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ORIGINAL ARTICLE

Evaluation of fetal medicine foundation algorithm in predicting small-for-gestational-age neonates

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ABSTRACT

Objectives: To examine the performance of the Fetal Medicine Foundation (FMF) 2012 predictive model and of isolated biophysical markers (uterine artery pulsatility index and mean arterial pressure) for small-for-gestational-age (SGA), in patients from Rio de Janeiro, Brazil.

Methods: For this cross-sectional study, SGA was diagnosed when a newborn presented birth weight below the fifth percentile for gestational age. FMF2012 algorithm sensitivity and specificity, positive (PPV) and negative (NPV) predictive value, positive likelihood ratio (LR +) and area under the ROC curve (AUC) were calculated to predict total and preterm SGA (SGA < 37). The performance of isolated biophysical markers – mean arterial pressure (MAP) and mean uterine artery pulsatility index (UtAPI) were studied.

Results: The final sample consisted of 1480 cases: 69 (4.6%) developed SGA, including 12 patients (0.8%) who were SGA < 37. The AUC showed that the performances of the FMF2012 combined model for SGA prediction was 0.687 and for preterm SGA was 0.824. With risk cutoff of 1:150, SGA screening yielded the following: sensitivity, 47%; specificity, 75%; LR +, 1.88; PPV, 8.66%; NPV, 96.72%. When screening for preterm SGA, we found sensitivity 66.6%, specificity 74.59%, LR +: 2.58, PPV 2%, and NPV 99.63%.

Conclusions: Performance of the FMF2012 algorithm in predicting SGA in our population was similar to that obtained in the reference population, according to sensitivity, but our false positive rate is significantly higher than the reference population.

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Clinical prediction model; mass screening; reproducibility of results; sensitivity and specificity; small for gestational age

Introduction

There is a known relationship between birthweight and gestational age at birth, first published by Lubchenco et al. in 1963 [1], that categorizes neonates as adequate, small or large for gestational age at birth, according to a numerical cutoff.

Small-for-gestational-age (SGA) neonates is a heterogeneous situation that includes constitutionally small fetuses and growth restricted fetuses (FGR) due mainly to impaired placentation [2–5].

Birthweight and neonatal death are inversely related, and FGR is reported in association with ~50% of stillbirths without malformations [1,6,7]. Also, there is a relationship between cerebral palsy and fetal reprogramming. The latter can lead to consequences in adulthood because of cardiovascular alterations, metabolic changes, and neural development [8–13]. Furthermore, respiratory discomfort, intraventricular hemorrhage, and necrotizing enterocolitis [14] are more frequent when birth occurs before 37 weeks of pregnancy.

Centralizing care to SGA high-risk pregnancies reduces perinatal death, compared with outcomes in newborns for whom restricted growth was detected after birth. Prenatal identification, adequate monitoring, timely delivery, and appropriate neonatal care are required [15].

SGA detection rate is only 15% in low-risk pregnancies and 25% in high-risk pregnancies. These low detection rates increase the risk of perinatal complications and stillbirth [13,16–18].

The potential value of early SGA screening is the possibility of elaborating prophylactic measures, such as the introduction of low-dose acetylsalicylic acid (ASA), which reduces the prevalence and/or delays symptoms to later gestational ages, reducing perinatal consequences [2,19]. Challenges in the management of these gestations include the accurate detection of

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fetuses with risk for adverse outcomes, prevention of fetal death, and appropriate choice of intervention threshold [20]. Any strategy that demands the prevention of SGA requires effective screening to identify high-risk patients during the first trimester of pregnancy [21]. These strategies may be employed to achieve a 30% reduction in low birth weight by 2025, which is the stated goal of the World Health Organization (WHO) Global [22].

The Fetal Medicine Foundation (FMF) provides a predictive model that estimates the risk for SGA and other adverse obstetric outcomes [23]. This study aimed to examine the performance of FMF2012 predictive model and of isolated biophysical markers (uterine artery pulsatility index and mean arterial pressure) for SGA, in patients from Rio de Janeiro, Brazil.

Materials and methods

This is a retrospective analysis of a prospectively collected cohort of all singleton pregnancies screened for adverse obstetric outcomes (aneuploidies, PE, SGA, and preterm spontaneous delivery) at $11–13^{+6}$ weeks' gestation. This study was part of a larger ongoing study examining the performance of the FMF2012 algorithm.

