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A comparative analysis of INTERGROWTH-21st and the World Health Organisation fetal growth chart in detection of term small for gestational age newborns and prediction of short-term adverse perinatal outcomes

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ABSTRACT

Objectives To compare the INTERGROWTH-21st and the WHO fetal growth chart in detecting term small for gestational age (SGA) neonates and predicting short-term adverse perinatal outcomes.

Design A retrospective cohort study.

Setting Department of Obstetrics and Gynaecology at the Aga Khan University Hospital Karachi.

Subjects Term singleton pregnancies between July and December 2018 with ultrasound growth scan done within 4 weeks of delivery. Pregnancies with structural and chromosomal abnormalities and multiple gestations were excluded.

Outcome The estimated fetal weight (EFW) was calculated using the INTERGROWTH-21st and the WHO fetal growth chart based on ultrasound measurements. Fetuses with EFW below the 10th percentile were classified as SGA. Neonates were confirmed as SGA based on similar postnatal weight percentile. Short-term adverse perinatal outcomes were also analysed.

Results A total of 932 records were screened, and 478 were included in the analysis. The sensitivity of the WHO fetal growth chart (70.2%; 95% CI: 60.4%, 78.8%) was higher than the INTERGROWTH-21st (45.2%; 95% CI: 35.4%, 55.3%) for predicting neonatal SGA. The WHO fetal growth chart predicted more SGA neonates when compared with the INTERGROWTH-21st (AUC=0.75, 95% CI: 0.71, 0.80 and AUC=0.63, 95% CI: 0.58, 0.68, respectively). Both charts were similar in predicting the short-term adverse perinatal outcomes; AUC (95% CI) was 0.77 (0.70, 0.83) for INTERGROWTH-21st and 0.78 (0.72, 0.85) for the WHO fetal growth chart.

Conclusion The WHO fetal growth chart demonstrates significantly better accuracy in predicting term SGA neonates compared with INTERGROWTH-21st. Further, both charts have similar prediction abilities for short-term adverse perinatal outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ INTERGROWTH-21st, a fetal growth chart, has been compared with various reference charts, but there is a lack of evidence on its comparison with the WHO fetal growth chart in predicting term small for gestational age (SGA) and short-term adverse perinatal outcomes in Pakistan.

WHAT THIS STUDY ADDS

⇒ The study compares the diagnostic accuracy of INTERGROWTH-21st and the WHO fetal growth chart for the prediction of term SGA and its short-term adverse neonatal outcomes in Pakistan. The findings demonstrate significantly better performance of the WHO fetal growth chart in predicting SGA neonates in comparison to INTERGROWTH-21st.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In clinical settings, healthcare practitioners may consider adopting the WHO fetal growth chart as the preferred method for assessing fetal growth and identifying SGA neonates for better management of pregnancies. This will potentially reduce the risk of adverse neonatal outcomes associated with SGA in Pakistan.

⇒ It highlights the need for health policymakers to review existing guidelines for fetal growth assessment and consider the adoption of the WHO fetal growth chart in antenatal care practices locally.

⇒ Examining additional data across diverse healthcare settings of the country will ensure the accuracy and reliability of the study findings.

INTRODUCTION

Fetal growth monitoring is one of the essential components of the standard antenatal

care.[1] Small for gestational age (SGA) characterised by birth weight <10th percentile for gestational age reflects decreased fetal growth secondary to intra-uterine undernutrition.[2] In South Asia, the prevalence of the term SGA stands at 41.5%, while in Pakistan, this figure is as high as 36%.[3 4] Sufficient evidence exists regarding the association between SGA and short-term adverse perinatal outcome.[2 5 6]

It was estimated that globally about 23.4 million, that is, 17.4% liveborn babies were born SGA in 2020.[7 8] In low and middle-income countries, 21.9% of all neonatal deaths is attributed to SGA while in Pakistan SGA, accounts for 26% of all neonatal mortalities.[3 9] Various country-specific tables, curves and charts were produced in different world zones to estimate the fetal birth weight, but they vary in methodology, quality of data and strength of the study. The INTERGROWTH-21st and the WHO fetal growth charts are the two most commonly used international standards for assessment of fetal growth.[10] These are based on 'healthy' subjects comprising of well-nourished pregnant women, without important risk factors for fetal growth restriction.[10 11] WHO has made provision of standards for the estimated fetal weight (EFW) as its top most priority and underscores that their chart suits best as the fetal growth chart for international use than those commonly applied today.[11]

