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Research Article

Evaluation of the INTERGROWTH-21st Fetal Growth Standards in the United Arab Emirates: A Pilot Study.

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ABSTRACT

Objectives: To evaluate the use of recently published INTERGROWTH-21st (IG-21) fetal growth standards in United Arab Emirates native population.

Method: This prospective cohort study analyzed fetal ultrasound measurements of head circumference, abdominal circumference and femur length. Z-scores and percentiles of fetal and neonatal growth measurements were calculated using IG-21 and compared with a standard reference.

Results: Measurements were performed in 120 pregnancies at a median gestational age of 25.8 weeks (range, 16 to 35). Thirteen out of 15 mean IG-21 Z-scores for all measurements remained between −0.5 and +0.5 at all gestational-ages. Actual standard deviations (SD) using IG-21 charts gave an acceptable SD (0.8 to 1.2) for 13 out of 15 measurements.

The proportions of most antenatal measurements <3rd, <10th, >90th and >97th percentiles were identical between standard and IG-21st charts. The median gestational age was 39 weeks (range, 29 to 41) and 14 (13%) were delivered by cesarean section.

The mean z-scores of all biometric measurements were close to zero while the mean percentiles were close to the 50th percentile, thus, describing appropriately the neonatal growth parameters in our population.

Conclusions: Fetal size in our population was comparable to the IG-21 standards. The IG-21 neonatal growth standards were more similar to that of the anticipated population distribution than to the standard charts. These preliminary results, if confirmed in a larger study in the UAE, would support use of IG-21 standards in UAE instead of the currently used standard charts.

Keywords: Prenatal ultrasound; Fetal growth; Fetal biometry; INTERGROWTH-21st

INTRODUCTION

Fetal biometry is routinely used for evaluation of gestation and fetal health. One limitation of this assessment tool is the availability of more than 80 antenatal growth charts of various qualities [1-3]. Their use in different populations from the one which they were derived raise the possibility of errors in estimating growth anomalies [4].

This may result in improper intervention, especially that the prenatal recognition of intrauterine growth restriction (IUGR) substantiated at birth has been proven to be suboptimal, particularly in high-risk pregnancies [5,6]. Therefore, development of reliable measurements and validated assessments are critical.

Recently, the international INTERGROWTH-21st (IG-21) study for fetal growth population standards has shown similar growth patterns in healthy pregnancies from different geographic

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locations [7,8]. This methodology used the same approach of the WHO Multicenter Growth Reference Study [9].

Its view was based on the World Health Organization's belief that fetal growth in normal pregnancies is similar across different ethnicities [10]. A main aim was to improve the detection of growth anomalies, such as IUGR and macrosomia [11]. Notably, the percentiles of IG-21 newborn standards were similar at term to those of the WHO Child Growth Standards [7,10,12].

Many countries have validated the IG-21 standards in a large cohort of their populations and encouraged adopting IG-21 in their practice [13,14].Other studies, on the other hand, have recommended further research for defining abnormal growth categories, especially for small-for-gestational-age (SGA) fetuses [15-17].

In the United Arab Emirates (UAE), fetal measurements are currently compared to reference values from Western pregnancies, although a regional study has shown variation in fetal growth among Arabs [18]. As it is essential to accurately assess fetal growth this cross-sectional pilot study aims to evaluate whether fetal biometry measurements in low-risk Emirati mothers in keeping with the IG-21 standards [7,13].

METHODS

This prospective, population-based cohort study involved ultrasound measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) in a cohort of pregnant women.

The study was approved by Al Ain Medical District Human Research Ethics Committee-UAE University and Ambulatory Health services Research Committee-SEHA-UAE. Pregnant native Emirati women attending prenatal clinics of the Ambulatory Health Services in Alain city-SEHA were recruited to participate in the study between September 2016 and January 2018.

Ultrasound scan was performed routinely in the first, second and third trimester of low risk mothers, and as recommended by the obstetricians managing high risk mothers. Only women with regular menstrual cycles and who were certain of the first day of their last menstrual period (LMP) and with a normal singleton pregnancy were enrolled, with the dating of each pregnancy based on that crown-rump length (CRL) in the first trimester.

