Customized GROW vs INTERGROWTH-21st birthweight standards to identify small for gestational age associated perinatal outcomes at term

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BACKGROUND: Fetal growth restriction is associated with stillbirth and other adverse pregnancy outcomes, and the use of the correct weight standard is an essential proxy indicator of growth status and perinatal risk.
OBJECTIVE: This study aimed to assess the performance of two international birthweight standards for their ability to identify perinatal morbidity and mortality indicators associated with small for gestational age infants at term.
STUDY DESIGN: This retrospective cohort study used data from a multicenter perinatal quality initiative, including a multiethnic dataset of 125,826 births from 2012 to 2017. Of the singleton term births, 92,622 had complete outcome data including stillbirth, neonatal death, 5-minute Apgar score <7, neonatal glucose instability and need for newborn transfer to a higher level of care or neonatal intensive care unit admission. The customized GROW and INTERGROWTH-21st birthweight standards were applied to determine small for gestational age (<10th percentile) according to their respective methods and formulae. The associations with adverse outcomes were expressed as relative risks with 95% confidence intervals and population attributable fractions.
RESULTS: GROW and INTERGROWTH-21st classified 9578 (10.3%) and 4079 (4.4%) pregnancies as small for gestational age, respectively. For all of the outcomes assessed, GROW identified more small for gestational age infants with adverse outcomes than INTERGROWTH-21st, including more stillbirths, perinatal deaths, low Apgar scores, glucose instability, newborn seizure, and transfers to a higher level of care. Moreover, 13 of 27 stillbirths (48%) that were small for gestational age by either method were identified as small for gestational age by GROW but not by INTERGROWTH-21st. Similarly, additional cases of all other adverse outcome indicators were identified by GROW as small for gestational age, whereas INTERGROWTH-21st identified in only 1 category (glucose instability) 9 of 295 cases (3.1%), which were not identified as small for gestational age by GROW.
CONCLUSION: Customized assessment using GROW resulted in increased identification of small for gestational age term infants that were at significantly increased risk of an array of adverse pregnancy outcomes.

Keywords: customized charts, fetal growth restriction, GROW, INTERGROWTH 21st, perinatal morbidity, small for gestational age, stillbirth

Introduction

Fetal growth restriction (FGR) is an important antecedent of perinatal death.[1] Small for gestational age (SGA) is often used as a proxy for FGR, as the information to determine whether FGR was present is often not available, because it was not recorded or missed during antenatal care.

However, SGA includes pathological (FGR) and constitutional small size, and hence, there has been an endeavour to adjust for such constitutional or physiological factors to improve the definition of "SGA" to better represent pathological small size.

Customized fetal growth and birthweight charts adjust for physiological variables which have been found to affect growth and birthweight in low-risk[2] and high-risk[3] pregnancies with normal outcomes: maternal height and weight within normal body mass index (BMI) limits, parity and ethnic origin as well as fetal sex when known. For example, in the absence of pathology, large and small mothers with normal BMI have neonates with similar perinatal mortality risk, and, if the standard of their weight is customized, also the same SGA rate.[4]

The same physiological variables are found to be significant in different countries and populations,[5] and coefficients have now been developed for more than 120 ethnic groups and incorporated into a "global" customized growth chart and birthweight percentile software (www.gestation.net). The effects of pathological factors such as smoking, obesity and diabetes mellitus are also identified in the data analysis but then excluded.[4] The principle of such customization is to produce a "Gestation Related Optimal Weight" (GROW) standard for each pregnancy.

Another method, which has recently been put forward to assess fetal growth and birthweight, is the INTERGROWTH-21st (IG21) standard.[6,7] This has been developed on the principle that the same standard can apply to all populations, as long as the data are derived only from healthy, well-nourished mothers who had a normal pregnancy. The data were collected in a standard manner prospectively in 8 countries. The standard assumes that downward variation in growth and birthweight by maternal size and ethnic origin represents stunting and malnutrition, and should not be adjusted for.[6,7]

Cite this article as: Fay E, Hugh O, Francis A, et al. Customized GROW vs INTERGROWTH-21st birthweight standards to identify small for gestational age associated perinatal outcomes at term. Am J Obstet Gynecol MFM 2022;4:100545.

2589-9333/$36.00

http://dx.doi.org/10.1016/j.ajogmf.2021.100545

AJOG MFM at a Glance

Why was this study conducted?

