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CLINICAL ARTICLE

Obstetrics

Performance of the INTERGROWTH-21st and World Health Organization fetal growth charts for the detection of small-for-gestational age neonates in Latin America

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Synopsis

The contents of this page will be used as part of issue TOC only. It will not be published as part of main article.

Comparison of fetal growth charts in Latin America. Although using the World Health Organizations standard increases the proportion of small for gestational age and fetal growth restriction neonates in Latin America, the INTERGROWTH-21st standards have better diagnostic performance in ruling in and out adverse neonatal outcomes.

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Abstract

Objective: To evaluate the performance of INTERGROWTH-21st (IG-21st) and World Health Organization (WHO) fetal growth charts to identify small-for-gestational-age (SGA) and fetal growth restriction (FGR) neonates, as well as their specific risks for adverse neonatal outcomes.

Methods: Multicenter cross-sectional study including 67 968 live births from 10 maternity units across four Latin American countries. According to each standard,

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neonates were classified as SGA and FGR (birth weight <10th and less than third centiles, respectively). The relative risk (RR) and diagnostic performance for a low Apgar score and low ponderal index were calculated for each standard.

Results: WHO charts identified more neonates as SGA than IG-21st (13.9% vs 7%, respectively). Neonates classified as having FGR by both standards had the highest RR for a low Apgar (RR, 5.57 [95% confidence interval (CI), 3.99–7.78]), followed by those who were SGA by both curves (RR, 3.27 [95% CI, 2.52–4.24]), while neonates with SGA identified by WHO alone did not have an additional risk (RR, 0.87 [95% CI, 0.55–1.39]). Furthermore, the diagnostic odds ratio for a low Apgar was higher when IG-21st was used.

Conclusion: In a population from Latin America, the WHO charts seem to identify more SGA neonates, but the diagnostic performance of the IG-21st charts for low Apgar score and low ponderal index is better.

KEYWORDS
developing countries, fetal growth, fetal growth restriction, growth standard, low birthweight, perinatal morbidity, perinatal outcomes, pregnancy, small for gestational age

1 | INTRODUCTION

Small-for-gestational-age (SGA) neonates are at increased risk of mortality and several morbidities,[1] suboptimal neurodevelopment,[2] and susceptibility to cardiovascular disease later in life.[3] Furthermore, the rate of perinatal death is significantly higher in unrecognized SGA fetuses than in those who are antenatally detected, appropriately followed, and managed accordingly.[4] Current guidelines recommend the 10th centile as a cutoff to define SGA and the third centile to define fetal growth restriction (FGR)[5,6] since several studies have demonstrated an increased risk of perinatal morbidity and mortality beyond these cutoffs. However, there is disagreement on which charts should be used worldwide.[7]

Two international standards for fetal growth have been constructed and published as a global effort to reduce the reported variability and the worldwide discrepancy when defining FGR. First, the INTERGROWTH-21st (IG-21st) project reported fetal biometry standards constructed with 20486 low-risk pregnancies delivered between 33 and 42 weeks.[8] Using a similar concept and methodology, the World Health Organization (WHO) multicenter growth reference study proposed an alternative standard.[9] However, previous studies evaluating the diagnostic performance of these fetal growth standards in different populations have reported conflicting results, preventing their worldwide adoption and implementation.[10–16]

Latin America is one of the most unequal regions globally regarding maternal and perinatal health. The region demonstrates an excess in stillbirths, with an estimated rate of 8.2 stillbirths per 1000 births (95% confidence interval [CI], 7.5–9.2),[17] and approximately 60% of deaths before the age of 5 years in the region occur during the first year of life, with 50% of those during the first 28 days.[18] Potential differences in the diagnosis of SGA among physicians in Latin America can exacerbate inappropriate use of the limited health resources, disadvantaging outcomes of SGA infants. Currently, no studies have been performed comparing the performance of both standards to identify SGA neonates in Latin America. Therefore, the objectives of this study were to evaluate the diagnostic performance of IG-21st and WHO fetal growth charts to identify SGA and FGR neonates and to assess the specific risks of adverse perinatal outcomes of SGA and FGR neonates identified by each fetal growth chart in a large cohort of deliveries from Latin America.

2 | MATERIALS AND METHODS

This was a multicenter cross-sectional study including all singleton livebirths between 24^{+0} and 41^{+6} weeks of gestational age occurring in 10 obstetric centers from four Latin American countries (Colombia, Peru, Mexico, and Chile) between January 2017 and December 2018. Table S1 summarizes the contribution of each country and participating center. The exclusion criteria were as follows: (1) stillbirth; (2) missing data on birth weight, gestational age, infant sex, or maternal country of birth; (3) birth weight <500 g; and (4) multiple gestation.

