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

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Abstract

Objective: To evaluate the performance of INTERGROWTH-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. Design: Multicenter cross-sectional study. Setting: Ten maternity units across four Latin American countries, 2016-2018. Population: 67,968 singleton live births. Methods: According to each standard, the neonates were classified as SGA and FGR (birthweight <10th and <3rd centiles, respectively). Main Outcomes Measures: The relative risk (RR) and diagnostic performance for the occurrence of a low Apgar score and low ponderal index were calculated for each standard. Results: The WHO charts identified more neonates as SGA than IG-21st (13.9% vs. 7%, respectively). 6.9% babies were considered SGA only by the WHO chart. Compared to normally grown babies, neonates classified as FGRs by both standards had the highest RR for a low Apgar (RR: 5.57; 95% CI: 3.99–7.78), followed by those SGA by both curves (RR:

3.27; 95% CI: 2.52–4.24), while SGAs 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 INTERGROWTH-21st was used than when SGA and FGR were defined by WHO charts. Conclusions: In a large population of singleton deliveries from Latin America, the WHO fetal growth charts seem to identify significantly more SGA neonates than the INTERGROWTH-21st charts, but the diagnostic performance of the latter for low Apgar score and low ponderal index is better.

Introduction

Small-for-gestational-age (SGA) neonates are at increased risk of mortality and several morbidities (1,2), suboptimal neurodevelopment (3–7), and susceptibility to cardiovascular disease later in life (8–10). Unrecognized SGA fetuses are at increased risk of perinatal death compared with those who are appropriately followed and managed (11). Its opportune identification allows timely interventions to reduce the risk of adverse perinatal outcomes (APOs) (12–15). Current guidelines recommend the 10^{th} percentile as a cutoff to define SGA and the 3^{rd} percentile to define fetal growth restriction (FGR) (16–18) since several studies have demonstrated an increased risk of perinatal morbidity and mortality beyond these cutoffs (17–23). However, there is disagreement on which charts should be used (16–21,24,25).

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 fetal growth restriction. First, the INTERGROWTH-21^{st} (IG-21^{st}) project reported fetal biometry standards constructed with 20,486 low-risk pregnancies delivered between 33 and 42 weeks (26–29). Using a similar concept and methodology, the World Health Organization (WHO) multicenter growth reference study proposed an alternative standard (30). 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 (31–37).

Latin America represent one of the most unequal regions globally regarding maternal and perinatal health (38–41). The region demonstrates an excess in stillbirths with an estimated rate of 8.2 stillbirths per 1000 births (95% CI 7.5-9.2) (42–44) and approximately, 60% of deaths before the age of five years old in the region occur during the first year of life, with 50% of those during the first 28 days (45). Potential differences in diagnosis of SGA among physicians in Latin America region can exacerbate an inappropriate use of the limited health resources, disadvantaging outcomes of SGA infants. At present, 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 INTERGROWTH-21^{st} 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.

Methods

Design and study population

This was a multicenter cross-sectional study including all singleton livebirths between 24^{+0} and 41^{+6}weeks of gestational age occurring in ten obstetric centers from four Latin American countries (Colombia, Peru, Mexico, and Chile) between January 2017 and December 2018. Participating centers included 1) ESE Clínica de Maternidad Rafael Calvo (Colombia) (n=11009); 2) Clínica Santa Cruz de Bocagrande (Colombia) (n=6264); 3) ESE Hospital Local Cartagena de Indias (Colombia) (n=641); 4) ESE Hospital la Divina Misericordia (Colombia) (n=4526); 5) Clínica Versalles (Colombia) (n=16976); 6) Hospital Universitario de la Fundación Santa Fe de Bogotá (Colombia) (n=869); 7) Hospital Materno Nacional San Bartolomé de Lima (Perú) (n=11182); 8) Instituto Mexicano Seguro Social (Hospital General de Zona N014, Unidad de Quemados, Hermosillo, México) (n=4,799); 9) Hospital Clínico Universidad de Chile (Chile) (n=1705) and 10) Clínica Dávila (Chile) (n=9997). 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 below 500 grams; and 4) multiple gestation.

Variables

Maternal baseline characteristics, including demographic details, obstetric history, and anthropometric measures at birth and perinatal outcomes, were collected from the hospital maternity records. Gestational age was calculated using maternal menstrual history or early prenatal ultrasound (before 20 weeks). A low Apgar score was considered below seven at the fifth minute. We used the standardized formula to calculate the ponderal index and applied reference ranges to the entire population (46,47). Similarly, the cephalization index (head circumference [cm]/birth weight [g] $\times$ 100) was calculated and applied to the entire population (48). The study protocol was approved by the ethics committee of the University of Cartagena (Ethics committee N 139, August 31, 2020).

