were carried out by sonographers who had received the Certificate of Competence in second trimester anomaly scan of The Fetal Medicine Foundation (http://www.fetalmedicine.com). Participants gave written informed consent to take part in the study, which was approved by the NHS Research Ethics Committee. The inclusion criteria were women with a singleton pregnancy who delivered a phenotypically normal live birth or stillbirth ≥ 24 weeks' gestation. Pregnancies with aneuploidy, major fetal abnormality, and those ending in a miscarriage, termination of pregnancy or stillbirth due to intrapartum causes were excluded.

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).[18] 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).[18] The Fetal Medicine Foundation fetal and neonatal population weight charts were used to convert birth weight and EFW to percentiles and Z scores.[19]

Statistical analyses

We updated the history model by fitting it in a population of 96,678 singleton pregnancies. The methodology is described in detail in a previous study.[11] We developed a likelihood for EFW by fitting a regression model conditional to Z and GA, with an interaction term. This model assumes that the coefficient for Z is a function of GA. The *prior* joint distribution of Z and GA according to the history model was combined with the EFW likelihood to obtain a pregnancy specific *posterior* distribution that was used to compute risks for different cut-offs. We found significant gestational age dependent effects of some maternal factors on EFW, however these effects were less than 0.1 standard deviations; therefore, we assumed independency between EFW and maternal factors.

We assessed the discrimination 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, were also obtained.

Model fitting was carried out within a Bayesian framework using Markov chain Monte Carlo (MCMC).[20] The statistical software package R was used for data analyses.[21]

RESULTS

Maternal and pregnancy characteristics

The maternal and pregnancy characteristics of the study population that included 96,678 singleton pregnancies 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. All elements of maternal characteristics and medical history are as self-reported by the patients.

For SGA defined by the FMF charts,[19] the birth weight was <10th and <3rd percentiles in 390 (42.0%) and 315 (34.0%), respectively, of the 928 pregnancies delivering at <32 weeks' gestation, in 1971 (31.9%) and 1283 (20.8%) of the 6,172 pregnancies delivering at <37 weeks and in 10052 (11.1%) and 3755 (4.2%) of the 90506 pregnancies delivering at ≥37 weeks.

Competing risks approach

We refitted our previously reported history model[11] in the larger dataset of the current study. The inferences for the parameters that define the joint prior distribution of Z and GA are presented in Table 2. The distribution of EFW expressed in Z scores was expressed in relation to Z and GA by fitting a regression model with an interaction term between Z and GA. 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 1). The inferences for the parameters of the EFW likelihood model are presented in Table 3. A three dimensional representation of the likelihood's structure is depicted in Figure 2. The linear relation between EFW and birth weight is evident beyond the predicted mean of zero Z EFW; a large fetus at 19 to 24 weeks predicts a large fetus at delivery. The crucial feature is that this association is more abrupt for lower gestational age and this trend is captured by the interaction model. The EFW likelihood updates the prior distribution of Z and GA. In the high risk cases the joint distribution is shifted towards earlier gestational ages and lower birth weights resulting in a higher risk for SGA, as we have previously demonstrated.[11-14]

Model evaluation

The discrimination of the model improved by the addition of EFW. The DRs for several cut-offs independently with or without PE at fixed FPRs are presented in Table 4. The prediction of SGA improved almost linearly for increasing degree of prematurity and higher severity of smallness (Table 4). Screening by maternal factors predicted 31%, 34% and 39% of SGA neonates with birth weight <10th percentile delivered at ≥37, <37 and <30 weeks' gestation, at 10% false positive rate, and after addition of EFW these rates increased to 38%, 43% and 59%, respectively; the respective rates for birth weight <3rd percentile were 43%, 50% and 64%.

The new model was well calibrated and the addition of EFW improved the calibration indices (Table 5).

DISCUSSION

Main findings

In the competing risks model for prediction of SGA the performance of screening by maternal characteristics and medical history is improved by the addition of second trimester EFW. The study provides further evidence that SGA is a spectrum disorder.[11-14] The Z score of EFW has a continuous association with Z score of birth weight and gestational age at delivery; EFW and birth weight are linearly correlated and this association becomes steeper for earlier gestational ages. The prediction of SGA was better for increasing degrees of prematurity (<30 vs. <37 weeks) and for higher severity of smallness (<3rd vs. <10th percentiles).