Maternal baseline characteristics were collected from the hospital maternity records, including demographic details, obstetric history, anthropometric measures at birth, and perinatal outcomes. Gestational age was calculated using maternal menstrual history or early prenatal ultrasound (before 20 weeks). A low Apgar score was considered <7 at the fifth minute. The ponderal index is determined by the ratio of birth weight to birth length (birth weight [g] × 100/length [cm^3]), and was used as an indicator to assess the growth pattern of SGA infants,[19] allowing the differentiation between symmetric and asymmetric growth restriction.[20] When the ponderal index is low, it is considered evidence of fetal malnutrition or severe fetal wasting, and it is associated with higher rates of morbidities such as hypoglycemia, polycythemia, early hyperbilirubinemia, hypothermia, perinatal resuscitation, perinatal asphyxia, fetal distress, or long hospital stay in the neonatal period.[19,20] Similarly, the cephalization index (head circumference [cm]/birth weight [g] × 100) was calculated and applied to the entire population. The study protocol was approved by the ethics committee of the University of Cartagena (ethics committee N 139, August 31, 2020). According to their distribution, continuous variables were reported as the means or medians using interquartile ranges (IQRs) or standard deviations. Categorical variables are reported as percentages. For each growth chart (IG-21st and WHO standards), we calculated the proportion of live births with a birth weight below the <10th centile (SGA) and below the third centile (FGR).

To evaluate the relative validity of each reference growth chart, neonatal outcomes (i.e. low Apgar rate, ponderal, and cephalization indexes) between the "nonoverlapping" populations were determined and compared with neonates ≥10th centile using the χ^2 test. Finally, relative risk (RR) was calculated as the ratio of the incidence of adverse perinatal outcomes among SGA and FGR neonates. To account for a country-specific effect, we further evaluated the association of SGA by different standards with the adverse outcome using multilevel regression analyses (Supplemental Material). Finally, diagnostic performance (sensitivity, specificity, positive and negative likelihood ratio, and the diagnostic odds ratio [OR]) was estimated and used to compare the accuracy of the two fetal growth standards to identify neonates at risk for adverse perinatal outcomes. We compared the likelihood and diagnostic ORs by bootstrapping 2000 replicates with replacement. The receiver operating characteristic curve analysis determined the performance for predicting a low Apgar score and ponderal index by each fetal growth standard. Data processing was performed using R Studio (version 4.0) software. A value of $P < 0.05$ was considered statistically significant.

3 | RESULTS

The study included 70 852 pregnant women who delivered live births. A total of 1293 (1.82%) pregnancies were excluded because of multiple gestations, 1273 (1.8%) for a birth weight <500 g, and 318 (0.45%) for missing data. Following exclusions, we considered 67 968 (95.9%) deliveries for the analysis. Table S1 summarizes each country's contribution to the overall population. The median maternal age was 26 years (IQR, 22–31 years), with differences across countries. There were also differences in nulliparity rate, ethnicity, and educational level. The median gestational age at delivery in the study population was 39.5 weeks (IQR, 38.5–39.5 weeks). The rate of preterm delivery was 7.9% (5359/67968). The proportion of neonates classified as SGA was significantly different between the two standards. The WHO growth standard classified the neonates as follows: ≥10th percentile: 58 542 (86.1%) and SGA: 9426 (13.9%), while for IG-21st, 63 244 (93%) neonates were ≥10th percentile and 4724 (7%) neonates were identified as SGA. Thus, the rate of neonates classified as SGA by IG-21st was almost two times lower than that classified by the WHO (7% vs 13.9%, $P < 0.001$). Similarly, the proportion of neonates classified as having FGR was significantly different between the two standards. The WHO growth standard classified the neonates as follows: at or above the third centile: 63 730 (93.8%) and FGR: 4238 (6.2%), while for IG-21st, 66 517 (97.9%) neonates were at or above the third centile, and 1451 (2.1%) neonates were classified as having FGR. Thus, the rate of neonates classified as having FGR by the IG-21st was almost three times fewer than that classified by the WHO (2.1% vs 6.2%, $P < 0.001$).

Figure 1a,b are Venn diagrams describing the classification of newborns according to the birth weight centiles of each standard using both standards simultaneously. Specifically, 86.1% (58 523/67968) were considered ≥10th centile by both standards, 6.95% (4721/67968) of neonates were classified as SGA only by the WHO standard (SGA-WHO only), 0.03% (19/67 968) of neonates were classified as SGA only by the IG-21st standard (IG-21st-only), and 6.92% (4705/67 968) were classified as SGA by both standards (Figure 1a). All neonates identified as SGA by IG-21st alone were preterm births. With respect to FGR, 93.7% (63 718/67 968) were considered above the third centile by both standards, 4.1% (2799/67 968) of neonates were classified as FGR only by the WHO standard (FGR-WHO only), 0.02% (12/67 968) of neonates were classified as FGR only by the IG-21st standard (IG-21st-only), and 2.1% (1439/67968) were classified as SGA by both standards (Figure 1b).

