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Developing a predictive model for perinatal morbidity among small for gestational age infants

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Abstract

Background: While neonates with birth weight <10th percentile are at increased risk of morbidity and mortality, most of these are constitutionally small and not at increased risk. There are no current strategies that reliably distinguish constitutionally small neonates from small neonates at highest risk of morbidity, so additional tools for risk stratification are needed.

Objective: Our objectives were to identify factors that are independently associated with perinatal morbidity among neonates with birth weight <10th percentile (small for gestational

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age, SGA) and to create predictive models of perinatal morbidity among SGA neonates based on timing of information availability.

Study Design: This secondary analysis of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be, was a nested case-control study. Participants were prospectively enrolled at eight U.S. centers, with data collection occurring at three standard time points during pregnancy and again after delivery. Our analysis included neonates with birth weights <10th percentile and excluded those with major congenital malformations or suspected or confirmed aneuploidy. The primary outcome was a composite of perinatal morbidity, defined as NICU admission > 48 hours, NEC, sepsis, RDS, mechanical ventilation, retinopathy of prematurity, seizures, grade 3 or 4 IVH, stillbirth, or death before discharge. Cases were SGA neonates that experienced the primary outcome, and controls were SGA neonates that did not. Maternal factors for potential inclusion in predictive modeling were drawn from a broad list of variables collected as part of the NuMoM2B study, including demographic, anthropometric, clinical, ultrasound, social/behavioral, dietary, and psychological variables. Characteristics that were different in bivariate analysis between cases and controls then underwent further evaluation and refinement. Continuous and multi-category variables were assessed using multiple approaches, including as continuous variables, using standard categories (such as for BMI) as well as empirically-derived cut-points identified by receiver-operating characteristics methodology. The approach for each variable that resulted in the best performance was selected for use in modeling. After variable optimization, multivariable analysis was used to derive prediction models using factors known at mid-pregnancy (Model 1) and at delivery (Model 2).

Results: Of the original cohort, 865 were eligible and analyzed, with 134 (15.5%) experiencing the primary outcome. After bivariable and multivariable analysis, these variables were included in Model 1: BMI, stress level, diastolic blood pressure, narcotic use (all in 1st trimester), and uterine artery pulsatility index at 16–21 weeks. Model 2 added the following variables to Model 1: preterm delivery, preeclampsia, and suspected fetal growth restriction. When models 1 and 2 were empirically tested and compared to predicted performance to demonstrate calibration, observed morbidity rates approximately followed expected rates within deciles. Models 1 and 2 had respective areas under the receiver-operating characteristic curve of 0.72 (95% CI 0.67 – 0.76) and 0.84 (0.80–0.88), to predict the composite morbidity.

Conclusion: Using a deeply phenotyped cohort of nulliparous women, we created two models with moderate-good prediction of perinatal morbidity among SGA neonates.

Keywords

perinatal morbidity; small for gestational age; fetal growth restriction; risk prediction

Introduction

A small for gestational age (SGA) birth weight, often defined as being below the 10th percentile for gestational age, is associated with both perinatal and long-term morbidities and mortality [1–3] As such, SGA birth weight is used as a surrogate outcome to confirm prenatal suspicion of fetal growth restriction (FGR), and is included as a core outcome measure for research on FGR [4]. Furthermore, SGA is often included as a core adverse

pregnancy outcome, along with preterm birth, stillbirth, and hypertensive disorders of pregnancy [5–7]. However, SGA is a statistical designation rather than a clinical one, and the fact that it is based on size-for-age alone without taking other factors into account hampers its performance as a predictor of morbidity. Indeed, most SGA neonates do not experience serious morbidity [8,9].

Given the prominence of SGA as both a research and clinical outcome and its poor performance as a sole predictor of morbidity, there is a critical need for new tools to improve prediction of perinatal morbidity in SGA neonates. Indeed, the need for such risk stratification of neonates identified as SGA is widely recognized and is acknowledged in recommendations jointly published by the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine [10,11]. Hence, our objective was to identify maternal, social, clinical, and other factors from early and late pregnancy that are independently associated with perinatal morbidity among neonates with birth weight < 10^{th} percentile and to develop risk prediction model. Because counseling by neonatologists often takes place when imminent delivery is possible but not certain, such discussions are contingent on factors that are anticipated but not yet known, such as SGA status and gestational age at birth. For this reason, our secondary objective was to generate a predictive model using factors that would routinely be available when imminent delivery is suspected but before the exact timing of delivery would be known.