The role of birth weight population charts

An important determinant of performance, in addition to the method of screening, is the birth weight chart used for defining SGA neonates. Historically birth weight standards, such as the one be Poon *et al* [23] and that of Intergrowth 21,[23] were developed in datasets with neonates delivered from 24 weeks onwards. This seemingly reasonable study design has a major hidden bias, because many of the preterm births arise from pathological pregnancies and their inclusion in the construction of reference ranges would inevitably lead to underdiagnosis of SGA neonates, especially those that are born preterm. This issue has been overcome in the construction of the FMF fetal and neonatal population weight charts in which the reference population was all babies at a given gestational age including those still *in utero*.[19] In the FMF charts the median birth weight for a given gestational age is the same as the median EFW; data on EFW from routine scans at early gestations were combined with birth weight at term to produce reference charts for birth weight for gestational ages from 20 to 42 weeks. Figure 3 illustrates the 10th percentile of the FMF and Intergrowth 21 charts.[19,23] There is a marked deviation between the two charts, especially for preterm cases, and babies classified as being on the 10th percentile at gestational ages <37 weeks according to Intergrowth 21 charts are well below the 1st percentile of the FMF chart. Consequently, in the comparison of performance of screening between different methods of predicting SGA care should be taken that the outcome measure is the same.

Implications for clinical practice

A routine ultrasound scan at 36 weeks' gestation is effective for the identification of term SGA but it will miss more than half of the stillbirth cases due to impaired placentation, because they occur before 36 weeks.[4-6] Therefore, a prediction model applied at 19-24 weeks is fundamentally important in selecting pregnancies that will benefit from monitoring before 36 weeks. In most developed countries a mid-trimester anomaly scan with fetal biometry is offered routinely, therefore additional resources are not required. The prediction is marginally better for SGA without PE, and it is therefore anticipated that the addition of biomarkers, such as uterine artery Doppler, mean arterial pressure and serum placental growth factor, will improve further the overall prediction by picking up the PE related component of SGA.

In screening for SGA it is important to tie stillbirth and morbidity rates with SGA cut-offs. There is evidence that adverse outcomes in small neonates are a function of both birth weight deviation and gestational age at birth.[24-31] The smaller the birth weight and the earlier the delivery occurs the higher the risk for stillbirth and morbidities. A single continuous competing risks model provides the capability of examining any desired cut-off and link it with important outcomes. Moreover the new model is ideal for clinically implementing such a rationale by giving risks for any clinically relevant cut-offs. This applies to both population screening and the follow up of high risk cases.

The competing risks model builds a new rationale where SGA is a continuum and challenges the concept of the existence of early and late SGA phenotypes if they present before or after the arbitrary gestational age of 32 weeks.[32]

Strengths and limitations

The strengths of the study are: first, large sample size with prospectively collected data; second, use of a continuous likelihood that best describes the distribution of EFW; third, use of a joint probability model that allows estimation of patient-specific risks for any desired definition of SGA; fourth, use of Bayes rule that allows the application of a single updateable model throughout pregnancy. Internal validation has demonstrated that the new model is stable and better than other screening methods.[11,12] Generalization of our method in other populations requires external validation.

Conclusion

The new competing risks model for SGA prediction has important conceptual and practical ramifications; it proves that SGA is a spectrum disorder and expands the precision medicine paradigm for SGA. This study designates the need to shift from the artificial concept of early and late growth restriction to a unified approach. Use of appropriate reference ranges for diagnosis of SGA, an effective unified screening modality and the investigation of new biomarkers are the three pillars that will expand the path for SGA prediction and management.

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

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Data availability statement: Research data are not shared

REFERENCES

1. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational-age fetuses significantly improve their outcome? *Ultrasound Obstet Gynecol* 2005; **25:** 258–264.

2. Bais JMJ, Eskes M, Pel M, Bonsel GJ, Bleker OP. Effectiveness of detection of intrauterine retardation by abdominal palpation as screening test in a low-risk population: an observational study. *Eur J Obstet Gynecol Reprod Biol* 2004; **116:** 164-169.

3. Lindhard A, Nielsen PV, Mouritsen LA, Zachariassen A, Sørensen HU, Rosenø H. The implications of introducing the symphyseal-fundal height measurement. A prospective randomized controlled trial. *Br J Obstet Gynaecol* 1990; **97:** 675–680.

