J. Fetal Med. (September 2021) 8:177–184
https://doi.org/10.1007/s40556-021-00312-8

ORIGINAL ARTICLE

Impact of Selection of Growth Chart in the Diagnosis of Suboptimal Fetal Growth and Neonatal Birthweight and Correlation with Adverse Neonatal Outcomes in a Third Trimester South Indian Antenatal Cohort; A Prospective Cross-Sectional Study

Seneesh Kumar Vikraman[1] · Rinshi Abid Elayedatt[2] · Aditi Dubey[1,3] · Nithya Elango[4]

Received: 23 April 2021 / Accepted: 3 July 2021 / Published online: 16 August 2021

Abstract Objectives: To compare fetal and neonatal growth charts pertaining to different models (population-specific, universal reference, universal standard and fully customised) in detecting suboptimal fetal growth in the third trimester. Methods: This was a prospective observational study conducted at two fetal medicine centers. After applying the inclusion criteria [singleton pregnancies between 28 and 40 weeks, verified dates and estimated fetal weight (EFW) $\leq$ 25th centile as per the Hadlock chart], 292 women were consecutively recruited. Four fetal growth charts (Hadlock, Intergrowth, fully customised GROW, Sonocare) and three neonatal charts (Fenton, Intergrowth and fully customised GROW) were used in the study. The EFW and birthweight centiles were categorized into three groups: $<$ 3.0, 3.1–10th and $>$ 10th centiles. The charts were evaluated by their ability to detect pregnancies with uteroplacental insufficiency and/or development of adverse neonatal outcomes in the third trimester. Results: Significant difference was noted between the fetuses/neonates assigned as $<$ 3rd centile (Hadlock-9.3%, Sonocare-4.8%, Intergrowth- 6.8% and the fully customised GROW-6.5%) and the neonatal charts (Fenton-18.5%, Intergrowth-20.2% and fully customised GROW- 13.4%). At a cut-off of 3rd centile, the GROW chart had the highest sensitivity (84.2%) followed by Intergrowth (78.9%), Hadlock (70.37%) and Sonocare (64.29%). Similarly, for a cut-off of $<$ 10th, the sensitivity was GROW 70.27%, Sonocare 64%, Intergrowth 60.8% and Hadlock 50%. Amongst the neonatal charts, fully customised GROW chart had the greatest detection rate ($<$ 3rd = 74.36%, $<$ 10th = 70.27%). However, there was no significant difference between the charts in the detection of pregnancies with suboptimal fetal growth associated with uteroplacental insufficiency and/or adverse neonatal outcomes. Conclusion**:** Despite substantial discrepancy between the growth charts in diagnosing fetal smallness, adding multivessel Doppler negates significant differences between them in diagnosing suboptimal fetal growth associated with uteroplacental insufficiency and adverse neonatal outcomes.

Keywords Fetal growth restriction · Suboptimal fetal growth · Growth Charts · Growth standards · Reference charts · Multivessel Doppler · Third trimester growth scan · Customised growth chart

Introduction

Fetal growth restriction (FGR) is the state of constrained fetal growth in utero, wherein the genetic growth potential of the fetus has not been attained due to placental and non-placental pathologies [1, 2]. Practically and clinically, constrained fetal growth in utero is diagnosed from the suboptimal centiles of the gestational age-dependent biometric parameters, impaired growth velocity and abnormal indices of the multivessel Doppler performed during the prenatal ultrasound examination [3]. The identification and red flagging of pregnancies with impaired fetal growth is

✉ Seneesh Kumar Vikraman
drseneeshkv@gmail.com

[1] Consultant in Maternal-Fetal Medicine, ARMC AEGIS hospital, Bypass road, Perinthalmana, Malappuram, Kerala 679322, India

[2] Fetal Medicine, Consultant in Maternal-Fetal Medicine, Nahas Hospital, Malappuram, Kerala, India

[3] Fellow in Fetal Medicine, ARMC AEGIS hospital, Perinthalmana, Kerala, India

[4] Fetal Medicine, ARMC, Salem, Tamil Nadu, India

essential to escalate surveillance, pre-decide the health setting for perinatal care, and schedule timing for delivery [4, 5]. This is particularly relevant in case of late onset FGR, where identification of pregnancies with suboptimal fetal growth is the chief concern [6].

