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Comparative performances of five neonatal anthropometric charts in classifying small- and large-for-gestational age Nigerian term neonates and predicting insulin resistance: An exploratory cross-sectional analysis

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TITLE PAGE

Comparative performances of five neonatal anthropometric charts in classifying small- and large-for-gestational age Nigerian term neonates and predicting insulin resistance: An exploratory cross-sectional analysis

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Abstract

Background: Abnormal intrauterine foetal growth, manifesting as small-for-gestational-age (SGA) or large-for-gestational-age (LGA) birth, increases the risk of insulin resistance (IR), a precursor of later adverse cardiometabolic outcomes. Neonatal anthropometric charts are used for identifying SGA or LGA babies, but their identification of these and association with neonatal outcomes vary across populations but sparingly reported from sub-Saharan Africa with largest burden of SGA worldwide. Notably, their association with neonatal IR is not known. We thus compared the performances of five charts—INTERGROWTH-21ST, Fenton-2013, Mokuolu, Lubchenco and WHO Multicentre Growth Reference Study (MGRS)—in identifying SGA/LGA and predicting neonatal IR associated with SGA/LGA.

Methods: This exploratory secondary cross-sectional analysis included 121 term neonates from a prospective maternal-infant cohort at Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria. Birthweights were classified with each chart. Neonatal IR was defined as Homeostatic Model Assessment of Insulin Resistance >1.195. We calculated frequencies of SGA/LGA, diagnostic accuracy (sensitivity, specificity) of detecting IR associated with SGA or LGA and inter-chart agreement (Cohen's κ).

Results: One-quarter of neonates (24.8%) had IR. The frequency of SGA and LGA varied widely across charts (SGA: 4.2–10.1%; LGA: 4.1–14.2%). INTERGROWTH-21ST and Fenton-2013 identified more SGA (10.1% and 10.0%, respectively), while INTERGROWTH-21ST and Mokuolu identified more LGA (12.6% and 12.5%, respectively). Across charts, sensitivities for predicting IR were low (13.3–40.0%), while specificities were higher (73.3–76.6%). Lubchenco and WHO charts showed relatively better balance of sensitivity and specificity, albeit with very wide confidence intervals. Concordance was highest between INTERGROWTH-21ST and Fenton-2013 for SGA (κ=1.0), and between

Mokuolu, INTERGROWTH-21ST, and Lubchenco for LGA (κ=0.93).

Conclusion: This largely exploratory findings suggests that neonatal anthropometric charts vary widely in their classification of neonatal birthweight. While none of the charts reliably predicted neonatal IR, Lubchenco and WHO-MGRS charts performed relatively better but unreliably due to wide confidence intervals. There is need for larger, multicentre studies in African populations.

Clinical Trial Number

Not applicable

Keywords

Insulin resistance, anthropometric charts, INTERGROWTH-21ST, birthweight, validation, sub-Saharan Africa

Background

Insulin resistance (IR) is a state of impaired cellular response to insulin, resulting in hyperglycaemia and, over time, increased risk of cardiometabolic disorders including diabetes.[1, 2] Epidemiologically and clinically, IR is commonly measured with the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), calculated from fasting serum insulin and glucose levels.[1] In childhood, the risk of developing IR and its consequences can be influenced by factors such as intrauterine growth patterns, genetic predisposition, and environmental influences.[1, 2] Rising global incidence of IR and its associated metabolic disorders makes its early detection and management critical to optimal cardiometabolic outcomes.[1, 2] Compared to appropriate-for-gestational-aged (AGA) neonates, those with abnormal intrauterine foetal growth (aIFG)- which may manifest as small-for-gestational-age (SGA) or large for-gestational-age (LGA)- may be at higher risk of

