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Review Article

Foetal Growth Standards: Does One Size Fit All?

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Antenatal ultrasonography to monitor foetal growth and well-being is an essential component of obstetric care. Measurement of foetal anthropometric parameters including head circumference, bi-parietal diameter, abdominal circumference and femur length, and the estimated foetal weight derived from these parameters is used for diagnosing restricted or excessive foetal growth and congenital anomalies, such as, small or large head size and skeletal dysplasias. These diagnoses have major therapeutic implications.Thus, it is quite imperative that the reference data should be accurate and representative of the population for which it is being used.

There are two major categories of foetal growth charts—those based on serial foetal measurements by ultrasonography, and those based on measurements at birth plotted against gestational age based on last menstrual period. Many different charts of both categories are currently being used to serve as reference normative data. Recently, Intergrowth-21st Consortium has published international foetal growth standards, based on prospectively collected foetal biometric data. The study has been conducted with highly standardized methodology on healthy, affluent, low-risk pregnant women in 8 countries, including India. For the present paper, we have reviewed the merits and drawbacks of these standards, as well as, several other Indian and international charts. None of the currently available charts come up to our expectations from an 'ideal' foetal growth chart. We suggest that for a country of our magnitude and diversity, there is an urgent need to construct our national foetal growth standards based on carefully selected population and using robust techniques and methodology.

Keywords: Foetus; Ultrasonography; Small for Gestational Age; Standards; Growth Charts, Intrauterine Growth Restriction, Intergrowth, India

Introduction

Monitoring foetal growth is an essential component of antenatal care. Recognition of altered foetal growth can improve neonatal outcome by allowing timely planning of interventions. Several charts have been created over the last five decades to provide reference data for assessment of foetal growth. A majority of the earlier charts, including the widely used charts by Lubchenco *et al.*, were based on anthropometric measurements at birth of live born babies at known gestational ages, starting from 24-30 weeks, till 42-44 weeks (Lubchenco *et al.*, 1963). Although, the stated aim of these charts was to classify the infants at birth into small appropriate or large for gestational age, these have been additionally used as references for assessing foetal growth. In subsequent years, ultrasound-based reference charts of foetal anthropometric parameters have also been published by several groups working in different geographically and/ or ethnically defined populations. In 2014, a major stride in the area of foetal growth monitoring was made by the Intergrowth-21st Consortium. International foetal growth 'standards' were published based on prospectively made foetal anthropometric measurements, using standardized sonological techniques in healthy affluent women from eight countries (Papageorghiou *et al.*, 2014).

In this review, we will be discussing the physiology of foetal growth, the need for and characteristics of 'ideal' foetal growth charts, and

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the strengths and limitations of the various foetal growth charts available to us today. Finally, based on our review, we shall be presenting our recommendations.

Physiology of Foetal Growth

Foetal period represents the most dynamic phase of growth in human life. In the initial period of gestation, the increment in size is small - at 9 weeks, the embryo measures less than 5 cm in length and 9 g in weight. Foetal weight gain is less than 10 g per week till about 16 weeks. Weight increment accelerates between 16-28 weeks of gestation to roughly 80g per week, and is maximal between 28-37 weeks at nearly 200g per week. From 37-42 weeks, foetal weight gain decelerates to about 70g per week.

Growth of the foetus is determined by its own genetic potential and modulated by maternal placental and environmental factors. Maternal height and weight are strongly correlated with birth weight. This 'maternal constraint' serves to limit foetal overgrowth, so as to prevent dystocia (difficult labour) and preserve mother's capacity for future successful pregnancies (Vasak *et al*., 2015). Other important maternal factors that influence foetal growth are her nutrient intake during pregnancy, anaemia, smoking, alcohol consumption, infections, chronic disease and pregnancy-induced complications such as hypertension or diabetes (Kramer *et al*., 2013). The important foetal factors that affect its growth include; congenital anomalies, infections and genetic syndromes.

Several aspects of placental function, including adequate trophoblast invasion, increase in utero-placental blood flow during later half of gestation, transport of glucose and amino acids from mother to foetus, and, production and transfer of growth regulating hormones are critical for foetal growth (Sferruzzi-Perri *et al*., 2016). Adequate placental adaptation in early pregnancy can overcome maternal under-nutrition, so that foetal nutrition is maintained during the phase of rapid growth in later gestation (Hayward *et al*., 2016). In a recent animal study, use of proteomics and Western blotting has revealed a significant difference in the expression of proteins involved in the pathways of energy metabolism, nutrient transport, stress response, and cell proliferation and apoptosis in the placenta and endometrium of normal and growth-restricted foetuses (Chen *et al*., 2015).

Foetal Growth Charts

The Need for Foetal Growth Charts

Monitoring foetal growth by ultrasonography was initiated in the 1960's and is now a standard of care in obstetric practice. Foetal biometry includes measurement of bi-parietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL). Foetal weight is estimated from these parameters.

The chief purpose of foetal growth monitoring is to diagnose foetal growth restriction (FGR), as this has an important bearing on perinatal morbidity and mortality, and guides decisions such as timing, mode and place of delivery. Growth restricted foetuses are at higher risk of not only several short- term morbidities, such as, birth asphyxia, sepsis, and hypoglycaemia, but are also at higher risk of adverse long -term cardio-metabolic outcomes.

Comparison of the foetal dimensions with the normal are also the basis of ultrasound-based dating of pregnancy as well as antenatal diagnoses of macrosomia (big baby), micro- or macrocephaly, and abnormalities or disproportion of limb length as in skeletal dysplasias. It goes without saying that unless the normal is well defined the abnormal or pathological cannot be diagnosed with accuracy.

