



Original Research Article

A longitudinal study of fetal growth using antenatal INTERGROWTH-21ST reference standard charts and perinatal outcome

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Abstract

Background: Neonatal growth charts reveal compromised growth only at the extreme of growth abnormalities. They cannot be used to identify the fetus whose birth-weight is above the 10th percentile but has failed to achieve its growth potential. Hence we performed a longitudinal study of antenatal fetal growth assessment using INTERGROWTH-21st (IG-21st) reference standard charts and correlated with neonatal outcome.

Aim & Objectives: To assess the predictive value of antenatal fetal INTERGROWTH-21st (IG-21st) reference standard charts in diagnosing the neonatal growth abnormalities and the perinatal outcome

Materials and Methods: A prospective longitudinal study was done on 100 patients visiting outpatient department (OPD) of Department of OBG, SDMCMSH, Dharwad, Karnataka, for regular ante natal care (ANC), booked at <14 weeks of gestation.

Serial ultrasounds (USG) were done, i.e. Dating Scan, nuchal translucency scan (NT scan), Anomaly Scan, Growth Scan at >32weeks and one at near term. Fetal biometry measured (CRL-crown rump length, BPD-Biparietal diameter, HC-head circumference, AC-abdominal circumference, FL-femoral length, EFW-estimated fetal weight) were plotted on IG-21st charts and monitored the fetal growth. The neonatal parameters at birth and perinatal outcome were noted.

Results: Ninety six (96%) fetuses had normal growth curves (NGC) for all assessed parameters. Four (4%) had growth curves (GC) for AC and EFW falling below NGC indicating fetal growth restriction (FGR). At birth, all these 4 babies (100%) had LBW indicating that fetal monitoring using IG-21st had accurately identified all (100%) fetuses at risk for FGR and AC and EFW were better parameters for assessment of FGR compared to HC, BPD and FL.), but were AGA (appropriate for gestational age); thus, indicating applicability of IG-21st.

Conclusion: The IG-21st reference standards have a high predictive value for growth deviations and applicable to our population for antenatal fetal growth monitoring.

Keywords: INTERGROWTH-21st Reference Standard Charts, Fetal growth monitoring, FGR, SGA, LBW, Perinatal outcome, Fetal biometry, NT scan, Anomaly scan, Growth scan.

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1. Introduction

Fetal growth restriction (FGR), is a common complication of pregnancy that has been associated with a variety of APO (Adverse perinatal outcome). An optimal management and

timing of delivery of FGR fetuses improves perinatal outcome.

In a given population, fetal size shows a normal distribution at a given gestational age. Consequently, a fraction of fetuses are either large for gestational age (LGA)

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or small for gestational age (SGA) regardless of their growth potential. Currently, fetal-growth disorders at both ends of the spectrum are major problem in obstetrics with APO.¹ The majority of SGA fetuses (50%-70%), are constitutionally small.¹

The incidence of FGR is around 3-9% in higher socioeconomic group, whereas in low socioeconomic group it is as high as 30%.² Almost 20-50% of stillborn are growth restricted. FGR represents the second primary cause of perinatal mortality after prematurity,³ accounting for 30% of still births, besides determining a higher frequency of preterm births and intrapartum asphyxia.⁴ FGR is also associated with neonatal complications⁵⁻⁹ and higher incidence of coronary diseases, arterial hypertension and diabetes in adult life have also been reported.¹⁰

Antenatal and postnatal care consist mostly of a series of screening tests of varied complexity, implemented at different levels of care, which together contribute to evaluating the overall health and nutritional status of each pregnant women and new born baby.¹⁰⁻¹² Objective assessments of fetal and neonatal growth deviations can play a major role in routine clinical care, as well as maternal and neonatal health research. The usefulness and limitations of such screening methods have been evaluated in randomized controlled trials over the last decade.^{13,14}

In affected pregnancies especially those that have not reached term, there is a need to monitor growth more closely to decide if clinical interventions are required. However, international antenatal growth charts analogous to the World Health Organization (WHO) Multicenter Growth Reference Study (MGRS) standards for infants and young children,^{15,16} developed using prescriptive approaching, are not available.