Growth charts constitute an essential tool in the clinical armamentarium of growth assessment by providing nomograms of biometric variables facilitating the interpretation of their adequacy[7]. Inspite of the progressive understanding of the phenotypes of placenta-based FGR and the introduction of a refined objective criteria for its diagnosis, the choice of fit-for-all growth chart is debatable and elusive [8, 9]. The heterogeneity in the design and constructional methodology of growth charts evades the efforts for contriving a universally acceptable standard or reference [10, 11]. The choice of growth charts has the potential to impact the prenatal diagnosis of fetal growth restriction. The impact of selection of growth charts with/without added multivessel Doppler necessitates introspection in their ability to identify pregnancies with suboptimal fetal growth and adverse neonatal outcomes especially in a low resource setting.

The objective of our study was to evaluate fetal and neonatal growth charts pertaining to varying conceptual models (population-specific, universal reference, universal standard and fully customised) in a south Indian antenatal population during routine third trimester ultrasound examination for growth assessment and correlating them with the presence of uteroplacental insufficiency and adverse neonatal outcomes. By interrogating a population with a high prevalence of fetal growth restriction (FGR) and non-uniform distribution of anthropometric characteristics, this study purposedly aims at providing information of immense practical utility for clinicians involved in perinatal care to optimize the diagnosis of FGR and their evidence-based management.

Materials and Methods

This was a prospective study conducted from 1st January 2019 till 30th March 2020, at two institutions- ARMC AEGIS hospital, Perinthalmana and Nahas hospital, Parapanagadi; both tertiary level, private healthcare institutions with dedicated obstetric, assisted reproduction, fetal medicine and advanced neonatal intensive care (NICU) facilities in the district of Malappuram, Kerala, India. The study protocol was approved by the institutional review board (ARMC/HRD/311/10/2019).

The study sample was constituted by women receiving regular antenatal care from the above institutions recruited in a consecutive fashion. All women were of south Indian origin belonging to mid-to-high socioeconomic class. An informed written consent was obtained from all women. The inclusion criteria were singleton pregnancies seeking antenatal care in the above institutions, gestational age between 28 and 40 weeks, availability of a dating scan done between 8–14 weeks of gestation and the estimated fetal weight (EFW) $\leq$ 25th centile on the Hadlock chart. The exclusion criteria were pregnancies with known fetal chromosomal or morphological abnormalities. An inclusion criteria of EFW $\leq$ 25th centile on the Hadlock chart was used for three reasons: (1) this was the initial chart used in the ultrasound reporting software, (2) the low incidence of adverse neonatal outcomes genuinely related to FGR in fetuses weighing $> 25^{th}$ centile [12], and (3) a previous study that had shown that the Hadlock chart (amongst the charts used in the present study) had the greatest sensitivity for detecting fetuses with EFW $\leq 10^{th}$ centile in our population [13].

All ultrasound examinations were performed using a GE Voluson E6 radiance BT18 unit, using a transabdominal curvilinear transducer with a frequency of 1–5 MHz (C1-5-D) by two fetal medicine specialists (SK and RAE). The fetal biometry was obtained adhering to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) [14]. The estimated fetal weight (EFW) of each fetus was calculated from the head circumference (HC), abdominal circumference (AC) and the femoral diaphyseal length (FL) using the Hadlock III formula: Log10 (weight) = 1.326–0.00326 * AC*FL + 0.0107*HC + 0.0438*AC + 0.158*FL [15]. A single set of measurements was obtained from each woman. Multivessel Doppler (Umbilical artery, Uterine artery and middle cerebral artery) was performed in all cases.