After providing written and verbal information regarding the study, a signed consent form was obtained from the eligible women who agreed to enroll. A standardized questionnaire was administered to all participants.

It included information on the first day of the LMP and its certainty, the regularity and duration of the menstrual cycle, number of previous pregnancies, the presence of diabetes, hypertension, hemoglobinopathies, medical conditions, and smoking. We intentionally enrolled both low and high risk mothers in order to represent the current clinical practice, and, for both groups, we used the same growth standard reference charts [19-21].

Mothers were excluded from the study if the first ultrasound showed multiple pregnancy, fetal anomaly, miscarriage, or fetal death. Standard fetal ultrasound measurements were used as previously described and similar to the IG-21 standard, using GE Voluson® E6 (General Electric Medical Systems, Zipf, Austria) [22].

Briefly, at transthalamic plane of the head identified the brain structures (thalamic nuclei, third ventricle, falx cerebri, cavum septum pellucidum, frontal and occipital horns) in order to measure the biparietal 48 diameter (BPD) and Head circumference (HC). Biparietal diameter measurements were excluded from the analysis as they were measured differently in our clinical practice (outer-inner) than in the IG-21 standards (outer-outer). HC was measured by tracing the outer perimeter of the head.

In the transaxial view of the fetal abdomen, the abdominal circumference (AC) was measured from the surface of the soft tissues, at the level of the liver, using as anatomical reference the umbilical portion of the left portal vein. Measurement of the osseous portion of the femur from one end to the other, disregarding the curvature, the femoral neck and both epiphyseal cartilages, defined femur length (FL).

The ultrasound machines which we used were standardized to use the same formulas that incorporate BPD, AC, HC and FL measurements to calculated fetal weight. The variation between predicted and actual fetal weights was be expressed in the form of mean, SD, and standard errors per 1,000gm.

Three main Voluson® transducer Probes were used during obstetrics assessments: Endocavity RIC5-9-D (6.6 MHz), abdominal RAB4-8-D (4.4 MHz) and curved array C1-5D (3.4 MHz). Measurements were performed by three physicians (LA, MA, RA) certified in sonography.

The standard fetal medicine guidelines used were those from the National Institution for Health and Care Excellence and the American Congress of Obstetricians and Gynecologists. Inter-observer reproducibility, assessed in 12 pregnancies, showed a coefficient of variation (CV) ≤ 4% for all the measurements by the three physicians except for FL (≤ 7.7%).

Fetal crown-rump length (CRL) was measured on all women between 12-13 gestational weeks to validate the gestational age (GA) estimated from last menses [8,23]. The CRL was obtained from the longest image of the fetus and measured the length from end to end.

Only the measurements obtained during one assessment per pregnancy, at a gestational age chosen between the 15th and the 36th week of gestation, was used for this study. Therefore, each fetus contributed only to one set of measurements to the analysis.

The Z-scores of the obtained measurements were calculated from the IG-21 standards, using the gestational age estimated from the LMP and were expressed in completed weeks of gestation as recommended by WHO International Statistical Classification of Diseases and Related Health Problems 10th Revision [7,24].

They were compared with the Z-scores obtained from the reference equations by Chitty et al., as they were demonstrated to give the best results to identify fetuses with abnormal growth parameters [19,21,25]. For each standard, Z-scores were calculated using the formula:

Z-score=Measured value-predicted mean value from the respective equation/Predicted standard deviation from that equation

A mean Z-score between -0.5 and +0.5, and a standard deviation (SD) of Z-scores ranging from 0.8 to 1.2 were judged to indicate good accord between observed and reference-derived expected measurements. Using both charts, we also compared the proportions of fetal measurements <3rd, <10th, >90th and >97th percentiles [13].

Computing all Z-scores, percentiles, proportions and all statistical analyses were performed with the statistical software STATA version 15 (StataCorp, College Station, Texas, USA).

We calculated and compared the Z-scores of weight, length and head circumference of the neonates from the IG-21 International Newborn Size at Birth Standards, and from the WHO charts [7,26,27]. We compared at birth the proportions of neonates <3rd, <10th, >90th and >97th percentiles with the IG-21 International Newborn Size versus the WHO charts [13].