The study was conducted at Maternidade Escola da Universidade Federal do Rio de Janeiro (ME/UFRJ), a university and nonprofit hospital located in the city of Rio de Janeiro, in the southeast region of Brazil. The estimated sample size was based upon the prevalence of SGA at the institution in 2011–2012 (3.1%) [24], an α error of 5% and a power of 95%. A sample of at least 1556 pregnant women, with 47 cases of SGA was required. GPower version 3.1.9.3 for Mac OS X software [25] (GPowerMac, Universität Düsseldorf, Düsseldorf, Germany) was used for the calculation of sample size.

Women were screened between October 2010 and December 2015. We excluded pregnancies with aneuploidies and major fetal abnormalities, pregnancies ending in termination, miscarriage or fetal death before 24 weeks, pregnancies that developed preeclampsia (PE), and patients that started the use of ASA before 16 weeks.

The study was approved by Research Ethics Committee – CAAE 25575913.2.0000.5275.

Patients were asked to complete a questionnaire identifying ethnicity, and some aspects of clinical, obstetric and family history, essential for risk calculation by the FMF2012 algorithm. These variables are the maternal factors: (i) weight in kilograms and height in centimeters; (ii) maternal age at the time of screening, in years; (iii) ethnicity: skin colour (self-reported; white, black or mixed); (iv) parity: number of previous deliveries that occurred after 24 weeks. (If equal to 0, the patient was classified as nulliparous. If $\geq$1, the patient was classified based upon the previous history of PE and/or SGA.); (v) history of smoking during pregnancy (yes or no); (vi) presence of diabetes mellitus (type 1, 2 or no); (vii) chronic hypertension (yes or no); (viii) systemic erythematous lupus (yes or no); (ix) antiphospholipid antibody syndrome (yes or no); (x) family history of PE (yes or no) and (xi) gestation from assisted reproductive technology (ART; yes or no).

Biophysical markers considered as variables of the study were: (i) crown-rump length (45–84 mm); (ii) mean arterial pressure (MAP): measured with the patient in the seated position, following $\geq$10 min of rest. MAP was simultaneously measured in both arms with an appropriately sized cuff (3BTO-A2, Microlife, Taipei, Taiwan; ONROM, Omron Corporation, Kyoto, Japan). Values were reported in mm Hg and in multiples of median (MoM) [26]; (iii) mean uterine artery pulsatility index (UtAPI): arithmetic mean of UtAPI, according to FMF (also described in MoM) [27]. All data, including those from patients screened between 2010 and 2012, were entered into FMF 2012 software for calculation of SGA risk.

Risk scores were calculated according to the logistic regression model described by Poon et al. [23]. Screen positivity is defined by the risk cutoff of 1:150 using the algorithm for preterm-SGA.

The screening results did not interfere with professional conduct during prenatal care. As FMF algorithm was not validated in our hospital, ASA was prescribed at a dose of 100 mg/d, at bedtime for PE prophylaxis based on WHO recommendations [28,29].

Data on pregnancy outcome were collected from hospital records. GA at birth was calculated based on the date of the last menstrual period or first-trimester ultrasound screening. When the difference between those timepoints was greater than 7 d, the ultrasound estimation was used. The final sample was classified in accordance with the original work as follows [23,30]: normal, newborns with birthweight $>$5th percentile for gestational age; SGA, all newborns with birth weight $<$ 5th percentile for gestational age (term and preterm); preterm SGA, newborns with birthweight $<$ 5th percentile for gestational age, if delivery occurred before 37 weeks of pregnancy. We only considered cases with known birthweight.

Statistical analysis

Statistical software package Stata version 13.0 (StatCorp, College Station, TX) and MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium) were used for data analysis. It was determined preterm and total SGA prevalence in the final sample and in the excluded subgroups: ASA use before or at 16 weeks of gestation and PE development. The median of continuous variables and ratios of categorical variables were compared between outcome groups by Mann–Whitney U test and by chi-squared test or Fisher test (when the expected value was < 5). Differences between groups were considered statistically significant if p-value $< .05$.

A box plot was created to illustrate the distribution of screening results in the following groups: (i) final sample, normal cases and those that developed SGA and SGA < 37; (ii) excluded cases (as previously described); (iii) loss to follow-up, cases with unknown outcomes.