Characteristics of an 'Ideal' Foetal Growth Chart

For an obstetrician, monitoring a particular pregnancy, the ideal normative data should be a), *representative* of the expected longitudinal growth pattern of foetuses from a population similar to the one from which the patient comes; b), should provide median and centiles or standard deviations of the biometric parameters of interest; and c), should be easy to interpret, or incorporated within the ultrasonography machine. Characteristics of an 'ideal' foetal growth chart are summarized in the accompanying panel (Box 1). However, as we will discuss further in the review, probably all the currently available foetal growth charts fall short of these ideals in terms of their applicability to the Indian population.

Box 1: Characteristics of an 'ideal' foetal growth chart

1. *Representative* of the typical growth pattern of healthy foetuses in that population
2. Gestational age assessment and measurement of foetal biometric parameters should be accurate.
3. *Comprehensive*: Information on all parameters of interest across the gestational age range from early pregnancy to term (14-42 weeks).
4. The interpretation of whether the foetal dimensions and estimated foetal weight are within or outside the normal range, and whether there is any deviation across centiles on longitudinal follow-up should be simple.

Reference vs. Standards

Broadly speaking, growth 'reference' curves provide a snapshot of how foetuses are actually growing in the population, while growth 'standards' depict the ideal growth that could be achieved in the absence of factors that confound or constrain growth. It seems logical that the normative data for foetal growth should be based on how foetuses 'should grow'.

As noted in subsequent sections, several exclusion criteria are applied in most studies of foetal growth, aiming to bar the entry of foetuses with a 'non-standard' or deviant growth pattern into the study. Thus. the curves produced in these studies are intermediate between reference and standard curves. The stricter the entry criteria would be, the nearer the curves would move towards being 'standard'.

However, the focus of the exclusion criteria so far has been predominantly on factors that may restrain foetal growth, with inadequate attention to excluding factors that can cause excessive foetal growth, such as maternal obesity or excessive gestational weight gain.

There are two intrinsic problems with creation of standard foetal growth curves. Firstly, there are several known, as well as, unknown factors (environmental, maternal, placental and foetal) that may either restrain or enhance foetal growth, and it is not possible to identify and exclude all such factors. Secondly, if too strict eligibility criteria are applied for selection of subjects for generating the standards, this will limit their inherent applicability to the wider population.

Universal vs. Racial/Ethnic Standards

The jury is still out on the question of preferring a 'one size fits all' universal standards approach or charts based on the local population. The WHO international growth standards for children are now accepted in most countries across the world, but there is no such consensus regarding foetal growth standards. The recently published data from the NICHD Foetal Growth Study favours the use of racial/ethnic standards for foetal growth. As part of the study, 2334 healthy women from four self-identified US racial/ ethnic groups underwent serial antenatal ultrasonography. The estimated foetal weight (EFW) was noted to differ significantly by race/ethnicity beyond 20 weeks. At 39 weeks, the 5th, 50th, and 95th percentiles of weight differed from each other by 169-349 g (adjusted global $P < .001$). The racial/ ethnic differences in humerus and femur lengths became apparent by 10 weeks, in AC by 16 weeks, in HC by 21 weeks, and in BPD by 27 weeks. The authors noted, that if standards based on white group are used, as many as 15% of non-white foetuses would be erroneously classified as growth restricted. Racial/ ethnic-specific standards improved the precision in evaluating foetal growth. (Buck Louis *et al.*, 2015). We will be discussing this question in Indian context in subsequent sections.

Foetal Biometry vs Neonatal Anthropometry Based Foetal Growth Charts

Foetal growth charts can be broadly categorized into two types — those based on serial foetal measurements by ultrasonography, and those based on measurements at birth plotted against gestational age based on last menstrual period. A succinct comparison of the two types is provided in Table 1.

Table 1: Comparison of foetal biometry and neonatal anthropometry based foetal growth charts

Foetal biometry based charts	Neonatal anthropometry based charts
Serial foetal measurements are made in pregnant women using ultrasonography (USG). The biometric parameters are:· Bi-parietal diameter (BPD) Head circumference Abdominal circumference (AC) Femur length Foetal weight and length are estimated from these. Charts are constructed by plotting foetal biometric variables (BPD, AC etc) as well as estimated foetal weight and length against gestational age.	Neonatal anthropometric measurements (birth weight, length and head circumference) are made at birth and plotted against gestational age based on last menstrual period (LMP).
In a majority of these charts, gestational age assessment is more reliable as it is based on combination of LMP and early pregnancy USG.	Gestational age in several of these charts is based on recall of LMP alone and hence may not be reliable.
These charts typically provide foetal growth data beginning from 14-20 weeks of gestation.	These charts typically begin from 28-33 weeks of gestation.
Not gender-based.	Several of these charts are available separately for male and female babies.
Mainly used by obstetricians and ultrasonologists for serial monitoring of foetal parameters, diagnosis of FGR, macrosomia, micro-or macrocepahlay, skeletal dysplasia or disproportionate growth.	Mainly used by neonatologists and paediatricians for classifying babies at birth into appropriate, small or large for gestational age.
The charts incorporated into the USG machine or ICMR charts are chiefly used.	Local charts are preferred.
Examples: Hadlock's charts incorporated in many USG machines (Hadlock *et al.,* 1982), ICMR multicentricfoetal growth charts (Berry *et al.,* 1990), Intergrowth -21st FGLS charts (Papageorghiou *et al.,* 2014)	Examples: Lubchenco's charts (Lubchenco *et al.,* 1963), AIIMS charts (Singh *et al.,* 1974), Vellore charts (Kumar *et al.,* 2013), Intergrowth-21st NCSS charts (Villar *et al.,* 2014)