To estimate the predictive value of fetal biometry for neonatal growth measurements, we measured, for each individual fetus, the relationship between the Z-scores of all the biometry measurements and the neonatal growth parameters (AC and birth weight, FL and length at birth, antenatal and HC at birth), using correlation and regression modelling (a correlation coefficient R>0.6 and a P value<0.05 defining statistical significance).

RESULTS

From the 124 pregnant women initially enrolled in the study, four (3%) were excluded because of missing data and/or a history of irregular menstrual periods. Biometric measurements were performed in the remaining 120 pregnancies, whose characteristics are shown in Table 1. The median gestational age at the time of biometric measurements was 25.8 weeks (range, 16 to 35).

Ten pregnancies (8.3%) were between 15 and 20 weeks' gestation, 33(27.5%) between 20 and 24 weeks, 61(50.8%) between 24 and 32 weeks, and 16(13.3%) above 32-weeks. The Z-scores (and their SD) of all the measurements using both the IG-21 and the standard references are displayed in Table 2.

To assess the effect of substituting the IG-21 for the standard charts, we also compared between the two sets of charts, and for each fetus, the Z-scores and their SD for AC, FL and HC (Table 2) [13].

While 13 out of 15 mean Z-scores from the IG-21 chart for all measurements remained between -0.5 and +0.5 at all gestational-ages, they never exceeded this range in any measurement in the standard chart. Comparing the SDs derived from the IG-21 and with those obtained from the standard charts, the former gave an acceptable SD (between 0.8 and 1.2) for 13 out of 15 measurements of HC, AC FL, while the standard charts had no acceptable SDs for any of the parameters, indicating, therefore, that the IG-21 charts were more similar to that of the expected population than to the standard charts.

When displayed across gestational ages, the IG-21 Z-scores of fetal measurements remained all between -0.5 and +0.5 except for head circumference Z-scores which were consistently above +0.5 but showed a steady decline with advancing gestational age (Figure 1).

The proportions of antenatal measurements of HC, AC, and FL <3rd, <10th, >90th and >97th percentiles were identical between the standard and the IG-21st standard, except for HC>90th percentile was higher with the IG-21st standard while the AC was higher in the standard chart when <10th or >90th percentile (Table 3).

Thus, using the standard charts seem to overestimate the proportions of fetuses with abnormal growth measurements when compared with the IG-21st standards.

All 120 pregnancies resulted in live newborns, but data were missing from 15 infants. There were 56 boys (53%); median gestational age was 39 weeks (range 29 to 41) and 14(13%) were delivered by cesarean section. Median values were 3,100gm for birth weight (range 1,200 to 4,200), 50cm for length (range 36 to 60), and 34 cm for head circumference (range 27 to 37).

The distribution of the IG-21st Z-scores and percentiles for growth measurements at birth are shown in Figure 2. The mean Z-scores were close to zero while the mean percentiles were close to the 50th percentile, thus, describing appropriately the neonatal growth parameters in our population.

Except for length exceeding the 90th percentile, the proportions of measurements at birth of HC, weight, and lengths <3rd, <10th, >90th and >97th percentiles were also consistently higher with the standard as compared to the IG-21st chart (Table 4).

The proportion of neonates with a birth weight <10th percentile was closer to the expected prevalence of small for gestational age (up to 7%) with the standard chart (10%) than the IG-21st charts (<5%).

Similarly, the standard charts overestimate the proportion of macrosomic infants (>90th percentile) with a prevalence of 26% when compared to the IG-21st charts (5.87%) which is closer to the expected prevalence (5 to 9%). Using the standard charts thus seem to overestimate the proportions of newborn with abnormal growth measurements when compared to the IG-21st standards.

We found no significant relationship, for each individual fetus, between the Z-scores of all the biometry measurements and the neonatal growth parameters (correlation coefficients R<0.2 and P>0.05).

Table 1: Characteristics of the 120 enrolled pregnancies.