Widely used INTERGROWTH-21st, after multiple implementation projects, has been compared with various customised, local and international charts in order to evaluate if it can predict SGA newborn and consequent adverse perinatal morbidity and mortality.[10 11] There is no study yet that has compared INTERGROWTH-21st with the WHO fetal growth chart in Pakistan, highlighting the need for a comparative study to fill this gap. In a study from China, the WHO fetal growth chart identified one in six fetuses as SGAs which was 50% more than those identified by the INTERGROWTH-21st.[12] Similarly, a study conducted in six states of the USA concluded no significant differences in accuracy between the growth standards for predicting adverse perinatal outcomes.[13] Similar results were reported by Savirón-Cornudella R *et al*.[14] Despite a substantially high burden of SGA in Pakistan, no such comparative analysis of growth charts on local data is available. Hence, this study aimed to compare the ability to predict term SGA at birth and its associated short-term adverse perinatal outcomes based on INTERGROWTH-21st and WHO fetal growth chart.

METHODS

Study design and setting

This single-centred retrospective cohort study was conducted at the Department of Obstetrics and Gynaecology of the Aga Khan University Hospital (AKUH) Karachi, Pakistan. AKUH is a well-equipped tertiary care hospital accredited by the Joint Commission of International Accreditation (JCIA). It is one of the few tertiary care hospitals in Pakistan that uses the fetal growth chart during antenatal assessment.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Eligibility criteria

From the electronic medical records (EMR) between July and December 2018, singleton pregnant women who had their last ultrasound scan done within 4 weeks of delivery and were between 37 and 40 completed weeks of gestation were included. Neonates with structural and chromosomal abnormalities were excluded due to potential variations in their estimated measurements. We also excluded observations with missing values. A total of 932 patient records were screened. 454 women did not meet the eligibility criteria and 478 women were included in the analysis. The study was approved by the ethical review committee of AKUH (Reference # 2019-1337-3472).

Data collection and variables

Using a structured questionnaire, data was collected on maternal characteristics including age, occupation, ethnicity, parity (nulliparous and multiparous), comorbidities, height and weight at booking visit; fetal characteristics included gestational age at the last scan and at birth, birth weight and mode of delivery; and short-term adverse perinatal outcomes including stillbirth, Apgar score at 5 min (categorised with a cut-off of 7), admission to the neonatal intensive care unit (NICU) and postnatal survival at 1 week. Due to the small numbers, neonates with any of the short-term adverse perinatal outcomes were grouped together for the purpose of analysis.

To identify SGA neonates, we calculated EFW for INTERGROWTH-21st (EFWIG) and WHO fetal growth chart that uses the Hadlock formula (EFWHD) using the ultrasound measurements near term of abdominal circumference (AC), head circumference (HC) and femur length (FL):[12] Following formula was used for:

(a) INTERGROWTH-21st fetal growth chart

'ln(EFWIG)=5.084820–54.06633×(AC/100)3–95.80076×(AC/100)3×(ln(AC/100))+3.136370×(HC/100)'

(b) WHO fetal growth chart:[12]

'ln (EFWHD)=ln (10) × (1.326+0.01107×HC+0.0438×AC+0.1581×FL–0.00326×AC×FL)'

Fetuses were considered SGA if their EFW were below the 10th percentile against any of the charts.

Statistical analysis

Continuous variables were presented as means and SD, while categorical variables were expressed as frequencies and percentages. To compare the characteristics between SGA and non-SGA groups, independent t-tests and Pearson χ^2 tests were employed for continuous and categorical variables, respectively. A p value less than 0.05 was deemed significant. The agreement between