Currently Available Foetal Growth Charts in India: Merits and Drawbacks

Foetal Biometry Based Growth Charts

A recent systematic review has looked at the methodology of generation of ultrasnography-based foetal growth charts in 83 studies from 32 countries (Loannou *et al*., 2012). The authors have assigned a 'quality score' to these studies based on various indicators of quality of study design, statistical techniques and reporting methods. For example, some of the indicators of high quality of study design included a priori sample size calculation, well defined population, prospective study with inclusion of each foetus only once, clearly described method of dating pregnancy and precise calculation of gestational age.

In only 20 of the studies, data had been collected prospectively and explicitly for research purpose and only 22 studies had reported all four biometric parameters, HC, AC, FL and BPD. Other common pitfalls of these studies were convenience sampling, use of a mix of cross-sectional and longitudinal data, inclusion of high-risk pregnancies, gestational age either not assessed by ultrasonography -or assessed beyond 14 weeks, and inadequate statistical methods.

The only Indian study included in this review was conducted at Christian Medical College, Vellore with nearly 500 scans on 120 pregnant women (Mathai M *et al*., 1995). The salient features of this study are presented in Table 2. This was a prospective study with both longitudinal and cross-sectional data collection and reported BPD, AC and FL between 20-40 weeks of gestation. The authors had noted that growth patterns of BPD and FL were comparable to Western population, but AC lagged behind, especially after 28 weeks such that 90th centile of these charts corresponded to the 50th centile of Western charts. This suggested that skeletal growth of Indian and western foetuses was similar, but soft tissue growth was lesser. Another notable finding was the median

Table 2: Summary of Indian studies on ultrasonography based fetal growth assessment

S.N.	Author, Year, City	Objective	Methodology	Results	Remarks/Drawbacks
1.	Sood *et al.,* 1988, Delhi	To study different foetal parameters in the diagnosis of IUGR and establish normal USG based fetal standards in Indian women	Serial USG was done in 85 pregnant women, 57 clinically normal and 27 with suspected IUGR 2 weekly from 28 weeks onwards. The recruited women had singleton pregnancy, known LMP and regular periods. BPD. HC and AC were measured.	Normative data (from 57 foetuses) was presented in tabular form as mean ± SD for BPD, HC and AC at 2-weekly intervals from 28 to 41 weeks. All parameters had reasonable accuracy in discriminating between normal and IUGR foetuses, but AC was found to be most useful. AC was noted to be smaller in comparison to available Western data.	This was a small study. Foetal biometry has been done only in third trimester and data has not been converted to smoothened centile charts.
2.	Chellani *et al.,* 1990 Delhi	To assess fetal growth by serial USG and compare it with previously established postnatal growth curves	BPD, AC and FL measured every 4 weeks from 20-36 weeks of gestation and biweekly thereafter in 241 low-risk pregnant women	Estimated foetal weight (EFW) and length from 20-40 weeks reported as growth curves (3^{rd} to 97^{th} centiles). These curves corresponded closely with the postnatal curves (Ghosh *et al.,* 1971; Mohan *et al.,* 1991) from 28 week onwards.	The data has been reported only in terms of EFW and foetal length, derived from FL. The values or curves for the actual foetal biometric parameters (AC, HC, BPD, FL) have not been provided
3.	Berry *et al.,* 1992 Multicentric- Delhi, Mumbai, Belgaum, Gauhati, Pune, Ahmedabad	To develop norms for clinical and USG parameters of foetal growth and to compare them as tools for monitoring foetal growth	2831 women with known LMP and no history of medical or obstetric problem were followed within one week of 20, 28, 32 and 36 weeks of gestation for clinical (maternal weight, fundal height and abdominal girth) and USG (BPD, AC and FL) parameters	Data from 2106 mothers who delivered babies with BW ≥ 2500g at >36 weeks was used to create curves showing mean ± SD for FL and AC. The mean ± SD of F*L.*, AC and BPD, and clinical parameters (mothers' weight, fundal height and abdominal girth) was also presented separately for babies with BW in three categories (<2500, 2500-2999 and> 3000g) at 20, 28, 32 and 36 weeks.	GA is based only on LMP. Smoothened curves given only for FL and AC.It was noted that 72% of low birth weight babies can be correctly identified by clinical parameters alone as compared to 65% with USG. Hence, it was concluded that USG does not help in early detection of IUGR.
4.	Mathai *et al.,* 1995 Vellore	To assess the pattern of foetal growth and gestation at delivery in pregnant Indian women	120 women with known LMP, regular cycles, first antenatal examination < 20 weeks with USG confirmation of dates and no known obstetric or medical risk factor recruited from CMC, Vellore. Serial USG measurement of BPD, AC and FL at 20, 24, 28, 32 and 36 weeks and weekly thereafter till delivery, birth weight recorded.	Median, 10^{th} and 90^{th} centiles were presented for BPD, AC and FL in *tabular* form as *discontinuous* data at 20, 24, 28, 32, 36, 37, 38, 39 and 40 weeks. Median gestation at spontaneous delivery was 38+3 days. BPD and FL were comparable to those of western populations, but AC lagged behind especially after 28 weeks, so that 90^{th} centile of this data corresponded to 50^{th} centile of Western data from 28 to 40 weeks	Smoothened curves have not been produced for foetal growth parameters.
5.	Kinare *et al.,* 2010 Pune	To describe foetal size in a rural Indian population and compare it with European and urban Indian populations	Serial USG measurement of F*L.*, AC, BPD and HC at approximately 18, 30, and 36 weeks' gestation in 653 singleton pregnancies. Compared with data from French population and Vellore study (Mathai *et al.,* 1995)	Curves for foetal AC, HC, BPD and FL constructed. These foetuses were smaller than the French reference and the urban Vellore sample even at the first scan.	Poor recall of LMP leading to inaccurate GA No exclusions made, with 64% of the mothers being under-weight. Study not intended to generate reference data

