OBSTETRICS

# Personalized stratification of pregnancy care for small for gestational age neonates from biophysical markers at midgestation

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**BACKGROUND:** Antenatal identification of pregnancies at high risk of delivering small for gestational age neonates may improve the management of the condition and reduce the associated adverse perinatal outcomes. In a series of publications, we have developed a new competing-risks model for small for gestational age prediction, and we demonstrated that the new approach has a superior performance to that of the traditional methods. The next step in shaping the appropriate management of small for gestational age is the timely assessment of these high-risk pregnancies according to an antenatal stratification plan.

**OBJECTIVE:** This study aimed to demonstrate the stratification of pregnancy care based on individual patient risk derived from the application of the competing-risks model for small for gestational age that combines maternal factors with sonographic estimated fetal weight and uterine artery pulsatility index at midgestation.

**STUDY DESIGN:** This was a prospective observational study of 96,678 singleton pregnancies undergoing routine ultrasound examination at 19 to 24 weeks of gestation, which included recording of estimated fetal weight and measurement of uterine artery pulsatility index. The competing-risks model for small for gestational age was used to create a patient-specific stratification curve capable to define a specific timing for a repeated ultrasound examination after 24 weeks. We examined different stratification plans with the intention of detecting approximately 80%, 85%, 90%, and 95% of small for gestational age neonates with birthweight <3rd and <10th percentiles at any gestational age at delivery until 36 weeks; all pregnancies would be offered a routine ultrasound examination at 36 weeks.

**RESULTS:** The stratification of pregnancy care for small for gestational age can be based on a patient-specific stratification curve. Factors from maternal history, low estimated fetal weight, and increased uterine artery pulsatility index shift the personalized risk curve toward higher risks. The degree of shifting defines the timing for assessment for each pregnancy. If the objective of our antenatal plan was to detect 80%, 85%, 90%, and 95% of small for gestational age neonates at any gestational age at delivery until 36 weeks, the median (range) proportions (percentages) of population examined per week would be 3.15 (1.9—3.7), 3.85 (2.7—4.5), 4.75 (4.0—5.4), and 6.45 (3.7—8.0) for small for gestational age <3rd percentile and 3.8 (2.5—4.6), 4.6 (3.6—5.4), 5.7 (3.8—6.4), and 7.35 (3.3—9.8) for small for gestational age <10th percentile, respectively.

**CONCLUSION:** The competing-risks model provides an effective personalized continuous stratification of pregnancy care for small for gestational age which is based on individual characteristics and biophysical marker levels recorded at the midgestation scan.

**Key words:** Bayes theorem, competing risks, fetal growth restriction, precision medicine, pyramid of prenatal care, second trimester screening, small for gestational age, stratification, survival model

## Introduction

Small for gestational age (SGA) fetuses/neonates are at increased risk of stillbirth and adverse perinatal outcome,[1−3] and these risks can be potentially reduced if the fetuses can be identified prenatally and the pregnancies receive appropriate monitoring and timely delivery.[4] Studies have now established that: (1) approximately 85% of SGA neonates are born at ≥37 weeks' gestation,[5] (2) the predictive performance for SGA neonates is higher if the method of screening is routine third-trimester ultrasonographic fetal biometry rather than selective ultrasonography based on maternal risk factors and serial measurements of symphysial-fundal height,[6] and (3) the third-trimester scan is carried out at 36 rather than 32 weeks of gestation.[7,8] However, such late third-trimester scanning will miss the diagnosis of SGA and possible stillbirth occurring at <36 weeks; we have previously reported that fetuses are SGA in approximately 70% of antepartum stillbirths at <32 weeks' gestation, in 45% at 32 to 36 weeks, and in 30% at ≥37 weeks.[9] Therefore, it would be necessary that, in addition to a routine ultrasound examination at 36 weeks of gestation for all pregnancies, a scan be carried out at <36 weeks in pregnancies identified at the routine midtrimester scan as being at high risk for SGA at <36 weeks.[10]

We have recently proposed that the best method for predicting SGA is the competing-risks model, which is mainly based on 2 concepts: first, growth restriction is a spectrum condition, and second, the elements of SGA are smallness and prematurity, which are related to each other (Appendix 1).[11−18] We have merged these 2 elements in a single continuous Bayesian model. The mathematical basis of the new approach is a joint Gaussian continuous distribution of Z score in birthweight for gestational age ($Z_{BW}$) and gestational age at delivery ($GA_{Delivery}$).[11] We have also demonstrated that the proposed methodology is superior to risk scoring systems in the prediction of SGA and SGA-related stillbirth.[19−21] Screening by a combination of elements from maternal

Cite this article: Papastefanou I, Wright D, Syngelaki A, et al. Personalized stratification of pregnancy care for small for gestational age neonates from biophysical markers at midgestation. Am J Obstet Gynecol 2023;229:57.e1-14.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2022.12.318

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## AJOG at a Glance

### Why was this study conducted?

This study aimed to define the pregnancy-specific appropriate timing for a follow-up ultrasound scan at <36 weeks of gestation by using a competing-risks model for small for gestational age (SGA) neonates that combines maternal demographic characteristics and medical history and midgestation sonographic estimated fetal weight and uterine artery pulsatility index.

### Key findings

Timely recognition of SGA is feasible. Each pregnant woman could be examined at a different gestational age after 24 weeks, depending on the individual characteristics and the biophysical marker levels at the midgestation assessment.

### What does this add to what is known?

A new competing-risks model based on a midgestational age assessment provides an effective personalized continuous stratification of pregnancy care pertinent to SGA.

demographic characteristics and medical history, together with sonographic estimated fetal weight (EFW) and uterine artery pulsatility index (UtA-PI) at midgestation, provides effective discrimination between pregnancies at high and low risk of birth of SGA neonates.[16]

The objective of this study was to demonstrate the stratification of pregnancy care based on an integrated assessment at 19 to 24 weeks of gestation that combines maternal risk factors with EFW and UtA-PI in the context of a new competing-risks model for SGA.