Table 1 Distribution of maternal characteristics by SGA status at birth

Variable	SGA (n=104)	Non-SGA (n=374)	Mean difference (95% CI)/p value
Age (years)*	28.4 (±4.8)	28.1 (±4.4)	0.3 (–0.68, 1.28)
Height (cm)*	157.7 (±6.4)	158.3 (±6.1)	0.6 (–0.74, 1.94)
Weight (kg)*	66.7 (±7.7)	69.8 (±8.4)	3.1 (1.30, 4.98)
BMI*	26.9 (±3.5)	28.0 (±4.1)	1.1 (0.23, 1.96)
Gestational age at booking (weeks)*	12.8 (±2.9)	13.0 (±2.9)	0.2 (–0.43, 0.83)
Gestational age at delivery (weeks)*	37.6 (±0.8)	38.2 (±1.0)	0.6 (0.39, 0.81)
Parity†			
Nulliparous	41 (39.4)	153 (40.9)	0.13‡
Multiparous	63 (60.6)	221 (59.1)	
Ethnicity†			
Urdu	58 (55.8)	233 (62.3)	0.01‡
Sindhi	27 (26.0)	92 (24.6)	
Others	19 (18.2)	49 (13.1)	
Occupation†			
Home-maker	102 (98.1)	347 (92.7)	0.06§
Working women	2 (1.9)	27 (7.2)	
Pre-pregnancy comorbidities†			
Essential hypertension	2 (1.9)	6 (1.6)	0.83§
Essential diabetes mellitus	1 (1.0)	3 (0.8)	
Others	4 (3.8)	21 (5.6)	
None	97 (93.3)	344 (92.0)	
Antenatal complications†			
Gestational diabetes mellitus	12 (11.5)	54 (14.4)	0.008§
Pregnancy-induced hypertension	1 (1.0)	11 (2.9)	
Others	7 (6.7)	7 (1.87)	
None	84 (80.8)	302 (80.7)	
Type of delivery†			
Vaginal delivery spontaneous	4 (3.8)	113 (30.2)	0.42‡
Induction of labour	30 (28.8)	105 (28.1)	
C-section	50 (67.4)	156 (41.7)	

*Mean and SD, p value by independent T-test.
†Frequency and percentages reported.
‡P value by χ^2 test.
§P value by Fisher's exact.
BMI, Body Mass Index; SGA, small for gestational age.

INTERGROWTH-21st and the WHO fetal growth chart was assessed using Gwet's AC1.[15] Cross-tabulations between INTERGROWTH-21st and the WHO fetal growth chart with at birth weight percentile was used as a gold standard for diagnostic analysis, evaluating sensitivity, specificity, positive predictive value, negative predictive value, accuracy and area under the curve (AUC) in detecting SGA. Subsequently, additional diagnostic values for short-term adverse perinatal outcomes were computed using these tools. All the analysis used STATA version 16.0, while R version 4.3.2 was used for Gwet's AC1. The formula for Gwet's AC1 is:

$$\gamma = pa - pe/1 - pe$$

Where pa is the probability of agreement and pe is the probability of chance agreement.[15]

RESULTS

Maternal characteristics

The analysis included 478 subjects who were classified as having SGA and non-SGA neonates based on their postnatal weight centile status. The two groups showed significant differences with regard to their ethnicity and

Table 2 Distribution of neonatal characteristics by SGA status at birth

Variable	SGA (n=104)	Non-SGA (n=374)	P value
Birth weight (kg)*	2.3 (2.1–2.4)	3.0 (2.7–3.2)	<0.01†
Apgar at 5 min‡			
<7	2 (1.9)	0 (0.0)	0.05§
≥7	102 (98.1)	374 (100)	
NICU admission‡			
Yes	2 (1.9)	3 (0.8)	0.30§
No	102 (98.1)	371 (99.2)	
Mortality‡			
Death	1 (0.9)	0 (0.0)	0.22§
Alive	103 (99.0)	374 (100)	
C-section due to fetal distress¶			
Yes	22 (21.2)	30 (6.3)	<0.01**
No	48 (46.2)	230 (48.1)	
Vaginal delivery	34 (32.6)	218 (45.6)	
Composite short-term adverse perinatal outcome			
Yes	29 (27.9)	36 (9.6)	<0.01**
No	75 (72.1)	338 (90.4)	

*Median and IQR reported, for others, frequency and percentages reported.
†P value by Mann-Whitney U test.
‡Short-term adverse perinatal outcomes.
§P value by Fisher's exact.
¶Not a neonatal outcome, maternal outcome referred to as one of the adverse perinatal outcomes.
**P value by χ^2 test.
NICU, neonatal intensive care unit; SGA, small for gestational age.

employment status with a greater proportion of Sindhi speaking (provincial language) and home-makers in the SGA group. Additionally, women with SGA fetuses showed significantly lower Body Mass Index and earlier gestational age at delivery compared with the non-SGA group (table 1).

Perinatal outcomes

SGA and non-SGA groups differed significantly in terms of occurrence of short-term adverse perinatal outcomes (table 2). This was reflected not only in the cumulative data but also when examining outcomes such as Apgar score <7 at 5 min.