Abbreviations: USG- ultrasonography, BW- birth weight, GA-gestational age, LMP-last menstrual period, AC-abdominal circumference, BPD-bi-parietal diameter, HC-head circumference, Fl- femur length, EFW- estimated foetal weight, IUGR:intra uterine growth retardation

gestation in Indian babies (delivered following spontaneous labour) was 38 weeks and 3 days, more than a week lesser than that reported in studies from Caucasian population. The slower growth in the third trimester and shorter gestation were considered to be the reason for lower birth weight in Indian babies. However, this study was assigned a quality score of only 17% in this systematic review, as some of the methodological details are missing. In the paper, gestational age has been truncated to completed weeks, statistical analysis is inadequate and smoothened curves have not been produced.

There are few other Indian studies based on serial antenatal USG that have not been included in the above review. Table 2 summarizes the methodology, results and some of the lacunae in the published Indian studies on USG based foetus growth assessment. The first study was conducted at All India Institute of Medical Sciences, Delhi, on 85 pregnant women. Serial USG for measurement of BPD, AC and HC was done from 28 week onwards, and presented in tabular form as mean ± SD (Sood *et al*., 1988). The second study was conducted on 241 low-risk pregnant women at Safdurjang Hospital Delhi (Chellani *et al*., 1990). BPD, AC and FL were measured every 4 weeks from 20-36 weeks of gestation and bi-weekly thereafter. A paper based on a multicentre study conducted by Indian Council of Medical Research during 1984-87, with the objective of developing norms for clinical and ultrasonographic parameters of foetal growth and comparing their utility was published in 1992 (Berry *et al*., 1992). This study was conducted at 9 sites in 6 cities (Table 2), and curves were generated for AC, FL and fundal height. USG had limited availability at that time and the study concluded that it doesn't score over clinical parameters in identifying FGR. Apart from these studies on urban women recruited from tertiary care centres, there is one study from a rural cohort near Pune (Kinare *et al*., 2010). However, this study was not intended for generation of reference data. Its major drawbacks are that most of the women were under-weight and they did not recall their last menstrual period (LMP).

If we look at the current situation in India, most of the obstetric USG machines have Hadlock's data incorporated in their software. Hadlock *et al*., had published their cross-sectional data, collected from 400 'middle-class white' women in Texas in 1982 (Hadlock *et al*., 1982 a; Hadlock *et al*., 1982 b; Hadlock *et al*., 1982 c; Hadlock *et al*., 1982 d). Their studies have been assigned a quality score of about 40% by Ioannou *et al.* (2012) based on the relatively small sample size, data collection not done explicitly or primarily for research, and inadequate statistical methodology (Ioannou *et al*., 2012). Hence, this data is definitely not very useful for identifying abnormal growth of Indian foetuses. Few obstetricians and radiologists use the data on foetal AC, BPD, FL and HC generated by Indian studies, such as; that by Berry *et al*., 1992. The practice at several centres is to calculate estimated foetal weight from foetal biometry and compare it with a local reference chart based on measurements at birth (described in the next section) for classifying foetuses as normal growth restricted or macrosomic.

Neonatal Anthropometry Based Foetus Growth Charts

There are several Indian studies that have generated 'foetal growth' charts, based on measurements at birth at different gestational ages (Ghosh *et al*., 1971; Singh *et al*., 1974; Mohan *et al*., 1990; Singhal *et al*., 1991; Mathai *et al*., 1996; Kandraju *et al*., 2012; Kumar *et al*., 2013; Alexander *et al*., 2013). A summary of these studies is presented in Table 3. However, these charts are not really representative of foetal growth *in utero*, as these are not based on foetal measurements by ultrasonography, and babies born pre-term may have had some growth restriction prior to birth. Another common drawback is that many of these studies are based on retrospective data collected over several years (Mathai *et al.*, 1996; Kandraju *et al.*, 2012; Kumar *et al.*, 2013; Alexander *et al.*, 2013). Gestational age was not confirmed by early pregnancy USG in several studies (Ghosh *et al*., 1971; Singh *et al.*, 1974; Mohan *et al.*, 1990; Singhal *et al.*, 1991; Alexander *et al.*, 2013). Postnatal gestational age confirmation by physical/neurological assessment has not been done (Ghosh *et al*., 1971; Mathai *et al.*, 1996; Kandraju *et al.*, 2012; Kumar *et al.*, 2013; Alexander *et al.*, 2013), and high-risk pregnancies have not been excluded (Ghosh *et al*., 1971; Singhal *et al.*, 1991; Mathai *et al.*, 1996; Kandraju *et al.*, 2012).