IR[3] and its consequent later adverse cardiometabolic outcomes.[4–7] Thus, identifying these neonates early can inform interventions that may reduce these risks.[7, 8] Neonatal anthropometric charts serve as benchmarks for evaluating measured birth sizes (weight, length, head circumference) relative to a reference or standard population.[8, 9] These charts are used to classify the birth-weight of neonates as SGA, AGA or LGA. In Nigeria, various charts are used for newborn birth-size classification, ranging from locally-derived (e.g. Mokuolu et al[10] chart) to foreign or international charts (Lubchenco et al[11]; World Health Organization (WHO)'s Multicentre Growth Reference Study [WHO-MGRS];[12] International Foetal and Newborn Growth Consortium for the 21st Century [INTERGROWTH-21ST];[13] and Fenton et al's 2013 charts[14]). However, these charts differ in their methodology and sample population base; thus, their performances in classifying a given neonate as SGA, LGA or AGA may differ.[9, 15] Generally, charts are classified as *standard*, *reference* or *customised* charts.[9] Standard charts are *prescriptive* charts developed from newborn babies of an internationally-representative population of stringently-selected healthy mothers, aimed at describing *how babies should grow* (e.g. WHO-MGRS,[12] INTERGROWTH-21ST charts[13]). Reference charts are *descriptive* charts developed from babies of less-stringently selected population of mothers, aimed at describing *how babies are actually growing* in a given population (e.g. Lubchenco,[11] Mokuolu[10] and Fenton-2013 charts[14]). Customised charts are designed to be specific to a given population by accounting for maternal characteristics such as weight, height, etc. along with neonatal anthropometrics.[9] Published in 1963 from Caucasian neonates of gestational age 24-42 weeks in Colorado, USA, the Lubchenco et al[11] chart is one of the oldest charts. Mokuolu et al[10] chart was developed cross-sectionally from over 5,000 Nigerian babies born at 25-44 weeks in North-central Nigeria (Ilorin). Specifically, its validity among Nigerian children has not been assessed although the need for this was recognised by the

authors.[10, 16, 17] The Fenton et al chart,[14] published in 2013, was developed through a meta-analysis of six large population-based datasets comprising nearly 4 million Caucasian infants (gestational age 22–36 weeks) from Germany, the United States, Italy, Australia, Scotland, and Canada, and was extrapolated to cover up to 50 weeks gestational age. The Fenton-2013 charts demonstrate smooth transition to WHO-MGRS charts standards at term and so is sometimes used for term babies.[18]

Because of the concern for multiplicity of local/regional charts across the world, the WHO, in 2004, published the WHO-MGRS chart as a global growth standard derived from a multinational population of term newborn infants from six countries (Brazil, Ghana, India, Norway, Oman, and the United States) who were prospectively followed up from birth to 24 months.[12] Using similar methodology to the WHO-MGRS, the International Foetal and Newborn Growth Consortium (INTERGROWTH-21st) sought to complement the WHO-MGRS by developing charts from preterm and term infants enrolled from eight countries-Brazil, Italy, Oman, UK, USA, China, India and Kenya. Although the WHO-MGRS and INTERGROWTH-21ST charts are recommended for global use, Africa was represented only by Ghanaian and Kenyan infants, respectively, raising concerns about generalisability to other African populations, given genetic and environmental diversity across populations.[16, 19–21] There is thus need to objectively determine which chart is best for our population, to minimise misclassification. [4, 9] Objective validation of charts is often determined by the extent to which they predict or are associated with short- or long-term clinical outcomes like postnatal growth failure,[22] poor neurodevelopmental outcomes,[22] adverse perinatal/neonatal outcomes,[4, 21, 23–25] preterm outcomes[26] and mortality.[27] However, the predictive performances of charts with respect to long-term cardiometabolic consequences of aIFG is scarcely reported. Since these cardiometabolic consequences are partly mediated via IR, determining which of the charts is most associated with IR may

suggest which is best for predicting later cardiometabolic outcomes. We thus aimed to (1) determine and compare the frequency of SGA, LGA and aIFG (SGA/LGA) among five neonatal charts (INTERGROWTH-21ST, Fenton-2013, Mokuolu, Lubchenco and WHO-MGRS); (2) explore their predictive association with IR associated with SGA and LGA; (3) determine the agreement (concordance) among the charts with respect to classifying neonates as SGA, LGA and SGA/LGA.

Methods

Study design and population

This is an exploratory secondary cross-sectional analysis of the infant data of a larger prospective cohort study in which we consecutively enrolled non-diabetic healthy singleton pregnant women at late third-trimester and followed them up till birth to determine the association between maternal and neonatal IR at the Obstetrics Unit of the Lagos State University Teaching Hospital (LASUTH), a tertiary hospital in Ikeja, Lagos, Nigeria. The methodology, including study design, study population, eligibility criteria, sampling, sample size determination, assay and data collection procedures are detailed in previous publications,[17, 28] but summarised here. All neonates with birthweight data were included in this secondary analysis. The primary study was conducted, in line with the Declaration of Helsinki,[29] between September 2020 and May 2021 after being approved by the Health Research & Ethics Committee (HREC) of LASUTH and written informed consent obtained from participants.