In our study, we used four prenatal charts and three postnatal charts (Table 1). The EFW centiles obtained from these charts was categorized into three groups for comparative and correlation purpose:< 3.0 centile, 3.1–10th centile and > 10th centile. The neonatal birthweight centiles were categorised in a similar fashion. The presence of uteroplacental insufficiency [Uterine artery pulsatility index (PI) > 95th centile, Umbilical artery PI > 95th centile, middle cerebral artery PI < 5th centile, cerebroplacental ratio < 5th centile] and/or the development of adverse neonatal outcomes was considered as a single composite variable for correlational purpose. Adverse neonatal outcomes were defined as one or more of the following events: the need for emergency cesarean section for fetal distress, NICU admission > 48 h, development of fetal hypoglycemia, hyperbilirubinemia and/or thrombocytopenia. The prenatal and postnatal charts were evaluated using the parameters of sensitivity, specificity, positive and negative predictive values.

Descriptive and inferential statistical analysis was performed in our study. Results on continuous variables are

Table 1 Growth charts used in our study

Growth Chart	Details
A. PRENATAL	
1. Hadlock [16]	Growth reference, constructed from a cross-sectional data of 392 women in Texas, US, published in 1991
2. INTERGROWTH-21 [17, 18]	Growth standard, highly prescriptive in nature; based on the concept that under ideal conditions of sound health, adequate nutrition, proper educational status, and with minimal environmental constraints, ethnic or genetic influences would be minimal (less than 4%). The study was conducted in eight countries across the world, with India being one of them
3. GROW [19]	The fully customized prenatal standards from the Perinatal institute were applied to our data. This uses a software known as GROW (gestation related optimum weight) [Gestation Network; Birmingham, UK, www.gestation.net]. In this software, maternal characteristics are entered to calculate an individually adjusted weight at 40.0 weeks. This predicted weight is then combined with a standard proportionality curve to provide a GROW curve. The Hadlock EFW curve is used for this purpose. It is converted from a weight- by-gestation curve to a percent of term weight by gestational age curve. Full customization was used in our study
4. Sonocare [20]	A population specific growth chart developed from a local south Indian population
B. POSTNATAL	
1. Fenton [21, 22]	The Fenton's chart is one of the most common neonatal charts used across the world including India. It has the advantages of being based on more recent data on size at birth, harmonizes the preterm growth chart with the new WHO Growth Standards, smoothens the data between the preterm and WHO estimates while maintaining integrity with the data from 22 to 36 and at 50 weeks, provides sex specific growth curves, and re-scales the chart x-axis to actual age rather than completed weeks, to support growth monitoring
2. INTERGROWTH 21st [17, 18]	It is based on integrated monitoring of growth and development from pregnancy to school age by providing a single international standard. Described above
3. GROW [19]	Fully customised standard (adjusted to Indian ethnicity, weight, height and parity) from the Perinatal institute; GROW customised neonatal growth standard (GROW; gestation network; Birmingham, UK)

EFW- estimated fetal weight, GROW- gestation related optimum weight, UK- United Kingdom, WHO- World Health Organization, US- United Stated

presented as mean ± standard singleton and median with interquartile range (IQR). The Chi-square and Fisher Exact tests were used to assess the significance of study parameters on a categorical scale between two or more groups, and non- parametric setting for qualitative data analysis. Statistical software SPSS (Statistical Package for the Social Sciences Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.), and R environment version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/.) was used for data analysis.

Results

During the study period from 1st January 2019 till 30th March 2020, 292 women fulfilled our inclusion criteria, all south Indian. The median age of our study group was 24 years [IQR, 21- 28]. The median height was 154 cm [IQR, 150.5–157; range 36 (141–177)], the median weight was 54 kg [IQR, 46–60; range 55 (33–88)] and the mean BMI was 22.7 ± 4.23 kg/m^2. In our study sample, 39.7% (n = 116/292) were nullipara.

The median gestational age was 34 5/7 weeks, range 7.5 weeks [31 1/7–38 6/7 weeks]. Preterm birth (< 37 weeks) was observed in 10.9% (n = 32/260) pregnancies. Low birth weight (birthweight < 2500 g) was noted in 33.2% (n = 97/292). In our study group, 15.4% (n = 45/292) had a BMI of less than 18.5 kg/m^2.