## Materials and Methods

### Study population and design

The data for this study were derived from prospective screening for adverse obstetrical outcomes in individuals attending for routine pregnancy care at $19^{+0}$ to $24^{+6}$ weeks of gestation at King's College Hospital and Medway Maritime Hospital, United Kingdom, between 2011 and 2020. During this visit, we: (1) recorded maternal demographic characteristics and medical history, (2) carried out an ultrasound examination for fetal anatomy and growth, and (3) measured the left and right UtA-PI either by transvaginal or transabdominal color Doppler ultrasound and calculated the mean value of the 2 arteries.[22,23] Most UtA-PI measurements were carried out transvaginally because we were simultaneously measuring cervical length; the transabdominal approach was used when participants declined transvaginal sonography. The ultrasound scans were carried out by sonographers who had extensive training in ultrasound scanning and had obtained the appropriate Fetal Medicine Foundation (FMF) Certificate of competence in ultrasound and Doppler examinations (http://www.fetalmedicine.com). The fetal head circumference, abdominal circumference, and femur length were measured, and the EFW was calculated by the Hadlock formula[24] because a systematic review identified this as the most accurate model.[25] Gestational age was determined by the measurement of fetal crown–rump length at 11 to 13 weeks or the fetal head circumference at 19 to 24 weeks.[26,27] Participants gave written informed consent to participate in the study, which was approved by the National Health Service Research Ethics Committee. The inclusion criteria for this study were singleton pregnancies delivering a nonmalformed live birth or stillbirth at >24 weeks of gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities. The same study population was used in previous publications on the prediction of SGA.[15,16,19]

### Outcome measures

Data on pregnancy outcome were collected from hospital maternity records or the general medical practitioners of the study participants. The outcome measures of the study were birth of a neonate at or below different thresholds of birthweight percentile for different cutoffs of $GA_{Delivery}$. The FMF fetal and neonatal population weight charts were used to convert birthweight and EFW to percentiles and Z scores.[28]

### Statistical analyses

#### Competing-risks approach

The competing-risks approach for SGA is a model for the personalized joint distribution of $Z_{BW}$ and $GA_{Delivery}$. The proposed method assumes competing events in 2 dimensions, which are simultaneously merged in a joint distribution. In the $Z_{BW}$ dimension, the competing events are birthweight below or ≥10th percentile, whereas in the $GA_{Delivery}$ dimension, the competing events are delivery before or ≥37 weeks. We used the Bayes theorem to combine the maternal factor–driven previous joint distribution of $Z_{BW}$ and $GA_{Delivery}$ with the likelihoods of biophysical markers, and obtain a pregnancy-specific posterior joint distribution, predictive of any desired cutoff in $Z_{BW}$ and $GA_{Delivery}$.[16]

#### Personalized stratification

We used maternal factors, EFW, and UtA-PI to produce patient-specific risks according to the competing-risks model from 24 weeks until any given gestational point up to 36 weeks of gestation. This process is described by a personalized risk line that shows the changing cumulative risk for SGA up until any gestational age (Supplemental Figures 1 and 2). We also calculated the risks from 24 weeks until delivery for the SGA cases delivered before 36 weeks of gestation. The distribution of risks until delivery for the SGA cases enabled as to obtain a cutoff line that changed according to the desired detection rate (Supplemental Figures 1 and 3). The cutoff line, to a certain extent, represents the incidence of the condition at any given gestational age point considering

that this is a well-calibrated model, as we have previously demonstrated.[11–18] For each pregnancy, the point where the individual risk for SGA described by the personalized stratification line exceeds the cutoff line was the suggested gestational age for a follow-up ultrasound examination (Figure 1). In this modeling, we examined different stratification plans with the intention of detecting approximately 80%, 85%, 90%, and 95% of SGA neonates with birthweight <3rd and <10th percentiles at any gestational age at delivery until 36 weeks.

We converted UtA-PI and mean arterial pressure to multiples of the median values, as previously described.[29] Model fitting was carried out within a Bayesian framework using Markov chain Monte Carlo.[30] The statistical software package R (R Core Team, Vienna, Austria) was used for data analyses.[31]

## Results

### Study population

The maternal and pregnancy characteristics of the study population that included 96,678 singleton pregnancies are given in the Supplemental Table 1 and are the same as in our previous publications.[15,16,19] In the SGA group, compared with the non-SGA group, there was a lower median maternal age, weight, height, and body mass index; lower prevalence of White individuals; and higher prevalence of individuals of Black, South Asian, and mixed race, individuals with a history of chronic hypertension, systemic lupus erythematosus, or antiphospholipid syndrome, smokers, nulliparous individuals, and parous individuals who had previously developed preeclampsia or delivered SGA neonates. The parous individuals in the SGA group, compared with those in the non-SGA group, had longer interpregnancy intervals.

### Personalized stratification

The process of developing a stratification curve specific for each pregnancy is described in Figure 1. The personalized risk curve shows continuously the risk for SGA until any given point of pregnancy. The risk increases as we would expect because the condition becomes more common with advancing gestational age. The point where the individual risk becomes higher than the risk threshold defined by the cutoff line is the suggested gestational age for reexamining the particular pregnancy. The cutoff line changes according to the desired detection rate. Figure 1 shows 3 different clinical scenarios according to the individual characteristics and biomarker levels: a very high-risk case, a very low-risk case, and an intermediate-risk case. The new approach indicates the gestational age at which the follow-up scan should be carried out.

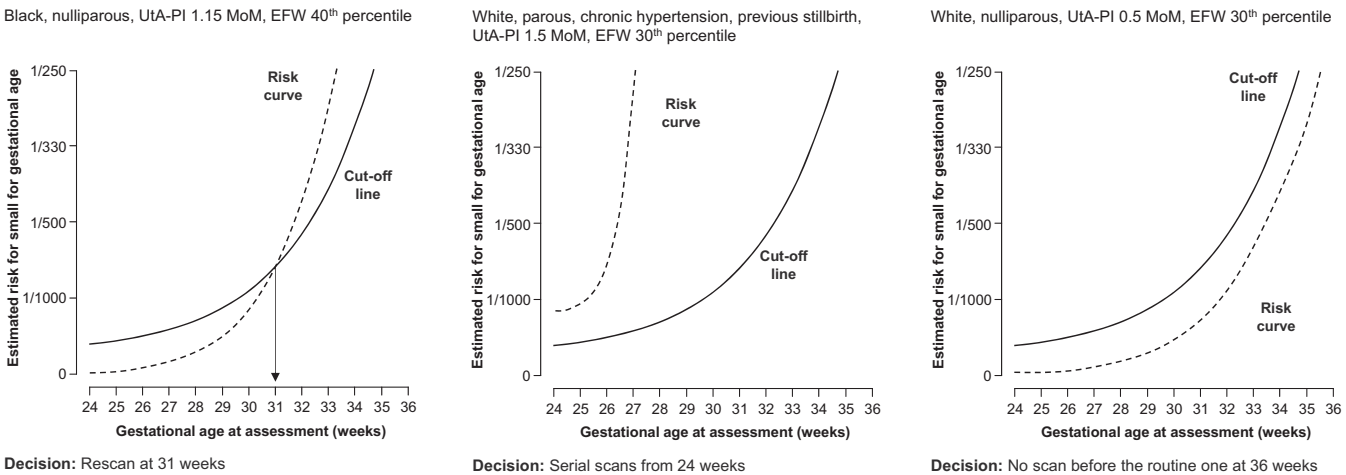
If the objective of our antenatal plan was to detect 80%, 85%, 90%, and 95% of SGA neonates at any gestational age at delivery until 36 weeks, the median (range) proportions (percentages) of population examined per week would be 3.15 (1.9–3.7), 3.85 (2.7–4.5), 4.75 (4.0–5.4), and 6.45 (3.7–8.0) for SGA <3rd percentile and 3.8 (2.5–4.6), 4.6 (3.6–5.4), 5.7 (3.8–6.4), and 7.35 (3.3–9.8) for SGA <10th percentile, respectively. The proportions of the population examined per week for each policy are given in the Table. The graphical demonstration of the stratification plan for SGA <third percentile is depicted in Figure 2.