4. Ciobanu A, Khan N, Syngelaki A, Akolekar R, Nicolaides KH. Routine ultrasound at 32 vs 36 weeks' gestation: prediction of small-for-gestational-age neonates. *Ultrasound Obstet Gynecol* 2019; **53:** 761–768.

5. Souka AP, Papastefanou I, Pilalis A, Michalitsi V, Panagopoulos P, Kassanos D. Performance of the ultrasound examination in the early and late third trimester for the prediction of birth weight deviations. *Prenat Diagn* 2013; **33:** 915-920.

6. Akolekar R, Tokunaka M, Ortega N, Syngelaki A, Nicolaides KH. Prediction of stillbirth from maternal factors, fetal biometry and uterine artery Doppler at 19-24 weeks. *Ultrasound Obstet Gynecol* 2016; **48**: 624-630.

7. Lesmes C, Gallo DM, Panaiotova J, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by fetal biometry at 19-24 weeks. *Ultrasound Obstet Gynecol* 2015; **46:**198-207.

8. Papastefanou I, Pilalis A, Chrelias C, Kassanos D, Souka AP. Screening for birth weight deviations by second and third trimester ultrasound scan. *Prenat Diagn* 2014; **34**: 759-764.

9. Ciobanu A, Rouvali A, Syngelaki A, Akolekar R, Nicolaides KH. Prediction of small for gestational age neonates: screening by maternal factors, fetal biometry, and biomarkers at 35-37 weeks' gestation. *Am J Obstet Gynecol* 2019; **220:** 486.e1-486.e11.

10. Bakalis S, Silva M, Akolekar R, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by fetal biometry at 30-34 weeks. *Ultrasound Obstet Gynecol* 2015; **45:** 551-558.

11. Papastefanou I, Wright D, Nicolaides KH. Competing risks model for prediction of small for gestational age neonates from maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2020; **56**:196-205

12. Papastefanou I, Wright D, Syngelaki A, Lolos M, Anampousi K, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonates from maternal characteristics and serum pregnancy-associated plasma protein-A at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol.* 2020; **56**: 541-548.

13. Papastefanou I, Wright D, Lolos M, Anampousi K, Mamalis M, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonates from maternal characteristics, serum PAPP-A and PlGF at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol* 2020. doi: 10.1002/uog.23118.

14. Papastefanou I, Wright D, Syngelaki A, Souretis K, Chrysanthopoulou E, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonates from biophysical and biochemical markers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol* 2020. doi: 10.1002/uog.23523.

15. Royal College of Obstetricians and Gynaecologists. The Investigation and Management of the Small–for–Gestational–Age Fetus. Green-top guideline No. 31. RCOG January 2014.

16. Snijders RJ, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34–48.

17. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *Br J Obstet Gynaecol* 1975; **82**: 702–710.

18. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol* 2019; **133**: e1-e25

19. Nicolaides KH, Wright D, Syngelaki A, Wright A, Akolekar R. Fetal Medicine Foundation fetal and neonatal population weight charts. *Ultrasound Obstet Gynecol* 2018; **52**: 44-51.

20. Gilks WR, Thomas A, Spiegelhalter DJ. A language and program for complex Bayesian modelling. *The Statistician* 1994; **43**: 169-177.

21. R Development Core Team. R: a language and environment for statistical computing: R Foundation for Statistical Computing, Vienna, Austria. Available at: https://www.r-project.org/.

22. Poon LCY, Volpe N, Muto B, Syngelaki A, Nicolaides KH: Birthweight with gestation and maternal characteristics in live births and stillbirths. *Fetal Diagn Ther* 2012; **32**: 156-165.

23. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, Lambert A, Papageorghiou AT, Carvalho M, Jaffer YA, Gravett MG, Purwar M, Frederick IO, Noble AJ, Pang R, Barros FC, Chumlea C, Bhutta ZA, Kennedy SH. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet 2014; 384: 857-868.

24. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. *N Engl J Med* 1999; **340**: 1234-1238.

25. Boulet SL, Alexander GR, Salihu HM, Kirby RS, Carlo WA. Fetal growth risk curves: defining levels of fetal growth restriction by neonatal death risk. *Am J Obstet Gynecol* 2006; **195**: 1571–1577.

26. Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. *Am J Obstet Gynecol* 2012; **207**: 318-416.

27. McIntyre S, Blair E, Badawi N, Keogh J, Nelson KB. Antecedents of cerebral palsy and perinatal death in term and late preterm singletons. *Obstet Gynecol* 2013; **122**: 869-877.