Statistical analysis

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. First, the birth weight percentile was calculated using IG-21st software, and the calculation coefficients derived from the WHO study were used to calculate the WHO birth weight percentile. Then, for each growth chart (IG-21st and WHO standards), we calculated the proportion of live births with a birth weight below the $<10^{th}$ percentile (SGA) and $<3^{rd}$ percentile (FGR). To evaluate the relative validity of each reference growth chart, neonatal outcomes (i.e., low Apgar rate, ponderal, and cephalization indexes) between the "non-overlapping" populations were determined and compared with neonates at or above the 10^{th} percentile using the chi-squared 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, where the subjects were at the lower level and countries at the upper level. The relationships between patient-level and country-level variables and the adverse perinatal outcomes were examined with multilevel linear regression using the R 'lm4' package. Fixed effects were estimated for maternal education and nulliparity. The multilevel analysis was implemented in a stepwise manner. First, an unconditional means model was used to determine the attributable variance explained by the multilevel design. Second, using a backward elimination approach, all selected variables for inclusion were added to the unconditional means model as fixed effects, and nonsignificant variables were removed sequentially until only significant (i.e., $p<0.05$) variables remained. Finally, diagnostic performance (sensitivity; specificity; positive and negative likelihood ratio; and the diagnostic odds ratio) was estimated and used to compare the accuracy of the two fetal growth standards to identify neonates at risk of adverse perinatal outcomes. We compared the likelihood and diagnostic odds ratios by bootstrapping 2000 replicates with replacement. The receiver-operating characteristics (ROC) curve analysis determined the performance for predicting a low APGAR score and ponderal index by each fetal growth standard was determined by the receiver–operating characteristics (ROC) curve analysis. The resulting areas under the ROC curves (AUCs) were compared using the DeLong method, and a p-value <0.05 was considered statistically significant. Data processing was performed using R software. A value of $p<0.05$ was considered statistically significant.

Results

The study included 70,852 pregnant women who delivered live births. A total of 1293 (1.9%) pregnancies were excluded due to multiple gestations (n=1273), birth weight less than 500 grams (n=9), and missing data (n=309).

Population description

Following exclusions, we considered 67,968 deliveries for the analysis. Table S1 summarizes each country's contribution to the overall population. The median maternal age was 26 (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 (IQR: 38.5 – 39.5) weeks. The rate of preterm delivery was 7.9% (5359/67,968). The proportion of neonates classified as SGA was significantly different

between the two standards. The WHO growth standard classified the neonates as follows: at or above the 10^{th} percentile: 58,542 (86.1%) and SGA: 9426 (13.9%), while for IG-21^{st}, 63,244 (93%) neonates were at or above the 10^{th} percentile, and 4724 (7%) neonates were identified as SGA. Thus, the rate of neonates classified as SGA by the IG-21^{st} 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 FGR was significantly different between the two standards. The WHO growth standard classified the neonates as follows: at or above the 3^{rd} percentile: 63,730 (93.8%) and FGR: 4238 (6.2%), while for IG-21^{st}, 66,517 (97.9%) neonates were at or above the 3^{rd} percentile, and 1451 (2.1%) neonates were classified as FGR. Thus, the rate of neonates classified as FGR by the IG-21^{st} was almost three times fewer than that classified by the WHO (2.1% vs. 6.2%, $p<0.001$).

Figures 1A and 1B are Venn diagrams describing the classification of newborns according to the percentiles of each standard (at or above the 10^{th} percentile vs. SGA and FGR) using both standards simultaneously. Specifically, 86.1% (58,523/67,968) were considered at or above the 10^{th} percentile by both standards, 6.95% (4721/67,968) 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-21 standard (IG-21^{st}- only), and 6.92% (4705/67,968) were classified as SGA by both standards (Figure 1A). All neonates identified as SGA by IG-21^{st} alone were preterm births. With respect to FGR, 93.7% (63,718/67,968) were considered above the 3^{rd} percentile 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-21 standard (IG-21 only), and 2.1% (1439/67,968) 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 at or above the 10^{th} percentile for both curves. The rate of preterm delivery was higher in the newborns classified as FGR by WHO alone and by both standards than in those classified as above the 10^{th} percentile by the two standards (all p values <0.001). However, the rate of preterm delivery was significantly higher in those classified as SGA by the two curves than in those classified as AGA (16.3% vs. 7.32%, $p<0.05$). In addition, there were significant differences in the cesarean section rate among the groups, being significantly higher in neonates classified as SGA and FGR by both standards compared to those classified as above the 10^{th} percentile by the two standards (59.4% vs. 46.2%, $p<0.001$) (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 at or above the 10^{th} percentile 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 at or above the 10^{th} percentile by both curves (0.40% vs. 0.46%, $p=0.64$, Table 1). Figures 2A and 2B 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 below seven at five minutes (RR: 3.27; [95% CI: 2.52 – 4.24], and 5.57 [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 above the 10^{th} percentile by both standards (FGR by both standards: 22.5 [IQR: 20.6 – 24.7] & SGA by both standards: 23.5 [IQR: 21.7 – 25.4] vs. 26.7 [24.9 – 28.6]; all p values <0.001). Similarly, the rate of a ponderal index below the 5^{th} percentile was significantly higher in these groups. Neonates classified as SGA and FGR by both standards exhibited the most significant RR for a low ponderal index (RR: 11.95; [95% CI: 10.7 – 13.4], and 14.9 [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 odds ratios 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 five minutes and 4.14 (95% CI: 3.52 – 4.86) and a ponderal index below the 5th percentile, respectively.