## Comment

### Main findings

In this study, we describe an approach for personalized stratification of

**FIGURE 1**
**Patient-specific risk curve**




The point where the individual cumulative risk for small for gestational age described by the personalized risk curve (*interrupted curve*) exceeds the cutoff line (*solid curve*) is the suggested gestational age to carry out the next ultrasound examination. The 3 panels present patient-specific risk curves according to the individual characteristics and biomarker measurements.

*EFW*, estimated fetal weight; *MoM*, multiples of the median; *UtA-PI*, uterine artery pulsatility index.

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**TABLE**
**Proportion of population (95% confidence intervals) examined per week according to the personalized stratification plan**

| Gestational age for assessment (wk) | Small for gestational age <3rd percentile | | | | Small for gestational age <10th percentile | | | |
|---|---|---|---|---|---|---|---|---|
| | Desired detection rate | | | | | | | |
| | 80% | 85% | 90% | 95% | 80% | 85% | 90% | 95% |
| $24-24^{+6}$ | 1.9 (1.8–2.0) | 2.7 (2.6–2.8) | 4.3 (4.2–4.4) | 8.0 (7.8–8.2) | 2.5 (2.4–2.6) | 3.6 (3.5–3.7) | 5.5 (5.4–5.6) | 9.8 (9.6–10.0) |
| $25-25^{+6}$ | 2.0 (1.9–2.1) | 2.8 (2.7–2.9) | 4.1 (4.0–4.2) | 6.6 (6.4–6.8) | 2.7 (2.6–2.8) | 3.7 (3.6–3.8) | 5.2 (5.1–5.3) | 8.4 (8.2–8.6) |
| $26-26^{+6}$ | 2.2 (2.1–2.3) | 3.0 (2.9–3.1) | 4.2 (4.1–4.3) | 6.4 (6.2–6.6) | 3.0 (2.9–3.1) | 3.9 (3.8–4.0) | 5.6 (5.5–5.7) | 8.1 (7.9–8.3) |
| $27-27^{+6}$ | 2.5 (2.4–2.6) | 3.3 (3.2–3.4) | 4.6 (4.5–4.7) | 6.7 (6.5–6.9) | 3.2 (3.1–3.3) | 4.4 (4.3–4.5) | 5.8 (5.7–5.9) | 8.2 (8.0–8.4) |
| $28-28^{+6}$ | 2.7 (2.6–2.8) | 3.7 (3.6–3.8) | 4.9 (4.8–5.0) | 6.6 (6.4–6.6) | 3.7 (3.6–3.8) | 4.7 (4.6–4.8) | 6.2 (6.0–6.4) | 7.8 (7.6–8.0) |
| $29-29^{+6}$ | 3.1 (3.0–3.2) | 4.0 (3.9–4.1) | 5.2 (5.1–5.3) | 6.5 (6.3–6.7) | 4.1 (4.0–4.2) | 5.1 (5.0–5.2) | 6.4 (6.2–6.6) | 7.6 (7.4–7.8) |
| $30-30^{+6}$ | 3.3 (3.2–3.4) | 4.3 (4.2–4.4) | 5.3 (5.2–5.4) | 6.5 (6.3–6.7) | 4.3 (4.2–4.4) | 5.4 (5.3–5.5) | 6.3 (6.1–6.5) | 7.1 (6.9–7.3) |
| $31-31^{+6}$ | 3.6 (3.5–3.7) | 4.5 (4.4–4.6) | 5.4 (5.3–5.5) | 6.1 (5.9–6.3) | 4.6 (4.5–4.7) | 5.4 (5.3–5.5) | 6.1 (5.9–6.3) | 6.5 (6.3–6.7) |
| $32-32^{+6}$ | 3.7 (3.6–3.8) | 4.4 (4.3–4.5) | 5.1 (5.0 –5.2) | 5.6 (5.5–5.7) | 4.5 (4.4–4.6) | 5.2 (5.1–5.3) | 5.8 (5.7–5.9) | 5.6 (5.5–5.7) |
| $33-33^{+6}$ | 3.6 (3.5–3.7) | 4.4 (4.3–4.5) | 5.0 (4.9–5.1) | 5.0 (4.9–5.1) | 4.4 (4.3–4.5) | 4.9 (4.8–5.0) | 5.3 (5.2–5.4) | 4.0 (3.9–4.1) |
| $34-34^{+6}$ | 3.5 (3.4–3.6) | 4.0 (3.9–4.1) | 4.5 (4.4–4.6) | 4.5 (4.4–4.6) | 3.9 (3.8–4.0) | 4.5 (4.4–4.6) | 4.6 (4.5–4.7) | 4.1 (4.0–4.2) |
| $35-35^{+6}$ | 3.2 (3.1–3.3) | 3.6 (3.5–3.7) | 4.0 (3.9–4.1) | 3.7 (3.6–3.8) | 3.5 (3.4–3.6) | 3.9 (3.8–4.0) | 3.8 (3.7–3.9) | 3.3 (3.2–3.4) |

*CI*, confidence interval.
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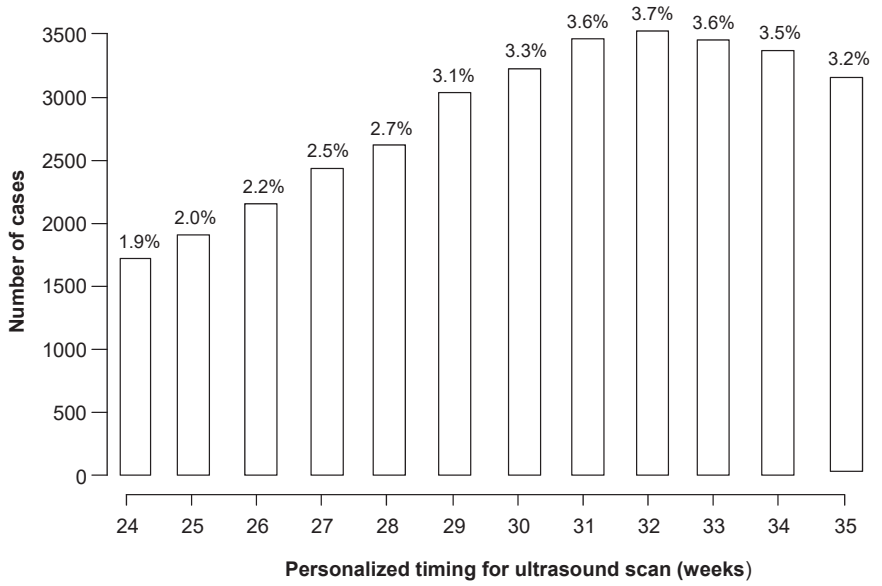
pregnancy care for the timely identification of SGA fetuses. Midtrimester assessment identifies a group at high risk for delivery of SGA infant at <36 weeks of gestation and defines the appropriate timing of a subsequent examination at between 24 and 36 weeks. The proposed methodology identifies a large proportion of SGA fetuses with the use of minimum resources. Detection rate is translated to a timely identification of SGA, targeting at a reduced number of scans performed. The new method is fully customizable with regard to birthweight percentile cutoff and gestational frame for which stratification is desired.

