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ORIGINAL ARTICLE

Individualized fetal growth assessment: critical evaluation of key concepts in the specification of third trimester size trajectories

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Abstract

Objectives: To characterize second and third trimester fetal growth using Individualized Growth Assessment methods in a larger cohort of fetuses with normal neonatal growth outcomes.
Methods: A prospective longitudinal study of 119 pregnancies was performed from 18 weeks, MA, to delivery. Measurements of several 1D and 3D fetal size parameters were obtained from 3D volume data sets at 3–4 week intervals. Regression analyses were used to determine Start Points (SP) and Rossavik model ($P = c\ \{t\}^{k+st}$) coefficients *c*, *k* and *s* for each parameter in each fetus. Second trimester growth velocity reference ranges were determined and size model specification functions re-established, the latter used to generate individual size models. Actual measurements were compared to predicted third trimester size trajectories using Percent Deviations. New age-specific reference ranges for the Percent Deviations of each parameter were defined using 2-level statistical modeling.
Results: Rossavik models fit the data for all parameters very well (R^2: 99%), with SP's and *k* values similar to those found in much smaller cohorts. The c^* values were strongly related to the second trimester slope (R^2: 97%), as was predicted s^* to estimated c^* (R^2: 54–95%). Rossavik models predicted third trimester growth with systematic errors close to 0%; random errors (95% range) ranged between 5.7 and 10.9% and 20.0 and 24.3% for 1D and 3D parameters, respectively.
Conclusions: IGA procedures for evaluating second and third trimester growth are now established based on a larger cohort (4–6 fold larger). New, more rigorously defined, age-specific standards for the evaluation of third trimester size deviations are now available for nine anatomical parameters and a weight estimation procedure that incorporates a soft tissue parameter (fractional thigh volume). These results provide a means for more reliably assessing fetal growth on an individualized basis, thus minimizing the effect of biological differences in growth.

Keywords

Fetal growth, Rossavik size models, ultrasound

History

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Introduction

Obstetricians typically evaluate fetal growth on the basis of a single anatomic parameter, such as estimated fetal weight (EFW), which is compared to a population-based reference range [1]. One alternative is Individualized Growth Assessment (IGA) that uses Rossavik models to specify expected third trimester size trajectories and birth characteristics from second trimester measurements of several anatomic parameters in individual fetuses [2]. This approach minimizes the biological variability that is inherently associated with a population standard because each fetus acts as its own control. Unlike more conventional methods, IGA can detect growth aberrations by comparing measurements to standards that are based on the growth potentials of each fetus for a set of anatomical parameters. This comprehensive procedure has been used for fetal growth evaluation in the United States [2], Netherlands [3], Japan [4] and Italy [5]. However, the fundamental components were largely based on a relatively small sample of 18–30 fetuses where the neonatal growth status was either subjectively assessed or compared to cross-sectional standards [6,7]. Furthermore, these earlier studies did not consistently examine a complete set of anatomical parameters in all fetuses of a given sample.

To further refine our understanding of this personalized approach, a prospective longitudinal study of fetal growth was undertaken in which pregnancies were scanned serially during the second and third trimesters. Our primary objective was to investigate IGA in a large, rigorously defined sample of fetuses with normal neonatal growth outcomes [8]. A complete set of growth parameters was

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measured in nearly all fetuses at all time points. For each fetus, assessment of neonatal growth status was made using a modified Neonatal Growth Assessment Score [8]. This type of scoring system combines multiple neonatal size parameters (Growth Potential Realization Index values [2]) that correct for differences in age at delivery, growth potential, fetal growth cessation at term and systematic errors in the prediction of neonatal size characteristics. Our results provide a more comprehensive rationale for use of IGA in clinical practice. Practical implementation of IGA is now facilitated by the availability of an accompanying free computer program.

Methods

Sample selection

This prospective longitudinal study was initially performed in a sample of 142 pregnant women recruited from the Fetal Imaging Unit at William Beaumont Hospital (the Detroit metropolitan area) between 2006 and 2011. Research subjects were identified on the basis of an apparently normal second trimester ultrasound screening examination and the absence of medical or obstetrical complications. Pregnancies with multiple gestations or anatomical anomalies were excluded. All participants were enrolled under signed Informed Consent. The protocol was approved by the Human Investigation Committee at William Beaumont Hospital and the Institutional Review Board at the National Institute of Child Health and Human Development.

At the end of pregnancy, modified Neonatal Growth Assessment Scores (m_3NGAS_{51}), determined using IGA methods independently developed in Houston [8], were obtained. A subset of 119 (83.8%) cases with normal neonatal growth outcomes was identified using a sample-specific normal range, based on preliminary studies described below. These pregnancies were used in all subsequent IGA procedures of this study.