Table 2 displays the diagnostic performance of the WHO and IG-21st for identifying an APGAR score below seven at 5 minutes and a ponderal index below the 5thpercentile. Both charts exhibited low sensitivities for low Apgar scores (below 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 odds ratios (DORs) (Table 2). As an overall measure of diagnostic performance for a low Apgar score, the diagnostic odds ratio was higher when SGA (3.70 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 odds ratio 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-value = 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 and ponderal index, the IG-21st fetal growth charts marginally improved the prediction of a low APGAR score based on the area under the receiver operating characteristic (ROC) curve (AUC), estimated using 2,000-fold bootstrapping to account for overfitting (Table S3). Specifically, for low APGAR scores, the AUC of the identification of SGA neonates for WHO fetal growth charts were 55.3 (95% CI: 53.1 – 57.5) vs. 57.3 (55.2 – 59.4) for IG-21st, p *=0.005* (two-sided) (Table S3).

Discussion

Main findings

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

Comparison with results of previous studies and interpretation of results

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 (31,32,34,36,49) or customized charts (31). Moreover, undiagnosed SGA fetuses are at increased risk of adverse perinatal outcomes and stillbirth (31,37,50). Importantly, similar to other reports from developed countries (37,42–44), we reported that the IG-21st chart identified fewer neonates as SGA and that the Latin American population turns to the right in the distribution percentiles within the IG-21st standard.

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 EFW in the WHO study was based on the Hadlock formula (53), while IG-21st created a new formula based only on HC and AC.(54) 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 to 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 US reported limited accuracy of the IG-21st, NICHD, and WHO standards for identifying neonates at risk of adverse perinatal outcomes (including death) (49). IG-21st has been compared to customized charts reporting that IG-21st failed to detect SGA neonates, particularly among ethnic groups with larger maternal size.(31) Similar to our results, IG-21st classified fewer newborns as being below the 5th and 10thpercentiles by birth

weight than WHO and NICHD standards (49).

Human body proportions are thought to be the product of environmental and gene interactions, and they are notable differences across different races/ethnicities and countries (55). The ponderal index is an indicator of leanness in neonates. Previous studies have shown that asymmetric fetal growth (characterized by a low ponderal index) reflects fetal malnutrition (56), is associated with cerebral palsy (57,58), and increases the risk of perinatal morbidity and mortality (59). Developing countries might welcome using the cephalization index due to its low cost. Based on this index, some recommendations postulated that the greater the brain weight: body ratio (the more severe the intrauterine malnourishment), the higher the chances are for suboptimal brain development despite compensatory mechanisms such as brain sparing (48). Since intrauterine adverse events might not be clinically relevant until late in child development, it is crucial to identify as early as possible those small neonates at risk for neurodevelopmental disabilities who need early life interventions. This is especially relevant in deprived environments, where these interventions can improve cognitive performance and reduce antisocial behavior at a young age (60,61).

Strength and limitations

The strength of this study is that this birth dataset 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 simultaneously 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 due to population characteristics, culture, and obstetric practice. However, non-black Hispanics are 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 used 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 birth weight. Other large series have shown that IG21st standards miss a fraction of babies at risk for this complex event (62). It is also a limitation of our study that we could not compare the performance of customized standards due to the lack of published and validated coefficients for all the participating countries. Although customized curves have been proposed (63–65), their superiority in identifying adverse perinatal outcomes has not been supported by more recent literature (66,67). Finally, although WHO 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.

Interpretation

There is a trade-off between maximizing sensitivity (few false negatives) and specificity (few false positives) in the chart selection. 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 (68). In absolute terms (according to a prevalence of stillbirth among detected SGA of 1%), this means one additional fetal death for each 87 non-detected 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 UK showed that two otherwise normal small babies are picked up for every SGA fetus with complications identified (69). 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 odds ratio [DOR] (+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 thirty phenotypes) was better when SGA and FGR were defined using the IG-21st charts.