Table 1 describes clinical characteristics and perinatal outcomes for pregnancies assigned as SGA and FGR by WHO standard alone, by both standards, and those classified as ≥10th centile for both curves. The rate of preterm delivery was higher in the newborns classified as having FGR by WHO alone and by both standards than in those classified as >10th centile by the two standards (all P values <0.001). In addition, there were significant differences in the cesarean section rate among the groups (Table 1). The rate of a low Apgar score was significantly higher for neonates classified as SGA and FGR by both standards (1.51% and 2.64%, respectively), followed by neonates classified as FGR only by the WHO (0.82%), being significantly lower in neonates classified as ≥10th centile by both curves (0.46%). Notably, there were no significant differences in the rate of low Apgar scores between those neonates classified as SGA only by WHO and neonates classified as ≥10th centile by both curves (0.40% vs 0.46%, $P = 0.642$) (Table 1). Figures 2a,b show the RRs for a low Apgar score or ponderal index, respectively, in neonates identified as SGA and FGR. Neonates classified as SGA and FGR by both standards exhibited the most significant RR for an Apgar score <7

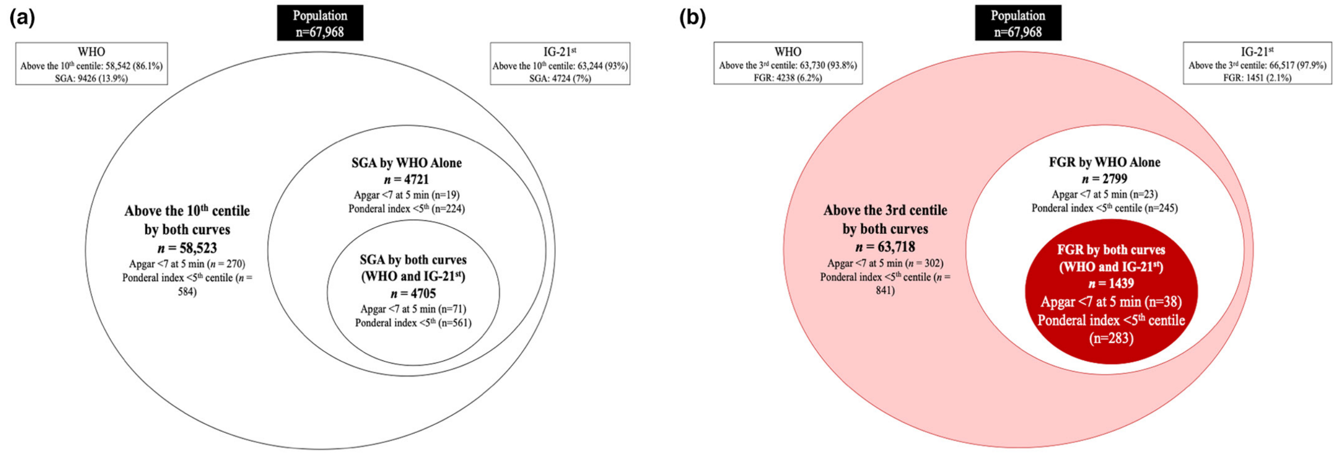

FIGURE 1 Venn diagrams describe newborns' classification according to the centiles of each standard (≥10th percentile vs small for gestational age [SGA] and fetal growth restriction [FGR]) using both standards simultaneously. IG-21st, INTERGROWTH-21st; WHO, World Health Organization.

TABLE 1 Clinical characteristics and perinatal outcomes for pregnancies assigned as SGA and FGR by each standard and those classified as above the 10th percentile for both curves.