Data collection procedures

At enrolment, trained research assistants used a self-designed proforma to collect baseline maternal characteristics from consenting eligible pregnant women. Venous blood was sampled from each woman and assayed for fasting plasma insulin and glucose levels to calculate maternal HOMA-IR: *fasting insulin (μU/mL) ✕ fasting plasma glucose (mmol/L)/22.5*.[17, 28] Enrolled mothers were followed-up till birth, and their babies' blood were sampled within 48 hours of life for fasting plasma glucose and insulin to calculate HOMA-IR.[17] Neonatal IR was defined as HOMA-IR >1.196 for Nigerian neonates.[17] Neonatal data (gestational age, birthweight, sex) were abstracted from routinely-collected delivery records.

Data analysis

Statistical analysis was conducted with the *R*-based JASP Statistics software version 0.18.0 (University of Amsterdam, The Netherlands; https://jasp-stats.org/). We derived birthweight percentile and Z scores using the INTERGROWTH-21ST Neonatal Size Calculator (https://intergrowth21.tghn.org/newborn-size-birth/) and Fenton-2013-2013 Growth Calculator for Preterm Infants (https://www.peditools.org/fenton2013/). The percentiles were used to classify each neonate as either SGA, LGA or AGA defined as birthweight-for-gestational-age <10th percentile, >90th percentile and between 10-90th percentiles, respectively. Mokuolu, Lubchenco and WHO charts/tables were also used to classify each neonate. WHO's Anthro Survey Analyser (https://www.who.int/tools/child-growth-standards/software) was used to generate z scores based on WHO-MGRS standards. We defined *abnormal intrauterine growth* (***aIFG)*** as SGA, LGA or either of SGA or LGA (SGA/LGA).[24] Normality of continuous variables was assessed with Shapiro-Wilk test and Q-Q plot. Continuous and categorical variables were summarised with mean (standard deviation [SD]) (or median with interquartile range [IQR], if skewed) and proportion, respectively. We used student t-test (or Mann-Whitney U-test, if skewed) to compare continuous variables between two groups (high vs low IR). Paired t-test or repeated-measure analysis of variance (RM-ANOVA) was used to compare mean percentile and Z-score values among dependent groups (charts) with significant *P*-values corrected with Holm's correction for multiple comparisons. We assessed the diagnostic accuracy (sensitivity, specificity, likelihood ratio) of each chart with respect to identifying IR among SGA, LGA and SGA/LGA compared to non-SGA, non-LGA and non-SGA/LGA, respectively. Thus

Sensitivity for detecting IR among SGA babies (i.e. probability of IR among SGA babies)=

True Positive (SGA babies with IR)/(True Positive

[SGA babies with IR]+ false negative [SGA babies without IR])

Specificity for detecting *no IR* among non-SGA babies (probability of *no IR* among non-SGA babies)= True Negative (non-SGA babies without IR)/ (True Negative [non-SGA babies without IR]+ false positive [non-SGA babies with IR])

Likelihood Ratio for detecting IR among SGA babies= Sensitivity/(1-Specificity)

The formulae were similarly applied to LGA and SGA/LGA categories**.** To determine possible alternative charts with best concordance with the most sensitive chart(s) we conducted pair-wise concordance (agreement) tests among the charts using Cohen's kappa statistics (κ), interpreted as *none* if 0.0-0.2, *minimal* if 0.21-0.39, *weak* if 0.40-0.59, *moderate* if 0.60-0.79, *strong* if 0.80-0.90 and *almost perfect* if above 90.[30] Generally, κ < 60 was regarded as clinically unacceptable. $P<0.05$ was set as statistical significance.

Results

General characteristics of the study population

Of 150 term newborn infants, 121 had birthweight data and were thus included in this analysis. Table 1 shows that the babies were born at a mean±SD gestational age of 39.2 ± 1.0 weeks, with a male/female ratio of 1.3:1.0 and mean birthweight of 3251.4 ± 424.5 g. The mean birthweight percentile value was significantly larger with INTERGROWTH-21ST than Fenton-2013 charts (mean difference= 8.49 [95% CI=7.39, 9.59], paired t(df=118) =15.2, p<0.001). The mean birthweight z-score value was significantly larger with INTERGROWTH-21ST than WHO-MGRS and Fenton-2013 charts (0.06, -0.12 and -0.24, respectively; F=45.43, t[df=118]= ;p<0.001); post-hoc Holm's correction showed that INTERGROWTH-21ST was significantly larger than WHO-MGRS (mean difference =0.29[0.25,0.33], t[df=118] =18.52, Cohen's d =0.30 p) and Fenton-2013 while WHO-MGRS was larger than Fenton-2013.