This study aimed to compare the performance of the INTERGROWTH-21st birthweight standard, promoted as internationally applicable to all populations, with the performance of GROW, which is individually adjustable according to maternal characteristics, in defining "small for gestational age" (SGA) and their respective strength of association with adverse pregnancy outcomes.

Key findings

GROW identified more SGA infants with adverse outcomes than INTERGROWTH-21st, and infants identified as SGA by INTERGROWTH-21st but not by GROW were not at increased risk.

What does this add to what is known?

The results were in agreement with other comparisons between these standards, but thanks to a larger and more detailed dataset, this study was able to extend the analysis to include a wider array of indicators of perinatal morbidity and mortality.

This study aimed to test these two standards on a database of comprehensive clinical outcomes (Obstetrics Clinical Outcomes Assessment Program [OB COAP]), to determine which method best identifies SGA birthweight that is associated with adverse outcomes.

Materials and Methods

Study cohort

This retrospective cohort study used data from the OB COAP database from 2012 to 2017. The OB COAP is a multicenter clinician-led, quality initiative in Washington and has been previously described in detail.[8] The OB COAP collected medical record–abstracted data on consecutive deliveries at 14 sites that participated in the program for some or all of the study period. These included centers providing level I, II, and III neonatal care and both urban and rural locations.

Calculation of percentiles

Birthweight percentiles were determined according to (1) the US customized GROW birthweight percentile calculator,[9] which is based on data from three American multiethnic datasets[5,8,10] and (2) the INTERGROWTH-21st neonatal standard.[6] The prevalence of SGA (<10th birthweight percentile) according to these standards and their association with SGA-related perinatal outcomes were compared.

The two standards differ in their assessment of preterm births: IG21 is based on cross-sectional birthweight averages derived from term and preterm deliveries, whereas GROW uses a term optimal weight adjusted, fetal growth based trajectory throughout the whole gestational age range,[11] which identifies an increased rate of preterm deliveries known to be associated with SGA.[12,13] To exclude this variation between the standards, we truncated the analysis to term deliveries only.

Outcomes

Outcome variables derived from the dataset were (1) stillbirth; as time of fetal death was not recorded, an average of 2 days was deducted from the gestational age at delivery[14,15]; (2) Apgar score <7 at 5 minutes; (3) neonatal glucose instability or hypoglycemia; (4) newborn seizure; (5) transfer to a higher level of neonatal care; and (6) neonatal death (up to 28 days).

Analysis

Descriptive statistics were used to compare participant characteristics for the whole cohort and stratified by four mutually exclusive groups: SGA by GROW only, SGA by IG21 only, SGA by both, and SGA by neither standard. SGA rates according to each standard were compared for their association with outcome using relative risks (RRs), 95% confidence intervals (CIs), and population attributable fractions (PAFs)[16] PAF is the proportion of outcome that can be attributed to being SGA. All statistical analyses were performed using Stata software (version 15.1; StataCorp, College Station, TX).[17]

Ethics

The Western Institutional Review Board has determined that the OB COAP is not engaged in research on human subjects and is therefore deemed exempt from institutional review. All data were fully anonymized for analysis.

Results

Table 1 summarizes the exclusions from the original database of 125,826 deliveries, which left 92,622 singleton, normally formed pregnancies with complete data for customization.

The characteristics of the study population are listed in Table 2 and show a multiethnic population, with the main minority groups being Hispanic (18.4%) and Asian (17.6%). A more detailed subgroup count of the "Asian" category towards the end of the data collection period (n=1011) found that most Asian mothers were from South Asia (60.0%), followed by Far East (24.5%) and South East Asia (15.5%).