The standard of care for the antenatal detection of SGA involves using risk scoring systems, such as the one proposed by the Royal College of Obstetricians and Gynaecologists in the United Kingdom.[21] Recently, the DESiGN (DEtection of Small for Gestational age Neonate) trial has found that the Growth Assessment Protocol (GAP) developed by the Perinatal Institute[32] was not superior to standard care for the antenatal detection of SGA.[33] We have previously demonstrated that the performance of screening of the new model is superior to that of risk scoring systems.[19,21] Therefore, it is reasonable to assume that our approach yields better results than the GAP care pathway.

In addition, logistic regression models do not provide a clinically useful suggestion for subsequent management.[11–18] Fixed gestational periods may also be problematic. For example, 32-week universal assessment is too late for severe early SGA delivering at <32 weeks and too early for late SGA. The proposed methodology is based on a personalized stratification curve. Factors from maternal history, low EFW, and increased UtA-PI shift the personalized curve upward to a higher risk domain (Figure 1). The degree of shifting defines the timing for assessment for each pregnancy. It is also apparent that it is important to rely on the combination of the information rather than fixed isolated criteria.[21]

FIGURE 2
**Distribution of the proportion of the population (percentage) examined weekly for timely identification of 80% of SGA neonates with birthweight <3rd percentile**




*SGA*, small for gestational age.

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## Implications for clinical practice

The competing-risk approach is based on the notion that growth restriction is a spectrum condition rather than a fragmented outcome consisted of an early and a late form. Consequently, we avoided fixed intervals for scanning in the third trimester, and we established continuous personalized stratification. The impact on clinical practice could be profound. The timely recognition of SGA could prevent hypoxia and potentially stillbirth, and the effective allocation of resources would allow improvement of antenatal care for the whole population. The new model addresses 2 important clinical issues. The first is the identification of high-risk pregnancies for any desired outcome definition, and the second is the timing for assessing this high-risk group. Assessment at midgestation identifies a group at high risk for early SGA and defines the best gestational time for a follow-up scan at <36 weeks. All pregnancies, irrespective of their risk at midgestation, should be offered a routine ultrasound examination at 36 weeks of gestation for assessment of risk for term SGA.

An important component of the introduced personalized stratification is that it incurs no additional cost; consequently, immediate clinical implementation is feasible. Ultrasound biometry in the context of a midtrimester anomaly scan is the standard of care worldwide. Although the addition of uterine artery Doppler requires adequate training, it incurs no additional cost because it can be carried out by the same operators, at the same clinical visit, and using the same ultrasound machines. An important merit of our model is the capability to use any desired biomarkers by leveraging the Bayes theorem. Therefore, where uterine artery Doppler is not possible, maternal factors and EFW can be used alone. Conversely, biochemical markers, such as serum placental growth factor, could be added in the model, enhancing the prediction of very small and very preterm infants, as we have previously demonstrated.[17]

## Strengths and limitations

The strengths of this study are: (1) examination of a large population of individuals having a routine ultrasound scan at midgestation for assessment of fetal anatomy and growth; (2) recording of data on maternal characteristics and medical history to define the previous model; (3) use of a specific methodology and appropriately trained doctors to measure UtA-PI; (4) use of the Bayes theorem to combine maternal factors with biomarkers and achieve a patient-specific individual plan for a subsequent ultrasound scan; and (5) providing a fully customizable method according to local preferences and health economic considerations.

Future clinical trials are needed to examine whether the implementation of this personalized stratification method could improve perinatal outcome.

## Conclusions

Assessment of risk for SGA at midgestation by a combination of maternal factors, EFW, and UtA-PI provides the basis for determining the gestational age for a follow-up ultrasound examination at between 24 and 36 weeks of gestation (Video). ■

## References


1. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. N Engl J Med 1999;340:1234–8.
2. Steer P. The management of large and small for gestational age fetuses. Semin Perinatol 2004;28:59–66.
3. 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.
4. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol 2018;218:S855–68.
5. 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.e1–11.
6. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet 2015;386:2089–97.
7. Roma E, Arnau A, Berdala R, Bergos C, Montesinos J, Figueras F. Ultrasound screening for fetal growth restriction at 36 vs 32 weeks'

gestation: a randomized trial (ROUTE). Ultrasound Obstet Gynecol 2015;46:391–7.
**8.** 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;53:761–8.
**9.** Poon LC, Volpe N, Muto B, Syngelaki A, Nicolaides KH. Birthweight with gestation and maternal characteristics in live births and stillbirths. Fetal Diagn Ther 2012;32:156–65.
**10.** Poon LC, Lesmes C, Gallo DM, Akolekar R, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by biophysical and biochemical markers at 19-24 weeks. Ultrasound Obstet Gynecol 2015;46:437–45.
**11.** Papastefanou I, Wright D, Nicolaides KH. Competing-risks model for prediction of small for gestational age neonate 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 neonate from maternal characteristics and serum pregnancy-associated plasma protein-A at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2020;56:541–8.
**13.** Papastefanou I, Wright D, Lolos M, Anampousi K, Mamalis M, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonate from maternal characteristics, serum pregnancy-associated plasma protein-A and placental growth factor at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2021;57:392–400.
**14.** Papastefanou I, Wright D, Syngelaki A, Souretis K, Chrysanthopoulou E, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonate from biophysical and biochemical markers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2021;57:52–61.
**15.** Papastefanou I, Nowacka U, Syngelaki A, et al. Competing-risks model for prediction of small-for-gestational-age neonate from estimated fetal weight at 19-24 weeks' gestation. Ultrasound Obstet Gynecol 2021;57:917–24.
**16.** Papastefanou I, Nowacka U, Syngelaki A, et al. Competing risks model for prediction of small-for-gestational-age neonates from biophysical markers at 19 to 24 weeks' gestation. Am J Obstet Gynecol 2021;225:530.e1–19.
**17.** Nowacka U, Papastefanou I, Bouariu A, Syngelaki A, Akolekar R, Nicolaides KH. Second-trimester contingent screening for small-for-gestational-age neonate. Ultrasound Obstet Gynecol 2022;59:177–84.
**18.** Nowacka U, Papastefanou I, Bouariu A, Syngelaki A, Nicolaides KH. Competing risks model for prediction of small for gestational age neonates and the role of second trimester soluble Fms-like tyrosine Kinase-1. J Clin Med 2021;10:3786.
**19.** Papastefanou I, Nowacka U, Buerger O, Akolekar R, Wright D, Nicolaides KH. Evaluation of the RCOG guideline for the prediction of neonates that are small for gestational age and comparison with the competing risks model. BJOG 2021;128:2110–5.
**20.** Nicolaides KH, Papastefanou I, Syngelaki A, Ashoor G, Akolekar R. Predictive performance for placental dysfunction related stillbirth of the competing risks model for small-for-gestational-age fetuses. BJOG 2022;129:1530–7.
**21.** Royal College of Obstetricians and Gynaecologists. The investigation and management of the small—for—gestational—age fetus. Green-top guideline, No. 31. Royal College of Obstetricians and Gynaecologists; 2014.
**22.** Papageorghiou AT, Yu CKH, Bindra R, Pandis G, Nicolaides KH. Fetal Medicine Foundation Second Trimester Screening Group. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. Ultrasound Obstet Gynecol 2001;18:441–9.
**23.** Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. Obstet Gynecol 2000;96:559–64.
**24.** Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements-a prospective study. Am J Obstet Gynecol 1985;151:333–7.
**25.** Hammami A, Mazer Zumaeta A, Syngelaki A, Akolekar R, Nicolaides KH. Ultrasonographic estimation of fetal weight: development of new model and assessment of performance of previous models. Ultrasound Obstet Gynecol 2018;52:35–43.
**26.** Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. Ultrasound Obstet Gynecol 1994;4:34–48.
**27.** Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. Br J Obstet Gynaecol 1975;82:702–10.
**28.** 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.
**29.** Litwinska M, Litwinska E, Lisnere K, Syngelaki A, Wright A, Nicolaides KH. Stratification of pregnancy care based on risk of pre-eclampsia derived from uterine artery Doppler at 19-24 weeks' gestation. Ultrasound Obstet Gynecol 2021;58:67–76.
**30.** Gilks WR, Thomas A, Spiegelhalter DJ. A language and program for complex Bayesian modelling. Statistician 1994;43:169–77.
**31.** R Development Core Team. R: a Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Available at: https://www.r-project.org/. Accessed April 20, 2022.
**32.** Clifford S, Giddings S, South M, Williams M, Gardosi J. The Growth Assessment Protocol: a national programme to improve patient safety in maternity care. MIDIRS Midwif Dig 2013;23:516–23.
**33.** Vieira MC, Relph S, Muruet-Gutierrez W, et al. Evaluation of the Growth Assessment Protocol (GAP) for antenatal detection of small for gestational age: the DESiGN cluster randomised trial. PLoS Med 2022;19:e1004004.

