EVALUATION OF THE INTERGROWTH-21ST PROJECT NEWBORN STANDARD FOR NEONATAL PHENOTYPES AND NEONATAL MORBIDITY AND MORTALITY

EVALUACIÓN DE FENOTIPOS NUTRICIONALES DEL RECIÉN NACIDO CON EL ESTÁNDAR INTERGROWTH-21ST PARA PREDICCIÓN DE MORBILIDAD Y MORTALIDAD NEONATALES

AVALIAÇÃO DE FENÓTIPOS NUTRICIONAIS DO RECÉM-NASCIDO COM O PADRÃO INTERGROWTH-21ST PARA PREDIÇÃO DE MORBIMORTALIDADE NEONATAL

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Abstract:

The use of local references or standard for neonatal studies still requires their validation through indicators of morbidity and mortality. Objective: evaluate the performance of the INTERGROWTH-21st Project (IG-21) standard and a commonly used Argentinian reference (Urquia) by examining the differences in the frequency of growth phenotypes, and the associated neonatal morbidity and mortality. Methods: Retrospective cohort study of all singleton live-births from Sarda Maternity Hospital (Buenos Aires, Argentina) between 33 and 42 gestational age, using information obtained from a Perinatal Surveillance System (Agustina) dataset between 1996-2001 (n = 25948). Phenotypes small- and large-for-gestational age, stunting and waisting and a composite of neonatal morbidity/mortality (CNMM) were contrasted between the IG-21 standard and Urquia reference. Results: the Urquia 3rd centile value was lower than IG-21 before 37 weeks, but then it surpassed IG-21 until term. Among Sarda, 2.3%, 5.9% and 8.9 were <3rd, <10th and >97th centile, respectively, under the IG-21 standard, while 3.7%, 10.1% and 8.4% were <3rd, <10th and >97th centile, respectively, under the Urquia reference. Stunting and waisting were 16.1% and 0.9%, respectively under IG-21. The IG-21 detection rates of CNMM showed that 28.5%, 19.6% and 8.5% occurred among weight<3rd,<10th and >97th centile, respectively, while 21.8%, 14.2% and 8.0% occurred among <3rd, <10th and >97th centile under the Urquia criteria. Newborn weight <3rd,<10th and >97th centile under IG-21 showed higher neonatal CNMM risk compared with Urquia reference. Conclusions: The IG-21 standard identified a higher risk of neonatal morbidity and mortality than the Urquia reference.

Keywords: fetal nutrition disorders; stature by age; body mass index; morbidity; infant mortality.

Resumen:

Introducción: El uso de referencias locales o estándares para estudios neonatales aún requiere su validación a través de indicadores de morbilidad y mortalidad. Objetivo: Comparar la capacidad predictiva del estándar INTERGROWTH-21st (IG-21st) y una referencia argentina (Urquia) mediante los fenotipos de crecimiento fetal y morbi-mortalidad neonatales. Métodos: Estudio de cohorte retrospectivo de recién nacidos vivos entre 33 y 42 semanas del Hospital Materno-Infantil Ramón Sarda (Buenos Aires, Argentina), entre 1996-2001 (n = 25948). Los fenotipos pequeños (PEG) y grandes para la edad gestacional, acortado y emaciado y un índice compuesto de morbilidad / mortalidad neonatal (CNMM) se contrastaron entre IG-21st y la referencia Urquia. Resultados: El 3er percentil del peso al nacer de Urquia fue menor que el de IG-21st antes de las 37 semanas; 2.3%, 5.9% y 8.9 de los RN fueron <3º, <10° y > 97° percentil, respectivamente, bajo el estándar IG-21st, mientras que 3,7%, 10,1% y 8,4% fueron <3 °, <10 ° y> 97 ° percentil, respectivamente, bajo la referencia Urquia. Acortados fueron 16.1% y emaciados 0.9%, bajo IG-21st. CNMM bajo IG-21st fueron 28.5%, 19.6% y 8.5% en peso<3º, <10º y >97º percentil, respectivamente, mientras que 21.8%, 14.2% y 8.0% ocurrieron en peso< 3°, <10° y > 97° percentil bajo Urquia. Acortados fueron 17.3% y emaciados 18.3%. Los RN <3er°, <10° y > 97° percentil bajo IG-21st mostraron mayor riesgo de CNMM en comparación con la referencia Urquia. Conclusiones: El estándar IG-21st identificó mayor riesgo de morbilidad y mortalidad que la referencia Urquia.