The International Fetal and Newborn Growth Consortium for the 21st century, or INTERGROWTH-21st,¹⁷ is a global, multidisciplinary network of more than 300 researchers and clinicians from 27 institutions in 18 countries worldwide and coordinated from the University of Oxford, dedicated to improving perinatal health globally and committed to reducing the millions of preventable newborn deaths that occur as a result of preterm birth or FGR. They have developed INTERGROWTH-21st Global Perinatal Package which comprises of new, globally-validated standards for fetuses, newborn infants and the postnatal growth period of preterm infants through the INTERGROWTH-21st Project.

INTERGROWTH-21st project is the first, population based, large, multi-ethnic, longitudinal, fetal growth standard based on early assessment of gestational age¹⁷ and their reference standards for antenatal fetal growth monitoring are according to the most recent data and globally validated.

2. Aims

To assess the sensitivity and predictive value of antenatal fetal INTERGROWTH-21st (IG-21st) reference standard charts in diagnosing the neonatal growth abnormalities in our population and to study the perinatal outcomes of such neonates.

3. Materials and Methods

2.1. Study subjects

Patients booked for regular ANC Checkup at Department of Obstetrics and Gynecology, Sri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Dharwad, Karnataka. (SDMCMSH).

2.2. Inclusion criteria

1. Patients booked at SDMCMSH between December 2018 to May 2019 in 1st trimester (< 14 weeks)
2. Patients willing to participate in study

2.3. Exclusion criteria

1. Patients refusal
2. Multiple pregnancies
3. Termination of pregnancy due to anomalous fetus

2.4. Study period

December 2018 to May 2019 – Recruitment of patients for the study from January 2019, follow up of the patients recruited in the study until delivery and 7 days post natal.

2.5. Study instrument

A pre-designed and pre-tested proforma and the INTERGROWTH-21st reference standard charts.

2.6. Statistical analysis

Data was entered in Microsoft Excel and imported to the SPSS 29.0 version. Descriptive data was assessed in mean, standard deviation, and percentage. The Wilk-Shapiro test was used to assess the normality of the data.

2.7. Data collection

After obtaining ethical clearance and informed consent from the patients, 100 patients were included in this prospective longitudinal study. High risk factors affecting fetal growth were identified by detailed obstetric/past medical and surgical /significant family history and general physical and systematic examination and noted down.

All patients underwent a minimum of four ultrasounds (USG) i.e. dating scan / NT scan (if dating is done <11 weeks), anomaly scan, growth scan one after 32 weeks and one near term.

The USG values were plotted on the INTERGROWTH-21st charts for each of the fetal growth measures (CRL, BPD,

HC, AC, FL and EFW). Also if any additional USG were done, its values also were plotted on graphs. At least one of the scans was done by 2 different doctors to look for inter observer errors.

The perinatal outcome of all these patients i.e. gestational age at delivery (term/preterm), mode of delivery, baby details (apgar score, live/ still born, birth weight) and early neonatal events (up to 7 days of life) if any were noted down.

2.8. Sample size

100

$$n = Z^2 P (1 - P) / d^2$$

According to the study by Lee et al.² prevalence of FGR was 10%

P=10, Z=1.96 for 95% CI, error of 6%, sample size obtained is 96,

So approximately n=100 was considered

2.9. Sampling procedure

All patients falling under inclusion criteria were numbered and included in the study until the sample size of 100 was reached according to convenient sampling technique.

4. Results

This study included 100 patients booked at SDMCMHS from 1st trimester till delivery and the neonates were followed up till 7 days post-delivery.

Among the 100 patients included in the study 5 were Elderly Gravida (Age > 35 yrs) which constituted 5% of the study population, among which 2 were Elderly Primigravida and 3 were multigravida.