All pregnancies had a live birth. In 23.9% (n = 70/292) pregnancies, there were Doppler signs of uteroplacental insufficiency in the prenatal ultrasound. Adverse neonatal outcomes were noted in 4.5% (n = 13/292) of the pregnancies with 4.1% (n = 12/292) of them having both adverse neonatal outcomes and uteroplacental insufficiency.

Tables 2, 3 and 4 summarises the relative performance of the prenatal and postnatal charts of our study by their ability in detecting pregnancies with adverse outcomes.

Discussion

Our study showed, firstly, that when the prenatal growth charts were used alone without applying hemodynamic parameters, they differed significantly from each other in assigning fetal smallness, irrespective of the cut-off used

Table 2 Distribution of fetal estimated weights and neonatal birthweights in different categories of centiles for comparative purpose

Category of EFW/neonatal weight centiles (all figures in %)			
	< 3rd centile	3-10th	> 10th
A. Prenatal *			
Hadlock	9.6	20.9	69.5
Sonocare	4.8	13.4	81.8
Intergrowth$^{\delta}$	6.8	9.2	83.9
GROW$^{\delta\delta}$	6.5	6.2	87.3
B. Postnatal #			
Fenton	18.5	31.8	49.7
Intergrowth $^{\delta}$	20.2	25.3	54.5
GROW $^{\delta\delta}$	13.4	15.4	71.2

*The distribution between the prenatal charts was significantly different ($P < 0.001$, significant. Chi-Square test)

The distribution between the postnatal charts was significantly different ($P < 0.001$, significant. Chi-Square test)

δ The difference in the category wise distribution was significantly different between the prenatal chart vs postnatal charts of Intergrowth ($p = < 0.001$ for < 3rd, 3–10th, > 10th respectively)

δδ The difference in the category wise distribution was significantly different between the prenatal chart vs postnatal charts of GROW ($p = 0.004$, < 0.001,0.014 for < 3rd, 3-10th, > 10th respectively)

EFW- estimated fetal weight, GROW- gestation related optimum weight

(< 10th or < 3rd centiles). Further, a significant difference was noted between the prenatal and the neonatal charts, and amongst the neonatal charts. Secondly, once the hemodynamic parameters (multivessel Doppler) were added, the difference between the prenatal and postnatal charts in identifying pregnancies with uteroplacental insufficiency and/or adverse outcome due to suboptimal fetal growth was not significantly different. Thirdly, the customized growth chart showed enhanced sensitivity for detecting pregnancies with adverse neonatal outcomes while the population-specific growth chart had a propensity to underestimate suboptimal fetal growth. This observation, however, lacked statistical significance.

In a previous study, we had demonstrated the wide variation between the commonly used fetal and neonatal growth charts in assigning fetal smallness without considering multivessel Doppler assessment [13]. In the present study, we showed a considerable difference between the prenatal vs postnatal chart (such as Intergrowth prenatal vs postnatal) as well, with much higher detection in the latter (Table 2). In general, the prenatal detection of fetal smallness is impaired due to the interplay of factors such as errors in estimating fetal biometry and restrictive ability of single growth scan to detect falling growth velocity near term [23–25].

The differences between the charts is explained by their varying methodology and the anthropometric difference

Table 3 Distribution of fetuses/neonates (n = 292) in the two EFW/BW centile categories of < 3rd centile and 10th centile and association with abnormal parameters (UPI and adverse neonatal outcomes)