We hypothesize that integration of factors across demographic, social, psychological, and clinical domains would yield models with at least moderate prediction of perinatal morbidity in SGA neonates.

Materials and Methods

This was a secondary analysis of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) study, in which 10,038 nulliparous women underwent prospective demographic, clinical, and biomarker data collection in order to study predictors of adverse pregnancy outcomes. There were eight participating U.S. centers, which collected data from participants at 3 study visits during pregnancy and again after delivery. The three visits occurred at 6 weeks 0 days – 13 weeks 6 days (visit 1), 16 weeks 0 days – 21 weeks 6 days (visit 2), and 22 weeks 0 days – 29 weeks 6 days (visit 3), with a minimum interval of 4 weeks between visits. Details of the nuMoM2b protocol have been previously published by Haas et al [12]. Ultrasounds were performed for fetal size at all study visits (crown-rump length at visit 1, estimated fetal weights at visits 2 and 3). Uterine artery Doppler velocimetry was assessed in participants at visit 2. Experimental parameters that were assessed in sub-cohorts of the parents study (such as fetal adrenal measurements) were not assessed in our study.

This was a nested case control study, in which we included data only from women who delivered singleton neonates with an SGA birth weight and then identified variables that were different between groups who did and did not experience the primary outcome. SGA was defined as a birth weight < 10^{th} percentile according to the Alexander standard [13]. We chose to define the study population using a birth weight SGA designation rather than

by ultrasonographic fetal size because study ultrasounds were only performed prior to 30 weeks' gestation, before the majority of abnormal fetal growth becomes apparent [14]. Women were excluded if their neonate had known major congenital malformations (those associated with neonatal morbidity), confirmed or suspected aneuploidy, if they did not attend visits 1 or 2, and for missing outcome data.

The primary outcome of composite perinatal morbidity was defined as neonatal intensive care (NICU) admission > 48 hours, necrotizing enterocolitis (NEC), sepsis, respiratory distress syndrome (RDS), mechanical ventilation, retinopathy of prematurity (ROP), seizures, grade 3 or 4 intraventricular hemorrhage (IVH), stillbirth (defined as fetal death occurring after 20 weeks), or death before discharge. Definition of these outcomes for the nuMoM2b study were previously published [12].

Potential maternal factors were drawn from a broad list of variables collected as part of the NuMoM2B study. Demographic factors were collected in the first trimester and included maternal and paternal demographics (age, self-reported race, ethnicity, level of highest education, income). Maternal anthropometrics such as weight, BMI, and resting blood pressure were collected at all three antepartum study visits. Maternal clinical factors included medical conditions such as hypertension, pre-gestational diabetes, thyroid disease, and autoimmune disease; medication use (i.e. total number and class); early pregnancy factors (vaginal bleeding, use of assisted reproductive technology for conception); and uterine artery Doppler velocimetry (assessed at 16 weeks 0 days – 21 weeks 6 days). Maternal social and behavior measures included tobacco and illicit drug use, self-reported sleep quality, dietary habits, physical activity, validated assessments for stress (Perceived Stress Scale), depression (Edinburgh Postnatal Depression Scale), anxiety (State Trait Anxiety Index – Trait scale), and social support (Multidimensional Scale of Perceived Social Support) assessments [15–18].

Analysis

First, characteristics were compared between neonates with and without the perinatal morbidity endpoint using t-tests for continuous and chi-square tests for categorical measures. See Appendix A for all analyzed variables. Characteristics that were significantly different between groups (defined as $p < 0.05$, see Appendix B) were further evaluated prior to model selection, as follows. Multi-category variables (education and hypertensive disorders of pregnancy) were reduced in number of categories where magnitude of association with morbidity was similar and not significantly different between ordinal-adjacent groups, and fewer categories were associated with marked improvement of the Akaike information criterion (AIC) and minimal loss in the area under the receiver-operator characteristics curve (AUC) in a simple bivariate logistic regression (see Appendix C). The AIC is an estimate of prediction error and is helpful in model development [19]. BMI and blood pressure were evaluated as both continuous and categorical variables. Categorization approaches were tested by combining integer values into categories using both standard, clinically relevant categories [20] as well as using cut-points identified by the receiver-operating characteristics (ROC) curve using the Youden index [21]. The approach that resulted in the lowest AIC and highest AUC was selected for use in modeling. Colinearity was avoided by pre-selecting

among two or more characteristics expected to represent redundant assessments of a single underlying factor (e.g. systolic and diastolic blood pressure), the characteristic with the lower AIC was selected for inclusion.