	≥10th percentile by both curves	<10th percentile (SGA)		Above or equal the third percentile by both curves	Below the third percentile (FGR)	
		By WHO alone	By both standards		By WHO alone	By both standards
	n = 58 523	n = 4721	n = 4705	n = 63 718	n = 2799	n = 1439
		(IQR or %)	(IQR or %)	(IQR or %)	(IQR or %)	(IQR or %)
Gestational age (weeks)	39 (SD ± 1.66)	39.4 (SD ± 1.7)*	38.5 (SD ± 2.7)	39 (SD ± 1.7)	38.9 (SD ± 2)	37.5 (SD ± 3.5)
Preterm delivery (<37 weeks)	4282 (7.3)	289 (6.1)*	769 (16.3)	4618 (7.25)	317 (11.3)	412 (28.6)
Route of delivery						
Cesarean	27 031 (46.2)	1779 (37.7)	2247 (47.8)	28 978 (45.5)	1228 (43.9)	854 (59.4)
Instrumented	751 (1.3)	41 (0.9)	25 (0.5)	797 (1.3)	15 (0.5)	5 (0.4)
Vaginal	30 730 (52.5)	2900 (61.4)	2432 (51.7)	33 931 (53.3)	1556 (55.6)	579 (40.3)
Birth weight (grams)	3340 (3100–3610)	2866* (2690–3004)	2514 (2230–2710)	3300 (3020–3595)	2620 (2420–2790)	2180 (1783–2438)
WHO centile	52.4 (29.9–77.3)	8.16* (6.75–9.06)	0 (0–0)	48.3 (24.5–75.4)	0 (0–0)	0 (0–0)
IG-21st centile	63 (42.1–83)	14.6* (12.2–17.3)	5.1 (2.3–7.5)	59.1 (36.5–81.7)	6.2 (4.7–9.5)	1.2 (0.4–2.2)
Apgar score <7 at 5 min	270 (0.46)	19 (0.4)	71 (1.5)	302 (0.5)	23 (0.8)	38 (2.6)
Ponderal Index	26.7 (24.9–28.6)	24.5* (23–26)	23.5 (21.7–25.4)	26.5 (24.7–28.5)	23.7 (22.2–25.3)	22.5 (20.6–24.7)
Ponderal index below the fifth centile	584 (1)	224 (4.7)*	561 (11.9)	841 (1.3)	245 (8.7)	283 (19.7)
Cephalization index	1 (0.9–1.1)	1.2 (1.1–1.2)*	1.3 (1.2–1.5)	1.04 (0.9–1.1)	1.26 (1.2–1.4)	1.48 (1.34–1.8)

Note: Data are median (interquartile range [IQR]) or number (percentage). In this table, there are not included IG-21st only cases.
Abbreviations: FGR, fetal growth restriction; IG-21st, INTERGROWTH-21st; SGA, small for gestational age; WHO, World Health Organization.

at 5 min (RR, 3.27; [95% CI, 2.52–4.24] and 5.57 [95% CI, 3.99–7.78], respectively). Importantly, neonates classified as SGA only by WHO alone did not have a significantly higher risk of a low Apgar score (RR, 0.87 [95% CI, 0.55–1.39]) (Figure 2a).

The median ponderal index was significantly lower in the group of neonates classified as SGA and FGR by both standards than in those classified as >10th centile by both standards (FGR by both standards: 22.5 [IQR, 20.6–24.7] and SGA by both standards: 23.5 [IQR,