28. Trudell AS, Cahill AG, Tuuli MG, Macones GA, Odibo AO. Risk of stillbirth after 37 weeks in pregnancies complicated by small-for-gestational-age fetuses. *Am J Obstet Gynecol* 2013; **208**: 376.e1-7.

29. Moraitis AA, Wood AM, Fleming M, Smith GC. Birth weight percentile and the risk of term perinatal death. *Obstet Gynecol* 2014; **124**: 274-283.

30. Iliodromiti S, Mackay DF, Smith GC, Pell JP, Sattar N, Lawlor DA, Nelson SM. Customised and non customised birth weight centiles and prediction of stillbirth and infant mortality and morbidity: A cohort study of 979,912 term singleton pregnancies in Scotland. *PLoS Med* 2017; **14**: e1002228.

31. Ciobanou A, Jabak S, De Castro H, Frei L, Akolekar R, Nicolaides KH. Biomarkers of impaired placentation at 35-37 weeks' gestation in the prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol* 2019; **54**: 79-86.

32. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol* 2016; **48:** 333-339.

FIGURE LEGENDS

Figure 1. Association between estimated fetal weight Z scores and birth weight Z scores at 28 (solid line), 35 (dashed line) and 42 (dotted line) gestational weeks.

Figure 2. Three dimensional demonstration of the regression plane for the estimated fetal weight Z scores likelihood, conditionally to birth weight Z scores and gestational age at delivery.

Figure 3. Fetal Medicine Foundation (FMF) birth weight charts showing the median 10^{th} and 90^{th} percentiles (solid curves) and the 10^{th} percentile of the Intergrowth 21 chart (interrupted curve).

Table 1. Maternal and pregnancy characteristics in the study population. Descriptive measures are reported within each group.

Variables	Total (n=96,678)	Non-SGA (n=84,655)	SGA (n=12,023)	p value
Maternal age (years)	31.4 (27.1-35.1)	31.5 (27.2-35.2)	30.8 (25.15-34.9)	<0.0001
Maternal weight (kg)	67.6 (59.7-79.0)	68.0 (60.0-79.5)	63.8 (56.0-74.0)	<0.0001
Maternal height (cm)	165 (160-169)	165 (161-169.7)	163.0 (158-167)	<0.0001
Body mass index (kg/m^2)	24.8 (22.1-28.8)	24.9 (22.2-29.0)	24.0 (21.3-27.9)	<0.0001
GA at assessment (weeks)	21.7 (21.1-22.1)	21.7 (21.1-22.1)	21.7 (21.1-22.1)	0.1308
Racial origin				
White	71349 (73.8)	63885 (75.5)	7464 (62.1)	<0.0001
Black	15972 (16.5)	13196 (15.6)	2776 (23.1)	<0.0001
South Asian	4672 (4.8)	3583 (4.2)	1089 (9.1)	<0.0001
East Asian	1965 (2.0)	1689 (2.0)	276 (2.3)	0.0315
Mixed	2720 (2.8)	2302 (2.7)	418 (3.5)	<0.0001
Conception				
Natural	93123 (96.3)	81578 (96.4)	11545 (96.0)	0.0668
Ovulation induction	637 (0.7)	548 (0.7)	89 (0.7)	0.2635
In-vitro fertilization	2918 (3.0)	2529 (3.0)	389 (3.2)	0.1445
Medical history				
Chronic hypertension	1188 (1.2)	897 (1.1)	291 (2.4)	<0.0001
Diabetes mellitus	1116 (1.2)	972 (1.2)	144 (1.2)	0.6672
SLE/APS	228 (0.2)	182 (0.2)	46 (0.4)	0.00057
Cigarette smokers	8323 (8.6)	6497 (7.7)	1826 (15.2)	<0.0001
Family history of preeclampsia	3725 (3.9)	3220 (3.8)	505 (4.2)	0.0367
Parity				
Nulliparous	44243 (45.8)	37595 (44.4)	6648 (55.3)	<0.0001
Parous with previous SGA	7119 (7.4)	5137 (6.1)	1982 (16.5)	<0.0001
Parous with previous preeclampsia and (or) SGA	9076 (9.4)	6899 (8.2)	2177 (18.1)	<0.0001
Inter-pregnancy interval (years)	2.9 (1.8 - 4.7)	2.9 (1.8 - 4.6)	3.2 (2.0 - 5.5)	<0.0001
GA of last birth (weeks)	40 (39 - 40)	40 (39 - 40)	40 (38 - 40)	<0.0001
Preeclampsia	2866 (2.9)	1988 (2.4)	878 (7.3)	<0.0001
Gestational hypertension	2641 (2.7)	2126 (2.5)	515 (4.3)	<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.