Place Table 1 here

HOMA-IR distribution among neonates

The median (IQR) HOMA-IR was 0.5 (0.2, 1.1) and it was not associated with gestational-age, sex or birth-weight (Table 1). One-quarter of the neonates (24.8% [95% CI:17.4, 33.5%], n=30/121) had IR (HOMA-IR>1.195).

Frequency of abnormal intrauterine growth among charts

Depending on the growth chart, the frequencies of SGA, LGA and SGA/LGA ranged from 4.1 to 10.1%, 5.8 to 14.2% and 11.6 to 22.7%, respectively (Table 2). More babies were classified SGA with INTERGROWTH-21ST (10.1%) and Fenton-2013 (10.0%) than with WHO-MGRS (7.4%), Mokuolu (4.2%) and Lubchenco (4.2%). More babies were classified as LGA with INTERGROWTH-21ST (12.6%) and Mokuolu (12.5%) and least (4.2%) by WHO-MGRS charts.

Place Table 2 here

Comparison of charts's diagnostic accuracy in identifying IR among neonates with aIFG

Although Lubchenco and WHO-MGRS charts appeared to have the highest sensitivity (both 40%) and likelihood ratio (both 1.6) in detecting IR among SGA infants, the confidence intervals (CIs) were very wide (Table 3). The specificities were comparable among the charts (74.8-76.6%) with fairly narrow CIs. For LGA, Lubchenco and WHO also demonstrated largest sensitivity (both 17.6%) and LR (both 0.7) for IR among LGA babies but the CIs were very wide. The specificities among LGA were similar among the charts (73.0-75.2%), with fairly narrow CIs.

Place Table 3 here

Concordance among growth charts in classifying infants' weight

The overall agreement among the five charts were 0.67 and 0.77 for SGA and LGA classification, respectively. Pair-wise agreement was best and perfect between INTERGROWTH-21ST and Fenton-2013 charts among SGA (Figure 1). For IR detection among SGA, Mokuolu chart had the best agreement with WHO-MGRS chart (κ =0.70) and with Lubchenco chart (κ =0.79). Among LGA, the pair of charts with the best and perfect agreement were INTERGROWTH-21ST-Mokuolu charts and Mokuolu-INTERGROWTH-21ST with near perfect agreement with Lubchenco (κ=0.93). For IR detection among LGA, Mokuolu and INTERGROWTH-21ST charts had the best agreement with Lubchenco chart (κ =0.93, respectively) while three charts (Mokuolu, Fenton-2013 and INTERGROWTH-21ST charts) had equal but weak agreement with WHO-MGRS chart (κ =0.43).

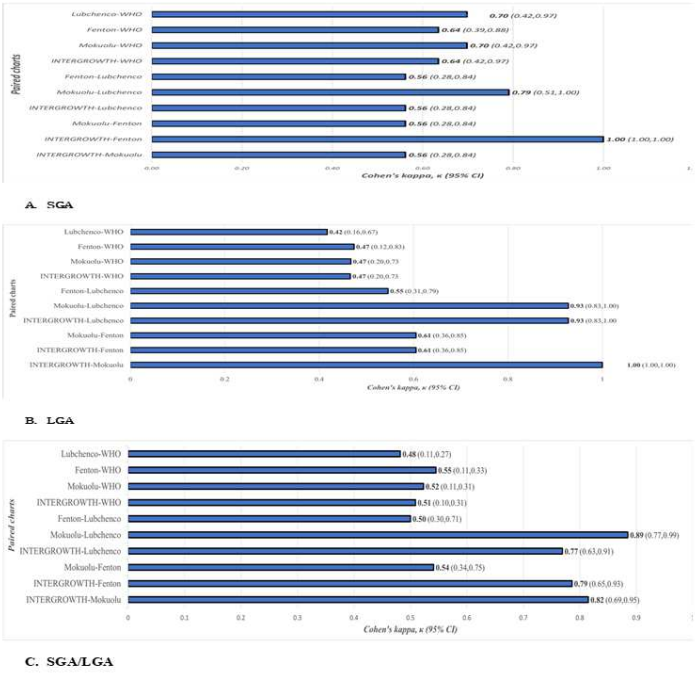


Figure 1. Paired agreement (concordance) among charts in classifying SGA (A), LGA (B) and SGA/LGA (C).

Legend: For SGA assessment (A), Mokuolu chart had the highest concordance both with WHO-MGRS and Lubchenco chart. For LGA assessment, Mokuolu, Fenton-2013 and INTERGROWTH-21ST charts had similar but low agreement with WHO-MGRS chart, while Mokuolu and INTERGROWTH-21ST both had the highest agreement with Lubchenco chart. For SGA/LGA assessment, Fenton-2013 had the highest but low agreement with WHO-MGRS chart while Mokuolu chart had the highest agreement with Lubchenco chart.