A model that was based on early pregnancy factors (up to 21 weeks 6 days), was estimated first (hereafter referred to as Model 1) because counseling of parents by neonatologists often takes place before birth based on the possibility of imminent birth before all factors leading up to birth are known. No more than 1 parameter estimate per 10 morbidity events was included as a starting point for model selection. When >9% of eligible participants were missing data for a factor that was associated with morbidity, the factor was excluded from the initial round of model selection and later reintroduced to assess significance and its effect on other variables within the model (see Appendix D). Variable selection utilized multiple logistic regression using backwards selection. When variables for a final early-pregnancy model were identified, a hospital clustering effect was investigated by including study site in a hierarchical model, with a plan to use the simple odds ratios (OR) if no clustering was found.

Once the model that only used factors known in early pregnancy had been established and evaluated, variables that could not be known until near the time of delivery were added to estimate a later-pregnancy model (hereafter referred to as Model 2).

Because of the anticipated effect of gestational age on morbidity, gestational age at birth was selected *a priori* for inclusion in Model 2. After adding late-pregnancy variables, backwards selection was utilized to achieve a parsimonious final model 2. Calibration of the final model was then demonstrated by comparing predicted values with the observed rate of morbidity within decile of predicted value.

Data analysis was performed using SAS software, Version 9.4 of the SAS System for Windows. Copyright © 2006 SAS Institute Inc. Graphics were created using GraphPad Prism version 8.1.1 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com. This analysis was approved by the University of Utah institutional review board.

Results

From the original nuMoM2b cohort of 10,038 women, 865 were eligible for analysis (Figure 1). Baseline characteristics are summarized in Table 1. Of eligible women, 134 (15.5%) of their perinates experienced the primary composite endpoint. The most common outcomes within the composite were NICU admission > 48 hours (12.6%, n=104), RDS (4.5%, n=39), and mechanical ventilation (3.1%, n=27). Each of the remaining individual outcomes in the composite occurred in <1% of pregnancies. The variables that were significantly different between the women whose neonates experienced the composite outcome and those who did not are summarized in Table 2, with all analyzed variables (both significant and not) available in Appendices A and B. There was no evidence of clustering by hospital (data not shown).

Variable selection for use in modeling

After removing overlapping variables and optimizing performance by reducing categories or collapsing continuous variables when indicated, nine variables associated with morbidity among SGA neonates were included in the initial model (Table 3; see Appendix C for details of variable omission and selection). The final model 1 included five variables: 1st trimester BMI (categorical), 1st trimester stress level (categorical), 1st trimester diastolic blood pressure (continuous), 1st trimester narcotic use (categorical), and maximum measured uterine artery pulsatility index at 16–21 weeks (continuous, Table 4). Model 1 had an area under the receiver-operating characteristic curve of 0.72 (95% CI 0.67 – 0.76).

Model 2, which added factors that become known only later in pregnancy, added preterm delivery, preeclampsia, and clinical suspicion for FGR to model 1. When incorporating these factors, 1st trimester diastolic blood pressure became non-significant and so was not included in Model 2. In Model 2, the factors with the strongest associations with morbidity were preterm delivery, 1st trimester narcotic use, 1st trimester high perceived stress score, and 1st trimester BMI ≥ 27. (Table 5). The ORs for all included variables are illustrated in Figure 2.

When models 1 and 2 were empirically tested and compared to predicted performance to demonstrate calibration, observed morbidity rates approximately followed expected rates within deciles, though Model 2 followed the line of agreement more closely (Figure 3). Each decile included between 82 and 84 women, and Model 2 had an area under the curve (AUC) of 0.84 (95% CI 0.80–0.88). We provide the formula to compute the probability of composite perinatal morbidity (Table 6).

Discussion:

We analyzed outcomes from 865 neonates from the nuMoM2b cohort to identify factors that were independently associated with perinatal morbidity among SGA neonates, and we developed two predictive models of morbidity. Model 1 included five variables using information that is available during the first half of pregnancy: 1st trimester maternal BMI, 1st trimester maternal perceived stress, 1st trimester diastolic blood pressure, 1st trimester narcotic use, and uterine artery pulsatililty index at 16–21 weeks. Each of these factors conferred similar odds of morbidity (OR 1.6–2.2), except for narcotic use and high perceived maternal stress, which both had ORs of 3.1.