Primigravida participating in the study were 51 and the remaining 49 patients were multigravida constituting 51% and 49% of the total study population respectively.

Comorbidities that would have an effect on fetal growth and likely to cause FGR were present in 18 patients. Diabetes Mellitus was diagnosed in 7 patients (7%) and hypertension in 11 patients (11%). Two patients in study group developed both GDM and HTN.

Entire spectrum of Diabetes Mellitus i.e. GDM on diet (43%), IGT (29%), GDM on OHA (14%) and Overt DM (14%). was seen. Hypertension was diagnosed in 11 of the 100 patients (11%), constituting Gestational Hypertension (37%), NSPE (27%), Chronic HTN (9%), SPE (9%), IE(9%) and APE (9%).(**Table 1**)

Table 1: Baseline characteristics and comorbidities of respondents

Baseline characteristics	No of respondents	% of respondents
Elderly Gravida (age>35 years)	5	5%
Parity		
Primigravida	51	51%
Multigravida	49	49%
Comorbidities	18	18%
Diabetes Mellitus	7	7%
1) Overt DM	1	1%
2) Gestational DM	4	4%
a) GDM - Diet	3	3%
b) GDM - OHA	1	1%
3) IGT	2	2%
Hypertension	11	%
1) Chronic Hypertension	1	1%
2) Gestational Hypertension	4	4%
3) NSPE	3	3%
4) SPE	1	1%
5) Imminent Eclampsia	1	1%
6) Antepartum Eclampsia	1	1%

DM: Diabetes mellitus, GDM: Gestational diabetes mellitus, OHA: Oral hypoglycemic agents, IGT: Impaired glucose tolerance, NSPE: Non severe pre Eclampsia, SPE: Severe pre Eclampsia

Table 2: Antenatal growth curve wise distribution of growth parameters

Growth Parameters	Normal	Below Normal	Percentage
BPD	100	0	100%
HC	100	0	100%
AC	96	4	100%
FL	100	0	100%
EFW	96	4	100%

BPD: Biparietal diameter, HC: Head circumference, AC: Abdominal circumference, FL: Femur length, EFW: Estimated fetal weight

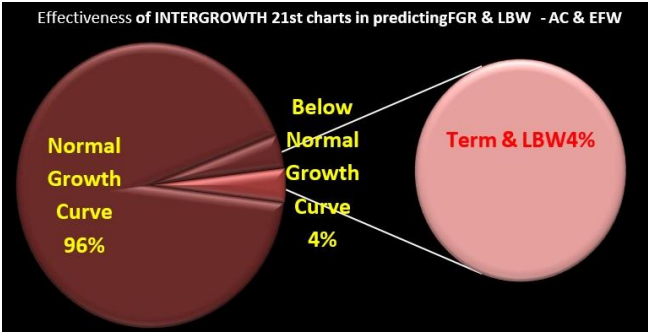


Figure 1: Effectiveness of INTERGROWTH 21st charts in predicting FGR & LBW

The fetal growth of all the patients was done using INTERGROWTH-21st reference standard charts. Fetal growth in 4 patients was below the normal curve for AC and EFW, indicating fetal growth restriction (4% of the study group). Other parameters i.e. BPD, HC and FL were within the normal curve in these fetuses. (Table 2, Figure 1)

All the FGR babies were born at term and had LBW confirming the diagnosis of FGR. None of them required NICU care.