The performance of screening for total and preterm SGA was determined by evaluating sensitivity and specificity, positive predictive value (PPV) and negative predictive value (NPV), positive likelihood ratio(LR), and receiver operator characteristic (ROC) curve analysis. MAP and UtAPI isolated performances for the prediction of total and preterm SGA were compared with the corresponding ROC curves. AUC was compared as described previously [31] and considered different when p-value $< .05$.

Results

First trimester combined screening for obstetric adverse outcomes was carried out in 1934 patients. We excluded 454 cases due to fetal aneuploidies ($n = 7$); major fetal malformation ($n = 28$); miscarriage, termination, or fetal death before 24 weeks of gestation ($n = 18$); ASA use before or at 16 weeks of gestation ($n = 103$); PE ($n = 120$); and missing outcome data ($n = 178$). The remaining 1480 cases were included in the study. The prevalence of SGA in the final sample was 4.6% ($n = 69$), with 0.8% ($n = 12$) of these cases categorized as preterm SGA. The two excluded subgroups: ASA use before or at 16 weeks of gestation and PE development presented SGA rates of 24.73 (95% CI: 16.89–34.68) in 23 of 93 cases of known birthweight (10 missing outcome data) and 13.68 (95% CI: 8.4–21.29) in 117 of 120 cases (3 missing outcome data).

Table 1 shows the characteristics of the final sample and the comparison of these characteristics between the normal group and those with SGA.

The distribution of risk values for SGA, UtAPI, and MAP is shown in Figure 1. Figure 2 presents the ROC curves and respective AUC with 95% confidence intervals (CI).

Table 1. Maternal and gestational characteristics in the outcome groups.

Characteristics	Normal $n = 1411$	SGA $n = 69$	p
Maternal age – mean, median (age)	27.27 [22–32]	27.27 [21–33]	.51
Maternal weight – mean, median (kg)	66.64 [57–74]	63.62 [54–73]	.07
Maternal height – mean, median (cm)	160.160 [156–165]	158.158 [154–162]	.0018*
Race/skin colour:			
White	548 (61.2)	31 (44.9)	
Black	269 (19.06)	13 (18.8)	.843
Mixed	593 (42.02)	25 (36.2)	>.99
Parity:			
Nulliparous	768 (54.4)	50 (72.4)	
Parous with no previous PE/SGA	684 (41.3)	17 (24.6)	.011*
Parous with previous PE/SGA	59 (4.18)	2 (2.89)	.931
Cigarette smoker	54 (3.82)	3 (4.34)	.82
Family history of PE	83 (5.88)	8 (11.59)	.05*
Assisted conception	2 (0.14)	1 (1.44)	.01*
History of chronic hypertension	33 (2.33)	3 (4.34)	.29
History of type I diabetes mellitus	11 (0.77)	4 (5.79)	.2
History of type II diabetes mellitus	15 (1.0)	0	>.99
History of SLE or APS	0	0	–
GA at birth	39.43 [38.57–40.29]	38.29 [37.43–39.29]	.002*
Birth weight	3290 [3035–3580]	2460 [2240–2690]	.000*
CRL – median (mm)	63.7 [58–70]	62 [57–69]	.21
UtAPI – median	1.72 [1.36–2.04]	2.02 [1.65–2.36]	.000*
MAP – median	83.8 [78.2–90]	86.6 [79.55–91.35]	.02*

Values between () are percentages and between [] are interquartile ranges. SGA: small for gestational age; PE: preeclampsia; CRL: crown-rump length; SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; GA: gestational age; CI: Confidence Interval; UtA: uterine artery; PI: pulsatility index; MAP: mean arterial pressure. Comparisons between outcome group and unaffected group: chi-square (χ^2) or Fisher's exact test for categorical variables and Mann–Whitney test for continuous variables.
*p-value $< .05$.