When the model was adapted using factors that only become apparent later in pregnancy or at delivery (model 2), preterm birth was the strongest driver of morbidity (OR 12.6), followed by 1st trimester factors: early pregnancy narcotic use (OR 4.32), BMI (OR 2.59), and high perceived stress (OR 2.59). While prenatal stress has been associated with adverse perinatal and childhood outcomes, we were surprised that its association was as strong as or stronger than that of better recognized factors such as BMI, blood pressure, and suspected FGR [22–26].

Our findings are consistent with previous studies reporting associations of each of these factors with adverse perinatal outcomes [3,26–33]. Indeed, the association of these factors

with neonatal morbidity is already recognized. However, data on the use of these factors for risk stratification of SGA births is limited. It is interesting that while the model identified multiple biomedical risk factors with intuitive links to perinatal morbidity, both moderate and high perceived maternal stress scores were independently associated with perinatal morbidity. Whether stress is a mere indicator of another exposure or is on the causal pathway cannot be inferred from this study design. However, its presence here as an independent risk factor underscores the need for biomedical research and healthcare communities to adopt a more holistic view of prenatal risk stratification.

Because methods to differentiate constitutional from pathologic smallness are inadequate, the development of multimodal approaches to risk stratification is critical to facilitate optimal counseling and management. Once validated, the models presented here will allow for improved stratification of SGA neonates with regard to their chance for morbidity. Furthermore, these models may provide insight into which factors may be relevant for the development of an analogous model for use when FGR is suspected during pregnancy. Such a model could be useful for aiding clinicians in identifying fetuses with suspected FGR who are at highest and lowest risk of morbidity, thereby reducing harm from unnecessary surveillance and intervention for fetuses not at elevated morbidity risk. Additionally, the identification of a set of risk factors for neonatal morbidity could help systems target resources preventively to reduce neonatal morbidity. Such approaches have the potential to reduce cost, increase value, reduce patient burden, and optimize utilization in systems with limited resources.

Prior to clinical application, this model needs to be externally validated and refined. Several factors included in the final model are objective measures that are readily available to clinicians, such as BMI and blood pressure. Although suspected FGR and the diagnosis of preeclampsia are not always easily determined, their dichotomous natures also make them appealing for use in such a model. However, the assessment of prenatal stress is more complex, as its ascertainment at this point in time is not routinely performed. In our cohort, prenatal stress was assessed using the Perceived Stress Scale [15], making it difficult to externally validate these models using datasets wherein stress was assessed using alternative methods. The most poorly defined factor in our model is narcotic use, which was recorded in the nuMoM2b dataset as a dichotomous variable in a section of the maternal interview dedicated to prescription medication use without clarification of the specific medication, dose, and frequency. Prior to further study or clinical application of this model, this factor will need to be further refined, ideally using objective measures, in order to clarify what type and level of narcotic use are associated with adverse outcomes. With projected AUCs of 0.72 (Model 1) and 0.84 (Model 2), both models offer the potential for clinical utility and thus could inform the development of a more refined model, especially when integrated with other ultrasound parameters or biomarkers.

In addition to external validation and refinement, there are multiple uncertainties that need to be addressed to optimize prediction of perinatal morbidity. The most pressing next step is the integration of biomarker data with clinical data. Promising biomarkers range from maternal serum angiogenic factors to placental analytes, to genomic, proteomic, and metabolomic data. Additional opportunities for clarification include the need to determine

whether other metrics for prenatal stress can be used in place of the Perceived Stress Scale, and how the dose and type of opioid relate to the risk of perinatal morbidity. Finally, novel applications of machine learning and computational biology methods are needed to fully leverage the depth of characterization in the nuMoM2b cohort to improve understanding and prediction of adverse pregnancy outcomes.

Our study has multiple strengths. First, data were prospectively collected at multiple centers using standardized methods and validated questionnaires, which maximized data quality and validity. Second, the breadth and high quality of information collected across various pregnancy epochs allowed for an in-depth and novel assessment of psychosocial variables that have previously been difficult to analyze alongside more traditional biometric factors. There were also several limitations of our study. The cohort was defined by birth weight rather than by ultrasonographic diagnosis of FGR, making our models valuable for stratification of neonates once they are known to have an SGA birthweight, but generally precluding their application at the time when FGR is first diagnosed. Ideally, a similar model could be developed for prenatal application when a fetus is suspected to have FGR. This analysis can be used as a starting point to identify factors that can later be tested for antepartum risk stratification in the setting of suspected FGR. Also, the use of birth weight percentile to define the cohort could have caused stillbirths of normally grown fetuses to be considered SGA at birth if a delay occurred between the fetal death and delivery. However, this was unlikely to affect the analysis, since only 2 of the 134 cases that suffered the primary morbidity endpoint had a stillbirth. Another limitation was our inability to elaborate further on certain factors within the model, such as dosing and indication for narcotic use, and specific types of stressors that the women in this cohort experienced and were associated with perinatal morbidity [15]. The variable “clinical suspicion for FGR” was collected via chart abstraction after delivery, so information on the reasons for the ultrasound that diagnosed FGR and the surveillance protocol after FGR diagnosis was not available. Finally, because of the size of the SGA sub-cohort and relatively infrequent perinatal morbidity, the entire sample was required to generate the model, such that use of an internal validation cohort was not possible.