Abbreviations: INTERGROWTH-21ST, International Foetal and Newborn Growth Consortium for the 21st Century charts;[13] Mokuolu, Mokuolu et al[10] charts for Nigerian neonates; Fenton-2013, Fenton-2013 et al's[14] neonatal growth chart; Lubchenco, Lubchenco et al's charts; WHO, World Health Organization (WHO)'s Multicentre Growth Reference Study chart;[12] SGA, small for gestational age; LGA, large for gestational age; AGA, appropriate for gestational age.

Discussion

Summary of key findings

Neonatal clinicians need to objectively determine which growth charts are most appropriate for benchmarking birth-weights in order to identify babies with SGA or LGA for appropriate anticipatory care against potential short- and long-term complications.[9] However, it is not known which of five neonatal charts is best for Nigerian neonates, including for identifying those most at risk of insulin resistance. In this exploratory secondary analysis of a cross-sectional data of offsprings of a prospective cohort of Nigerian pregnant women, we compared five neonatal anthropometric charts in their identification of SGA and LGA babies and their predictive association with IR associated with SGA and LGA. Overall, the frequencies of SGA and LGA varied widely, up to two-to-three-fold among the charts: 4.2-10.1% and 4.1-14.2%, respectively. Overall, all charts demonstrated low sensitivity and modest specificity in identifying IR, with Lubchenco and WHO charts performing relatively better albeit with wide CIs suggesting imprecise estimation. Mokuolu chart was most concordant with Lubchenco and WHO-MGRS charts for detecting IR among SGA infants and it was also most concordant with Lubchenco and WHO-MGRS charts for LGA (along with INTERGROWTH-21ST and Fenton-2013).

Comparison with previous studies

Similar to other authors,[4, 31] we found a two-to-three-fold variation in the frequencies of SGA and LGA among the charts. This implies that for a given neonate, the classification as being SGA or LGA is largely dependent on the chart used. Thus, clinicians need to ensure that the chart used is the best predictor of clinically-important short- or long-term outcomes. Singamala *et al.*[31] in India noted that Fenton-2013, INTERGROWTH-21ST and local charts also vary widely in detecting the incidence of SGA and LGA among term neonates. However, while we obtained the highest incidence of SGA with INTERGROWTH-21ST chart, they

found Fenton-2013 chart to yield highest incidence of SGA. Also, while we found INTERGROWTH-21ST to yield highest LGA incidence the earlier authors reported a local chart as the highest incidence of LGA. These observations suggest that the performances of different charts vary among racio-geographic populations of infants partly due to the differences in the sample populations from whom the charts were developed. Thus, the representativeness of a chart to given local neonatal population should be assessed objectively before routine clinical use to avoid over-/under-diagnosis of SGA/LGA with consequent under-/over-treatment.

Comparative diagnostic accuracy and concordance among growth charts

Anthropometric charts are not designed primarily to detect specific morbidities or their mediators like IR, but to identify neonates whose intrauterine or extrauterine growth/size deviate most from a given reference population.[9] Thus, the observed low sensitivities in detecting IR is not surprising, agreeing with previously reported low sensitivity of charts in detecting specific morbidities.[23–25]

Although INTERGROWTH-21ST and Fenton-2013 charts had the highest frequencies of SGA and LGA in our sample, they did not have the highest sensitivity. Rather, our result suggests that WHO-MGRS and Lubchenco charts may be more sensitive for detecting IR among both SGA and LGA babies. To explain this, we speculate that the inclusion of Ghanaian (West-African) babies in the WHO-MGRS cohort may make the chart more representative of Nigerian babies than the INTERGROWTH-21ST which had Kenyan (East-African) babies. However, this notion is not supported by our observation that the Lubchenco chart derived from Caucasian populations showed similar performance to the WHO-MGRS. Of note is that our observed sensitivities require cautious interpretation because of the very wide CIs, suggesting imprecision of our sensitivity estimates due to underpowered sample size for this question.

In contrast to our finding, Anne *et al.*[25] found the INTERGROWTH-21st chart to be the most sensitive (34%–50%) in identifying preterm-associated complications (bronchopulmonary dysplasia, hypoglycaemia and mortality), followed by Fenton-2013 and a local population-based charts. However, similar to ours, WHO-MGRS chart was the most sensitive in predicting neonatal morbidity among neonates in a New Zealand study[4] and hypoglycaemia among term neonates in a USA study.[18] The differences in diagnostic accuracies of given charts among studies may be due to differences in outcomes studied; whereas we studied IR, earlier authors have studied clinical outcomes.