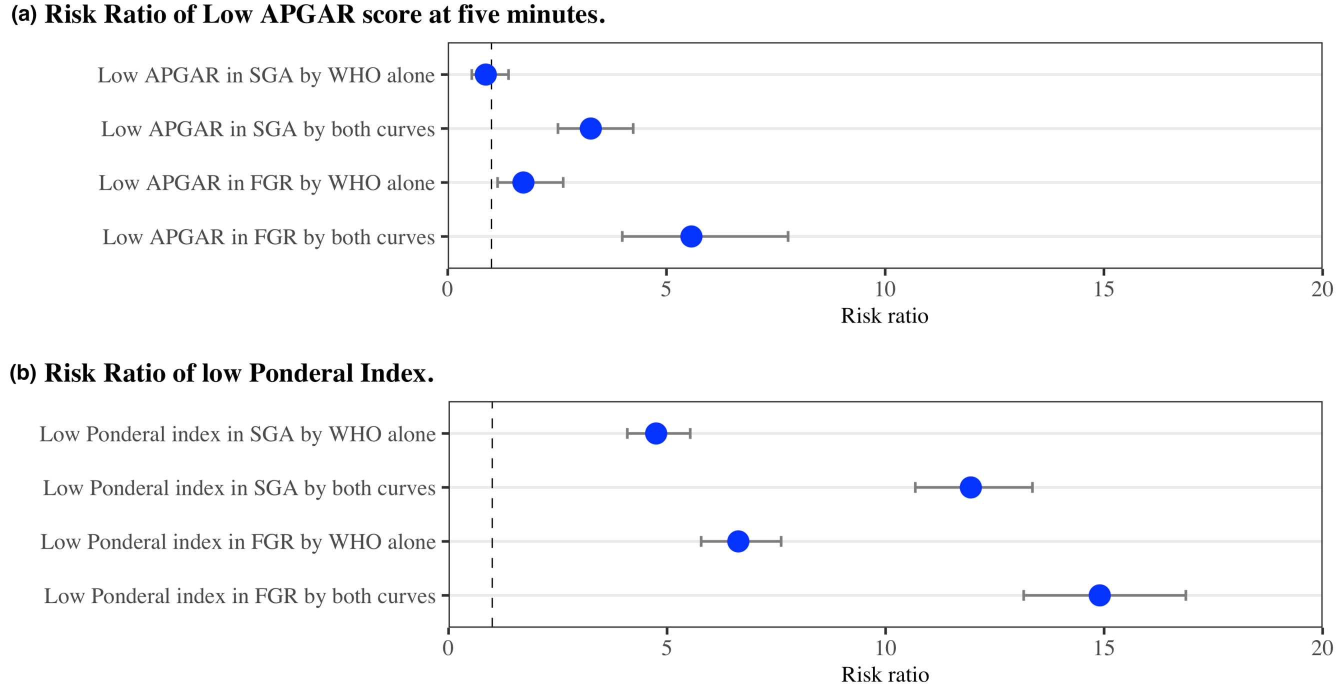

FIGURE 2 Risk ratios (RRs) of low Apgar scores and ponderal indexes in small-for-gestational-age (SGA) and fetal growth restriction (FGR) neonates according to the World Health Organization (WHO) and INTERGROWTH-21st (IG-21st) standards. (a) Neonates classified as SGA and FGR by both standards exhibited the most significant RR for a low Apgar score. However, neonates classified as SGA only by WHO alone did not have a significantly higher risk of a low Apgar score. (b) In terms of anthropometric measures, neonates classified as SGA and FGR by both standards exhibited the most significant RR for a low ponderal index. RRs were also increased in neonates identified as SGA by WHO fetal growth standard alone (SGA-WHO only), characterized by anthropometric measures resembling true FGR as reflected by a thrifty phenotype.

21.7–25.4] vs 26.7 [IQR, 24.9–28.6]; all *P* values <0.001). Similarly, the rate of a ponderal index below the fifth centile was significantly higher in these groups. Neonates classified as SGA and FGR by both standards exhibited the most significant RRs for a low ponderal index (11.95 [95% CI, 10.7–13.4] and 14.9 [95% CI, 13.2–16.8], respectively) (Figure 2). Furthermore, neonates classified as SGA only by WHO alone also had a significantly higher risk of a low ponderal index (RR, 4.75 [95% CI, 4.1–5.53]) (Figure 2b). Finally, the cephalization index was significantly higher in neonates classified as SGA by WHO alone and in those classified as SGA and FGR by both standards, displaying, in addition, a trend toward worst values in the latter groups (Table 2). Table S2 shows the ORs of SGA by each standard for neonatal outcomes under a hierarchical logistic regression model. In brief, we found that SGA babies only by WHO had an OR of 0.98 (95% CI, 0.61–1.57) for a low Apgar score at 5 min and 4.14 (95% CI, 3.52–4.86) and a ponderal index below the fifth percentile, respectively.

Table 2 displays the diagnostic performance of the WHO and IG-21st for identifying an Apgar score <7 at 5 min and a ponderal index below the fifth centile. Both charts exhibited low sensitivities for low Apgar scores (<30%) and high specificity. We next assessed the diagnostic effectiveness of both fetal growth charts for specific obstetric outcomes, demonstrating that the IG-21st had the highest diagnostic ORs (Table 2). As an overall measure of diagnostic performance for a low Apgar score, the diagnostic OR was higher when SGA (3.7 vs 2.02; mean difference, 0.61 [95% CI, 0.45–76.6]; $P<0.001$) and FGR (6.22 vs 3.01; mean difference, 0.72 [95% CI, 0.48–0.96], $P<0.001$) were defined by IG-21st than by WHO charts. Similarly, the diagnostic OR for a low ponderal index was also higher when SGA (10.4 vs 9.01; mean difference, 0.14, [95% CI, 0.06–0.23]; $P = 0.001$) and FGR (14.6 vs 10.6; mean difference, 0.32 [95% CI, 0.2–0.42]; $P<0.001$) were defined by IG-21st than by WHO charts. When we applied both fetal growth charts for the identification of a low Apgar score or ponderal index, the IG-21st fetal growth charts marginally improved the prediction of a low Apgar score based on the area under the ROC curve (AUC), estimated using 2000-fold bootstrapping to account for overfitting (Figure 3; Table 3). Specifically, using the 10th centile with the IG-21st detected more neonates that had a low Apgar score at 5 min (AUC, 57.3 [95% CI, 55.2–59.4]) when compared with the WHO standard (AUC, 55.32 [95% CI, 53.12–57.53]; $P = 0.005$) (Figure 3; Table 3). Importantly, there were no differences in the detection of a low Apgar when the third centile was used by both standards ($P = 0.575$). On the other hand, the identification of a neonate with a low ponderal index was significantly better when using the third centile with the WHO standard (AUC, 66.5 [95% CI, 65.21–67.79]) compared with IG-21st (AUC, 59.46 [95% CI, 58.39–60.53]; $P<0.001$) (Table 3; Figure 3).