Palabras clave: trastornos nutricionales en el feto; estatura por edad; índice de masa corporal; morbilidad; mortalidad infantil.

Resumo

Introdução: O uso de referências locais ou padrões para estudos neonatais ainda exige validação por meio de indicadores de morbimortalidade. Objetivo: Comparar a capacidade preditiva do padrão INTERGROWTH-21st (IG-21st) e uma referência argentina (Urquia) examinando as diferenças nos fenótipos de crescimento fetal neonatal e morbimortalidade. Métodos: Estudo de coorte retrospectivo de recém-nascidos vivos (RNV) entre 33 e 42 semanas do Hospital Materno Infantil Ramón Sarda (Buenos Aires, Argentina), entre 1996-2001 (n = 25948). Fenótipos pequeno (PEG) e grande para idade gestacional, encurtado e emaciado e um índice composto de morbimortalidade neonatal (CNMM) foram contrastados entre o IG-21st e a referência de Urquia. Resultados: o 3º percentil do peso ao nascer de Urquia foi inferior ao do IG-21st antes de 37 semanas; 2,3%, 5,9% e 8,9 dos RNV apresentaram percentil <3, <10 e> 97, respectivamente, segundo o padrão IG-21st, enquanto 3,7%, 10,1% e 8,4% foram < percentil 3, <10 e> 97, respectivamente, sob a referência Urquia. Encurtados foram 17,3% e emaciados 18,3% sob IG-21st. Os RNV <3º, <10º e> 97º percentil no IG-21st apresentaram maior risco de CNMM em comparação com a referência Urquia. Conclusões: O padrão IG-21st identificou um risco maior de morbimortalidade do que a referência Urquia.

Palavras-chave: transtornos da nutrição fetal; estatura-idade; índice de massa corporal; morbidade; mortalidade infantil.

Key concept:

A) What is known about it?

There is an incipient literature comparing the ability of different fetal and neonatal size charts to predict adverse perinatal outcomes. A consistent finding is that, for a wide array of adverse outcomes, all growth charts produce low predictive values. This applies to a variety of charts, including the IG-21st, WHO, population-specific, and ethnic-specific charts.

B) What does this job bring?

There are no published studies in Latin America that show the predictive value of different growth phenotypes at birth on neonatal morbidity and mortality. The present one demonstrate that IG-21st revealed a higher risk of neonatal morbidity and mortality than the local reference.

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Recibido: 2020-03-30 **Aceptado:** 2020-04-06

DOI: **http://dx.doi.org/10.31053/1853.0605.v77.n2.28064**

Introduction

There is an incipient literature comparing the ability of different fetal and neonatal size charts to predict adverse perinatal outcomes. A consistent finding is that, for a wide range of adverse outcomes, all growth charts produce low predictive values. This applies to a variety of charts, including the IG-21st, WHO, population-specific, and ethnic-specific charts [1].
INTERGROWTH-21st Project (IG-21st) selected a healthy cohort of fetuses from normal pregnancies in order to ensure that the resultant standard provides normative and prescriptive centiles of fetal and newborn growth for gestational age (GA) and sex, and is intended for use in clinical practice both within populations and for comparisons between nationalities [2-4].
The clinical and public health consequences of switching from currently used newborn references to the IG-21st standards are unclear. Its ability to identify infants at risk of adverse outcomes in a general obstetric population has been poorly studied [5,6]. More important, with the advent of the new standard, there is an urgent need to examine how the burden of growth abnormalities phenotypes status, which exists largely in low- and middle income countries, and its association with adverse health outcomes differ from previous estimate that have applied national reference [3,4].
We carried out an evaluation of the performance of the IG-21st Project standard and a commonly used Argentinian references by examining the differences in the frequency of growth abnormalities phenotypes and rates of associated severe neonatal morbidity and mortality.