Prediction of SGA and adverse perinatal outcomes by INTERGROWTH-21st and the WHO fetal growth chart

When predictive performance of the WHO fetal growth chart was compared with the INTERGROWTH-21st in identifying SGA newborns, the sensitivity of former was found to be 70.2%, surpassing that of the latter at 45.2% (table 3). However, the specificity of the two charts in correctly identifying non-SGA newborns was not significantly different (80.7% vs 80.5%). Additionally, the WHO fetal growth chart demonstrated a higher positive predictive value of 50.3% (vs 29.2%) and a higher negative predictive value of 90.7% (vs 84.1%), reflecting overall better accuracy (78.5% vs 72.8%).

Both the WHO fetal growth chart and INTERGROWTH-21st had AUC values in the moderate range, with the WHO reference growth chart having a slightly higher AUC (75.5% vs 70.3%), suggesting an overall better performance in distinguishing between SGA and non-SGA newborns compared with INTERGROWTH-21st (figure 1).

Furthermore, when assessing the sensitivity of both the charts in predicting composite short-term adverse perinatal outcomes, the WHO fetal growth chart showed a sensitivity of 25.5%, which, although was slightly lower than INTERGROWTH-21st (29.2%), still remained within a comparable range. The specificities for short-term adverse perinatal outcomes were also similar, with the WHO fetal growth chart at 90.9% and INTERGROWTH-21st at 91.1% (table 4). In contrast to INTERGROWTH-21st, the WHO fetal growth chart had a higher positive likelihood ratio that is, 3.65 (95% CI: 2.86, 4.05).

Agreement between INTERGROWTH-21st and the WHO fetal growth chart

The inter-rater reliability between the WHO and INTERGROWTH-21st fetal growth chart using Gwet's AC1 coefficient[15] calculated the value of 83.6% (CI: 78.9,

Table 3 Performance metrics for predicting small for gestational age newborns

Performance metrics	WHO growth standard % (95% CI)	INTERGROWTH-21st growth standard % (95% CI)
Sensitivity	70.2 (60.4 to 78.8)	45.2 (35.4 to 55.3)
Specificity	80.7 (76.4 to 84.6)	80.5 (76.1 to 84.4)
PPV	50.3 (41.9 to 58.7)	29.2 (30.4 to 48.5)
NPV	90.7 (87.1 to 93.6)	84.1 (79.9 to 87.8)
Accuracy	78.5 (74.5 to 82.1)	72.8 (68.6 to 76.8)
AUC	75.5 (70.1 to 80.3)	70.3 (66.5 to 73.8)

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

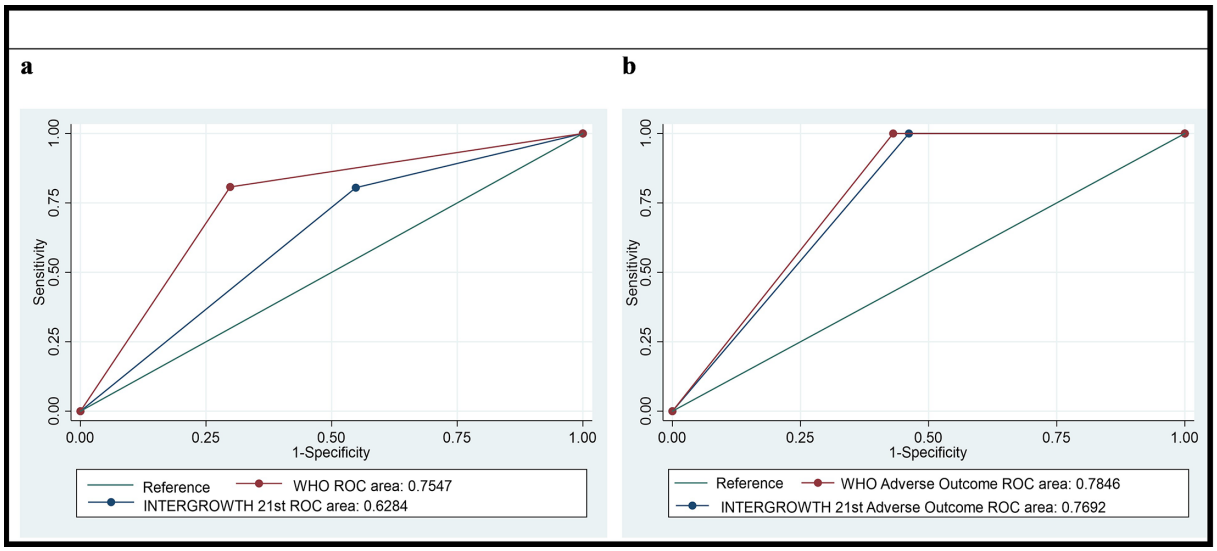

Figure 1 Growth chart comparison for SGA and short-term adverse perinatal outcome. SGA, small for gestational age.