The first major study on intra-uterine growth was by Ghosh *et al.* (1971) Growth charts for weight,

length and head circumference from 28-44 weeks of gestation were constructed based on the prospective measurements at birth of about 5000 consecutive single live born babies with known gestational age delivered at Safdurjang Hospital Delhi (Ghosh *et al.*, 1971). In comparison to the available Western growth charts (Lubchenco *et al.*, 1963, Usher and Mclean, 1969), weight curve of Indian babies showed a downward divergence starting from 34-36 weeks of gestation, while the length and head circumference showed a similar divergence from 37-38 weeks. This was attributed to interference in the placental 'supply line' by factors such as maternal under-nutriton, anaemia, toxaemia etc.

Similar findings were reported in a study conducted at All India Institute of Medical Sciences (AIIMS), New Delhi (Singh *et al*., 1974) (Table 3). In 1990, Mohan *et al*., published another prospective study from Safdurjang Hospital (Mohan *et al*., 1990). In this study, GA was confirmed after birth by Ballard's scoring (Ballard *et al*., 1977), and babies born to diabetic or toxaemic mothers were excluded. Weight and length curves were noted to diverge from those of Western populations from about 35 weeks onwards. No secular trend was noted compared to the previous study from the same hospital (Ghosh *et al*., 1971). At AIIMS also, birth weight data were again collected prospectively and plotted against gestational age (Singhal *et al*., 1991). A small trend towards improvement in mean birth weight was noted between 34-41 weeks, in comparison to the previous study from the same Institute (Singh *et al*., 1974).

The other four studies are from southern India (Table 3). Mathai *et al* have constructed birth weight and gestational age charts based on data from more than 11,000 babies born at CMC, Vellore (Mathai *et al*., 1996). The authors have presented separate centile charts and curves for male and female babies and for first born and later born babies. Kumar *et al*., from the same institution have published more recently (Kumar *et al*., 2013). Of note, customization was done for maternal height as an important variable that affected birth weight, by subtracting or adding 135 g to the birth weights of babies born to mothers with height < 151 cm or > 158 cm.

The study by Kandraju *et al*., is based on data from > 30,000 deliveries (Kandraju *et al*., 2012). Birth weights of Indian babies were lower than international charts across all gestational ages from 24-42 weeks. Both 10th and 90th centiles were lower than those in Lubchenco's charts, commonly used for classifying babies as small appropriate or large for gestational age (SGA, AGA and LGA). The authors concluded that using international rather than Indian growth charts would result in over diagnosis of SGA and under diagnosis of LGA babies.

Another notable recent Indian study is based on data from nearly 16,000 births at a rural block in Tamil Nadu (Alexander *et al*., 2013). This study provides data on babies born to healthy rural women, unlike all other studies that are from tertiary hospitals, which serve as referral centres for high-risk pregnancies. Data for deaths under 2 months of age was also collected. The authors noted that mortality was higher in babies with birth weight below the 3rd and above the 97th centiles of the study data. The 97th-centile here was at 3.8 kg as compared to WHO 97th centile of 4.3 kg. Therefore, assigning risk status to Indian babies based on WHO/Intergrowth birth weight centiles may lead to under-estimation of the risk to babies who are LGA according to Indian reference data.

The conclusions from these Indian studies can be summarized as follows:

- Foetal growth pattern of Indian babies from northern, southern, urban as well as rural regions is more or less similar to each other, but significantly different from widely used international charts.
- Studies from the same institutions published after a gap of 15-20 years (Ghosh *et al.*, 1971 and Mohan *et al.*, 1990; Singh *et al.*, 1974 and Singhal *et al.*, 1991; Mathai *et al.*, 1996 and Kumar *et al.*, 2013) have yielded very similar data, lacking any definite secular trend in foetal growth and birth weight.
- Erroneous interpretation of foetal growth status, and mis-classification at birth into SGA, AGA and LGA can result if international growth charts are used. This could lead to unwarranted investigations or hospitalization of infants who are AGA according to the references based on the local population, but mis-classified as 'SGA'

Table 3: Summary of Indian studies presenting birth measurements against gestational age

S.No.	Authors; year of publication	N; Population	Study design; GA estimation	Exclusion criteria	Parameters measured; GA range	Data presentation	Results and conclusions
1	Ghosh S *et al*; 1971	5031 liveborn singletons at Safdurjung Hospital, Delhi	Prospective; GA assessed by LMP alone	LMP not known, congenital anomalies, maternal diabetes	BW, length and HC;28-44 wk ± 1 SD	Combined (both genders) curves depicting mean	In comparison to western charts, flattening of curves noted in late gestation, attributed chiefly to poor maternal nutrition
2	Singh M *et al*; 1974	3550 liveborn singletons at AIIMS, Delhi	Prospective; GA by LMP and clinical scoring at birth	LMP not known or not matching with clinical score, congenital anomalies, maternal diabetes, toxemia	BW;30-44 wk	Tables of mean and SD of BW against GA for girls and boys separately and combined, combined centile curve (10^{th}-90^{th})	BW curve was similar to Ghosh's and divergent from western charts. Authors concluded that inclusion of high risk mothers, low SES and low maternal nutrition led to lower mean BW
3	Mohan M *et al*; 1990	2875 liveborn singletons at Safdurjung Hospital, Delhi	Prospective; GA by LMP & Ballard scoring	Congenital anomalies, maternal diabetes, toxemia	BW, length HC and Ponderal Index;28-42 wk	Combined data for both genders, mean, SD, smoothed centiles from 3^{rd}-97^{th}	Curves similar to Ghosh's showing lack of improvement in fetal growth over a period of 20 yrs
4	Singhal PK, *et al*; 1991	4748 liveborn singletons at AIIMS, Delhi	Prospective; GA by LMP and clinical assess-ment at birth	None	BW;26-44 wk	Combined data for both genders, mean, SD, smoothed centiles from 3^{rd} to 97^{th}	Trend towards higher BW from 37 wk onwards compared to previous AIIMS study. Recommendation of revising local intrauterine charts every 10-15 yrs
5	Mathai M, *et al*; 1996	11645 liveborn singletons at CMC, Vellore	Retrospective 4yr data; Best estimate of GA by LMP, early antenatal exam & USG	GA not known	BW; 33-42 wk	Separate centile charts and curves for male and female, first and later born infants	Gender, parity and maternal height were significantly correlated with birth weight. Girls were 113g lighter than boys, and first born 130g lighter than later born.