Preliminary studies

Growth Potential Realization Index (GPRI): sample-specific normal ranges for neonatal thigh circumference (ThC), abdominal circumference (AC) and weight (WT)

The $GPRI_{ThC}$ normal range (88–118%) for this sample was determined in 30 neonates with normal neonatal growth outcomes using IGA methods developed in Houston, TX [9]. Similarly, the normal range (90–110%) for $GPRI_{AC}$ was determined in 22 neonates with normal $GPRI_{ThC}$ and $GPRI_{WT}$ values. The $GPRI_{WT}$ normal range (85–125%) was determined in 53 neonates with normal $GPRI_{ThC}$ and $GPRI_{AC}$ values. Details of these calculations are given in the Preliminary Studies Supplemental File (S1).

Modified Neonatal Growth Assessment Score (m_3NGAS_{51}): sample-specific normal range

The m_3NGAS_{51} normal range (117–218%) for this sample was determined in 40 neonates with normal $GPRI_{HC}$. $GPRI_{AC}$, $GPRI_{ThC}$, $GPRI_{CHL}$ and $GPRI_{WT}$ values using IGA methods developed in Houston, TX [8]. The details of this calculation are included as Supplemental Material (S1, Preliminary Studies.pdf). This range was used to select the 119 cases studied in this investigation.

Sample characteristics

All neonates in our sample had m_3NGAS_{51} values within the sample-specific normal range (177–218%). Additionally, all included fetuses had well defined fetal ages, at least three scans between 17 and 28 weeks, MA, 2–4 scans after 28 weeks, MA, and a complete set of neonatal measurements (WT, ThC, AC, CHL, HC). Of the 119 selected, 22 (18.5%) had been used previously in IGA studies of arm parameters [10] and TVol [11]. These 22 fetuses and an additional 8 (6.7%) from the sample were used in an IGA study of ThC [9].

Fetal age determination

Fetal age in 98/119 (82.4%) was determined from first trimester CRL measurements [12], made as part of the ultrasound protocol (90.8%) or by referring physicians (9.2%). In 18/119 (15.1%) cases, fetal age was calculated from the LMP's (regular cycles) and confirmed by a second trimester ultrasound examination (agreement within 7 days). Ages in two cases (1.7%) were based on the average of age estimates derived from BPD, HC, AC and FDL measurements [13–16] obtained at 16 weeks, MA. There was one pregnancy (0.8%) that resulted from *in vitro* fertilization. Fetal age was calculated from the date of conception and 2 weeks were added to give an equivalent menstrual age [17].

Sonographic examinations

Ultrasound scans were carried out at 3–4 week intervals starting at approximately 18 weeks, MA (first scan: 18.6 ± 0.7 {SD} weeks) and ending after 37 weeks (last scan: 37.4 ± 1.5 {SD} weeks) in most cases. The number of ultrasound examinations per fetus averaged 6.8 ± 0.8 {SD} and the last-scan-to-delivery interval was 1.7 ± 1.1 {SD} weeks. Our protocol called for measurement of five standard anatomical parameters (BPD, HC, AC, FDL, ThC) [18], three arm parameters (HDL, ArmC, fractional arm volume (AVol) [10] and fractional thigh volume (TVol) [11]. HC and AC were calculated from their profile short and long axes [18]. Fetal weight was estimated from BPD, AC and TVol measurements using the method of Lee and colleagues [19]. All measurements were made using 3D volume data sets acquired with hybrid mechanical and curved array abdominal transducers (Medison 530 system, SVAW transducer, Cypress, CA: 18 cases; Voluson systems {730, 730 Expert, E8}, RAB 4-8 and RAB 2-5 transducers, GE Healthcare, Milwaukee, WI: 101 cases) [19]. Complete measurement sets were available for most fetuses but when measurements were missing, individual scans or complete scan sets were excluded from the analyses. This resulted in small variations (113–119) in the number of fetuses available for IGA evaluation of different anatomical parameters.

Neonatal evaluation

Within 48 h of delivery, six anatomical measurements (WT, CHL, HC, AC, ThC, ArmC) were made on each neonate as

previously described [10,20]. These measurements were used to classify neonatal growth status.

Individualized fetal growth assessment – data analysis

An important assumption of IGA is that the second trimester growth of a specific parameter is normal. Although some genetic syndromes or prenatal infections can cause early IUGR, most fetal growth abnormalities occur during the third trimester. The IGA approach requires an initial assessment of growth velocity for a given parameter. If the slope of the growth curve is within the expected reference range, it will reflect the growth potential of a specified growth parameter in that individual fetus. However, if the second trimester growth velocity is out of range, it would not be appropriate to use a Rossavik model to predict a normal third trimester growth trajectory because such velocities may indicate abnormal growth earlier in pregnancy.