Methods

Using prospectively gathered maternity data from a general obstetric population and according with the INTERGROWTH-21st project [3] we carried out a retrospective cohort study of all singleton live births at Sarda Maternity Hospital (Buenos Aires, Argentina) with a gestational age between 33 and 42 weeks, using information obtained from a Perinatal Surveillance System (*Agustina*) dataset between 1996-2001 (n = 25948). Exclusion criteria were twin infants, stillborn, without gestational age or sex, and infants with implausible birth weight–GA combinations [5].
The database include standardized definitions and information for all births occurring $\geq$ 20 weeks' gestation, including demographics, antenatal complications, delivery details (birth weight [with most measured within 72 hours of birth], birth length), and neonatal outcomes. Data are routinely checked for accuracy.
Gestational age was estimated by the date of the last menstrual period (LMP) and information from the earliest ultrasound examination (US). A margin of error of ± 7 days was calculated for the first US [6].
Maternal variables studied were: age (years), schooling (years), marital status (with or without partner), smoking during gestation (yes/no), parity (defined as the number of live born or stillborn infants from 20 weeks' gestation or where the infant weighed 400 g or more), hypertension (prior or gestational, yes/no), diabetes (prior or gestational, yes/no) and maternal pre-gestational body mass index (BMI, kg/m^2).
Growth phenotypes categories of interest were defined using the IG-21st newborn standard [3] and a national reference [7], and included small-for-gestational age (SGA, birth weight below <3rd and 10th centile), large-for-gestational age (LGA, >97th centile), stunting (length <3rd centile) and waisting (body mass index [BMI] <3rd centile) [4]. Stunting and waisting were calculated only with IG-21st, because the Urquía reference does not include newborn length.
The *primary outcome* was a composite of severe neonatal morbidity and mortality (CNMM) that identifies newborns with at least one of the following conditions: neonatal death (occurring within the first 28 days of life), birth asphyxia (Apgar score ≤7 at 5 minutes), positive pressure respiratory support >4 hours, and seizures. These neonatal morbidity measures have been shown to be important predictors of adverse neonatal outcome, requires limited standardization of clinical diagnoses and is well accepted as a marker in large, international, population based studies of severely ill newborns [2,8]. Data from previous population-based studies indicate that the incidence of this outcome is approximately 5% [9].

Statistical Analysis
Variables were summarized as means, medians, and proportions, as appropriate. The prognostic performance of the IG-21st and local reference were assessed in terms of the ability of the phenotypes categories to estimate risks of composite severe neonatal morbidity/mortality (CNMM) using rate ratios with 95% confidence intervals (CI) and detection (sensitivity) rates [10].
Rate ratio (RR) for primary outcomes were estimated using log-binomial regression analysis adjusting for maternal age, parity, BMI, smoking during pregnancy, hypertension, gestational diabetes and infant sex, with the non-phenotypes group as the reference.
Sensitivity, specificity, and predictive values were calculated for composite adverse neonatal outcome for both birthweight criteria. Also, Youden index, which reports the performance of a diagnostic test dichotomously (-1/+1) was calculated.

Sensitivity analyses
Because previous research has shown that children are at risk of both stunting and waisting, might be born with both, pass from one state to the other over time, and accumulate risks to their health and life through, the combined rate were calculated.

Ethical aspects
The study was carried out by using publicly accessible anonymized data, by means of encrypted individual health card numbers [11].

Results

The study included 25948 singleton live births. Mean maternal age was 25.7 years (SD 6.3), and near 50% had > 12 years of schooling. Mean BMI was 24.3 k/m^2, 14.6% were smokers, 7.0% hypertensive, and 3.1% diabetic. The distribution by newborn gender was similar. Mean birth weight was 3306 g (520) and prematurity 11.5% (Table 1).

Table N° 1: Maternal and infant characteristics, composite severe neonatal morbidity/mortality (CNMM) and neonatal phenotypes (N= 25948)

Maternal Characteristic	Mean (SD) or %	
Age, years	25.7	6.3
BMI (kg/m2)	24.3	4.6
Education		
High school	11499	46.6
University	771	3.1
Marital or cohabiting	19873	76.5
Nulliparous	10356	39.9
Previous miscarriage	7171	27.6
Previous preterm birth	279	1.1
Smoking in pregnancy	4566	14.6
Hypertension	1823	7.03
Diabetes	816	3.1
Bleeding during pregnancy	365	1.4
Urinary infection	1283	4.9
Infant		
Male	12992	50.1
Gestational age, wks	38.8	1.9
Preterm birth	2998	11.5
Birthweight, g	3306	520
Length, cm	48.1	2.5
Head circumference, cm	34.8	1.9
BMI (kg/m2)	14.3	1.8
Composite severe neonatal morbidity/mortality (CNMM)		
Neonatal death	217	0.84
Birth asphyxia (Apgar 5'<7)	324	1.2
Respiratory support >4 hs	1413	5.4
Seizures	130	0.5
CNMM	1878	7.2
Phenotypes		
Urquia		
< 3rd centile	961	3.7
< 10th centile	2609	10.1
> 97th centile	2188	8.4
INTERGROWTH-21st		
< 3rd centile	593	2.3
< 10th centile	1527	5.9
> 97th centile	2300	8.9
Stunting	4307	16.6
Wasting	207	0.9