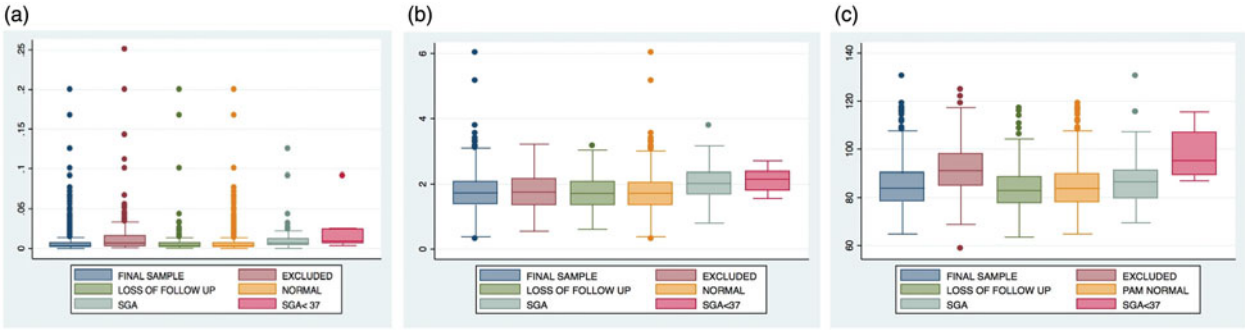
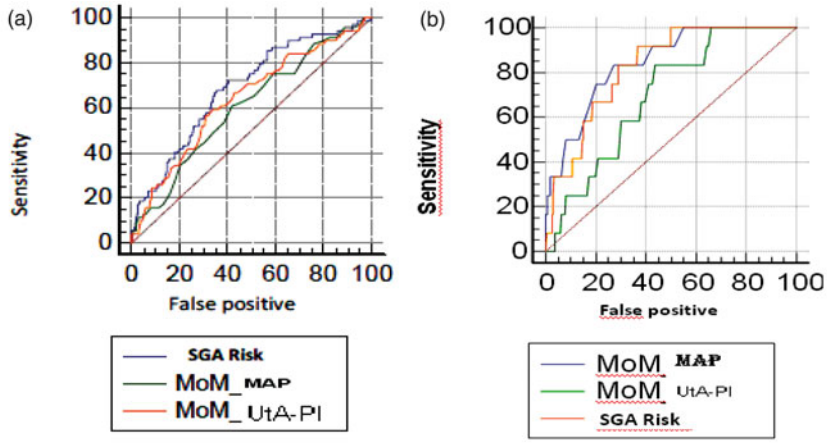


Figure 1. Box plot for (a) SGA risk; (b) UtAPI, and (c) MAP in studied groups. SGA: small for gestational age; UtAPI: mean uterine artery pulsatility index; MAP: mean arterial pressure.



	AUC	SD[a]	95%CI
SGA Risk	0.687	0.0326	0.663 –0.711
MoM_MAP	0.606	0.0348	0.581–0.631
MoM_UtAPI	0.639	0.0353	0.614–0.664

	AUC	SD[a]	95%CI
MoM MAP	0.843	0.0494	0.824 –0.861
MoM UtAPI	0.695	0.0605	0.671 –0.719
SGA Risk	0.824	0.0450	0.803 –0.843

Figure 2. ROC curves for (a) SGA and (b) SGA < 37. SGA: small for gestational age; MoM: Multiples of median; MAP: Mean Arterial Pressure; UtAPI: mean uterine artery pulsatility index; AUC: area under curve; SD: standard deviation; CI: confidence interval.

The performance of FMF2012 algorithm in predicting SGA, at any gestational age was: sensitivity of 47%; specificity of 75%; LR + of 1.88; PPV of 8.66%; NPV of 96.72%.

For the prediction of preterm SGA, the FMF 2012 algorithm showed the sensitivity of 66.6%; specificity of 74.59%, LR + of 2.58, PPV of 2%, and NPV of 99.63%.

The excluded subgroup of ASA users patients exhibited a sensitivity of 69.5% and specificity of 35.7%. PE development group presented a sensitivity of 62.5% and specificity of 63.3%.

Discussion

The present study evaluates the performance of the screening model for SGA < 37 included in the FMF2012 algorithm. The study was also extended to total SGA, which corresponds to newborns with birthweight below the 5th percentile, between 24 and 42 weeks, as term SGA newborns have a greater risk for morbidities over the long term when compared to newborns with adequate weight for gestational age [9,11,12]. We considered the same exclusion criteria as Poon et al. [23] to generate comparative results, as the main objective of the study was to evaluate the performance as an external validation of the FMF2012 algorithm.

The prevalence of total SGA in our sample was 4.6% and 0.8% for preterm SGA, compared with previously reported values of 5.1% and 0.6% [23]. In a prospective cohort of patients submitted to first-trimester screening, Crovetto et al. [32] found a prevalence of

10.9% for SGA newborns and 5.2% for fetuses with FGR. The authors [32] state that most IUGR prediction models consider the newborn, rather than the fetus, as the subject of the outcome, and the prevalence of FGR fetus or SGA newborns depends on the patterns assumed to define the condition.