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Received July 17, 2022; revised Dec. 26, 2022; accepted Dec. 28, 2022.

The authors report no conflict of interest.

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

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# Appendix

## Competing-risks approach for small for gestational age

The competing-risks model for small for gestational age (SGA) is a model for the joint distribution of birthweight Z scores ($z$) and gestational age ($g$, weeks) at delivery. This distribution is obtained using Bayes theorem to combine a prior distribution of $z$ and $g$, given maternal characteristics, with a likelihood function for $z$ and $g$ from biomarkers.

### Prior joint distribution – history model

The mean of the prior joint distribution is defined by the predicted mean of $z$ and the predicted mean of $g$, given the correlation between $z$ and $g$. The proposed method assumes competing events in 2 dimensions. In the $z$ dimension the competing events are birthweight below or above the 10th percentile, whereas in the $g$ dimension the competing events are delivery before or after 37 weeks. Gestational ages >37 weeks were treated as censored observations at 37 weeks and Z scores $> -1.2816$ were censored at $-1.2816$. The means of $z$ and $g$ were determined from maternal characteristics by using censored regression. Standard deviations for $z$ and $g$ and the correlation coefficient between $z$ and $g$ were assumed constant for all women, independent from maternal factors and they were inferred by the model. We assumed Gaussian distributions, constant standard deviations and constant correlation coefficient, independent from maternal factors, for simplicity of interpretation. The model was fitted in Bayesian framework using Markov chain Monte Carlo techniques which enabled all parameters for both model's elements and the correlation coefficient to be estimated within a single analysis (Supplemental Table 2).

### Likelihood for biophysical markers

The likelihood for Z scores of estimated fetal weight (EFW) was developed by fitting a regression model conditional to z and g, with an interaction term. This model assumes that the coefficient for z is a function of g. A folded plane regression model* was fitted for the likelihood of the $\log_{10}$ MoM values of UtA-PI and MAP. The folded plane method that we have developed expressed mean $\log_{10}$ MoM UtA-PI and MAP conditionally to both z and g. The mean $\log_{10}$ MoM depended on both z and g, until it reaches zero $\log_{10}$ MoM level and beyond a break line the mean was presumed to be constant and equal to zero. The new approach exceeds the conventional regression analysis, where parameters are driven mainly by pregnancies at term with normal birthweight and normal biomarker values that are the vast majority of cases. A single 2-dimensional continuous likelihood is now focused in the clinically relevant domain of small babies. The combination of different biomarkers was achieved by a multivariable Gaussian distribution*. The standard deviations of the biomarkers $\log_{10}$ MoM values and the correlation coefficients amongst them, were assumed constant and independent of the z, g and gestational age at measurement. Therefore variances, covariances and consequently the covariance matrix were constant. The likelihoods were fitted in Bayesian framework using Markov chain Monte Carlo techniques (Supplemental Tables 3 and 4).

### Posterior joint distribution

We used Bayes' theorem to combine the prior joint distribution of $z$ and $g$ according to the competing-risks history model with the likelihoods of biophysical markers. The resulting pregnancy-specific joint posterior distribution allows the calculation of risk for any specific cutoff for $z$ and $g$. The $z$ and $g$ cutoffs define the volume under the surface of the joint distribution which is essentially the risk for SGA for these particularly chosen cutoffs (Supplemental Figures 1 and 2).

The new model has important novel elements: first, the 2 dimensions of SGA ($z$ and $g$) are recognized and combined continuously, second, censoring enabled us to use all data while focusing the model in the small babies, third, the joint nature of the model links $z$ and $g$ explaining the association between prematurity and smallness, fourth, a single model allows computation of risk for an infinite number of combinations of $z$ and $g$ at any stage of pregnancy, and fifth, any newly examined biomarker can be added in the very same model according to Bayes' theorem.

The parameters for the prior model and the likelihood functions that can be used for the individual risk calculation are given in Supplemental Tables 2 to 4. We have also developed a freely accessible online calculator for our competing-risks model for SGA (https://fetalmedicine.org/research/assess/sga-risk).

## Personalized risk curve

The risk for SGA neonate is the volume under the density surface of the personalized posterior joint probability distribution $\boldsymbol{p}(z,g)$ for the region $R^2$ defined each time by the chosen cutoffs for $z$ and $g$. This quantity is essentially a 2-dimensional integral of the $\boldsymbol{p}(z,g)$ function for the limits defined by the chosen cutoffs for $z$ and $g$.