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

Table 2. Model for the joint distribution of birth weight Z score (Z) and gestational age (GA) at delivery according to maternal factors and medical history. Estimates of posterior means with 95% credibility limits and standard deviation.

	Estimates (95% credibility limits)	**Standard deviation**
Birth weight Z		
Intercept	0.444662 (0.404997 to 0.482800)	0.0198324
Black	-0.524625 (-0.56310 to -0.486797)	0.0193620
South Asian	-0.482211 (-0.53890to -0.426000)	0.0289344
Mixed	-0.280160 (-0.35891 to -0.199497)	0.0407331
Height (cm) -165	0.026730 (0.024430 to 0.029010)	0.0011768
Weight (kg) - 69	0.012648 (0.011449 to 0.013920)	0.0006290
(Weight (kg) - 69)^2	-0.000189 (-0.00022 to -0.000155)	0.0000166
In vitro fertilization	-0.098920 (-0.181002 to -0.019259)	0.0417037
Smoker	-0.693680 (-0.738802 to -0.64980)	0.0226538
Chronic hypertension	-0.706842 (-0.81700 to -0.597397)	0.0559370
SLE/APS	-0.443860 (-0.687707 to -0.19620)	0.1270514
Multiparous	0.138451 (0.049818 to 0.243202)	0.0495576
Last GA (weeks)- 40	0.068527 (0.060040 to 0.077340)	0.0043285
Previous BW Z	0.344370 (0.327300 to 0.361400)	0.0086454
Interval (years) $^{-1}$	-0.380348 (-0.47720 to -0.263297)	0.0545169
Interval (years) $^{-0.5}$	1.004172 (0.760094 to 1.202000)	0.1117701
SD for Z	1.399757 (1.378000 to 1.422000)	0.0112191
GA at delivery		
Intercept	45.490642 (45.2500 to 45.7500)	0.1296534
Mean birth weight (Z)	1.499151 (1.416710 to 1.582867)	0.0424478
Weight (kg) - 69	-0.024432 (-0.02943 to -0.019530)	0.0025118
In vitro fertilization	-1.214127 (-1.59700 to -0.819672)	0.2005893
Chronic hypertension	-0.989338 (-1.52103 to -0.439545)	0.2745230
Diabetes Mellitus	-3.964919 (-4.41400 to -3.515975)	0.2296087
Previous preeclampsia	-1.157569 (-1.52000 to -0.782300)	0.1903221
Previous stillbirth	-1.474475 (-2.12703 to -0.798980)	0.3388455
Multiparous	0.551989 (0.386397 to 0.727900)	0.0864940
Last GA (weeks)-40	0.865976 (0.789000 to 0.939800)	0.0384931
(Last GA (weeks)- 40)^2	0.041513 (0.034850 to 0.047960)	0.0033572
SD for GA	5.730152 (5.599000 to 5.868000)	0.0680466
Correlation	0.366211	

GA, gestational age; SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome.

Table 3. Fitted regression model for the mean estimated fetal weight Z score conditional to birth weight Z score and gestational age at delivery.

Term	Estimate (upper and lower credibility limits)	SD
EFW Z score		
Intercept	0.000582608 (-0.005139075 to 0.006283125)	0.0029054386
BW Z score	0.275778696 (0.270200000 to 0.281500000)	0.0028908233
(GA – 40)* BW Z score	-0.014074987 (-0.015780000 to -0.012380000)	0.0008691561
SD for EFW Z score	0.894125012 (0.890100000 to 0.898100000)	0.0020542869

EFW, Estimated fetal weight; BW, Birth weight; GA, gestational age at delivery; SD, standard deviation.

Table 4. Performance of screening based on maternal factors and estimated fetal weight Z score at 19 to 24 weeks. Detection rates are given for all SGA with birth weight <10th and <3rd percentile, SGA with preeclampsia and SGA without preeclampsia.