	< 3rd centile * No UPI and no adverse outcomes	< 10th centile # UPI and/or adverse outcomes	No UPI and no adverse outcomes	UPI and/or adverse outcomes
Prenatal *				
Hadlock	8 (40%)	19 (32.2%)	43 (47.3%)	43 (32.8%)
Sonocare	5 (25%)	9 (15.3%)	19 (20.9%)	34 (26%)
Intergrowth	4 (20%)	15 (25.4%)	18 (19.8%)	28 (21.4%)
GROW	3 (15%)	16 (27.1%)	11 (12.1%)	26 (19.8%)
Postnatal #				
Fenton	25 (46.3%)	29 (53.7%)	86 (58.9%)	60 (41.1%)
Intergrowth	24 (40.7%)	35 (59.3%)	78 (59.1%)	54 (40.9%)
GROW	10 (25.6%)	29 (74.4%)	37 (45.1%)	45 (54.9%)

BW = birthweight, EFW = Estimated fetal weight, GROW = Gestation related optimal weight, UPI = uteroplacental insufficiency

*The charts did not significantly differ in identifying severe small fetuses (< 3rd centile) with adverse outcomes ($p = 0.904$ for prenatal charts, not significant; $p = 0.240$ postnatal charts, not significant)

The charts did not significantly differ in identifying small fetuses (< 10th centile) with adverse outcomes

($p = 0.204$ for prenatal charts, not significant; $p = 0.085$ postnatal charts, not significant)

Table 4 Performance of the growth charts in detecting pregnancies with adverse prenatal (uteroplacental insufficiency) and postnatal events (neonatal adverse events), < 3rd and < 10th as Cut-offs

A. < 3rd cut-off for EFW (prenatal charts) and neonatal weights (postnatal charts)					
	Sensitivity	Specificity	PPV	NPV	Accuracy
Hadlock	70.37	23.08	32.20	60	39.24
Intergrowth prenatal	78.95	26.67	25.42	80	39.24
Sonocare	64.29	23.08	15.25	75	30.38
GROW prenatal	84.21	28.33	27.12	85.08	41.77
Fenton	53.7	34.69	31.18	57.63	41.45
Intergrowth					
Postnatal	59.32	37.63	37.63	59.32	46.05
GROW postnatal	74.36	43.36	31.18	83.05	51.32
B. < 10th cut-off for EFW (prenatal charts) and neonatal weights (postnatal charts)					
	Sensitivity	Specificity	PPV	NPV	Accuracy
Hadlock	50	35.29	32.82	52.75	40.99
Intergrowth	60.87	41.48	21.7	80.22	45.50
Sonocare	64.15	42.6	25.95	79.12	47.75
GROW postnatal	70.27	43.24	19.85	87.91	47.75
Fenton	41.10	56.10	40	57.21	49.86
Intergrowth					
Postnatal	40.91	53.95	33.96	61.12	49.17
GROW postnatal	54.88	58.99	26.38	81.59	58.06

EFW- estimated fetal weight, GROW- gestation related optimum weight

between the races [26, 27]. The growth standards are constructed from a population of supposedly healthy pregnancies with the fetuses growing in an optimal manner in the apparent absence of any constraints [17, 28]. The study design for such charts is therefore longitudinal with highly prescriptive inclusion criteria. On the other hand, reference charts are derived from a mixed population of low-risk and high-risk pregnancies [29]. The study design is usually cross-sectional and descriptive with often less stringent selection criteria[16]. From a different perspective, growth charts may be based on the data from a small population confined within a particular ethnic group or geographical border, termed as population-specific charts. In contrast, universal growth standards are developed from the data obtained from several countries, spanning different racial groups [29]. Finally, growth charts adapted for variables affecting fetal growth (maternal ethnicity, parity, height and weight) are referred to as customized growth charts [30]. In our study, the anthropometric aspects of the women varied considerably as mentioned in the aforementioned description. This along with the varying conceptual methodology explains the differences in the performance of the charts. Poljak et al. observed considerable variation in the diagnostic accuracy of antenatal tools in identifying small fetuses when correlated to adverse neonatal outcomes[31]. Similarly, considerable differences have been highlighted between the growth charts in assigning fetal smallness when applied to different ethnic populations [32–38] and within the ethnic sub-groups in certain growth standards [13].