We found a perfect concordance (κ =1.0) between INTERGROWTH-21ST and Fenton-2013 charts (perhaps the commonest used neonatal charts worldwide) for SGA detection, similar to a near perfect concordance (κ =0.93) reported between INTERGROWTH-21ST and Fenton-2013 charts by Yitayew *et al.*[22] Singamala et al[31] and Chan et al[32] reported lower concordances of 0.74 and 0.79 among Indian and Singaporean neonates

Clinical application

In utero, causes of aIFG may affect the metabolic programming of SGA/LGA babies causing maladapted glucose metabolism resulting in increased insulin sensitivity and reduced fat mass. While these adaptations may help the foetus survive in a nutrient-poor environment, they can predispose the infant to IR and its cardiometabolic consequences like diabetes.[2, 33, 34] LGA infants are often exposed to hyperglycaemia in utero, particularly if their mothers have gestational diabetes or obesity.[34] This exposure leads to increased insulin production by the foetal pancreas, resulting in hyperinsulinemia. Postnatally, these infants may continue to exhibit increased insulin levels and a higher risk of IR, obesity and metabolic syndrome later in life.[2, 3, 6, 7, 33]

Strengths and Limitations

A notable strength of our study is that it tested five charts used across neonatal settings in

Nigeria and elsewhere, potentially alerting neonatal care-providers of the implication of the choice of preferred chart. Most previous studies have explored the performances of INTERGROWTH-21ST and Fenton-2013, sometimes with local chart in predicting neonatal outcomes. Nonetheless, our study has several important limitations. First, the small sample size and the very small number of babies with IR suggests significant underpower to reliably determine the diagnostic accuracy (especially sensitivity) of detecting IR among SGA and LGA babies. Thus, our findings should be interpreted or applied cautiously and considered largely exploratory and hypothesis-generating especially in this respect. Nonetheless, it provides valuable data to design larger adequately-powered studies. Second, the single-centre design restricts generalisability to the larger population of Nigerian neonates. Third, IR was defined by HOMA-IR, an expensive biochemical surrogate of IR that may fluctuate in the neonatal period, rather than by long-term cardiometabolic outcomes. Short-term clinical outcomes like hypoglycaemia, respiratory distress, and mortality may be more relevant and cost-effective neonatal outcomes for bench-marking chart performances.[22] Another drawback is our retrospective use of routinely-collected birthweight values documented by multiple nursing/medical staff at birth, rather than those measured prospectively with standardised measurements. Perhaps, applying the Fenton-2013 chart in this term neonatal population was inappropriate as it was primarily designed for preterm birth-size assessment. However, its authors reported that it compares reasonably well with the MGRS chart,[14] and has thus been used in similar studies.[18]

Conclusion

In this exploratory study, the five charts demonstrated disparate frequencies of SGA and LGA among our sample in agreement with earlier studies. Overall, none of the five neonatal anthropometric charts reliably predicted neonatal IR, although Lubchenco and WHO-MGRS charts showed relatively better performance. Given the small sample size, especially with

respect to the few cases with IR, our findings should be interpreted with caution. They serve to inform the design of future multicentre studies with larger samples and validation against other clinical outcomes to determine which charts are most applicable to Nigerian neonates. Such studies should also use rigorously standardised anthropometric measurements, including length and head circumference.

List of abbreviations

AGA, appropriate-for-gestational age

aIFG, abnormal intrauterine foetal growth

IR, insulin resistance

HOMA-IR, Homeostatic Model Assessment of Insulin Resistance LASUTH, Lagos State University Teaching Hospital

INTERGROWTH-21ST, International Foetal and Newborn Growth Consortium for the 21st Century

LGA, large-for-gestational age

SGA, small-for-gestational age

WHO-MGRS, World Health Organization's Multicentre Growth Reference Study

DECLARATIONS

Ethics approval and consent to participate

The study was approved by the Health Research & Ethics Committee (HREC) of LASUTH (LREC/06/10/1323) and written informed consent were obtained from participants.

Consent for publication

Not applicable

Availability of data and materials

De-identified dataset used for this analysis are available on reasonable request to the corresponding author.

Competing interests

All authors declare no conflict of interest

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Author Contribution

POU and IJA conceptualized this analsis; POU conducted the statistical analysis and made the initial draft. AOD conducted all laboratory analyses. All authors participated in primary data collection, and reviewed and approved the manuscript. JOC and IJA supervised the project and obtained funding.