Table 1 shows the results of the bivariate analysis of maternal factors and biophysical markers. We did not observe the same differences between groups in maternal factors, as observed by Poon et al. [23]. However, the primary outcome investigated by Poon et al. [23] was the preterm SGA newborn, while our primary outcome was SGA, as we did not have statistical power to establish differences between the normal group and preterm SGA.

Our sample showed differences between groups in maternal height, previous pregnancies without PE or SGA, maternal family history of PE, and ART use. Poon et al. [23] found lower means for age and maternal weight and higher prevalence of nonwhite ethnicity, cigarette smoking, gestation from ART, previous pregnancy with SGA neonates, chronic hypertension, and type 2 diabetes mellitus. The authors also found a lower prevalence of type 1 diabetes mellitus in the SGA group compared to the normal group.

Ethnic differences remain controversial [33–35]. In our sample, we did not find statistical differences in SGA occurrence among maternal ethnic groups. However, the criterion we used as a proxy for ethnicity was skin color, as self-reported by the patient. Skin color is one of the phenotypic characteristics that constitutes race and is not necessarily related to ancestry, especially in a multicultural and mixed society such as Brazil [36].

The distributions of SGA risk, UtAPI, and MAP values were similar in the final sample and the group with unknown outcomes, which validates the final sample as representative of the eligible population (Figure 1).

Among 276 excluded patients, 120 developed PE, and 103 used ASA. The clinical criteria adopted by ME/UFRJ in prescribing ASA are the same criteria included in the predictive model as maternal factors. The score values of the excluded group were significantly higher than those of the final sample (Figure 1). This reinforces the exclusion criteria, as they succeeded in excluding high-risk SGA patients, who could have been counted as false positives (FP). The distribution of MAP in this group also exhibited higher values, as patients with chronic hypertension and/or clinical criteria for ASA use during gestation were included in this group. Finally, the distribution of UtAPI was similar in the excluded group and the final sample (Figure 1). We believe this happened because 120 cases were mostly late PE, and 103 cases involved ASA use. First-trimester UtAPI is not a good predictor for late PE and is not altered in chronic hypertension [27,37]. Cases that evolved with SGA have risk scores and isolated UtAPI values significantly higher than those of the normal group, which proves the ability of both to identify cases at high risk for SGA, particularly the preterm form (Figure 1). When we observed the SGA results in these excluded subgroups, we noticed that they were, as expected, a real high-risk group with an inflated SGA prevalence despite the prophylactic measure. Although the discussion about the reasons for ASA ineffectiveness, in this subgroup, is beyond the scope of this study, we believe that ASA prescription based on clinical factors is insufficient. Furthermore, we don't know what would happen if ASA had been prescribed for cases identified as high-risk by the FMF2012 algorithm.

The SGA predictive model provided by FMF presents an AUC from maternal factors plus UtAPI and MAP of 0.759. Our value was 0.824, similar to that of 0.822 observed by Poon et al. [23] when they used maternal factors plus all biophysical and biochemical markers. For a 10% FP rate, we observed a detection rate of 41% in our population, while they observed 44.8%.

Our reference predictive model [23] presented a detection rate of 30% for preterm SGA. We found a sensitivity of 66% with FP of 25% for prediction of preterm SGA. For SGA, at any gestational age, sensitivity was 47%, with FP of 25% the higher FP rate can be explained by the distinct impact of maternal characteristics in our sample. This aspect was not evaluated in this study.

Comparison between ROC curves showed that FMF score risk and isolated UtAPI yield statistically similar prediction of SGA, as well as MAP, in predicting preterm SGA (Figure 2) [23,38].

The limitations of our study include the small number of preterm SGA subjects, which represent the FMF2012 algorithm endpoint, and are the best cases for the examination of predictive performance. Changes in the institution's health care protocols in 2013 incorporated ASA prescription, based on clinical criteria, for patients at high risk for PE, which forced us to exclude a significant portion of cases that were high-risk for SGA, which may have been true positives.

Even with a large 95% CI, we obtained significant results regarding the performance of FMF2012 algorithm for preterm SGA prediction and extended the

same cut-off value to test the performance for SGA screening.

The high NPV was a favorable aspect of our research.

We conclude that the FMF2012 predictive model, which includes maternal factors and biophysical markers, applied in a Brazilian population presented comparable detection rate but a higher false positive rate than the reference population for a given risk cutoff.

Disclosure statement

No potential conflict of interest was reported by the authors.

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