The median gestational age in these term births was 277 days (interquartile range [IQR], 273–282), with a median birthweight of 3424 g (IQR, 3122–3726). SGA and large for gestational age (LGA) rates varied between GROW (SGA, 10.3%; LGA, 9.8%) and IG21 (SGA, 4.4%; LGA, 19.0%) standards, with substantially higher SGA and lower LGA rates according to GROW (Table 2). Table 2 also shows the attributes of the pregnancies that are identified as SGA by GROW only, IG21 only, SGA by both methods, and SGA by neither standard. Pregnancies that were SGA by IG21 only were smaller in terms of maternal height, weight, and BMI. These mothers were also more likely to be younger, nulliparous, and Asian, and a higher proportion

TABLE 1
Exclusion criteria

Criteria	Excluded (n)	Remaining (n)	Remaining (%)
Congenital anomalies and multiple pregnancies	4642	121,184	96.3
Missing or invalid gestational age or birthweight	886	120,367	95.7
Preterm deliveries (<259 d)	10,397	112,309	89.3
Planned out of hospital births	5670	106,836	84.9
Missing or invalid variables[a]	16,729	92,622	73.6

[a] Variables include sex, maternal height, weight, ethnicity, or parity.

Dataset comprises 125,826 births from 2012 to 2017.

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of infants identified as SGA according to IG21 were female.

Table 3 lists the incidence of the adverse outcome categories and the number and proportion that were identified as SGA by both GROW and IG21, as well as by GROW or IG21 only. Each of the outcome categories were significantly associated with SGA birthweight when SGA was identified by both standards.

Of the 60 stillbirths, 14 were SGA by both GROW and IG21 (RR, 9.17; 95% CI, 4.91−17.12). An additional 13 cases (48%) were SGA according to GROW only and had a significantly increased risk (RR, 5.68; 95% CI, 2.99−10.78), with a PAF of 23.3% (95% CI, 12.2−39.8). There were no additional stillbirths identified as SGA according to IG21.

A similar pattern was apparent for the four morbidity categories (low Apgar score, poor glucose control, newborn seizure, neonatal transfer to higher level of care), with GROW in each instance identifying a substantial number of additional cases as being SGA, which had significantly increased risk of the respective outcome. Only in the glucose instability category did IG21 identify 9 additional SGA cases with increased risk, whereas GROW identified an additional 94 SGA cases.

There were 18 neonatal deaths, 9 of which were identified as SGA by both standards (RR, 19.21; 95% CI, 7.42−49.76), with one additional case identified by GROW and none by IG21.

Comments

Main findings

Our analysis confirmed that SGA in the perinatal period is significantly associated with perinatal morbidity and mortality in term neonates. However, the strength of association and the number of cases identified depends on the standard applied to calculate the weight for gestation percentile to determine SGA. In each outcome category, the customized GROW standard performed better in that it identified a large number of additional cases as SGA that were not identified by IG21. No additional cases were identified by IG21, except for a few in the "glucose instability" group.

This difference in performance was, in part, because of the ability of the customized method to control for constitutional variation, thereby better identifying pathologically small cases. As shown in Table 2, neonates identified as SGA by IG21 were more likely to be female and had mothers who were younger, smaller, Asian, and in their first pregnancy. Such factors affecting birthweight and hence the definition of SGA are adjusted for by GROW as constitutional variation, which is supported by the fact that the group of pregnancies that were SGA by IG21 but not GROW had no stillbirths or neonatal deaths and had a reduced rate of perinatal morbidity.

A further observation was that the IG21 standard, although intended for international use, did not seem to reflect the birthweight distribution of the OB COAP population, with only 4.4% of birthweights being below the 10th percentile. This low level was consistent with findings when IG21 was used to define SGA in other populations.[18−20] As shown in the analysis in Table 3, the "missing" cases (SGA by GROW only) constituted in each outcome category a large proportion (e.g. 48% of stillbirths) that have significantly increased risks of adverse outcome but are not detected as SGA by IG21.

Research and clinical implications

The results are consistent with previous head-to-head comparisons between IG21 and customized GROW charts. GROW improved the association between SGA and adverse outcomes in populations from New Zealand,[18,21] Australia,[22] Sweden,[23] Florida,[24] a United Kingdom cohort with chronic hypertension,[25] a Spanish cohort with gestational diabetes mellitus,[26] and a 10-country database assessing stillbirth risk at term.[19]

This study of a birthweight database compared the IG21 newborn standard[6] with GROW,[11] which is a combined fetal growth and birthweight standard. The analysis was limited to term deliveries to avoid potentially placing IG21 at a disadvantage because of the known association between prematurity and FGR, which tends to be missed by a cross-sectional standard derived from newborn weights. A comparative study of the performance of fetal growth charts in preterm deliveries has also reported better results with the customized GROW chart than the IG21 fetal growth chart.[27]