Category	Median(range)	N (%)
Age (y)	31.6(19.1–41.5)	-
Body-mass index (kg/m^2)*	26.9(16.1–44.4)	-
Obesity (BMI>30 kg/m^2)	-	11(9.1%)
Gravity	4(1–14)	-
Parity	3(0–12)	-
Abortions	0(0–5)	-
Previous C-section	0(0–3)	-
Gestational diabetes	-	9(7.5%)
Bariatric surgery	-	2(1.6%)
Thyroid disease	-	3(2.5%)
Dyslipidemia	-	1(0.8%)
Vitamin D deficiency	-	50(41.6%)
Iron deficiency	-	71(59.1%)
Smoking/ alcohol use	-	0(0%)
Hypertension	-	0(0%)
Note: * At the date of the antenatal scan		

Table 2: Fetal growth parameters Z-scores estimates in 120 singleton pregnancies, based on standard reference (Chitty's equations) and IG-21st, expressed as mean value and standard deviation (SD).

Category	n	Mean (Chitty's reference)			Mean IG-21st			(Chitty's reference)			SD IG-21st		
		HC	AC	FL	HC	AC	FL	HC	AC	FL	HC	AC	FL
14-18 weeks	8	0.01*	-0.04*	-0.01*	0.13*	0.46*	0.08*	0.11	0.12	0.07	0.85*	1.27	0.96*
19-23 weeks	35	0.005*	0.06*	0.03*	-0.24*	0.49*	0.32*	0.25	0.24	0.25	0.82*	0.90*	0.92*
24-28 weeks	41	-0.05*	-0.01*	-0.04*	-0.16*	0.33*	0.47*	0.08	0.24	0.05	1.16*	1.07*	1.13*
29-33 weeks	31	-0.02*	0.04*	-0.04*	0.03*	0.43*	0.59	0.06	0.08	0.07	1.14*	0.98*	0.98*
34-41 weeks	5	0.004*	0.03*	-0.1*	-0.25*	0.12*	0.53	0.1	0.03	0.1	1.19*	1.13*	1.25
All	120	-0.02*	0.03*	-0.02*	-11	0.41	0.44	0.15	0.2	0.14	1.01	0.99	1

Note: IG-21st, INTERGROWTH-21st; HC, head circumference; AC, abdominal circumference; FL, femur length; *A priori acceptable values are between -0.5 and +0.5 for the mean Z-scores and between 0.8 and 1.2 for SD.

Table 3: Percentages of fetuses under 3rd or 10th centile, or above 90th or 97th centile, in 120 singleton pregnancies.

Category	n	<3rd centile (%)		<10th centile (%)		>90th centile (%)		>97th centile (%)	
		IG-21st	Chitty's equations	IG-21st	Chitty's equations	IG-21st	Chitty's equations	IG-21st	Chitty's equations
HC	120	0	0	0	0	7.8	0.8	0	0
AC	120	0	0	0	0.8	0	0.8	0	0
FL	120	0	0	0	0	0	0.8	0	0

Note: IG-21st: INTERGROWTH-21st, HC: head circumference, AC: Abdominal circumference, FL:femur length.

Table 4: Percentages of newborn infants under 3rd or 10th centile, or above 90th or 97th centile, in 105 neonates.

Category	n*	<3rd centile (%)		<10th centile (%)		>90th centile (%)		>97th centile (%)	
		IG-21st	WHO	IG-21st	WHO	IG-21st	WHO	IG-21st	WHO
HC	88	0	2.27	2.27	7.95	15.9	39.77	4.55	38.64
W	103	0	1.94	4.85	9.71	5.83	26.21	0.97	19.42
L	97	2.06	2.06	4.12	8.25	34	31.96	20.62	24.74

Note: IG-21st: INTERGROWTH-21st; HC: head circumference; W: weight; L: length; WHO: World health organization reference. *HC, W and L measurements were not available for all 105 neonates.