We identified prenatal factors associated with perinatal morbidity in a population of SGA neonates and integrated them into two predictive models with moderate-good performance. Prior to clinical application, these models need to be externally validated and refined. Future directions include the need for integration of biomarker data and novel computational approaches to assess the complex relationships between factors associated with perinatal morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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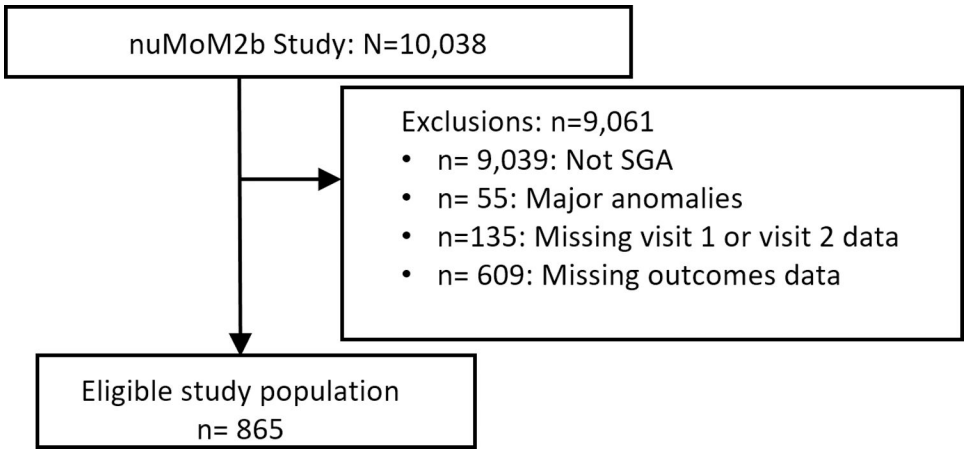

Figure 1: Study inclusion flow diagram.
SGA, small for gestational age.

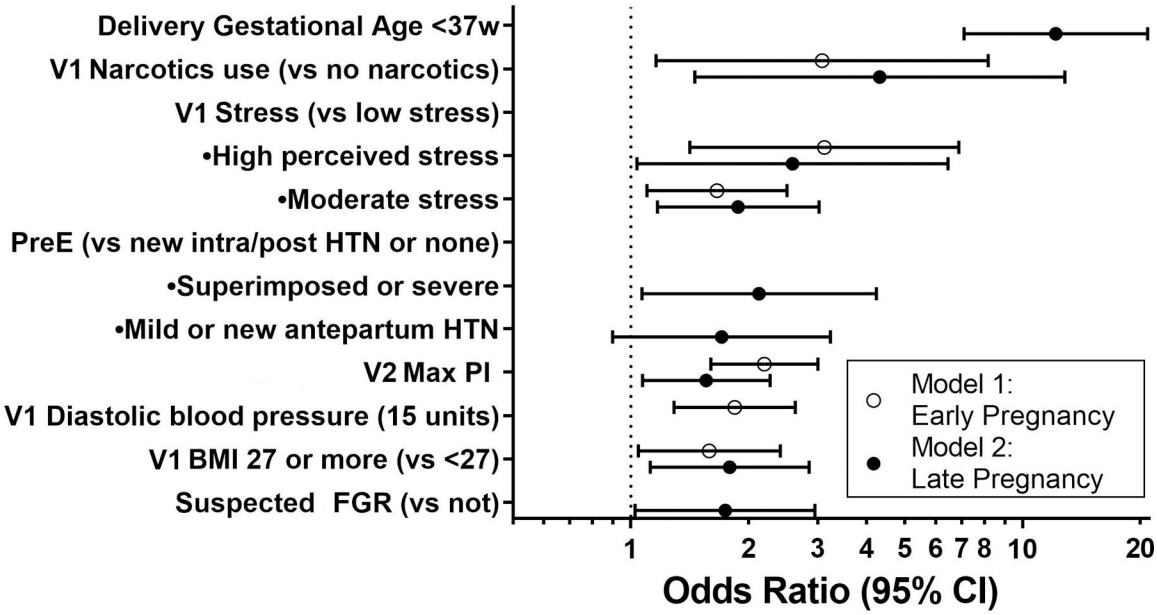

Figure 2: Association of factors with morbidity among SGA neonates when applied in both early and late pregnancy models.