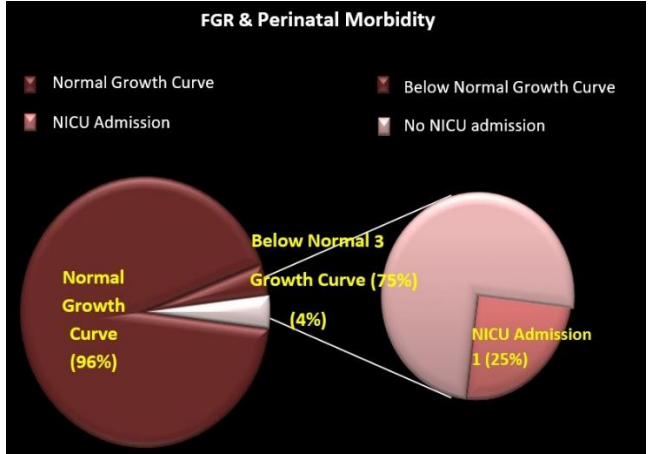


Figure 2: FGR and perinatal morbidity

One among the four FGR babies required NICU admission for LBW care. The remaining 3 babies (75%) had no perinatal morbidity. All the 4 babies (100%) were alive and healthy at the end of one week follow up post-delivery. (Figure 2, Figure 3)

Among the 96 fetuses falling under the normal growth curve, 93 fetuses were born at term and had normal birth weight; 2 babies had early preterm birth (< 34 weeks) and LBW; 1 baby had late preterm birth (≥34 weeks) with normal birth weight. Thus, all the fetuses falling under the normal growth curve were appropriate for gestational age. Hence it can be inferred that the INTERGROWTH 21st reference standard charts are applicable to our population. (Figure 4)

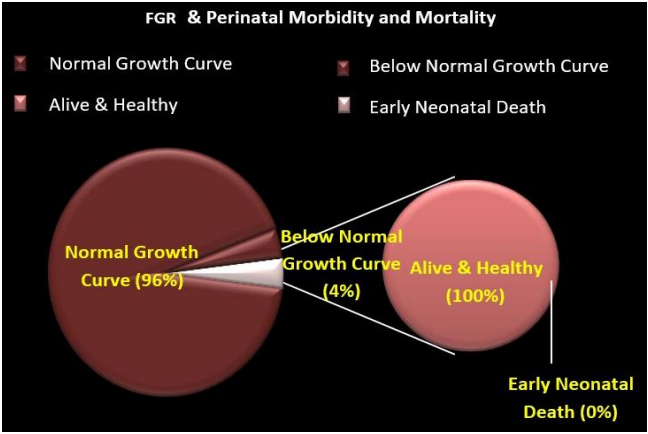


Figure 3: FGR & perinatal morbidity and mortality

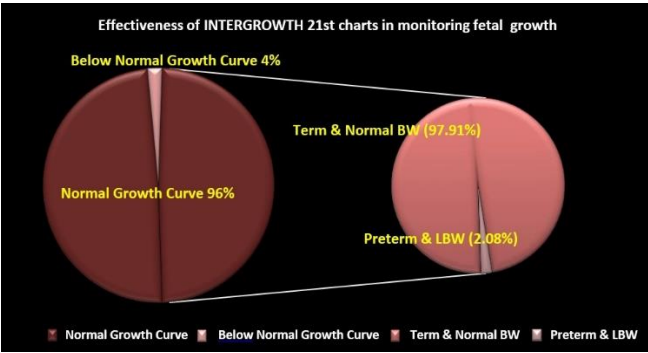


Figure 4: Effectiveness of INTERGROWTH 21st charts in monitoring fetal growth

Table 3: Mode of delivery and neonatal outcomes

Delivery	No. of respondents	% of respondents
Term	97	97%
Preterm	3	3%
Birth Weight		
Normal BW	94	94%
VLBW	1	1%
LBW	5	5%
Morbidity		
NICU admission	1	1%
Mortality	0	0

BW: Birth weight, VLBW: Very low birth weight, LBW: Low birth weight, NICU: Neonatal intensive care unit

Out of the 100 fetuses included in the study, 97 (97%) were born at term and 3 (3%) were born preterm.(Table 3)

Table 4: Birth weight- wise distribution of respondents

Birth Weight	No. of respondents	% of respondents
Normal BW	94	94%
VLBW	1	1%
LBW	5	5%

BW: Birth weight, VLBW: Very low birth weight, LBW: Low birth weight

Table 5: Association between Co-morbidity as DM with fetal growth and neonatal outcome