88.3%), indicating substantial agreement beyond chance and supported by a p value <0.05, emphasising the statistical significance of the observed agreement. This analysis provides evidence for a high level of reliability between the WHO and INTERGROWTH-21st fetal growth chart assessments, reinforcing the consistency and accuracy of the ratings.

DISCUSSION

Around 32 million infants are born as SGA in low and middle-income countries (LMICs) accounting for 27% of all live births.[16] We found a similar proportion of newborns (27.8%) born as SGA in our study population. Since SGA accounts for 26% of all neonatal mortalities in Pakistan,[16] it was relevant to examine the predictive performance of the WHO and INTERGROWTH-21st fetal growth chart. Hence, this study focused on identifying these high-risk neonates and their perinatal outcomes for our local obstetric population attending a tertiary care hospital where information regarding the relevant variables was available.

Our findings revealed that the WHO fetal growth chart is relatively better at distinguishing SGA and non-SGA neonates compared with the INTERGROWTH-21st . In contrast to the latter, the former showed a higher positive likelihood ratio, that is, 3.65 (95% CI: 2.86, 4.05). If used as a post-test screening modification test, it would result in a more significant risk alteration. We observed different rates of SGA for the two charts, and the INTERGROWTH-21st chart showed a lower rate of SGA prediction than the WHO fetal growth chart. Given this finding, it is crucial to question whether the INTERGROWTH-21st chart possesses the ability to accurately predict SGA in the Pakistani population if introduced into clinical service.

Table 4 Performance metrics for predicting short-term adverse perinatal outcomes

WHO growth standard				
Perinatal events	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV% (95% CI)**
NICU admission	1.4 (0.2 to 4.9)	99.1 (97.4 to 99.8)	40.0 (5.3 to 65.3)	69.8 (65.5 to 73.5)
Death	0.7 (0.02 to 3.8)	100.0 (98.9 to 100.0)	100.0 (2.5 to 100.0)	69.8 (65.5 to 73.9)
5 min Apgar <7.0	1.4 (0.2 to 4.9)	100.0 (98.9 to 100.0)	100.0 (15.8 to 100.0)	69.9 (65.6 to 74.1)
C-section due to fetal distress	21.4 (15.0 to 29.0)	93.7 (90.5 to 96.1)	59.6 (45.1 to 73.0)	73.2 (68.8 to 77.4)
Composite adverse outcome	25.5 (18.6 to 33.4)	90.9 (87.4 to 93.8)	55.2 (69.1 to 77.9)	73.7 (69.2 to 77.9)
INTERGROWTH-21st growth standard				
NICU admission	1.7 (0.2 to 5.9)	99.2 (97.6 to 99.8)	40.0 (5.3 to 85.3)	75.2 (71.0 to 79.0)
Death	0.8 (0.02 to 4.6)	100.0 (98.9 to 100.0)	100.0 (2.5 to 100.0)	75.1 (70.9 to 78.9)
5 min Apgar <7.0	1.7 (0.2 to 5.9)	100.0 (98.7 to 100.0)	100.0 (15.8 to 100.0)	75.2 (71.1 to 79.0)
C-section due to fetal distress	26.7 (19.0 to 35.5)	94.4 (91.5 to 96.6)	61.5 (47.0 to 74.7)	79.3 (75.2 to 83.1)
Composite adverse outcome	29.2 (21.2 to 38.2)	91.1 (87.6 to 93.8)	52.2 (39.7 to 64.6)	79.3 (75.1 to 83.1)

NICU, neonatal intensive care unit; NPV, negative predictive value; PPV, positive predictive value.