BMI: body mass index

Phenotypes

Overall between 1996 and 2001, the birth weight-for-gestational age <3rd centile was 3.7% of infants under the Urquia criteria, compared with 2.3% under the IG-21st criteria (p<0.001). Similarly, a substantially lower proportion of live births were <10th centile of birth weight-for-gestational age under the IG-21st criteria compared with the Urquia criteria (p<0.001). In contrast, a minimal difference was observed in the proportion of live births >97th centile under the IG-21st criteria compared with the Urquia criteria (P= 0.080) (Table 1). The Urquia 3rd centile value was lower than IG-21st 3rd centile before 37 weeks, but then it surpassed IG-21st until term (Figure 1). Stunting and waisting were 16.6% and 0.9%, respectively under IG-21st, whereas both combined rate was 0.26%.

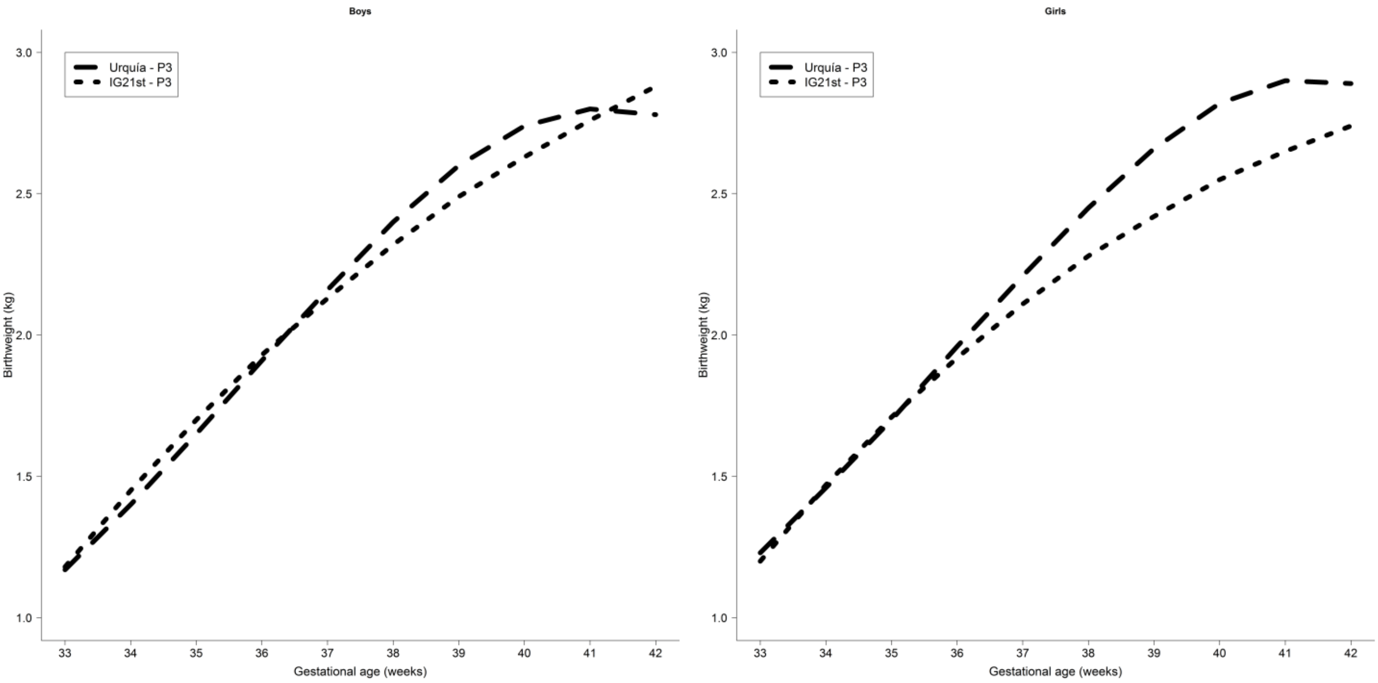

Figure N°1. Third percentile birthweight for Urquia reference and IG-21 Standard by gestational age and sex