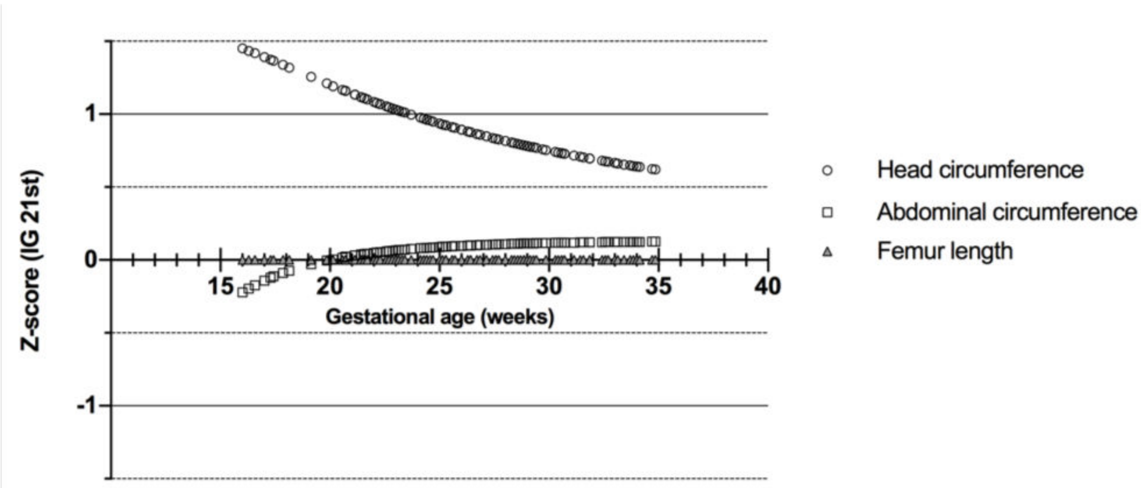

Figure 1: Distribution of Z-scores of fetal measurements (IG-21 standard) by gestational age in 120 singleton pregnancies. Except for head circumference, all the Z-scores did not exceed the range from =0.5 to +0.5, with the majority being much less and closer to zero, indicating small dispersion and therefore appropriately describing mean fetal size.

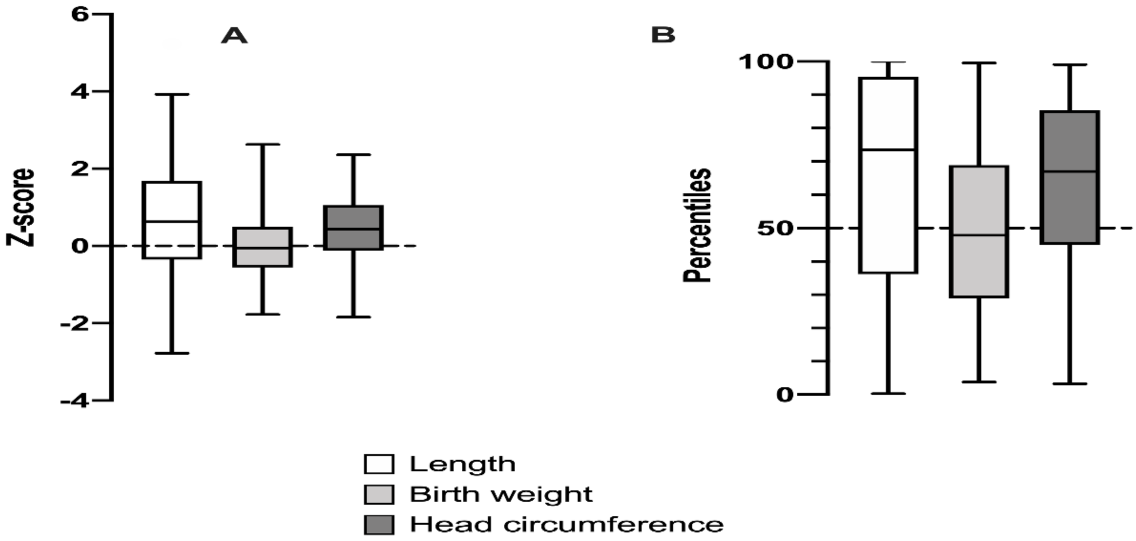

Figure 2: Z-scores (panel A) and percentiles (panel B) distribution of birth measurements in 105 singletons using the INTERGROWTH-21st. All the Z-scores had a median close to zero and a dispersion of approximately 0.1. All the percentiles had a median between 40 and 50 and a dispersion between 20 and 70, therefore appropriately describing mean neonatal size.