V1, visit 1 (6–13 weeks); V2, visit 2 (16–21 weeks), PreE, preeclampsia; intra, intrapartum; post, postpartum; HTN, hypertension; FGR, fetal growth restriction; Max PI, maximum measured pulsatility index; BMI, body mass index.

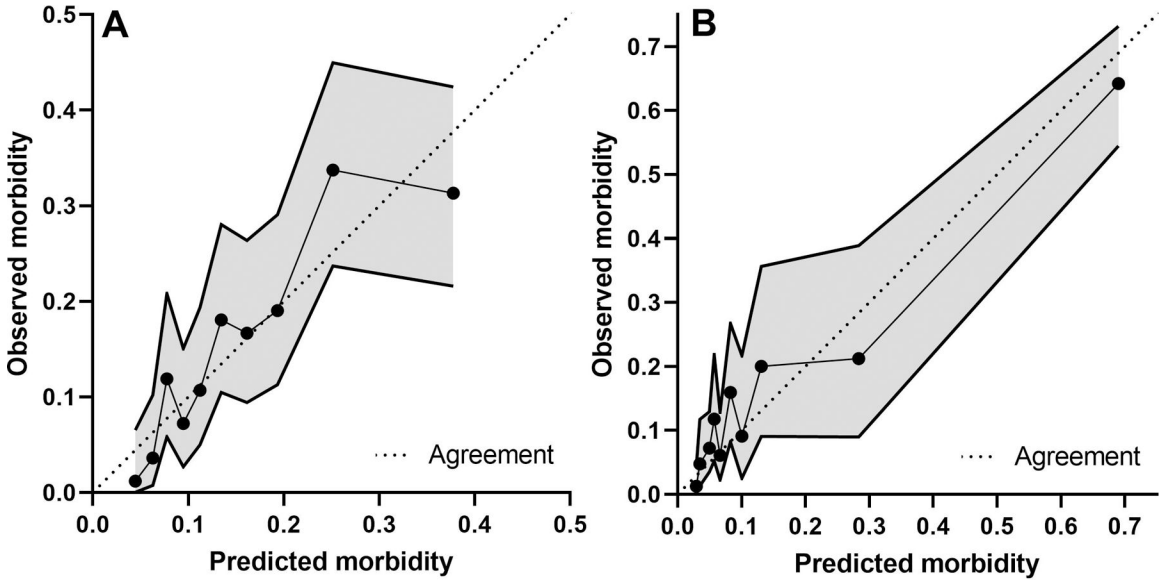

Figure 3: Application of models 1 and 2 for internal calibration

The median of the predicted decile is plotted on the X axis and observed probability of morbidity is plotted on the Y axis. All confidence intervals contain the line of agreement between predicted values and observed values for Early Pregnancy (A) and Late Pregnancy (B) models.

Table 1.

Study population baseline characteristics

	N=865
Maternal age category	
13–17	22 (2.5)
18–34	764 (88.4)
≥ 35	78 (9.0)
Race/ethnicity	
Non-Hispanic white	422 (48.8)
Non-Hispanic Black	182 (21.1)
Hispanic	157 (18.2)
Asian	53 (6.1)
Other	50 (5.8)
Maternal BMI category at visit 1	
<18.5	39 (4.6)
18.5–24.9	447 (52.9)
25–29.9	195 (23.1)
30–34.9	86 (10.2)
≥ 35	78 (9.2)
Chronic hypertension	35 (4.1)
Pre-gestational diabetes	11 (1.3)
Education attained	
Less than high school	105 (12.2)
High school or GED	121 (14.0)
Some college	179 (20.7)
Associate/ technical degree	79 (9.2)
Completed college	203 (23.5)
Any beyond college	176 (20.4)
Poverty category	
<100% FPL	126 (19.6)
100–200% FPL	90 (14.0)
≥200% FPL	426 (66.4)
Age at delivery < 37 weeks	117 (13.5)
Composite perinatal morbidity	134 (15.5)
NICU admission >48 hours	104 (12.6)
RDS	39 (4.5)
Mechanical ventilation	27 (3.1)
ROP	7 (0.8)
Death before discharge	6 (0.7)
Sepsis	2 (0.2)
NEC	2 (0.2)
Stillbirth	2 (0.2)

	N=865
Seizures	2 (0.2)
Grade III/IV IVH	1 (0.3)

Data are reported as n(%).