Morbidity and mortality

Table 2 shows rates of neonatal death and severe neonatal morbidity among live births within specific phenotypes categories. The rate of neonatal death among SGA<3rd centile was significantly higher under the IG-21st criteria compared with the Argentinean reference (9.4 vs 6.4 per 100 live births, p = 0.029). The rate of neonatal death was also higher among SGA <10th centile under the IG-21st criteria compared with the Urquia criteria (p = 0.006). However, rates of neonatal death among live births >97th centile of the IG-21st and Urquia criteria were similar (p = 0.08). Neonatal death was three times higher for stunting than for waisting; for combined group rate of neonatal death was 1.79%.

Patterns of all morbidities included in CNMM were also higher among SGA<3rd and SGA <10th centile under the IG-21st standard compared with the Urquia reference, but similar rates was found among >97th centile for both criteria. Consequently, rates of composite neonatal morbidity/mortality were significantly higher in all centile categories under INTERGROWTH criteria except for the large-for-gestational category (p=0.003 for SGA<3rd centile, p=0.002 for SGA<10th centile and p=0.553 for >97th centile). CNMM was extremely more common for stunting than for waisting under IG-21st criteria. For combined group rate was 1.51% (Table 2).

Table N° 2: Neonatal mortality and morbidity rates (per 100 live births) among phenotypes categories of the INTERGROWTH-21st Project standard and Urquia reference.

Phenotypes	All lives Births (n = 25948)		<3rd centile		<10th centile		>97th centile		Stunting		Wasting	
Standard or reference	**No.**	**Rate**	**No.**	**Rate**	**No.**	**Rate**	**No.**	**Rate**	**No.**	**Rate**	**No.**	**Rate**
INTERGROWTH 21st standard												
Neonatal death	217	0.84	56	9.4	79	5.1	16	0.7	205	4.7	3	1.4
Apgar 5'<7	324	1.2	67	11.2	105	6.8	58	2.5	295	6.8	7	3.3
Resp.support>4 hs	1413	5.4	99	16.7	145	9.5	145	6.3	451	10.4	30	14.5
Seizures	130	0.5	10	1.6	20	1.3	18	0.7	50	1.1	2	0.9
CNMM	1878	7.2	169	28.5	300	19.6	197	8.5	746	17.3	38	0.18
URQUIA reference												
Neonatal death	217	0.84	62	6.4	89	3.4	15	0.6	a		a	
Apgar 5'<7	324	1.2	78	8.1	127	4.8	54	2.4	a		a	
Resp.support>4 hs	1413	5.4	121	12.5	244	9.3	135	6.1	a		a	
Seizures	130	0.5	13	1.3	24	0.9	18	0.8	a		a	
CNMM	1878	7.2	210	21.8	370	14.2	185	8.0	a		a	

a: not applicable because the Urquia reference does not include newborn length

CNMM: composite severe neonatal morbidity/mortality; Rate: %

Analysis by gestational age

Rates among the different phenotypes were compared among live births at 33-36 weeks and 37-42 weeks gestation. For SGA <3rd centile prevalence under the Urquia references at 33 to less than 37 weeks' gestation were significantly higher compared with term infants (27.5% vs 3.7% respectively [p<0.001], whereas under the IG-21st standard a less reduction was observed (16.1% vs 2.1%, respectively [p <0.001]). At <10rd centile a significant decrease was observed with Urquia reference at 33-36 weeks compared with ≥37 weeks (7.4% vs 10.8%, respectively [p <0.001]), while for IG-21st standard figures were 7.0% vs 5.7%, respectively (p=0.002). For >97th centile, both Urquia and IG-21st significant reduction were similar at 33-36 weeks compared with ≥37 weeks (24.2% vs 6.3% [p <0.001]). Finally, under IG-21st standard the stunting rate was significant higher at 33-36 weeks than ≥37 weeks (20.4% vs 16.1%, [p<0.001]), whereas no difference was observed for wasting (0.90% vs 0.78%, [p<0.510]).