Research implications

Although, in the past years, the field's focus has been to answer which chart we should use, one alternative might be to identify cutoffs for each standard in which the perinatal morbidity increases, which might be not necessarily the 3rd or the 10thpercentile. Such perinatal risk-based cutoffs can be an opportunity to provide personalized care (52,70). This strategy might enhance the clinical applicability and use of the two standards while adapting to local scenarios. Environmental constraints are also a well-known factor influencing fetal growth, and usually, growth percentiles are not controlled adequately. Therefore, in addition to the argument about which chart should be used, the debate should move on to integrate functional parameters that enhance the fundamental objective in antenatal care, which is to assess placental function rather than fetal size.

Conclusion

In a large population in Latin America, the WHO fetal growth standard increases the identification of SGA and FGR neonates compared to 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.

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Disclosure of interest

The authors report no conflict of interest.

Contribution to Authorship

JM, FF, and AP analyzed the data and drafted the manuscript. NM, MPS, JC, AS, MP, AT, MP, PDC, DG, DS, NR, AS, JAB, SG, JAR, EG, and FF interpreted the results and revised the manuscript critically for important intellectual content. FF contributed to the design of the study. All authors approved the final version of the manuscript.

Details of Ethics Approval

The ethics committee of the University of Cartagena (Ethics committee N 139, August 31, 2020) approved the study protocol.

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

	Above or equal the 10^{th} percentile by both curves n=58,523	**Below the 10^{th} percentile (SGA)**	**Below the 10^{th} percentile (SGA)**	**Above or equal the 3^{rd} percentile by both curves** n=63,718	**Below the 3^{rd} percentile (FGR)**	**Below the 3^{rd} percentile (FGR)**
		By WHO Alone n=4721 **(IQR or %)**	**By both standards** n=4705 **(IQR or %)**	**(IQR or %)**	**By WHO Alone** n=2799 **(IQR or %)**	**By both standards** n=1439 **(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	27031 (46.2)	1779 (37.7)	2247 (47.8)	28978 (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	30730 (52.5)	2900 (61.4)	2432 (51.7)	33931 (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 minutes	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 <5th 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)

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

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% C**
APGAR score <7 at 5 minutes	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 <3rd 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 <3rd 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. – 8.59)
Ponderal Index below 5th 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. – 10.1)

Outcomes	Predictors	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	DOR (95% C
	WHO <3rd 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. – 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. – 11.6)
	IG-21st <3rd 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)

The proportions of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are given in percentages (%). DOR, diagnostic odds ratio, FN, False-negative; FP, false positive; LR, likelihood ratio; TN, true negative; TP, true positive.

Figure legends

Figure 1. Venn diagrams describe newborns' classification according to the centiles of each standard (at or above the 10th percentile vs. SGA and FGR) using both standards simultaneously.

Figure 2. Risk ratios of low APGAR scores and ponderal indexes in SGA and FGR neonates according to the WHO and 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 do 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.

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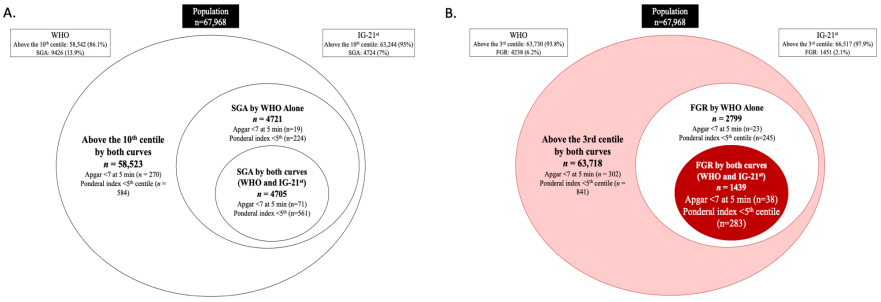
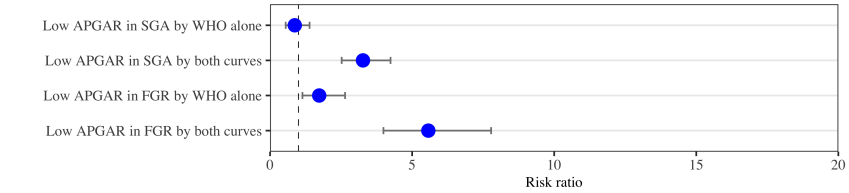


A. Risk Ratio of Low APGAR score at five minutes.



B. Risk Ratio of low Ponderal Index.