BMI, body mass index; GED, general education diploma; FPL, federal poverty level; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage.

Table 2.

All factors with significant differences between SGA neonates who did and did not experience the composite morbidity.

Variable	Morbidity[a] N=134	No Morbidity N=731	p
Education attained some college or less	75 (56.0)	330 (45.3)	0.023
BMI at visit 1, GMean (95% GMCI)	26.7 (25.5, 27.9)	24.8 (24.4, 25.2)	0.002
Maternal BMI category at visit 1 < 27	74 (56.1)	514 (72.1)	<.001
Chronic hypertension	11 (8.2)	24 (3.3)	0.008
Blood Pressure at 6w0d - 13w6d, mean (SE)			
Systolic	112 (1.18)	108 (0.41)	0.005
Diastolic	69.5 (0.82)	66.1 (0.31)	<.001
Pre-gestational diabetes	5 (3.7)	6 (0.8)	0.006
Hypertensive disorders of pregnancy			
Superimposed preeclampsia	5 (3.7)	4 (0.5)	
PreE with severe features	33 (24.6)	31 (4.2)	
PreE without severe features	5 (3.7)	26 (3.6)	<.001
New onset antepartum HTN	14 (10.4)	54 (7.4)	
New onset intrapartum or postpartum HTN	7 (5.2)	81 (11.1)	
No hypertensive disorder	70 (52.2)	534 (73.2)	
Narcotic use	8 (8.2)	12 (2.2)	<.001
Age Difference (Dad - Mom) (years) mean (SE)	3.15 (0.37)	2.30 (0.16)	0.037
Vegetable servings 10 or greater (goal)	4 (3.7)	59 (9.7)	0.04
HEI-2010 component 10, Sodium	8 (7.34)	19 (3.12)	0.033
Perceived Stress Scale, mean (SE)	15.0 (0.60)	13.2 (0.26)	0.006
Perceived Stress Scale category			
Low stress	57 (43.2)	402 (55.3)	0.005
Moderate stress	63 (47.7)	296 (40.7)	
High stress	12 (9.1)	29 (4.0)	
EPDS score, mean (SE)	6.56 (0.40)	5.69 (0.16)	0.046
EPDS category			
Low risk for depression	101 (76.5)	599 (84.5)	0.076
Possible depression	20 (15.2)	68 (9.6)	
Likely depression	11 (8.3)	42 (5.9)	
Uterine artery Doppler at 6w0d - 13w6d			
RI, GMean (95% GMCI)	.709 (0.698, 0.73)	.646 (0.64, 0.66)	<.001
PI, GMean (95% GMCI)	1.56 (1.46, 1.66)	1.26 (1.22, 1.29)	<.001
Diastolic notch present, n(%)	50 (37.3)	203 (27.8)	0.026
Adequate exercise[b]	25 (32.9)	238 (46.8)	0.023

Data are expressed as n(%) unless otherwise stated.

SGA, small for gestational age; HS, high school; GED, general education diploma, BMI, body mass index; preE, preeclampsia; HTN, hypertension; GMean, geometric mean; CI, confidence interval; SE, standard error; EPDS, Edinburgh Postnatal Depression Scale; RI, resistive index; PI, pulsatility index.

[a] Composite perinatal morbidity was defined as any of the following: NICU admission, NEC, sepsis, RDS, mechanical ventilation, ROP, seizures, grade III/IV IVH, stillbirth, or death prior to discharge.

[b] Defined as ≥ 150 minutes of moderate activity (3–6 metabolic equivalents of task (METs)) per week or ≥ 75 minutes per week of vigorous activity (≥6 METs) per week.

Table 3.