Risks of Composite neonatal morbidity/mortality rates

Table 3 highlights a decreasing risk in severe neonatal morbidity/mortality within phenotypes under the Urquia and INTERGROWTH criteria. Among all live births, infants <3rd centile had higher adjusted rate ratios of CNMM under IG-21st than the Urquia criteria (3.57 [95 % CI 2.90 – 4.40] vs 2.90 [2.40 – 3.49], respectively. For <10th centile RRs where 2.67 (2.27 – 3.14) and 1.99 (1.72 – 2.30) for IG21 and Urquia criteria, respectively. In contrast, there was no difference in the risks of CNMM among live births >97th centile under both criteria (1.27 [1.05 – 1.52] for IG-21st and 1.26 [1.05 – 1.52] for Urquia). Stunting and waisting showed near three times higher adjusted RRs of CNMM under IG-21st criteria compared with reference.

Table N° 3: Crude and adjusted RRs for composite adverse neonatal outcome among phenotypes categories of the Urquia reference and INTERGROWTH-21st Project standard

Phenotypes	Urquia reference		IG-21st standard	
	Crude RR (95% CI)	Adjusted RR a (95% CI)	Crude RR (95% CI)	Adjusted RR a (95% CI)
<3rd centile	1.18 (1.04-1.33)	2.90 (2.40- 3.49)	1.44 (1.28- 1.60)	3.57 (2.90- 4.40)
<10th centile	0.78 (0.67- 0.90)	1.99 (1.72- 2.30)	1.11 (0.99-1.23)	2.67 (2.27- 3.14)
>97th centile	0.17 (0.27- 0.32)	1.26 (1.05- 1.52)	0.18 (0.04- 0.33)	1.27 (1.05-1.52)
Stunting	b	b	1.19 (1.10-1.29)	2.91 (2.59-3.28)
Wasting	b	b	1.23 (0.91- 1.55)	3.37 (2.32- 4.89)

RR: relative risk; CI: confidence interval

a: adjusted for maternal age, parity, BMI, gestational age, hypertension, diabetes and infant sex. Non-phenotypes group as the reference.

b: not applicable because the Urquia reference does not include newborn length

Detection rates

Sensitivity rates by phenotype category showed that 9.02% and 16.0% of all cases of composite neonatal morbidity/mortality occurred among live births <3rd centile and <10th centile, respectively, under the IG-21st criteria, while 11.2% and 19.7% of CNMM occurred among live births <3rd centile and <10th centile under the Urquia criteria. For live birth >97th centile, sensitivity was slightly higher under IG-21st criteria compared with Urquia criteria (10.5% vs 9.9%, respectively). Under IG-21st criteria sensitivity was thirteen times higher for stunting than for waisting (39.8% vs 2.9%, respectively). Youden Index was extremely low for all phenotypes, except for stunting (Table 4).

Table N° 4: Sensitivity, specificity, and predictive values for composite adverse neonatal outcome among phenotypes categories of the INTERGROWTH-21st Project standard and Urquia reference.

INTERGROWTH-21 standard	Sen	Spe	PPV	NPV	Youden Index
<3rd centile	9.02	98.2	28.5	93.2	0.09
<10th centile	16.0	94.9	19.6	93.5	0.13
>97th centile	10.5	91.2	8.5	92.9	0.03
Stunting	39.8	85.2	17.3	94.7	0.27
Wasting	2.9	99.2	18.3	94.6	0.03
URQUIA reference					
<3rd centile	11.2	96.8	21.8	93.3	0.10
<10th centile	19.7	90.7	14.1	93.5	0.12
>97th centile	9.9	91.6	8.5	92.9	0.03

Sen: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value

Youden Index = Specificity + sensitivity – 1 [(12)]

When detection rates of CNMM by phenotypes were compared by gestational age categories, SGA <3rd centile sensitivity rate under Urquia reference showed no difference between 33-36 weeks and 37-42 weeks gestation (11.6% vs 11.0%, respectively). In contrast, under IG-21st standard, the rates showed a marked decrease between 33-36 weeks and 37-42 weeks (11.6% vs 7.7%, respectively).
At <10rd centile, sensitivity at 33-36 weeks were similar for both criteria but higher than <3rd centile (19.5% vs 19.0%), whereas at 37-42 weeks sensitivity rate under IG-21st decreased compared with Urquia reference (14.4% vs 19.8%, respectively). For >97th centile both criteria presented markedly decrease but similar rates at 33-36 weeks and 37-42 weeks (9.7% and 10.0% for Urquia criteria, and 10.3% and 10.6% for IG-21st criteria, respectively). Stunting showed the highest detection rates of CNMM under the IG-21st criteria at both 33-36 weeks and 37-42 weeks (42.6% and 38.4%, respectively). Finally, waisting exhibited the lowest rates in both GA categories under the IG-21st standard (3.3% at 33-36 weeks, and 2.6% at 37-42 weeks).