4 | DISCUSSION

In this large multicenter study, including an unselected population of singleton pregnancies from four countries in Latin America, the

TABLE 2 Diagnostic effectiveness of each standard for specific obstetric and perinatal outcomes.

Outcomes	Predictors	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	DOR (95% CI)
Apgar score <7 at 5 min	WHO <10th percentile	1.77 (1.48–2.12)	0.88 (0.83–0.93)	24 (20–29)	86 (86–86)	1 (1–1)	100 (99–100)	2.02 (1.59–2.57)
	WHO below the third percentile	2.68 (2.13–3.38)	0.89 (0.85–0.93)	18 (14–22)	93 (93–93)	1 (1–2)	100 (99–100)	3.01 (2.29–3.98)
	IG-21st <10th percentile	3.12 (2.56–3.81)	0.84 (0.80–0.89)	21 (17–26)	93 (93–93)	2 (1–2)	100 (99–100)	3.70 (2.88–4.76)
	IG-21st below the third percentile	5.61 (4.22–7.46)	0.90 (0.87–0.84)	12 (9–15)	98 (98–98)	3 (2–4)	100 (99–100)	6.22 (4.5–8.59)
Ponderal index below the fifth centile	WHO <10th percentile	4.42 (4.21–4.64)	0.49 (0.46–0.52)	57 (55–60)	87 (87–87)	8 (8–9)	99 (99–99)	9.01 (8.1–10.1)
	WHO below the third percentile	6.92 (6.43–7.45)	0.65 (0.62–0.68)	39 (36–41)	94 (94–95)	12 (11–13)	99 (99–99)	10.6 (9.5–11.9)
	IG-21st <10th percentile	6.56 (6.11–7.03)	0.63 (0.60–0.66)	41 (38–44)	94 (94–94)	12 (11–13)	99 (99–99)	10.4 (9.3–11.6)
	IG-21st below the third percentile	11.79 (10.5–13.3)	0.81 (0.79–0.83)	21 (19–23)	98 (98–98)	20 (17–22)	98 (98–98)	14.6 (12.6–16.8)

Note: The proportions of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are given in percentages.

Abbreviations: CI, confidence interval; DOR, diagnostic odds ratio, FN, false negative; FP, false positive; IG-21st, INTERGROWTH-21st; LR, likelihood ratio; TN, true negative; TP, true positive.

proportion of SGA and FGR neonates identified by the WHO fetal growth standard was significantly higher than that obtained using the IG-21st standards. Nevertheless, the overall diagnostic performance for the adverse neonatal outcome and the low ponderal index was better when IG-21st defined SGA and FGR.

Our study uses the fundamental approach of defining SGA and FGR using fetal growth charts in neonates. It has previously been reported that population-based standards that utilize neonatal birth weights are limited by the fact that the inclusion of premature growth-restricted infants incorrectly affects the norms resulting in a high rate of FGR misdiagnosis. The ability of the IG-21st standard to identify fetuses and neonates at risk of adverse outcomes has been recently challenged by several studies worldwide. Those studies have consistently reported that the use of IG-21st resulted in a lower prevalence of SGA compared with reference[10–12,14,16] or customized charts.[10] Another important finding is that the WHO identified an additional group of 4721 SGA babies who were not at significant risk of a low Apgar score. However, they have anthropometric features resembling intrauterine growth restriction. There have been several explanations for the discrepancy between the two standards. One explanation is that the calculation of estimate of fetal weight in the WHO study was based on the Hadlock formula, while IG-21st created a new formula based only on head circumference and abdominal circumference. On the other hand, IG-21st assumed a parametric distribution of the fetal growth trajectories under a linear mixed model. Researchers in the WHO project have used quantile regression to estimate percentiles directly and have fewer assumptions. It would be rational to assume, then, that compared with IG-21st, the aim of WHO was to be more of a reference, including pregnancies with complications. A previous study including 9409 women from the United States reported limited accuracy of the IG-21st, National Institute of Child Health and Human Development (NICHD), and WHO standards for identifying neonates at risk of adverse perinatal outcomes (including death).[16] Similar to our results, IG-21st classified fewer newborns as being below the fifth and 10th percentiles by birth weight than WHO and NICHD standards.[16]