6	Kandraju H *et al*; 2012	31,391 liveborn singletons at a tertiary care hospital at Hyderabad	Retrospective 10 yr data; GA by LMP or early pregnancy USG	GA not known or < 24 or > 42 wk	BW, HC and length; 24-42 wk	Smoothed centile curves (5^{th} -95^{th}) using LMS method for BW, length and HC, separately for male and female newborns	Compared to older Indian studies, mean BW and lengths were higher 34 wk onwards. In comparison with Lubchenco's charts, 10th and 90th centiles were lower. Use of Lubchenco's charts leads to many AGA infants labelled as SGA, and LGA infants being overlooked.
7	Kumar VS *et al*; 2013	19501 live-born singletons at CMC, Vellore	Retrospective 15 yr data; Best estimate of GA by LMP,	Mothers with obstetric risk factors, age <20 or >39 yr	BW adjusted for maternal height; 24-42 wk	Separate 'standards' for male and female, first and later born infants. Addition or subtraction of 135 g to early antenatal exam & USG BW of babies born to mothers with height <151cm &> 158 cm, respectively	Including normal mothers with no antenatal risk factors-'Standards'; appropriate statistical modelling. The increase in mean BW between years 1996 to 2010 was only 61 g. The authors recommend use of these charts for classifying Indian term & pre-term newborns as LGA, SGA and AGA.
8	Alexander AM *et al*; 2013	15,994 liveborn singletons at a rural block of 82 villages in Tamil Nadu	Retrospective 9 yr data; GA by LMP (majority) or early pregnancy USG	Mothers with medical or obstetric risk factors including stunting and anemia	BW, mortality in first 2 months of life; 32-42 wk	Smoothed centile curves (3^{rd} -97^{th}) using LMS method for BW, separately for male and female newborns; Comparison of under 2 month mortality in babies in different BW categories	All other Indian charts are from tertiary hospitals that serve asobstetric referral units. This study provides descriptive charts based on babies born to low risk rural women with good antenatal care. Flattening of BW curve at later gestation and lower median BW as compared to Western charts was noted. Higher mortality rates in SGA and LGA (>3.8 kg).

Abbreviations: AIIMS- All India Institute of Medical Sciences, CMC- Christian Medical College, GA-gestational age, LMP-last menstrual period, BW- birth weight, HC-head circumference, SES- socioeconomic status, SGA-small for gestational age, LGA- large for gestational age, AGA-appropriate for gestational age

by an international reference. On the other hand, the increased risk of perinatal morbidity in infants who are LGA as per local population based reference charts, but 'AGA' according to international charts may be overlooked.

International Foetal Growth Standards: The 'One Size Fits All' Approach

The INTERGROWTH-21st Project: A Summary

The INTERGROWTH-21st is a multi-centre study conducted in eight countries, including India. It had 3 components: Foetal Growth Longitudinal Study (FGLS), Newborn Cross-Sectional Study (NCSS) and Preterm Postnatal Follow-up Study (PPFS) (Villar J *et al.*, 2013). As part of FGLS, foetal anthropometric measurements were made prospectively from 14 weeks to birth in a cohort of women with adequate health and nutritional status, at low risk of intra-uterine growth restriction (Villar J *et al*., 2013).

The aim was to generate international standards of foetal growth; similar to the widely accepted WHO Multicentre Growth Reference Study (MGRS) child growth standards (de Onis *et al.*, 2004) (Box 2).

This is a great example of an elegantly designed international prospective observational study. Each and every aspect of the study, from site selection to defining eligibility and withdrawal criteria, standardization of USG measurements, statistical methods and reporting of data has been conducted following high methodological standards (Villar J *et al.*, 2013; Purwar *et al.*, 2013).

Out of more than 13,000 women commencing antenatal care at less than 14 weeks, only 4607 (35%) were found to be eligible, reflecting on the highly selective inclusion criteria. Of these, 625 women were enrolled from Nagpur, India. As per their initial premise, the investigators have reported that there was good inter-site agreement in foetus growth (Villar J *et al.*, 2014).