Variables included in the initial model after removing overlapping variables and collapsing continuous or multi-categorical variables to optimize performance

Variable	Morbidity[a] N=134	No Morbidity N=731	P
Education Some college or less	75 (55.97)	330 (45.27)	0.023
BMI ≥ 27	58 (43.94)	199 (27.91)	<.001
Diastolic BP at 6w0d - 13w6d Mean (SE)	69.5 (0.82)	66.1 (0.31)	<.001
Hypertensive disorder of pregnancy			
Superimposed PreE or PreE with SF	38 (28.36)	35 (4.79)	<.001
PreE without SF or new antepartum HTN	19 (14.18)	80 (10.96)	
New intrapartum/PP HTN or none	77 (57.46)	615 (84.25)	
Narcotic use	8 (5.97)	12 (1.64)	0.002
Parent Age Difference Mean (SE)	3.15 (0.37)	2.30 (0.16)	0.037
Perceived Stress Scale category			
Low stress	57 (43.18)	402 (55.30)	0.005
Moderate stress	63 (47.73)	296 (40.72)	
High stress	12 (9.09)	29 (3.99)	
EPDS score, mean (SE)	6.56 (0.40)	5.69 (0.16)	0.046
Uterine artery PI, GMean (95% GMCI)	1.56 (1.46, 1.66)	1.26 (1.22, 1.29)	<.001

Data are expressed as n(%) except where otherwise specified.

HS, high school; GED, general education diploma; BA/BA, bachelor's degree; BMI, body mass index; SE, standard error; preE, preeclampsia, SF, severe features; HTN, hypertension; PP, postpartum; GMean, geometric mean; EPDS, Edinburgh Postnatal Depression Scale; PI, pulsatility index.

[a]Alcohol score according to the Alternative Healthy Eating Index (AHEI-2010).[34]

[c]Defined as ≥ 150 minutes of moderate activity (3–6metabolic equivalents of task (METs)) per week or ≥ 75 minutes per week of vigorous activity (≥6 METs) per week.

Table 4.

Final model of early pregnancy variables (Model 1)

Variable	Odds Ratio	95% Wald Confidence Limits	
BMI ≥ 27	1.59	1.05	2.41
High perceived stress[a]	3.12	1.41	6.87
Moderate stress[a]	1.66	1.10	2.51
Diastolic BP at 6w0d - 13w6d[b]	1.84	1.29	2.63
Uterine artery PI at 16w0d – 21w6d[c]	2.19	1.60	3.00
Narcotic use (Yes vs No)	3.08	1.16	8.16

BMI, body mass index; BP, blood pressure; PI, pulsatility index.

[a]Perceived Stress Scale (referent group: low stress)[15]

[b]Diastolic blood pressure modeled continuously, with Odds Ratio provided for a 15-unit increment in diastolic blood pressure

[c]Maximum measured PI (rather than average)

Table 5.

Morbidity prediction model including factors known up to the time of delivery (Model 2).

Variable	Odds Ratio	95% Wald Confidence Limits	
Gestational Age at birth < 37 weeks	12.6	7.09	20.8
PreE [a]			
Superimposed preE or preE + SF	1.71	0.90	3.23
PreE without SF or new antepartum HTN	2.13	1.07	4.23
Stress [b]			
High perceived stress	2.59	1.04	6.45
Moderate stress	1.88	1.17	3.02
Narcotic Yes vs No	4.32	1.46	12.82
Suspected FGR Yes (vs No)	1.74	1.03	2.95
Diastolic Blood Pressure at 6w0d – 13w6d	1.56	1.07	2.27
Uterine artery PI [c] (16w0d – 21w6d)	1.79	1.12	2.85
BMI ≥ 27	2.59	1.04	6.45

preE, preeclampsia; SF, severe features; HTN, hypertension; FGR, fetal growth restriction; PI, pulsatility index; BMI, body mass index.

[a] Referent group: no hypertensive disorder or those with new intrapartum or postpartum hypertension.

[b] Perceived Stress Scale (referent group: low stress)[15]

[c] Maximum measured PI (rather than average)

Table 6.

Formula to calculate the probability of composite perinatal morbidity among SGA neonates

	Model 1 m-scores	Model 2 m-scores
Intercept	−6.1502	−3.8739
High perceived stress	1.1369	0.9504
Moderate stress	0.507	0.6309
PreE no SF or new antepartum HTN		0.5333
Superimposed preE or preE + SF		0.7538
Narcotic Use	1.1242	1.4634
Suspected FGR		0.5543
BMI ≥ 27	0.4609	0.5808
Diastolic BP at 6w0d - 13w6d	0.0407	
Uterine artery PI at 16w0d – 21w6d[a]	0.7854	0.4436
Delivery < 37 weeks		2.4977
Total M-score		

HTN, hypertension; preE, preeclampsia; SF, severe features; BMI, body mass index; BP, blood pressure; PI, pulsatility index.

The total M-score is computed as follows: for categorical variables: add the value of each variable (if present) to the intercept; for continuous variables: multiply the variable by its m-score and add to the intercept. The total M-score can then be used to calculate the probability of composite morbidity using the “Probability” formula.

[a]Maximum measured PI.