The posterior probability density $\boldsymbol{p}(z,g)$, up to a normalizing constant, is calculated by multiplying the likelihood by the prior, according to Bayes' Theorem:

$$\boldsymbol{p}(z,g) = \boldsymbol{dmvnorm}(\chi, \mu_\chi, \Sigma_\chi) * \boldsymbol{dmvnorm}\left(z, g, \mu_{z,g}, \Sigma_{z,g}\right)$$

In the above $\boldsymbol{dmvnorm}(\chi, \mu_\chi, \Sigma_\chi)$ is the multivariate Gaussian density for biomarkers, with mean vector $\mu_\chi$ expressed conditionally to $z$ and $g$ and covariance matrix $\Sigma_\chi$ and $\boldsymbol{dmvnorm}(z, g, \mu_{z,g}, \Sigma_{z,g})$ is the prior bivariate Gaussian density for $z$ and $g$ with mean vector $\mu_{z,g}$ and covariance matrix $\Sigma_{z,g}$, according to the history model. The

parameterization for both the history model and the likelihood of the biomarkers has been extensively described in previous publications.[11–18]

The risk curve used for the stratification of pregnancy care for SGA in our study represents the cumulative risk for SGA (***risk***) until any given gestational point (***time***) until 35 weeks, given a ***z0*** cutoff, which is user defined.

$$risk = g(time)$$

$$g(time) = \int_{-\infty,24}^{z0,time} p(z,g)d(z)d(g)$$

## Cutoff line

The stratification in our approach is based on 2 concepts. The first is that the personalized timing for assessment in the high-risk cases is driven by the gestational age where delivery for growth restriction becomes necessary; and the second concept is that for increasing risk the earlier the delivery takes place and therefore the earlier the required assessment. In our model the risk profile is reflected continuously to a patient-specific risk curve that shows the cumulative risk for SGA at any gestational point, as described in the previous section of the Appendix.

For the definition of the cutoff line, we assume that the distribution of $log_{10}$ risk for SGA until the actual delivery day, for the SGA cases, has ***mean*** which is a linear function of ***time*** and a standard deviation ***SD***.

$$log_{10}(risk_{SGA}) = f(time, mean, SD)$$

$$mean = a + b * time$$

The cutoff line will be defined by the following equation

$$cut - off\ line = a + b * time + z_{DR} * SD$$

$$z_{DR} = qnorm(1 - DR)$$

For example, for a desired detection rate (DR) of 90%

$$z_{DR} = qnorm(1 - 0.9) = -1.281552$$

Finally, we anti-log to obtain the cutoff line in original risk (Figure 1)

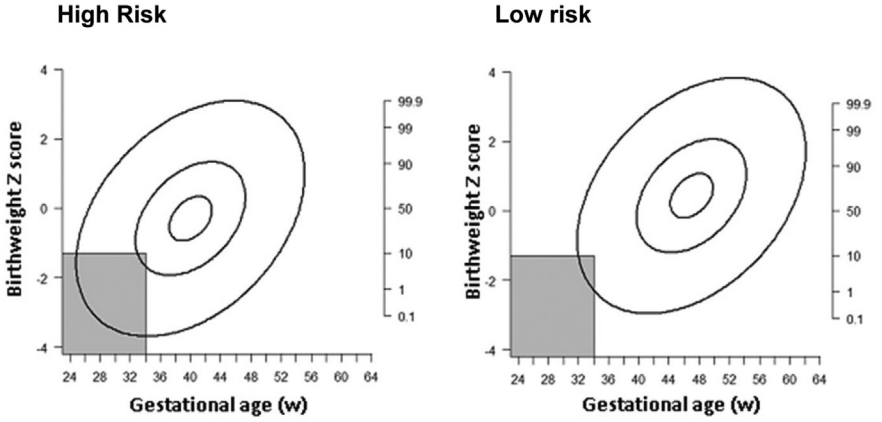
A relevant example for SGA<10th percentile and a desired DR of 90% is depicted in Supplemental Figure 3 (red dots are the SGA<10th percentile cases, deemed high risk by the model, that lay above the threshold).

## GLOSSARY

1. Joint distributionJoint distribution of 2 given random variables that are defined on the same probability space is the probability distribution on all possible pairs of the 2 variables. The probability distribution of each variable individually is called marginal distribution. The joint distribution is defined by the marginal distributions of the 2 variables and their correlation. The 2 variables could have a positive, negative or zero correlation.For example, consider a population in which we aim to describe the joint distribution of weight and height. The distributions of weight and height are the marginal distributions and the correlation is the degree of association between weight and height (the taller the person the more the weight). In our model the marginal distributions are the birthweight and gestational age at delivery. The means and standard deviations of these Gaussian distributions as well as the correlation coefficient are inferred by the competing-risks history model. The resultant prior joint distribution is then modified by the likelihood.
2. Multivariate likelihoodIn Bayesian prediction models a multivariate likelihood is a way to combine 2 or more biomarkers which are assumed to follow a Gaussian distribution with a given correlation between them. The simplest form of a multivariate likelihood is a number (ratio) that is multiplied with the prior odds to give the posterior odds that can be easily converted to a risk. In our model we use the general form of Bayes' theorem which involves the multiplication of whole probability distributions, rather than simple numbers. This give as the capability to calculate the risk for any desired cutoffs.
3. Folded plane regression modelA regression model y=a+b*x is graphically represented by a straight line. A regression model with 2 predictors y=a+b1*x1+b2*x2, is graphically depicted by a surface; a plane. Folded plane model is a novel technique that we developed to overcome the fact that least squares regression analysis do not describe adequately distribution tails, because inferences are driven by the more common cases which are clustered around the mean. In the growth restriction we are very much interested in the left tails of birthweight and gestational age distributions and their association with the biomarkers. With the competing-risks modeling and the folded plane method we achieved a continuous description of these extreme values by using simple Gaussian distributions.

SUPPLEMENTAL FIGURE 1

**The 50%, 75%, and 95% contours of the joint Gaussian distribution of birthweight Z scores and gestational age at delivery in a high-risk and a low-risk case, according to history model**




Birthweight is also expressed in percentiles in the vertical right axes. The shaded gray area corresponds to the risk of delivery before 34 weeks' gestation with small for gestational age neonates with birthweight <10th percentile. The cutoffs are user-defined.