Although the Apgar score has poor performance as a predictor of neurologic development, it remains a good predictor of neonatal outcome, both in preterm and term infants. In predicting survival, its performance is better than the measurement of umbilical-artery blood pH, even for newborn infants with severe acidemia.[21] Therefore, our finding that the IG-21st charts identify more babies with a low Apgar score is clinically relevant because this score captures an increased risk of neonatal mortality. Human body proportions are thought to be the product of environmental and gene interactions, and there are notable differences across different races/ethnicities and countries. The ponderal index is an indicator of thinness in newborns. It has been used to assess fetal growth, and when it is low it is associated with worse neonatal outcomes.[19,28] In infants with FGR, the deposit of adipose tissue and muscle mass decreases, which leads to a reduction in the ponderal Index. Being underweight, failing to thrive, and having a small thorax reflect different adaptations to malnutrition, hypoxia, and other factors. PI is

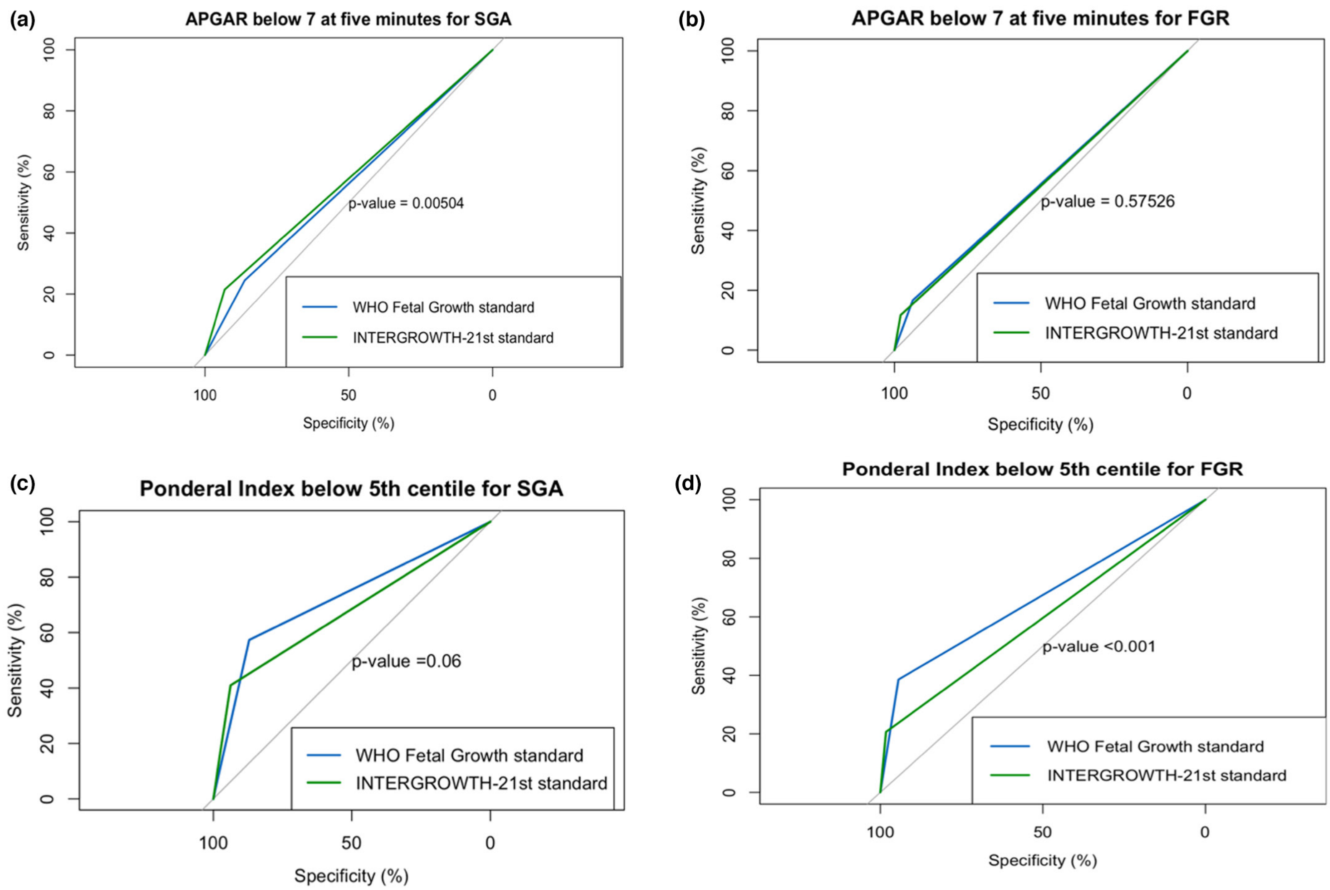

FIGURE 3 Receiver operating characteristic curve of the INTERGROWTH-21st (IG-21st) and World Health Organization (WHO) standard for each perinatal outcome.