In this study, with the addition of hemodynamic parameters (multivessel Doppler), the discriminatory ability of the charts was not significantly different in identifying pregnancies with adverse neonatal outcomes. Placenta-based FGR produces longitudinal changes in feto-placental and utero-placental circulations, reflecting the site and the severity of the underlying pathological lesions [3]. Consequently, the Doppler assessment of these vascular territories should be added to the diagnostic workflow. The diagnosis of suboptimal fetal growth should not solely rely on fetal smallness as inferred from the growth charts but should include additional information from the multivessel Doppler and the dynamic changes in the fetal growth velocity [3, 8, 39, 40].

However, the selection of a particular growth chart has potential implications in the initial screening growth scans performed in low resource settings [41]. It may be prudent to use a growth chart with a reasonable detection rate so that fetuses with suboptimal growth which requires increased surveillance are not overlooked. This is particularly pertinent in the third trimester where the optimum diagnosis of late onset FGR is important considering its significant contribution towards stillbirth. The fully customized growth chart in our study showed enhanced performance in terms of sensitivity and moderate false positive rate in detecting pregnancies which had adverse

neonatal outcomes. This is explained by the wide variation of the anthropometric variables in our study group and the true discrimination of the constitutionally small fetuses by the customized growth chart. A similar observation was noted in a large cohort study of 10 450 south Asian women when customised charts were used [42].

In actual clinical practice, achieving a true balance between a reasonable sensitivity and false positive rate is challenging as each has its own implications. A chart with high sensitivity may lead to a high false positive rate leading to increased hospitalization and financial burden. A chart with low sensitivity may lead to the omission of numerous true positives thus predisposing to an increased risk of stillbirths in the population. International growth standards have been proposed to address these concerns [17, 18]. Despite the concept of a single prescriptive chart being novel, they have received criticism [36, 43]. The significant anthropometric differences between various ethnic groups precludes the use of a single international growth standard seemingly untenable [44, 45]. In India, fetal size has been shown to be different between urban and rural populations [46]. The use of customized growth charts offers a rationale option as it adjusts to various parameters influencing individual fetal growth including maternal anthropometry. Customization showed improved sensitivity and accuracy in detecting pregnancies with suboptimal fetal growth and adverse neonatal outcomes [19, 47]. In our study, customised growth charts demonstrated enhanced sensitivity though the observations lacked statistical significance. However, the benefits of using customized growth chart remains inconclusive [48–50].

The strength of our study was its prospective design, correlation with adverse neonatal outcomes and focus on the third trimester, where the diagnosis of suboptimal fetal growth remains a concern. Selection of a non-referral population as the study group aids better assessment of the performance of growth charts as screening tools. Growth charts pertaining to different models were selected. A fully customized growth chart was studied for the first time in an Indian population. The limitation of our study was the small sample size and consequently the small outcome group of fetuses with adverse neonatal outcomes, thus being underpowered for deriving definite conclusions. The incidence of adverse neonatal outcomes in our population was limited due to adherence to an algorithmic approach for managing FGR [1, 2]. Being a cross-sectional study, cases with repeat ultrasound examinations were few and was not included for analysis. Prospective studies with a larger sample size and incorporating different ethnic populations are recommended to introspect the clinical utility of growth charts as screening tools for suboptimal fetal growth in the third trimester. The role of biomarkers in addition to biophysical parameters in improving their diagnostic ability in the third trimester should be explored. The utility of using ethnicity-specific and chart-specific centiles should be introspected in view of the considerable variation in the anthropometry.

Implications for Clinical Practice

While there is no consensus on a single ideal growth chart, the sonologist must be aware of the strengths and limitations of the chart being used in their ultrasound workflow prior to drawing affirmative conclusions on the adequacy of the fetal growth. Diagnosing suboptimal fetal growth warrants a multimodal approach with biometry, its interpretation based on the growth chart, application of multivessel Doppler and assessment of longitudinal fetal growth.

Declaration

Conflict of interest The author declares that he has no conflict of interest.

Informed consent Informed consent was obtained from all women.

Human and animal standards It is not an experimental research involving humans or animals.

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