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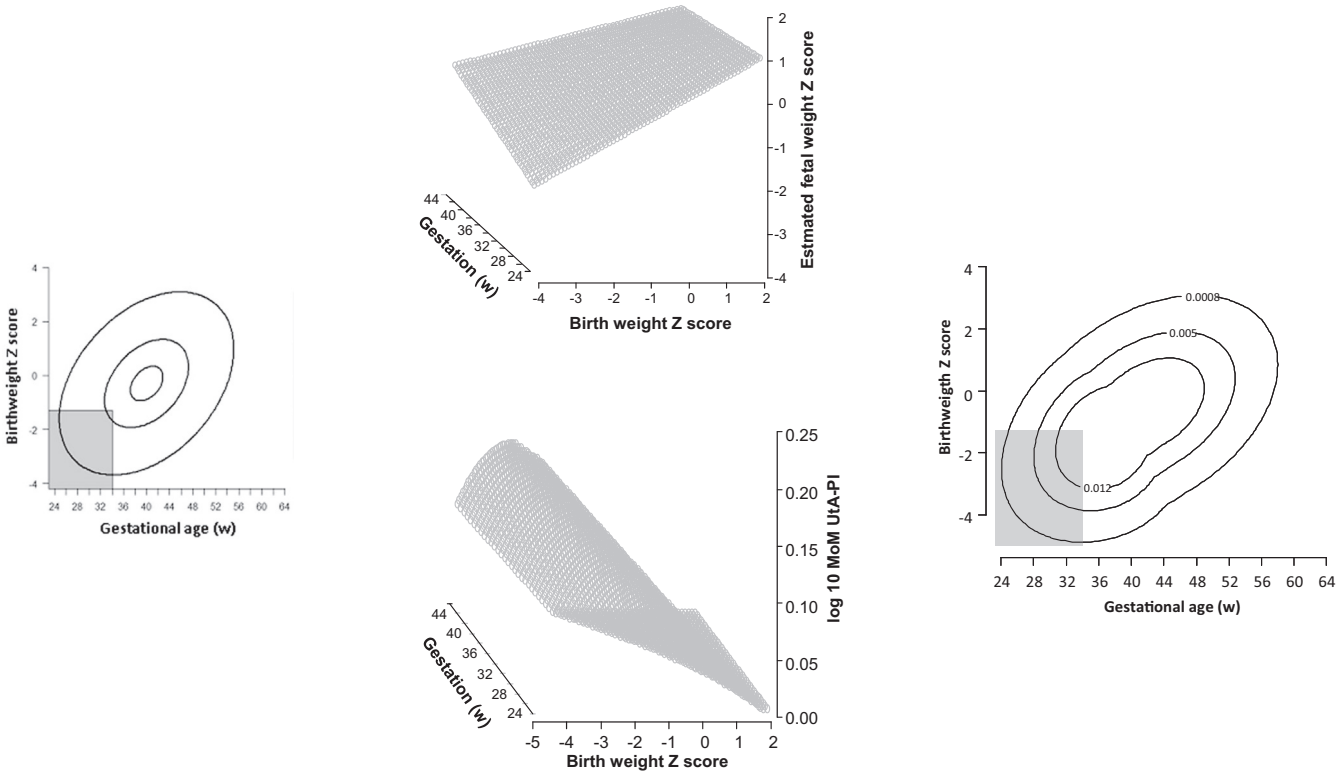
SUPPLEMENTAL FIGURE 2

**Graphical presentation of the application of Bayes' theorem in our model**




The previous joint distribution of birthweight Z scores (and gestational age at delivery) according to maternal factors (left graph) is updated by the likelihood of biomarkers (middle graphs), and the result is the posterior joint distribution that can be used to calculate the risk for any cutoff.

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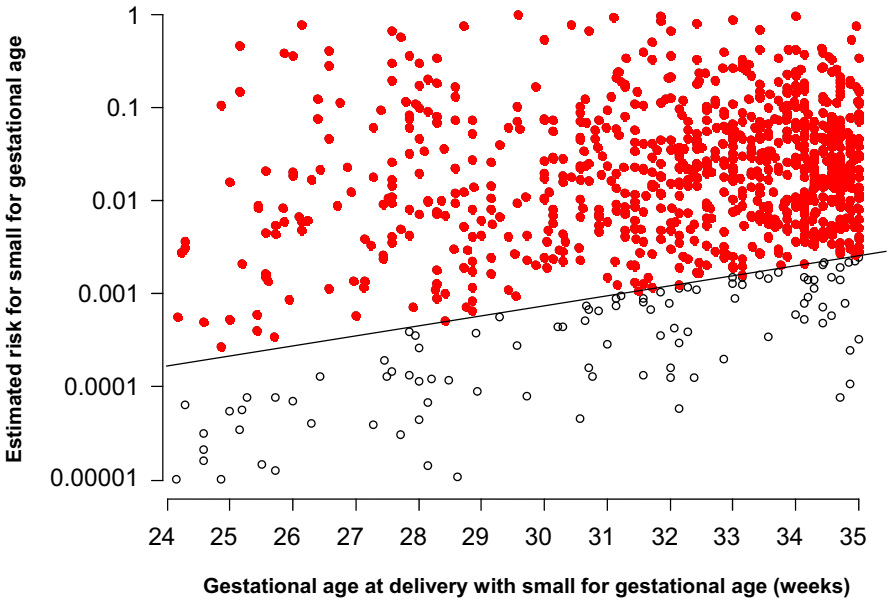
SUPPLEMENTAL FIGURE 3

**Association between the risk for SGA <10th percentile until the $GA_{Delivery}$ and the $GA_{Delivery}$ with SGA <10th percentile**




The cutoff line for the timely detection of 90% of SGA is superimposed, and the (*red dots*) represent the SGA cases that will be identified by the application of the personalized risk curve.

$GA_{Delivery}$, gestational age at delivery; *SGA*, small for gestational age.

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SUPPLEMENTAL TABLE 1
**Maternal and pregnancy characteristics of the study population**

| Variables | Total (n=96,678) | Non-SGA (n=84,655) | SGA (n=12,023) | *P* value |
|---|---|---|---|---|
| Maternal age (y) | 31.4 (27.1–35.1) | 31.5 (27.2–35.2) | 30.8 (25.15–34.9) | <.0001 |
| Maternal weight (kg) | 67.6 (59.7–79.0) | 68.0 (60.0–79.5) | 63.8 (56.0–74.0) | <.0001 |
| Maternal height (cm) | 165 (160–169) | 165 (161–169.7) | 163.0 (158–167) | <.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) | <.0001 |
| Gestation at assessment (wk) | 21.7 (21.1-22.1) | 21.7 (21.1–22.1) | 21.7 (21.1–22.1) | .131 |
| Race | | | | |
| White | 71,349 (73.8) | 63,885 (75.5) | 7464 (62.1) | <.0001 |
| Black | 15,972 (16.5) | 13,196 (15.6) | 2776 (23.1) | <.0001 |
| South Asian | 4672 (4.8) | 3583 (4.2) | 1089 (9.1) | <.0001 |
| East Asian | 1965 (2.0) | 1689 (2.0) | 276 (2.3) | .032 |
| Mixed | 2720 (2.8) | 2302 (2.7) | 418 (3.5) | <.0001 |
| Conception | | | | |
| Natural | 93,123 (96.3) | 81,578 (96.4) | 11,545 (96.0) | .067 |
| Ovulation induction | 637 (0.7) | 548 (0.7) | 89 (0.7) | .264 |
| In vitro fertilization | 2918 (3.0) | 2529 (3.0) | 389 (3.2) | .145 |
| Medical history | | | | |
| Chronic hypertension | 1188 (1.2) | 897 (1.1) | 291 (2.4) | <.0001 |
| Diabetes mellitus | 1116 (1.2) | 972 (1.2) | 144 (1.2) | .667 |
| SLE/APS | 228 (0.2) | 182 (0.2) | 46 (0.4) | .0006 |
| Cigarette smokers | 8323 (8.6) | 6497 (7.7) | 1826 (15.2) | <.0001 |
| Family history of preeclampsia | 3725 (3.9) | 3220 (3.8) | 505 (4.2) | .037 |
| Parity | | | | |
| Nulliparous | 44,243 (45.8) | 37,595 (44.4) | 6648 (55.3) | <.0001 |
| Parous with previous SGA | 7119 (7.4) | 5137 (6.1) | 1982 (16.5) | <.0001 |
| Parous with previous preeclampsia and/or SGA | 9076 (9.4) | 6899 (8.2) | 2177 (18.1) | <.0001 |
| Interpregnancy interval (y) | 2.9 (1.8–4.7) | 2.9 (1.8–4.6) | 3.2 (2.0–5.5) | <.0001 |
| Gestation of last birth (wk) | 40 (39–40) | 40 (39–40) | 40 (38–40) | <.0001 |
| Preeclampsia | 2866 (2.9) | 1988 (2.4) | 878 (7.3) | <.0001 |
| Gestational hypertension | 2641 (2.7) | 2126 (2.5) | 515 (4.3) | <.0001 |