TABLE 3 Receiver operating characteristic curve analyses for obstetric outcomes.

Outcome	Predictor	WHO AUC (95% CI)	IG-21st AUC (95% CI)	*P* value
Apgar <7 at 5 min	<10th centile	55.32 (53.12–57.53)	57.3 (55.2–59.4)	0.005
	Below the third centile	55.2 (53.29–57.1)	54.8 (53.16–56.45)	0.575
Ponderal index below the fifth centile	<10th centile	72.18 (70.87–73.5)	67.36 (66.06–68.67)	0.058
	Below the third centile	66.5 (65.21–67.79)	59.46 (58.39–60.53)	<0.001

Abbreviations: AUC, area under the curve; IG-21st, INTERGROWTH-21st; WHO, World Health Organization.

considered a better measure of FGR and complicating factors than SGA.[28] Previous studies have shown that asymmetric fetal growth (characterized by a low ponderal index) is associated with cerebral palsy and increases the risk of perinatal morbidity and mortality.[20] Developing countries might benefit using the ponderal index because of its low cost.

The strength of this study is that this birth data set is the most extensive compilation to date from Latin America, including data from four countries and more than 67 000 births. In addition to the increased data quantity, we evaluated the two current prescriptive international fetal growth standards to adjust the risk estimation of adverse perinatal outcomes and anthropometric measures associated with FGR. Differences in maternal age and antenatal care across countries might be attributable to population characteristics, culture, and obstetric practice. However, non-Black Hispanics have currently used to agglomerate the Latin American population worldwide, so we did not consider ethnic differences within our population. Study limitations include the retrospective nature of this study. Another limitation of our study is that we only reported Apgar scores. However, this is an objective measure to identify babies with a high risk of perinatal morbidity and poor neurological development. In addition, stillbirths were excluded because of uncertainty regarding their classification as SGA by birthweight. Finally, although WHO standards detected a significantly higher proportion of SGA fetuses, this fraction of small fetuses likely contains instances of adverse outcomes that the data available (only Apgar) could not reveal.

The chart selection has a trade-off between maximizing sensitivity (few false negatives) and specificity (few false positives). For SGA screening, using data from a previous large cohort study conducted in France, a false negative conferred an adjusted 2.1-increased risk for stillbirth.[22] In absolute terms (according to a prevalence of stillbirth among detected SGA of 1%), this means one additional fetal death for each 87 nondetected SGA. The WHO charts exhibited higher sensitivity for SGA-associated adverse outcomes and a low ponderal index. However, false positives are also an issue to consider. A false positive for SGA means unnecessary follow-up and planned delivery, which should be at term in adherence to the international guidelines. A large cohort study in the United Kingdom showed that two otherwise normal small babies are picked up for every SGA fetus with complications identified.[23] There is evidence from nationwide studies that compared with true negatives, iatrogenic preterm deliveries were 4.6 times higher than false positives. Thus, the ideal chart for fetal growth assessment should combine a good capacity to rule in and rule out SGA-associated complications. Under the assumption that the same weight is given to false negatives and positives, the diagnostic OR (+LHR/−LHR) estimates the performance. Especially for the definition of FGR, the IG-21st charts exhibited a better overall performance in predicting low Apgar scores. Furthermore, the diagnostic performance for a low ponderal index (a surrogate of the 30 phenotypes) was better when SGA and FGR were defined using the IG-21st charts.

In conclusion, in a large population in Latin America, the WHO fetal growth standard increases the identification of SGA and FGR neonates compared with the IG-21st project standard. Nevertheless, the former resulted in a lower overall diagnostic performance for a low Apgar score and low neonatal ponderal index.

AUTHOR CONTRIBUTIONS

Jezid Miranda, Francesc Figueras, and Ángel Paternina-Caicedo analyzed the data and drafted the manuscript. Natalia Maestre, Miguel Parra-Saavedra, Javier Caradeux, Álvaro Sepulveda-Martinez, Melisa Pelaez-Chomba, Andrés Torres, Mauro Parra-Cordero, Pilar Diaz-Corvillón, Dahiana M Gallo, Darío Santacruz, Nicolás Rodriguez, Andrés Sarmiento, Jesús A. Benavides, Sergio Girado, José A. Rojas-Suarez, Eduard Gratacós, and Francesc Figueras interpreted the results and revised the manuscript critically for important intellectual content. Francesc Figueras contributed to the design of the study. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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