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513 **Tables**

Table 1. Demographic, anthropometric and insulin resistance profile of neonates

Variables	Insulin Resistance (IR>1.195)				Total (N=121)	*P*[a] value
	Yes (N=30)		No (N=91)			
	Mean±SD	Range	Mean±SD	Range	Mean± SD	
GA, weeks	39.1 ± 0.9	37.6 – 41.1	39.3 ± 1.0	37.1 – 41.6	39.2 ± 1.0	0.42
Sex, n (%) M	17 (56.7%)		51 (56.0%)		68 (56.2%)	>0.99
F	13 (43.3%)		40 (44.0%)		53 (43.8%)	
Birthweight, g	3188.7 ± 371.0	2500.0 – 4000.0	3272.1 ± 440.6	2470.0 – 4900.0	3251.4 ± 424.5	0.35
Weight%ile (INTERGROWTH-21ST)	48.6 ± 28.9	4.0 – 96.0	51.7 ± 29.8	1.0 – 100.0	50.9 ± 29.5	0.63
Weight %ile	40.6 ±	4.0 –	43.0 ±	1.0 –	42.4 ±	0.69

(Fenton-2013)	25.5	91.0	28.8	100.0	27.9	
WeightZ (INTERGROWTH-21ST)	-0.07 ± 0.93	-1.73 – 1.72	0.10 ± 1.09	-2.25 – 3.26	0.06 ± 1.05	0.45
WeightZ (Fenton-2013)	-0.32 ± 0.82	-1.73 – 1.34	-0.21 ± 1.05	-2.54 – 3.09	-0.24 ± 0.99	0.61
WeightZScore (WHO-MGRS)	-0.26 ± 0.76	-1.73, 1.26	-0.09 ± 0.93	-0.97- 2.79	-0.12 ± 0.88	0.34
HOMA -IR	1.8 (1.4, 2.3)	1.2 – 4.2	0.3 (0.1, 0.7)	0.0 – 1.1	0.5 (0.2, 1.1)	< **0.001** *b)*

Abbreviations: %ile, percentile values; INTERGROWTH-21ST, International Foetal and Newborn Growth Consortium for the 21st Century charts;[13] Fenton-2013, Fenton-2013 et al's neonatal growth chart;[14] WHO-MGRS, World Health Organization (WHO)'s Multicentre Growth Reference Study chart;[12] HOMA-IR, homeostatic model assessment of insulin resistance; Weight%ile, birth-weight percentile derived with respective growth chart; WeightZ, birth-weight Z-score derived with respective growth chart.

a) p-values derived from Student t-tests

b) p-values derived from Mann-Whitney U-tests

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Table 2. Prevalence of abnormal intrauterine growth using different growth charts

Chart type	SGA		LGA		SGAL/LGA		AGA		Total, N [a]
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	
INTERGROWTH-21ST	12	10.1 (5.3, 17.0)	15	12.6 (7.2, 19.9)	27	22.7 (15.5, 31.3)	92	77.3 (68.7, 84.5)	119
Mokuolu	5	4.2 (1.4, 9.5)	15	12.5 (7.2, 19.8)	20	16.7 (10.5, 24.6)	100	83.3 (75.4, 89.5)	120
Fenton-2013	12	10.0 (5.3, 16.8)	7	5.8 (2.4, 11.6)	19	15.8 (9.8, 23.6)	101	84.2 (76.4, 90.2)	120
Lubchenco	5	4.2 (1.4. 9.5)	17	14.2 (8.5, 21.7)	22	18.3 (11.9, 26.4)	98	81.7 (73.6, 88.1)	120
WHO-MGRS	9	7.4 (3.5, 13.7)	5	4.1 (1.4, 9.4)	14	11.6 (6.5, 18.7)	107	88.4 (81.3, 93.5)	121

Abbreviations: INTERGROWTH-21ST, International Foetal and Newborn Growth Consortium for the 21st Century charts;[13] Mokuolu, Mokuolu et al[10] charts for Nigerian neonates; Fenton-2013, Fenton-2013 et al's[14] neonatal growth chart; Lubchenco, Lubchenco et al's charts; WHO-MGRS, World Health Organization (WHO)'s Multicentre Growth Reference Study chart;[12] SGA, small for gestational age; LGA, large for

gestational age; AGA, appropriate for gestational age; CI, confidence interval

a) N= 120, except for intergrowth where N=119

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Table 3. Diagnostic accuracy of charts in identifying IR in each class of aIFG