The second component of the INTERGROWTH-21st project was the Newborn Cross-Sectional Study (NCSS). Anthropometric data was obtained from 20,486 newborns from the same eight sites as in the FGLS study. Sex-specific centile curves (3rd to 97th) for weight, length, and head circumference for gestational age at birth have been

Box 2. The INTERGROWTH-21st Foetal Growth Longitudinal Study (Papageorghiou *et al.,* 2014)

- Aimed to generate international foetal growth standards similar to WHO MGRS child growth standards
- Based on the premise that foetal growth across populations would be similar, if nutrition and health needs are met and environmental constraints are low
- Conducted in 8 countries- Brazil, China, India, Italy, Kenya, Oman, UK and USA
- Highly standardized protocols for site selection, eligibility and withdrawal of participants and ultrasonography techniques
- Eligibility criteria included age ≥18 and <35 years, BMI ≥18.5 and <30 kg/m2, height ≥153 cm, singleton pregnancy, known LMP with regular cycles, no relevant past medical or obstetric history, no evidence of socio-economic constraints, no alcohol, tobacco or recreational drug intake, no hypertension or anaemia in current pregnancy
- Gestational age (GA) assessed by 2-step process. In women who were 9+0 to 13+6 weeks pregnant by LMP, GA was confirmed with crown–rump length (CRL) measurement by USG. LMP was considered valid and the women were included only if difference between CRL and LMP estimates was ≤ 7 days
- All women received standardised antenatal care package
- USG done six times at 5 ±1 week intervals, i.e.14–18, 19–23, 24–28, 29–33, 34–38 and 39–42 weeks
- 3rd to 97th centile curves published for AC, HC, F, BPD and occipito-frontal diameter from 14-40 weeks for 4607 foetuses

constructed from 33 to 42 weeks of gestation (Villar *et al.,* 2014).

Limitations in Recommending the use of INTERGROWTH-21st Foetal Growth Standards in India

The study has certain limitations, that prevent us from recommending the use of these charts as the default charts in the USG machines available in India. The authors have reported good inter-site agreement, but these inter-site comparisons have actually been made only for two foetal measurements—crown-rump length (CRL) between weeks 9 to 13 and HC between weeks 14 to 40, and not for other measurements, especially AC and BPD, which are used for calculating estimated foetal weight (Villar *et al*., 2014). Both CRL and HC of Indian babies were the lowest among all sites. Based on SD of the combined data from all sites, CRL of Indian newborns was at -0.36 SD at 13 weeks and 6 days, and HC at -0.58 SD between 34-40 weeks. At birth, the HC was again lowest among Indian babies (33.1±1.2 cm or at -0.55 SD) compared to the combined average of 33.9 ±1.3 cm.

Although, not specifically highlighted in the papers, the birth weight of the Indian babies (2.9 ± 0.4 kg) was also substantially lower than the combined average (3.3 ± 0.4 kg) (Villar *et al.,* 2014). This birth weight is at -1 SD of the combined average. These differences are by themselves striking, but become even more so, when we consider that the pregnant women selected were from perhaps the top 10th centile of Indian population, in terms of their nutritional and educational status, affluence, and access to healthcare (Purwar *et al.*, 2013). If the Indian babies delivered to these lowest risk women are at -0.55 SD for head circumference and -1SD for birth weight, we can well imagine that a majority of Indian foetuses would be falling short of these standards.

Another pertinent point is that the stringent eligibility criteria employed in this study (Villar *et al.,* 2013) make their validity for a significant proportion of Indians doubtful. Women with height ≤ 153 cm and vegetarians have been excluded. From a Western perspective, these may be seen as food faddism or short stature, but for India, where a third of the population is vegetarian (https://en.wikipedia.org/wiki/Vegetarianism_by_country), and women's mean height at 20 years in Indian states ranges from the lowest of 149.1 cm in Meghalaya to the highest of 154.6 cm in Jammu & Kashmir, these exclusion criteria are not valid (Deaton, 2007).

At the same time, some factors that increase the risk of foetal macrosomia have not been excluded. The BMI cut-off for exclusion is 30 kg/m^2, whereas for Indians, BMI cut-offs for overweight and obesity are ≥23 and 25, respectively (Misra *et al.,* 2009). Women overweight/ obese by Indian cut-off were found to have increased risk of gestational hypertension, gestational diabetes and LGA babies in a recent study (Aziz *et al.,* 2014). Similarly, gestational diabetes mellitus (GDM) is not listed as exclusion criterion, either at initial enrolment or during follow-up (Villar *et al.,* 2013, Purwar *et al.,* 2013). Recent studies indicate that GDM affects 35-40% of pregnant women in India (Gopalakrishnan *et al.,* 2015, Arora *et al.,* 2015), and has clear association with LGA. These are serious concerns, as this may have led to the inclusion of 'probably abnormal' larger foetuses amongst the 625 Indian foetuses in the study. At the same time, many 'normal' smaller foetuses might have been excluded, as foetal weight has a direct correlation with maternal height (Mathai *et al.,* 1996, Kumar *et al.,* 2013). Besides non-exclusion of GDM, another generic concern about the Intergrowth-21st data is that the information about maternal gestational weight gain is also not forthcoming. In recent studies from several countries, excessive gestational weight gain has been noted in approximately 35-65% of pregnant women, across all BMI categories. This has been associated with significantly higher risk of foetal macrosomia and LGA, independent of maternal pre-pregnancy BMI (Li *et al.,* 2015; Chen *et al.,* 2015; Dzakpasu *et al.,* 2015; Asvanarunat, 2014).

The limitations in recommending the use of INTERGROWTH-21st Foetal Growth Standards in India are summarized in Table 4.