DM	n	Deliveries		Growth Curve		Birth weight		NICU Admission/ neonatal death
		Preterm	Term	Normal	Below normal	Normal	LBW	
Overt DM	1	0	1	1	0	1	0	0
GDM DIET	3	0	3	3	0	3	0	0
GDM OHA	1	0	1	1	0	1	0	0
IGT	2	0	2	2	0	2	0	0
Total	7	0	7	7	0	7	0	0

DM: Diabetes mellitus, GDM: Gestational diabetes mellitus, OHA: Oral hypoglycemic agents, IGT: Impaired glucose tolerance

Table 6: Association of Hypertension with fetal growth

HTN	n	Deliveries		Growth Curve		Birth weight	
		Preterm	Term	Normal	Below Normal	Normal	LBW
GH	4	0	4	4	0	4	0
CH	1	0	1	1	0	1	0
NSPE	3	0	3	3	0	3	0
SPE	1	0	1	1	0	1	0
IE	1	0	1	0	1	0	1
APE	1	1	0	1	0	0	1
Total	11	1	10	10	1	9	2

CH: Chronic Hypertension, GH: Gestational Hypertension, NSPE: Non severe pre Eclampsia, SPE: Severe pre Eclampsia

Among the 100 babies included in the study, 94 (94%) had Normal BW, 5 (5%) had LBW, 1 (1%) had VLBW. (Table 4)

The fetal growth in all the patients with DM (including IGT, GDM on diet, GDM on OHA & Overt DM) was within the normal growth curve and all of them had a full term delivery (FTVD/Full term LSCS) with a normal weight newborn, indicating that all the patients with DM with well controlled sugar levels had normal fetal growth with no perinatal adverse outcomes.(Table 5)

The fetuses of Hypertensive patients had normal growth curves and AGA at birth, except one patient with SPE which had fetal growth below the normal curve for AC and EFW, developed imminent eclampsia and had LBW. One patient with Antepartum Eclampsia was induced, had preterm delivery, had LBW but AGA, and was shifted to NICU for preterm care. (Table 6)

5. Discussion

This prospective longitudinal study describes the use of INTERGROWTH 21st Reference standard charts for antenatal monitoring of fetal growth and perinatal outcome, in Department of Obstetrics and Gynecology, Sri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Manjushree nagar, Sattur, Dharwad. Cases constituted 100 antenatal mothers booked at our hospital between December 2018 and May 2019 and were followed up to delivery and 7 days postpartum.

According to an analysis of CHERG datasets, in 2012, an estimated 23.3 million infants (19.3% of live births) were born SGA in low and middle income countries which is higher than the incidence of 4% in our study, which could be attributed to the smaller sample size. Among the SGA

according to that analysis, 11.2 million (0.8 to 15.8%) were term and not LBW (≥ 2500 g), 10.7 million (7.6 to 15.0%) were term and LBW (< 2500 g) and 1.5 million (0.9 to 2.6%) were preterm; which again is lower according to our study-Term with LBW being 4% and preterm being 3%. South Asia had the largest burden, where the prevalence was the highest (34%); about 26% of neonatal deaths were attributable to infants born small for gestational age. Reduction of the prevalence of small for gestational age from 19.3% to 10.0% in these countries could reduce neonatal deaths by 9.2%.²

Among the fetal growth monitored in 100 patients using INTERGROWTH-21st reference standard charts in our study, fetal growth in 4% patients was below the normal curve for abdominal circumference and estimated fetal weight, but with biparietal diameter, head circumference and femur length were within the normal curve, indicating fetal growth restriction in 4% of the study group. This finding is consistent with findings of several studies that AC and EFW are the most sensitive parameters of fetal biometry affected in FGR and is used in very definition of FGR.