Discussion

We present a comparison of phenotypes prevalence and associated neonatal morbidity and mortality risk between a new standard on optimal fetal growth and existing local birthweight reference.
Applying the new INTERGROWTH-21st birth weight standard, we observed a roughly 40% reduction in the prevalence of SGA <10th centile among the cohorts (Urquia 10.1% vs IG-21st 5.8%). The SGA-less-than-10 percentile cutoff using the reference may have been too inclusive in identifying neonates at risk due to fetal growth restriction. On the other hand, the relative reduction in prevalence when applying the IG-21st standard vanished among infants born at 33 to less than 37 weeks' gestation (Urquia 7.4% vs IG-21st 7.0%) and was greater in Urquia term infants (10.4% vs IG-21st 5.7%); this may be attributed that, at preterm gestations, the IG-21st standard may not reflect optimal fetal growth because preterm birth is inherently pathological and is commonly associated with fetal growth restriction [(13)]. In addition, differences in SGA rates between criteria can be related to differences in maternal size. Increasing maternal height and weight are correlated with increasing infant birthweight, even for women of normal BMI [(14)].
When applying a more strict criteria (<3rd centile) the reduction among the cohorts slightly decreased (37%), but difference in prevalence was larger among infants born at 33 to less than 37 weeks' gestation (Urquia 27.5% vs IG-21st 16.1%) and was similar in term infants (3.7% vs IG-21st 2.1%) (Fig.1). This may be attributable to the prescriptive design of the IG-21st Project, the left shift in birth weight-for-gestational age centiles of the Urquia reference (skewness -0.701 [SE 0.015], K-S test = 0.162 [p<0.001]), and that mothers contributing births to the lower tail of the distribution may be more similar in risk profile between the IG-21st standard and the Urquia references; for example, they may comprise women who are genetically predisposed to having smaller children [(15)]. It is also unclear as to the extent to which miscategorization of gestational age due to the use of last menstrual period in the Urquia reference may have affected these findings.
Both the international IG-21st standard and Urquia reference has revealed a markedly high prevalence of LGA>97th centile infants than expected, but no difference was observed between them (Urquía 8.4% vs IG-21st 8.9%). In a previous population study of singleton live births, 0.87% and 9.63% were <3rd centile and >97th centile, respectively, under the IG-21st standard, while 2.27% and 3.55% were <3rd centile and >97th centile, respectively, of a Canadian reference [(2)]. Revollo et al. assessed the prevalence of SGA <3rd centile, stunting and wasting by gestational age in newborns of the Jujuy Province, Argentina at different altitude levels. Prevalence were 1.27%, 3.39% and 4.68% for of SGA<3rd centile, stunting and wasting, respectively, and significantly higher at >2.000 m.a.s.l. [(16)]. Finally, in an Australian study, >97th centile prevalence was 6.2% under IG-21st [(17)].
Observed differences in between-country and ethnic-specific fetal growth references potentially reflect differences in maternal socioeconomic status and health [(18)]. We highlight that the divergence between the IG-21st standard and the different studies may occur because several risk factors, such as overweight and obesity and gestational diabetes, that are linked to higher birth weight and preterm birth are more prevalent in the studies but excluded from the IG-21st study [(3)].
The international standards still need to be tailored to local populations and statistic-based cutoffs (such as < 10th or > 90th centile), should ideally be replaced by perinatal risk-based cutoffs to provide an evidence-based triage for neonatal care [(3)].
Differences were observed in neonatal morbidity and mortality rates within phenotypes of the IG-21st and Urquia criteria. The relatively less stringent INTERGROWTH criteria for identifying large-for-gestational age infants resulted in relatively low neonatal morbidity/mortality rates among such infants.
This overall picture suggests that, under IG-21st criteria, Sardá live births have low rates of growth restriction and high rates of excess growth, but higher morbidity/mortality rates in SGA infants, compared with the Urquia reference. The rate of a composite adverse neonatal outcome in a New Zeland study was 17.2% in infants identified as SGA <10th centile by IG-21st and 12.1% in those identified as SGA by customized criteria [(17)]. Differences were attributed to customized birthweight standards that differ from population standards in that they use ultrasound-based measures of fetal size. In a study from India, the infants identified as SGA <10th centile at birth by IG-21st charts had higher incidence of morbidities compared with Fenton growth charts [(19)]. Under the IG-21st standard infants <3rd centile and >97th centile had a higher composite neonatal morbidity/mortality rate than a Canadian reference [(2)]. Finally, the neonatal mortality risk of SGA status (< 10th percentile) did not differ significantly between IG-21st and a commonly used US references [(15)]. These findings are similar to our study, although the composite of adverse neonatal outcome were different.
Consistently, adjusted CNMM risks in SGA (<3rd and <10th) and >97th centiles where higher under IG-21st compared with Urquia reference. Elevated adjusted CNMM risks for stunting and waisting is worrisome, because the first accounted after a prolonged intrauterine growth restriction not amenable to rapid nutritional treatment, and is therefore considered to require prevention rather than treatment, whereas the late is an acute and reversible process with adequate nutritional intervention [(9)]. In addition, the combined rate (0.26 %) was small than children between 6 months and 59 months in 84 countries (3%, range 0% to 8%) [(20)], but mortality rate (1.79%) was higher than the most severe form of being wasted (1.4%), underpinning that they accumulate risks to their health and life course (such as promoting human capital and reducing the risk of non-communicable disease) through their combined effects.
In a sensitivity analysis, we find a larger relative reduction in neonatal mortality rate associated to SGA among infants born at term compared to 33 to less than 37 weeks' gestation (roughly 84% for Urquia vs 87% for IG-21st).
Despite the fact that children small or large for gestational age have an increased risk of adverse neonatal outcomes irrespective of the reference used for classification, most adverse outcomes occur in infants without this disorder. Consequently, the sensitivity, positive predictive values and Youden Index of these phenotypes for adverse perinatal outcomes were very low[(21)].
This study supports the case for an outcome-based determination of IG-21st centile cut-offs for surveillance and monitoring of abnormal growth [(4)]. The identification of optimal cut-offs for identifying infants at high risk for adverse outcomes needs to balance the proportion of severe neonatal morbidity and neonatal death identified by the cut-off (*sensitivity*) with the proportion of infants deemed to be high risk (*stratification capacity)* [(10)]. The optimal IG-21st centile cut-offs for identifying small- and large-for-gestational age live births will likely be resource/cost dependent and hence spatio-temporally specific.
Growth centiles (or phenotypes) are perhaps best viewed as one input for use in multivariable models for the screening and identification of high risk infants. Obstetric intervention for abnormal fetal growth is ideally guided by multivariable models that include fetal