DISCUSSION

The results show that normal and abnormal fetal and neonatal growth measurements by the IG-21 standards closely reflect the expected population distribution, validating previous observations [13,28,29]. Therefore, the routine implementation in the UAE of IG-21 standards would be appropriate. As these international standards were derived from different geographical regions and diverse ethnicities, their appropriateness to our multiethnic population is, therefore, justified. We acknowledge that their predictive value of neonatal growth measurements remains limited, similarly to the other standards.

Our findings also demonstrate that the IG-21 standards adequately estimate mean fetal size, as the mean Z-scores were within -0.5 and +0.5 in the majority of cases [13]. Some factors can explain the discrepancies found between the two sets of charts in (1) the mean Z-score, in (2) the differences in the proportions of fetuses with small and large mensurations, and (3) the absence of correlation, for each individual fetus, between the antenatal biometric Z-scores and the neonatal growth parameters, confirming previous reports [28]. Differences in ethnicities or in population demographics remains a theoretical possibility, but this remains unlikely since the IG-21 cohort included countries such Oman, with similar sociodemography to the UAE [13].

Although it is a main determinant of growth, socioeconomic status was not analyzed in this study. Discrepancies could also be explained by differences in the methodology of ultrasound measurement between the 2 standards in our study, calipers were placed on the middle of the skull bone (outer-inner method) to measure the HC, while the IG-21 standards relied on the outer-outer method [13]. Another possible factor for the observed differences, mainly for the FL, is the recent advances in ultrasound technology, with thinner ultrasound beam which yields shorter values, explaining therefore the lower FL values obtained with the IG-21standard compared to our measurements [13].

We used the standard reference equations to compare with the results of the IG-21 because they give the best results to identify fetuses with abnormal growth parameters [19-21,25]. As these reference ranges are descriptive, developed from the general population and encompassing all fetuses, whether growing adequately or not, their ability to identify abnormal biometric measurements is reduced as a result. On the contrary, as the IG-21 international standards are prescriptive, they define the expected optimal fetal size [13]. Their distribution, with a SD closer to the theoretical value of one, is narrower than with the standard references, resulting therefore in improved sensitivity of IUGR screening [13].

A strength of this study, in addition to its prospective nature, is that it was not only focused on fetal measurements but has, unlike previous reports, included the neonatal outcomes related to growth. The IG-21 standards confirmed that the measurements were more similar to that of the expected population than to the standard charts, not only with fetal measurements but also with neonatal growth parameters [13]. Evaluating neonatal growth outcome in this study is crucial as the International Fetal and Newborn Growth Consortium for the 21st Century Project has now extended the IG-21 prescriptive methodology to assess growth until the age of five years [10,26].

We acknowledge the limitations of this study. The sonographers enrolled in this study may not necessarily be representative of all sonographers. As they were not blinded when performing the fetal biometric measurements and comparing them to the existing standard references, a potential bias might have been introduced [13]. Instead of performing a longitudinal follow-up, routine cross-sectional ultrasound scans may have had an influence on our assessment of the IG-21 charts as the measured biometrics were scant between the intervals. The small sample size with the unequal distribution of pregnancies across the gestational ages constitutes another limitation. With data unavailable on 15 of the 120 infants, and with the calculation of Z-scores and percentiles for all measurements depending crucially on gestational age at birth, sex, the growth outcomes could not be assessed in all 120 infants; it was possible for weight in 103 newborns, length in 97 and head circumference in only 88. In addition, as the participants came from a selected population, an increased detection rate of abnormal fetal growth in the general population may result [13]. Any future implementation of the IG-21 growth standards should therefore be monitored, by assessing the abnormal growth detection rates and perinatal outcomes.

CONCLUSION

In this pilot study, fetal size in pregnant UAE women was similar to the international population that was used in the IG-21 project. In addition, and similar to the other standards, the IG-21 neonatal growth standards were close to the expected population distribution despite their limited predictive value of neonatal growth measurements. These preliminary results, if confirmed in a larger study in the UAE, would support the use of the IG-21 standards in our population instead of the currently used standard charts.

COMPETING INTERESTS

The authors declare that we have no conflicts of interests.

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