Values are given as median (interquartile range) or number (percentage). Comparisons between outcome groups were performed by chi-square or Fisher exact tests for categorical variables and Mann–Whitney U test for continuous variables.

*APS*, antiphospholipid syndrome; *SGA*, small for gestational age with birthweight <10th percentile; *SLE*, systemic lupus erythematosus.

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SUPPLEMENTAL TABLE 2

**Model for the prior joint distribution of birthweight Z score and gestational age at delivery according to maternal factors and medical history**

| Birthweight Z | Est | SD | LCL | UCL |
|---|---|---|---|---|
| Intercept | 0.444662 | 0.0198324 | 0.404997 | 0.482800 |
| Black | −0.524625 | 0.0193620 | −0.563100 | −0.486797 |
| South Asian | −0.482211 | 0.0289344 | −0.538900 | −0.426000 |
| Mixed | −0.280160 | 0.0407331 | −0.358905 | −0.199497 |
| Height (cm) -165 | 0.026730 | 0.0011768 | 0.024430 | 0.029010 |
| Weight (kg) - 69 | 0.012648 | 0.0006290 | 0.011449 | 0.013920 |
| Weight (kg) - $69^2$ | −0.000189 | 0.0000166 | −0.000221 | −0.000155 |
| IVF | −0.098920 | 0.0417037 | −0.181002 | −0.019259 |
| Smoker | −0.693680 | 0.0226538 | −0.738802 | −0.649800 |
| Chronic hypertension | −0.706842 | 0.0559370 | −0.817000 | −0.597397 |
| SLE/APS | −0.443860 | 0.1270514 | −0.687707 | −0.196200 |
| Multiparous | 0.138451 | 0.0495576 | 0.049818 | 0.243202 |
| Last GA (wk)- 40 | 0.068527 | 0.0043285 | 0.060040 | 0.077340 |
| Previous BW Z | 0.344370 | 0.0086454 | 0.327300 | 0.361400 |
| Interval (y) $^{-1}$ | −0.380348 | 0.0545169 | −0.477202 | −0.263297 |
| Interval (y) $^{-0.5}$ | 1.004172 | 0.1117701 | 0.760094 | 1.202000 |
| SD for Z | 1.399757 | 0.0112191 | 1.378000 | 1.422000 |
| GA at delivery | | | | |
| Intercept | 45.490642 | 0.1296534 | 45.250000 | 45.750000 |
| Mean birthweight (Z) | 1.499151 | 0.0424478 | 1.416710 | 1.582867 |
| Weight (kg) - 69 | −0.024432 | 0.0025118 | −0.029430 | −0.019530 |
| IVF | −1.214127 | 0.2005893 | −1.597000 | −0.819672 |
| Chronic hypertension | −0.989338 | 0.2745230 | −1.521025 | −0.439545 |
| Diabetes Mellitus | −3.964919 | 0.2296087 | −4.414000 | −3.515975 |
| Previous PE | −1.157569 | 0.1903221 | −1.520000 | −0.782300 |
| Previous IUD | −1.474475 | 0.3388455 | −2.127025 | −0.798980 |
| Multiparous | 0.551989 | 0.0864940 | 0.386397 | 0.727900 |
| Last GA (wk)-40 | 0.865976 | 0.0384931 | 0.789000 | 0.939800 |
| (Last GA (wk)- 40)$^2$ | 0.041513 | 0.0033572 | 0.034850 | 0.047960 |
| SD for GA | 5.730152 | 0.0680466 | 5.599000 | 5.868000 |
| Correlation | 0.366211 | | | |

*APS*, antiphospholipid syndrome; *Est*, Estimates of posterior means for the parameters; *IUD*, intrauterine demise; *IVF*, In vitro fertilization; *LCL*, lower credibility limits; *PE*, preeclampsia; *SD*, standard deviation; *SGA*, small for gestational age; *SLE*, systemic lupus erythematosus; *UCL*, upper credibility limits.

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SUPPLEMENTAL TABLE 3

**Likelihood functions for the mean $log_{10}$ MoM uterine artery pulsatility index and the mean estimated fetal weight Z score conditional to birthweight Z score and gestational age at delivery**

| Term | Estimate (upper and lower credibility limits) | SD |
|---|---|---|
| EFW Z score | | |
| Intercept | 0.00058261 (−0.0051391 to 0.0062831) | 0.0029054 |
| BW Z score | 0.27578 (0.27020 to 0.28150) | 0.0028908 |
| (GA−40) X BW Z score | −0.014075 (−0.01578 to −0.012380) | 0.00086916 |
| SD for EFW Z score | 0.89413 (0.89010 to 0.89810) | 0.0020543 |
| $log_{10}$ MoM UtA-PI | | |
| Intercept | −0.028947 (−0.03297 to −0.02517) | 0.0019212 |
| BW Z score | −0.033732 (−0.035670 to −0.031800) | 0.00097680 |
| GA−40 | −0.0097918 (−0.011310 to −0.0084240) | 0.00073230 |
| (GA−40)^2 | −0.00024759 (−0.0003855 to −0.0001238) | 0.000066442 |
| SD for $log_{10}$ MoM UtA-PI | 0.11881 (0.11830 to 0.11940) | 0.00027316 |

*BW*, birthweight; *EFW*, estimated fetal weight; *GA*, gestational age at delivery; *SD*, standard deviation; *UtA-PI*, uterine artery pulsatility index.

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SUPPLEMENTAL TABLE 4

**Correlation for the examined biophysical markers**

| Correlation | Correlation coefficient (95% confidence interval) |
|---|---|
| UtA-PI with EFW | −0.068655 (−0.074926 to −0.062378) |

*EFW*, estimated fetal weight; *UtA-PI*, uterine artery pulsatility index.

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