growth centiles and other risk factors such as uterine and middle cerebral artery blood flow [22].

Limitations include potential errors with regard to gestational age, which would have affected phenotypes under both criteria. In addition, some transcription errors are also possible with regard to the diagnoses of severe neonatal morbidity.

Another limitation was that only a *limited range of neonatal morbidity measures* could be reported, but these are objective measures that have been shown to identify infants at high risk of major morbidity [3,23-24]. Strengths of our study were sample size, the inclusion of objective morbidity measures that are infrequently included in other cohort studies, and combined evaluation of stunting and waisting.

Future work will standardize outcome measures because several core outcome sets have also been developed or are in development in the field of neonatology [25-26]. Lastly, our facility-specific estimates might not be representative for the country, but portray the population included in this study. The Urquia reference will remain useful in understanding the growth status of a newborn in relation to the population attended.

Conslusion

The IG-21 standard identified low rates of growth restriction and high rates of excess growth, but a higher risk of neonatal morbidity and mortality than the Urquia reference.

Limitaciones de responsabilidad

La responsabilidad del trabajo es sólo de los autores.

Exclusividad de publicación:

El estudio no ha sido publicado previamente, ni se ha presentado a otra revista.

Declaración de la originalidad del trabajo que se presenta.

Se trata de un artículo original.

Fuentes de apoyo:

Ninguna.

Conflicto de interés:

Los autores declaran que no existen conflictos de intereses con otros autores, instituciones, laboratorios, profesionales u otros.

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