Outcome measure	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												
History												
<10th percentile	0.7230	18.9	30.8	48.4	0.7213	18.8	27.8	46.1	0.7248	19.1	31.2	48.8
<3rd percentile	0.7469	22.1	35.0	53.0	0.7318	17.8	28.4	49.0	0.7493	22.5	35.8	53.5
History + EFW												
<10th percentile	0.7658	24.8	37.9	56.2	0.7367	20.4	31.8	51.3	0.7675	25.2	38.3	56.5
<3rd percentile	0.7904	28.4	43.0	61.9	0.7599	21.2	34.1	55.8	0.7925	28.8	43.6	62.3
<37 weeks												
History												
<10th percentile	0.7260	21.6	33.5	49.8	0.7212	22.5	32.8	48.1	0.7311	21.9	34.7	51.3
<3rd percentile	0.7302	22.5	34.9	51.4	0.7242	23.5	32.4	48.9	0.7363	22.6	36.5	52.9
History + EFW												
<10th percentile	0.7814	30.0	43.2	60.4	0.7745	30.4	41.8	58.6	0.7849	30.0	43.8	61.2
<3rd percentile	0.8088	35.4	49.7	65.6	0.7963	34.4	46.1	62.3	0.8148	36.2	51.1	67.2
<34 weeks												
History												
<10th percentile	0.7330	24.5	36.7	51.2	0.7406	26.6	39.0	49.5	0.7341	25.2	36.7	52.4
<3rd percentile	0.7314	24.4	36.6	51.4	0.7473	24.0	38.5	51.6	0.7266	25.0	35.8	51.9
History + EFW												
<10th percentile	0.8137	39.7	50.5	67.2	0.8166	40.4	50.5	68.4	0.8144	39.4	51.1	67.5
<3rd percentile	0.8301	44.5	56.1	70.5	0.8300	44.3	53.1	70.8	0.8319	44.9	58.2	70.6
<32 weeks												
History												
<10th percentile	0.7257	24.4	33.9	49.2	0.7342	23.7	30.5	48.3	0.7272	25.7	36.4	50.7
<3rd percentile	0.7234	23.8	34.0	49.5	0.7376	21.6	34.2	48.7	0.7210	25.0	35.3	51.0
History + EFW												
<10th percentile	0.8271	45.4	54.1	70.3	0.8433	46.6	55.1	72.0	0.8224	44.9	54.4	69.5
<3rd percentile	0.8444	51.1	61.0	74.6	0.8567	51.4	58.6	74.8	0.8397	52.5	62.3	74.5
<30 weeks												
History												
<10th percentile	0.7498	30.6	38.9	53.2	0.7374	30.9	38.2	48.5	0.7607	31.1	39.9	55.4
<3rd percentile	0.7426	28.9	38.3	52.8	0.7390	30.8	38.5	49.2	0.7501	31.3	40.0	54.8
History + EFW												
<10th percentile	0.8453	50.9	58.8	73.2	0.8639	55.9	61.8	76.5	0.8391	48.7	58.8	72.3
<3rd percentile	0.8518	57.8	64.4	77.8	0.8726	60.0	63.1	80.0	0.8420	57.4	65.2	77.4

SGA, small for gestational age neonates

Table 5. Calibration study for the new model for prediction of small for gestational age neonates by maternal history and estimated fetal weight Z score at 19 to 24 weeks.

Method of screening	Birth weight <10th percentile		Birth weight <3rd percentile	
	Calibration		Calibration	
	Slope	Intercept	Slope	Intercept
Birth ≥ 37 weeks				
History	1.16997	0.87155	1.12526	0.50600
History + EFW	1.10348	0.86096	1.04446	0.47672
Birth <37 weeks				
History	0.94378	-0.03058	0.86656	0.05935
History + EFW	0.88700	-0.08987	0.86043	-0.01187
Birth <34 weeks				
History	0.90321	-0.21577	0.83262	-0.02981
History + EFW	0.95522	-0.29644	0.87943	-0.13602
Birth <32 weeks				
History	0.80859	-0.02402	0.74903	0.18538
History + EFW	0.91025	-0.13488	0.86780	0.05250
Birth <30 weeks				
History	0.83296	0.23019	0.77084	0.43194
History + EFW	0.86824	0.07503	0.81856	0.24349