Despite the relative ease of application of a one-size-fits-all approach, uptake of the INTERGROWTH-21st consortium's standards has been patchy following several reports, consistent with the current study, that the standard does not reflect local populations in Australia,[28] China,[29] Europe,[30] and the United Kingdom.[31] The customized GROW charts and percentiles did not have this problem as they adjust for individual characteristics and hence also reflect the average

TABLE 2
Descriptives of dataset including SGA by GROW and INTERGROWTH-21st birthweight standards

Variable		SGA by GROW		SGA by IG21	
Pregnancies (N=92,622)		9578 (10.3)		4079 (4.4)	
	Total or average	SGA by GROW only	SGA by GROW and IG21	SGA by IG21 only	Not SGA by either standard
Pregnancies	92,622	5747 (6.2)	3831 (4.1)	248 (0.3)	82,796 (89.4)
Maternal height (cm), median (IQR)	163 (11)	165 (10)	160 (8)	152 (7)	163 (11)
Maternal weight (kg), median (IQR)	67 (21)	76 (25)	64 (18)	49 (7)	67 (20)
Maternal age (y)					
<20	3368 (3.7)	191 (3.3)	229 (6.0)	20 (8.1)	2928 (3.5)
20–28	32,285 (35.4)	2070 (36.0)	1366 (35.7)	94 (37.9)	28,755 (34.7)
29–34	36,479 (40.0)	2242 (39.0)	1436 (37.5)	96 (38.7)	32,705 (39.5)
≥35	19,147 (21.0)	1177 (20.5)	748 (19.5)	35 (14.1)	17,187 (20.8)
BMI (kg/m^2)					
<18.5	2514 (2.7)	46 (0.8)	160 (4.2)	54 (21.8)	2254 (2.7)
18.5<25.0	42,239 (45.6)	1681 (29.3)	1914 (50.0)	189 (76.2)	38,455 (46.4)
25.0<30.0	24,894 (26.9)	1627 (28.3)	1002 (26.2)	5 (2.0)	22,260 (26.9)
30.0<35.0	12,710 (13.7)	1192 (20.7)	425 (11.1)	0 (0)	11,093 (13.4)
≥35.0	10,265 (11.1)	1201 (20.9)	330 (8.6)	0 (0)	8734 (10.5)
Parity					
0	37,672 (40.7)	1957 (34.1)	2152 (56.2)	216 (87.1)	33,347 (40.3)
1	31,805 (34.3)	2041 (35.5)	1010 (26.4)	27 (10.9)	28,727 (34.7)
2	13,944 (15.1)	1039 (18.1)	359 (9.4)	5 (2.0)	12,541 (15.1)
≥3	9201 (9.9)	710 (12.4)	310 (8.1)	0 (0)	8181 (9.9)
Ethnic groups					
White or European	52,278 (56.2)	3708 (64.5)	1697 (44.3)	13 (5.2)	45,056 (54.4)
Hispanic	17,080 (18.4)	901 (15.7)	660 (17.2)	41 (16.5)	14,863 (18.0)
Asian	16,334 (17.6)	452 (7.9)	902 (23.5)	145 (58.5)	13,296 (16.1)
Other (<10%)	10,450 (11.2)	466 (8.1)	340 (8.9)	24 (9.7)	6273 (7.6)
Gestation at birth, median (IQR)	277 (9)	277 (11)	275 (11)	275 (11)	277 (9)
Sex					
Male	46,914 (50.8)	2907 (50.6)	1922 (50.2)	117 (47.2)	41,968 (50.7)
Female	45,479 (49.2)	2828 (49.2)	1902 (49.6)	131 (52.8)	40,618 (49.1)
Birthweight (g), median (IQR)	3424 (604)	2930 (278)	2588 (334)	2702 (248)	3483 (550)

Data are presented as number (percentage), unless otherwise indicated.

GROW, Gestation-Related Optimal Weight; IG21, INTERGROWTH-21st birthweight standard; *IQR*, interquartile range; *SGA*, small for gestational age.

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characteristics of each population. They are already in routine use in most hospitals in the United Kingdom and New Zealand, and uptake is gradually spreading internationally.