		N*				Diagnostic accuracy				
aIFG class	Chart	a (IFG with IR)	b (IFG without IR)	c (non-IFG with IR)	d(non-IFG without IR)	Sensitivity % (95% CI)	Specificity % (95% CI)	LR 95% CI	PPV % (95% CI)	NPV % (95% CI)
SGA										
	INTERGROWTH-21ST	4	25	8	82	33.3 (6.7, 60.0)	76.6 (68.6, 84.7)	1.4 (0.6, 3.4)	13.8 (1.2, 26.3)	91.1 (85.2, 97.0)
	Mokuolu	1	29	4	86	20 (-15.1, 55.1)	74.8 (66.8, 82.7)	0.8 (0.1, 4.7)	3.3 (-3.1, 9.8)	95.6 (91.3, 99.8)
	Fenton-2013	4	26	8	82	33.3 (6.7, 60.0)	75.9 (67.9, 84.0)	1.4 (0.6, 3.3)	13.3 (1.2, 25.5)	91.1 (85.2, 97.0)
	Lubchenco	2	28	3	87	40.0 (-2.9, 82.9)	75.6 (67.8, 83.5)	1.6 (0.5, 5.0)	6.7 (-2.3, 15.6)	96.7 (93.0, 100.4

									)
	WHO-MGRS	2	28	3	87	40.0 (-2.9, 82.9)	75.6 (67.8, 83.5)	1.6 (0.5, 5.0)	6.7 (-2.3, 15.6)	96.7 (93.0, 100.4)
LGA										
	INTERGROWTH-21ST	2	27	13	77	13.3 (-3.9, 30.5)	74.0 (65.6, 82.5)	0.5 (0.1, 1.9)	6.9 (-2.3, 16.1)	85.6 (78.3, 92.8)
	Mokuolu	2	28	13	77	13.3 (-3.9, 30.5)	73.3 (64.9, 81.8)	0.5 (0.1, 1.9)	6.7 (-2.3, 15.6)	85.6 (78.3, 92.8)
	Fenton-2013	1	29	6	84	14.3 (-11.6, 40.2)	74.3 (66.3, 82.4)	0.6 (0.1, 3.5)	3.3 (-3.1, 9.8)	93.3 (88.2, 98.5)
	Lubchenco	3	27	14	76	17.6 (-0.5, 35.8)	73.8 (65.3, 82.3)	0.7 (0.2, 2.0)	10.0 (-0.7, 20.7)	84.4 (77.0, 91.9)
	WHO-MGRS	3	27	14	76	17.6 (-0.5, 35.8)	73.8 (65.3, 82.3)	0.7 (0.2, 2.0)	10.0 (-0.7, 20.7)	84.4 (77.0, 91.9)
SGA/LGA										
	INTER	6	23	21	69	22.2	75.0	0.9	20.7	76.7

GROWTH-21ST					(6.5, 37.9)	(66.2, 83.8)	(0.4, 2.0)	(5.9, 35.4)	67.9, (85.4)
Mokuolu	3	27	17	73	15.0 (-0.6, 30.6)	73.0 (64.3, 81.7)	0.6 (0.2, 1.7)	10.0 (-0.7, 20.7)	81.1 (73.0, 89.2)
Fenton-2013	5	25	14	76	26.3 (6.5, 46.1)	75.2 (66.8, 83.7)	1.1 (0.5, 2.4)	16.7 (3.3, 30.0)	84.4 (77.0, 91.9)
Lubchenco	5	25	17	73	22.7 (5.2, 40.2)	74.5 (65.9, 83.1)	0.9 (0.4, 2.1)	16.7 (3.3, 30.0)	81.1 (73.0, 89.2)
WHO-MGRS	2	28	12	79	14.3 (-4.0, 32.6)	73.8 (65.5, 82.2)	0.6 (0.2, 2.1)	6.7 (-2.3, 15.6)	86.8 (79.9, 93.8)

Abbreviations: INTERGROWTH-21ST, International Foetal and Newborn Growth Consortium for the 21st Century charts;[13] Mokuolu, Mokuolu et al[10] charts for Nigerian neonates; Fenton-2013, Fenton-2013 et al's[14] neonatal growth chart; Lubchenco, Lubchenco et al's charts; WHO-MGRS, World Health Organization (WHO)'s Multicentre Growth Reference Study chart;[12]; SGA, small for gestational age; LGA, large for gestational age; AGA, appropriate for gestational age; aIFG, abnormal intrauterine growth which includes, SGA, LGA and SGA/LGA; LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

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