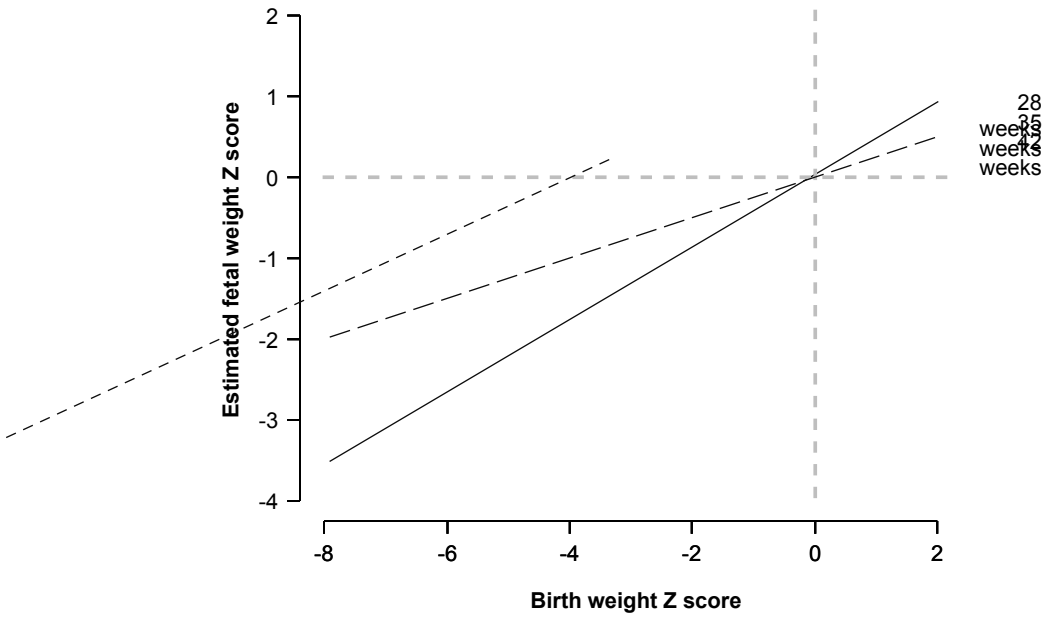

Figure 1

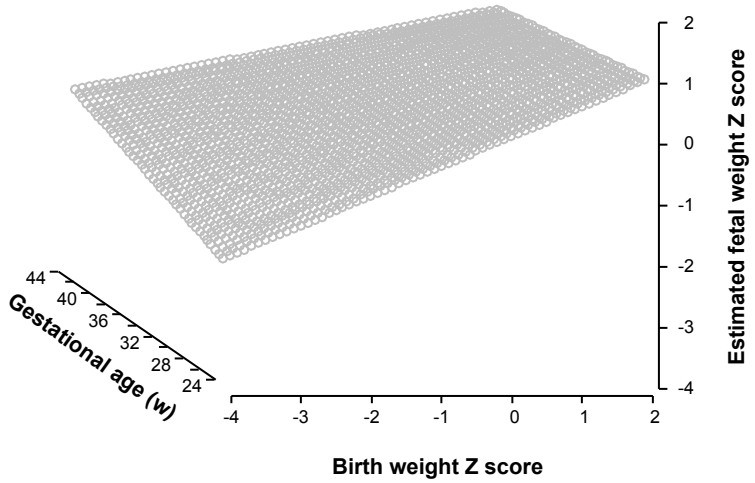

Figure 2

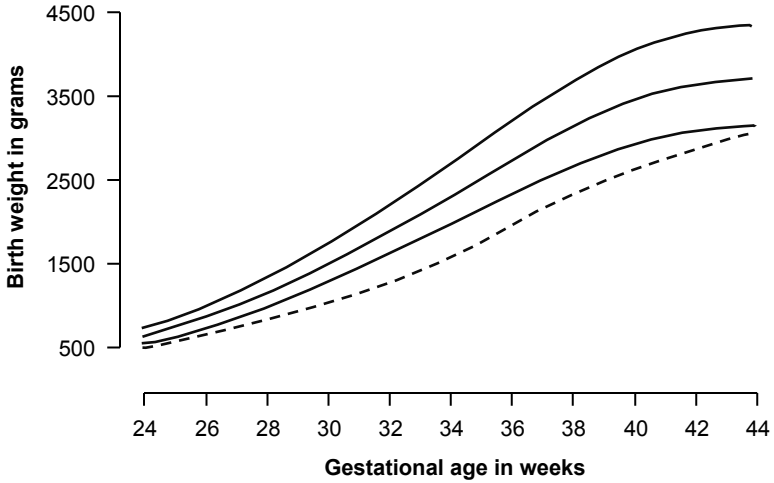

Figure 3