Hence, if the foetal biometric parameters based on INTERGROWTH-21st FGLS are included as default parameters in USG machines, there is likely to be over-diagnosis of FGR and under-diagnosis of foetal macrosomia, both with potentially significant clinical repercussions. A diagnosis of FGR may lead to undue stress in the mother; it may also lead to unwarranted interventions and cost, including hospitalization, investigations, and experimental

Table 4: Limitations in recommending the use of INTERGROWTH-21st Foetal Growth Standards in India

1.	Lack of true inter-site agreement
	• Inter-site comparison has not been provided for abdominal circumference (AC) and bi-parietal diameter (BPD), which are used for calculating estimated foetal weight
	• Crown-rump length (CRL) between 9-13 weeks and head circumference (HC) between 14-42 weeks of Indian foetuses is the lowest among all sites
	• At birth, weight of Indian babies is at -1 SD and HC at -0.55 SD of the combined average
2.	Exclusion of women with height ≤153 cm, when the mean height of Indian young women ranges from the lowest of 149.1 cm in Meghalaya to the highest of 154.6 cm in Jammu & Kashmir
3.	Non-exclusion of women with risk factor for foetal macrosomia
	• The BMI cut-off for exclusion is 30 kg/m^2, whereas for Indians, BMI cut-offs for overweight and obesity are 23 and 25 kg/m^2, respectively.
	• Gestational diabetes mellitus
	• Excessive gestational weight gain

'therapies', iatrogenic prematurity or caesarian section. On the other hand, missing or overlooking foetal macrosomia can also increase perinatal morbidity and mortality.

In the Newborn Cross-Sectional Study (NCSS) component of the INTERGROWTH-21st project also the mean weight, length as well as head circumference of the Indian babies (n=2493) was lower than that of babies from all the other seven countries (Villar *et al.,* 2014). Birth weight was at -1 SD of the combined mean, and birth length and head circumference were at -0.6 SD of the combined mean. Thus, use of the NCSS size at birth charts would also not be appropriate in Indian newborns.

The Regulatory Effect of Maternal Constraint on Foetal Growth: When Can We Expect Size of Indian Foetuses to Match Up With the International Standards?

Maternal body size is strongly associated with size of the offspring at birth. This is termed as 'maternal constraint' and regarded as an important *adaptive evolutionary mechanism* to reduce the risk of obstructed delivery (Vasak B *et al.,* 2015). In the cross-sectional component of the Intergrowth-21st Consortium study (n=51,200), maternal short stature is the strongest predictor of neonatal stunting and wasting (Victora *et al.,* 2015). Analysis of over a million singleton births between 28-43 weeks of gestation from the Netherlands Perinatal Registry indicated that perinatal mortality was the least in babies with birth weight between 80th and 84th centiles of the Dutch reference curves. It was concluded that the 'optimal' birth weight is higher than the median, but maternal constraint restricts foetal growth (Vasak B *et al.,* 2015). Thus, it follows that a secular trend in foetal growth will follow that in maternal size.

What Is The Expected Timeline for These Secular Changes?

In a recent large cross-sectional analysis of data from England and Wales, it was noted that the birth weight of offspring of South Asian women born in UK (i.e., second or later generation immigrants, presumably with better living conditions in their childhood than first generation immigrants) was actually somewhat lower than the offspring of first generation immigrant women (Leon DA and Moser KA, 2012). It was concluded that significant increase in the birth weight of South Asian newborns in UK is unlikely to occur in the next few decades. The secular trend in the mean height of Indian women is estimated at approximately 0.22 cm/ decade (Mamidi *et al.,* 2011). At this rate, it would take several centuries to close the approximately 10 cm gap in the median height of South Asian and Caucasian women. Hence, it would be imprudent to imagine that the foetal growth parameters of the average South Asian foetus would match those of the Western population in foreseeable future.

Conclusions

Monitoring foetal growth by USG is an integral component of antenatal care. However, the purpose is defeated if the references or standards are not

representative of the population, old or methodologically inaccurate. Of the available foetal ultrasonography based Indian foetal growth references, the data from the paper by ICMR multi-centric study (Berry *et al.*, 1992) is fairly good, and is being used by many ultrasonologists and obstetricians. However, there are limitations in that gestational age assessment is not very accurate, curves have been provided only for two foetal dimensions, and the data is nearly three decades old. Among the birth size based foetal growth charts, regional preference is seen among the neonatologists and obstetricians for the use of particular charts. For example, AIIMS charts (Singh *et al.*, 1974; Singhal *et al.*, 1991) are commonly being used in north India. These serve as reference tools for classification of newborns into AGA, SGA and LGA, but cannot be used for foetal growth monitoring.

The Intergrowth-21st study provides both foetal biometry and neonatal anthropometry based foetal growth standards. Although the study scores high in terms of its magnitude, study design and standardized methodology, the applicability of these standards to Indian foetuses has several limitations. A major problem is that the representation of population from Indian sub-continent is low. Secondly, the contention that foetal growth was similar irrespective of nationality or ethnicity, although attractive and biologically plausible, remains dubious and unconvincing. There is an obvious discrepancy in size, so much so, that the Indian newborns have the lowest weight, length as well as head circumference among all the eight countries.

More careful debate and discussion on the published and unpublished data of the Intergrowth-21st study are required before thinking of considering these as universal standards. Their immediate application without further discourse and adaptation is not desirable, as this will lead to over-classification of foetal growth restriction. This will lead not just to undue concern in the parents, but also has the potential for causing harm, by introduction of unsubstantiated therapies for improving foetal growth, or unnecessary hospitalization or investigations at birth.

It is evident that among the multitude of foetal growth charts available, none fulfils the requirements of an ideal foetal growth chart for our country. For a nation of our magnitude and diversity, it is desirable that we develop our own foetal growth standards based on carefully selected subjects, using robust techniques for tracking foetal biometry, and strong statistical methods.

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