Strengths and limitations

A strength of our study was that we had a comprehensive, multiethnic dataset with several indicators of perinatal morbidity and mortality. A potential weakness was that in 11% of cases, data were missing for customized assessment, but this still left a cohort of >90,000 cases for analysis of the various outcome indicators within the SGA subgroups. The retrospective

TABLE 3
GROW vs INTERGROWTH-21st birthweight standards: identification of small for gestational age neonates by outcome

Variable	Total or average	SGA by GROW only	SGA by GROW and IG21	SGA by IG21 only	Not SGA by either standard
Category	92,622	5747 (6.2)	3831 (4.1)	248 (0.3)	82,796 (89.4)
Stillbirth					
Frequency (n/1000)	60 (0.6)	13 (2.3)	14 (3.7)	0	33 (0.4)
Relative risk (95% CI)		5.68 (2.99–10.78)[a]	9.17 (4.91–17.12)[a]	0.00	—
PAF (95% CI)		23.3 (12.2–39.8)	26.5 (15.2–42.1)	0.0	—
Neonatal death					
Frequency (n/1000)	18 (0.2)	1 (0.2)	8 (2.1)	0	9 (0.1)
Relative risk (95% CI)		1.60 (0.20–12.63)	19.21 (7.42–49.76)[a]	0.00	—
PAF (95% CI)		3.8 (0.0–90.6)	44.6 (22.8–68.7)	0.0	—
5-minute Apgar score of <7					
Frequency, n (%)	1088 (1.2)	90 (1.6)	108 (2.8)	2 (0.8)	888 (1.1)
Relative risk (95% CI)		1.46 (1.18–1.81)[a]	2.63 (2.16–3.20)[a]	0.75 (0.19–2.97)	—
PAF (95% CI)		2.9 (1.5–5.6)	6.7 (5.0–9.0)	0.0	—
Glucose instability					
Frequency, n (%)	1248 (1.3)	94 (1.6)	192 (5.0)	9 (3.6)	953 (1.2)
Relative risk (95% CI)		1.42 (1.15–1.75)[a]	4.35 (3.74–5.07)[a]	3.15 (1.66–6.01)[a]	—
PAF (95% CI)		2.7 (1.3–5.3)	12.9 (10.8–15.3)	0.6 (0.2–1.6)	—
Newborn seizure					
Frequency, (n/1000)	99 (1.1)	11 (1.9)	3 (0.8)	1 (4.0)	84 (1.0)
Relative risk (95% CI)		1.89 (1.01–3.53)[a]	0.77 (0.24–2.54)	3.97 (0.56–28.43)	—
PAF (95% CI)		5.4 (1.5–18.0)	0.0	0.9 (0.1–11.0)	—
Transfer to higher level of care					
Frequency, n (%)	4586 (5.0)	337 (5.9)	545 (14.2)	15 (6.0)	3689 (4.5)
Relative risk (95% CI)		1.32 (1.18–1.47)[a]	3.19 (2.94–3.47)[a]	1.36 (0.83–2.22)	—
PAF (95% CI)		2.0 (1.3–3.1)	8.8 (7.9–9.9)	0.1 (0.0–0.7)	—

CI, confidence interval; *GROW*, Gestation-Related Optimal Weight; IG21, INTERGROWTH-21st birthweight standard; *PAF*, population attributable fraction; *SGA*, small for gestational age.

[a] $P<.05$ are statistically significant.

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nature of our study was a limitation in that we did not know the considerations that were included in the management of these pregnancies. However, we do not believe that this would have affected the comparative analysis of the two birthweight standards and their associations with indicators of pregnancy outcomes.

Conclusion

Our study confirmed and extended on a wider set of indicators that customized GROW charts are better at identifying SGA birthweight associated with adverse perinatal outcomes. SGA according to the IG21st newborn standard misses many babies with increased risk.

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Received Sept. 28, 2021; revised Nov. 17, 2021; accepted Nov. 30, 2021.

O.H., A.F. and J.G. work for the Perinatal Institute, a not-for-profit social enterprise that provides training and support services to healthcare organizations, including GROW charts used in this study. The other authors report no conflict of interest.

This study was supported by the Foundation for Health Care Quality, a 501(c)3 nonprofit organization that is supported by membership contributions. The study received no other funding.

This study was presented at the 39th annual meeting of the Society for Maternal-Fetal Medicine, Las Vegas, Nevada, February 11–16th, 2019.

A short video summarizing this study is available here: doi:10.1016/j.ajogmf.2021.100545.

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