A study conducted in Latin America compared the diagnostic performance of INTERGROWTH-21st and WHO fetal growth charts. Unlike the results of our study, the INTERGROWTH-21st demonstrated marginally better ability to predict low Apgar scores with AUC 57.3 (95% CI: 55.2 to 59.4) as compared with AUC 55.32 (95% CI: 53.12 to 57.53). However WHO fetal growth chart's identification of SGA was consistently higher (13.9% vs 7%).[17]

Other studies also reported that the SGA prediction ability of the INTERGROWTH-21st fetal growth chart was lower when compared with the WHO fetal growth chart and gestation-related optimal weight (GROW) customised chart.[18 19] Further, the Hadlock and the WHO fetal growth chart classified twice as many preterm infants as SGA compared with the INTERGROWTH-21st (18.4–19.4/100 births vs 10.0–10.8/100 births). This suggests that the results of our study are not unique to the Pakistani population but are consistent with those observed in other populations. On the other hand, a UK-based study that compared five fetal growth charts (namely Hadlock, GROW, Fetal Medicine Foundation (FMF), INTERGROWTH-21st and the WHO) showed that the latter two demonstrated similar performance and a higher sensitivity than the remaining charts.[20] Moreover, a study conducted in Bangladesh demonstrated that the INTERGROWTH-21st fetal growth chart significantly missed the diagnosis of SGA in the study population in comparison to the WHO fetal growth chart.[21] A systematic review of literature reveals that INTERGROWTH-21st estimation of fetal weight is useful for predicting adverse outcomes, particularly in cases classified below the 10th percentile. However, it also exhibits high false-negative rates, which necessitates the need for close monitoring especially for those at risk.[22]

Further, a study conducted in Hong Kong compared the precision of INTERGROWTH-21st with that of Hadlock and Shepard formulae. INTERGROWTH-21st predicted EFW within a 10% discrepancy from the actual birth weight in comparison to that of Hadlock and Shepard. However, INTERGROWTH-21st did not show any better prediction when compared with that with the other two formulae.[23] When compared with our study, their findings aligned with our research. In our study, although the INTERGROWTH-21st was not compared with the Hadlock fetal growth chart, the formula used by the WHO fetal growth chart was derived from the Hadlock. Thus, inferences from this study are relevant. Similarly, a study conducted in France concluded that INTERGROWTH-21st requires more validation before it could be considered for use as a standard for detecting SGA fetuses. The authors observed variations in ultrasound-based biometric measurements, noting that HC measurements aligned more closely with postnatal dimensions, while AC and FL did not correlate well. This discordance requires further investigation.[24]

When analysing the association between SGA neonates and short-term adverse perinatal outcomes, both charts performed poorly and showed similar results. In a study conducted in Sweden comparing a GROW-customised chart, the INTERGROWTH-21st, and a local population-based reference charts, the performance of these growth charts was poor for the prediction of adverse perinatal outcomes with a sensitivity of 29% among SGA neonates identified.[25] In our research, the assessment of perinatal mortality was not feasible due to the absence of such deaths in our sample. Similarly, the outcome of a low 5-min Apgar score was reported in only two neonates. Hence, a larger sample size would be required to achieve adequate statistical power for the evaluation of perinatal mortality and low Apgar score, given the rarity of these outcomes.

The strength of our study is that the ultrasound data used in this research was obtained by a single trained operator using a high-resolution ultrasound machine. Further, we included subjects with pregnancy complications such as pre-eclampsia and diabetes to ensure representation of the entire population rather than just the low-risk population. However, the retrospective nature of the study inherently carries certain limitations. First, the critical information on potential confounders, such as socioeconomic status and smoking status, was unavailable in the data, preventing the assessment or control of these variations during analysis. Second, ultrasound data needed for the study was only available for the subjects who visited the Maternal-Fetal Medicine (MFM) Unit, which is specialised for catering to high-risk populations, hence, limiting the study generalisability.

In summary, although the results of our study show better sensitivity of the WHO fetal growth chart in predicting SGA neonates, there are no significant differences between the WHO and INTERGROWTH-21st in predicting the short-term adverse perinatal outcomes, indicating good agreement that is beyond chance. There is a need for larger, multicentre studies to validate the results. However, given the absence of similar studies in Pakistan, this research can serve as a basis for the use of the WHO fetal growth chart until the results of any other prospective studies are available.

Contributors Study was conceptualised by NM, RN and AR. Methodology was developed by NM, RN, AR and IA. Study implementation and data extraction were done by AR under the supervision of NM. Data management and analysis were performed by AR under the supervision of IA. The initial and revised manuscript drafts were prepared by AR, KAR and SST and critically reviewed and edited by NM and RN. NM is the overall guarantor. All the authors reviewed and approved the final version of the manuscript.

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