All the 96 babies which had growth within the normal curve, had birth weight appropriate for gestational age. All the 4 babies detected to have FGR by the INTERGROWTH-21st reference standard charts were born at term and had low birth weight (LBW) indicating that the INTERGROWTH-21st reference standard charts had good predictive value in detecting neonatal SGA. Only one LBW baby (25%) had NICU admission and shifted mother side after optimal weight gain. All of the 4 LBW babies were alive and healthy (followed up to 7 days postpartum). Hence INTERGROWTH 21st fetal growth standard charts can be applied to monitor fetal growth in our population.

In the study by J. J. Stirnemann et al,¹⁹ the distribution of HC demonstrated clear similarity between the French population and the IG-21st population. Their observed centile curves closely matched those of IG-21st. The IG-21st standards performed as well as did locally derived charts in terms of screening for small-for-gestational age by AC, while they identified significantly fewer small FL values than were expected and then did the locally derived charts, which is similar to our study where in AC was a better parameter for identifying FGR and fetus at risk for SGA compared to all the other parameters (HC, BPD and FL) measured. Thus they concluded that under strict selection criteria, fetal size in France is similar to that of the international population used in the INTERGROWTH-21st Project which supports the results of our study where the fetal size in our population was similar to that of the IG 21st population. The discrepancies in FL were unlikely to impact on prenatal management. Therefore, switching from locally derived reference ranges to the IG-21st standards appears to be a better option.

In another study by Meselech Roro et al,²⁰ on Intrauterine growth patterns in rural Ethiopia comparing it with WHO and INTERGROWTH -21st growth standards, they found that the fetal growth patterns in a drought-affected rural community of Ethiopia determined using common ultrasound biometric measurements were similar to IntraUterine Growth patterns to those indicated in the WHO and INTERGROWTH-21st fetal growth reference standards further strengthening our inference.

The study by Jose Villar et al,¹¹ concluded that the satisfactory growth and development at 2 years of age of the INTERGROWTH -21st Fetal Growth Standards cohort support its appropriateness for constructing international standards. Our study followed up neonates up to 7 days postpartum. But further follow up through infancy is required for accurate validation of the appropriateness of the INTERGROWTH 21st Reference Standards for Indian population.

In the study by Anthony O Odibo et al,²¹ comparing customized fetal growth standard with the INTERGROWTH-21st century standard at predicting small-for-gestational-age neonates, concluded that both the growth standards had modest performance in detecting neonatal Small for GA fetus and were poor at predicting short-term adverse neonatal outcome.

In another study by Andre Francis et al,²² comparing Customized versus INTERGROWTH-21st standards for the assessment of birth weight and stillbirth risk at term, Customized assessment resulted in increased identification of small for gestational age and stillbirth risk.

Hence it can be inferred that unlike above study the INTERGROWTH-21st reference standards can be appropriate for our population, to monitor fetal growth and detect FGR / SGA. But further studies involving larger

population, are necessary to validate the applicability of these standards for the entire Indian population.

The strength of the study is that it is a prospective longitudinal design. All the recruited 100 patients could be followed up to delivery and seven days postpartum.

6. Limitations

Small sample size of only 100 patients it was done in a single-center setting limited follow-up (only 7 days postdelivery) was done.

Follow up of the neonates through infancy and long term follow up was not done.

7. Conclusion

Our study showed that the INTERGROWTH-21st reference standard charts developed using the same methods and conceptual approach as the WHO-MGRS standards for infants and young children, which are claimed to be based on most recent data and globally validated, are applicable to our population for antenatal fetal growth monitoring. It was effective in identifying fetal growth restriction in the study population, aiding proper monitoring and timely intervention when needed, thus improving the perinatal outcome.

But further studies need to be done using larger cohorts and also comparing the efficacy of the INTERGROWTH 21st standards with the customized standards for pregnancies at risk for neonatal SGA and adverse perinatal outcome. Also to validate the applicability of these charts to the Indian population.

8. Ethical Approval

SDMIEC/PG/0174/2018.

9. Source of Funding

None.

10. Conflict of Interest

None.

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