Rossavik size models are specified when the values of coefficients k, c and s are known. Seven fundamental steps were performed on this sample in the assessment of fetal growth using IGA [2]. The following fundamental procedures are each described in detail with a numerical example as Supplemental Material (S2, IGA Data Analysis.pdf):

(1) Determination of Start Points and Slopes of Second Trimester Fetal Growth Curves
(2) Determination of The Mean Value for Coefficient k
(3) Determination of Values for Coefficients c* and s*
(4) Specification of Second Trimester Size Model Functions
(5) Determination of Expected Third Trimester Size Trajectories
(6) Calculation of Percent Deviations
(7) Determination of Third Trimester Reference Ranges for Percent Deviations

Other analytical procedures

To compare the second trimester growth rates (slopes) of various anatomical parameters (total of 9 parameters per fetus), repeated measures analysis of variance (ANOVA) and the Tukey method (adjustments for non-independent multiple comparisons) were employed [21]. In this analysis, different anatomical parameters were considered ''occasions of measurements'' while the measurements at each ''occasion'' were the individual growth rates for the specified anatomical parameter. This procedure was carried out using PROC MIXED with a repeated statement in SAS (SAS, Cary, NC). $p < 0.05$ was considered statistically significant.

Results

Maternal and neonatal characteristics

Table 1 summarizes maternal and neonatal characteristics of the women and neonates in this sample. Our research subjects were primarily Caucasians, in their mid-child bearing years, with a wide range of parities. Most of the neonates (90%) delivered at term (>37 weeks, MA) with birth measurements within relatively narrow ranges (CV: 4–11%). There were 47.1% males and 52.9% females in the neonatal sample.

Table 1. Maternal and neonatal characteristics.

Maternal characteristics	
Age (years)	30.9 ± 5.2
Gravidity (%)	
1	40.3
2	25.2
3	18.5
4+	16.0
Race (%)	
White	88.2
Black	7.6
Asian	3.4
Hispanic	0.8
Neonatal characteristics	
Birth age (weeks)	39.0 ± 1.4
Male	47.1%
Female	52.9%
Weight (g)	3293 ± 354
Crown-heel length (cm)	49.6 ± 1.9
Head circumference (cm)	34.2 ± 1.4
Abdominal circumference (cm)	31.8 ± 1.7
Mid-thigh circumference (cm)	15.6 ± 1.4
Mid-arm circumference (cm)	10.6 ± 1.0

Mean values expressed $\pm$ 1 standard deviation.

Table 2. Size parameter slopes and start points.

	Slopes (cm/week)				Start points (week)
Parameter	*N*	Mean	SD	CV(%)	Mean $\pm$ SD
Biparietal diameter	118	0.320	0.037	11.6	4.9 ± 1.9
Head circumference	118	1.164	0.101	8.7	4.7 ± 1.4
Abdominal circumference	119	1.141	0.121	10.6	6.5 ± 1.5
Humerus diaphysis length	119	0.228	0.034	14.9	5.8 ± 2.3
Mid-arm circumference	119	0.378	0.062	16.4	7.3 ± 2.7
Fractional arm volume*	119	0.100	0.013	13.0	6.3 ± 2.0
Femur diaphysis length	118	0.272	0.035	12.9	7.7 ± 1.7
Mid-thigh circumference	114	0.572	0.073	12.8	8.9 ± 1.6
Fractional thigh volume*	119	0.146	0.015	10.3	8.5 ± 1.4

*Requires cube root of 3D fractional limb volume parameters to achieve linear slope.

Second trimester growth rates and start points

Table 2 presents the empirically determined Slopes of second trimester growth curves and their associated Start Points. Except for the HC and AC slopes, all mean slopes are significantly different ($p < 0.05$). The variability of individual slopes (CV's) was similar for all parameters except those for the limb parameters, which were somewhat greater (exception: TVol). The average growth rates for the arm parameters were significantly smaller than those for the corresponding thigh parameters.

Mean Start Points (Table 2) were consistent with the known embryological development of different body parts [22,23]. The earliest mean Start Points were for head parameters (BPD, HC), followed by the trunk (AC), upper arm (HDL, ArmC, AVol) and thigh (FDL, ThC, TVol) parameters. Mean Start Points for limb bones (HDL, FDL) were earlier than those for the soft tissue (ArmC, ThC) and would be in the cartilagenous stage of bone development. Start Point variability was similar for all anatomical parameters but somewhat higher for arm parameters.

Coefficient *k*

Coefficient *k* values strongly reflect the anatomy of the anatomical parameter studied [6]. Their values were related to the dimension of the parameter being measured (i.e. 1D: around 1.0; 3D: around 3), with 1D head parameters (BPD, HC) being more similar than those for the trunk and limb soft tissue (AC, ArmC, ThC) parameters (Table 3). However, skull *k* values were similar to those for the limb bones (HDL, FDL). The *k* values for the three upper arm parameters (HDL, ArmC, AVol) were quite similar to those for their corresponding thigh parameters (FDL, ThC, TVol) but that for the trunk soft tissue parameter (AC) was quite different from those for the limb soft tissue parameters (ArmC, ThC).

As found previously [6], fixing the Coefficient *k*'s at their mean values did not affect the quality of the fit (variable *k* R^2 values: all means above 99% with SD's of 0.3–0.7 % versus fixed *k* R^2's: all means above 99% with SD's of 0.3–0.8%). However, decreased variability for both Coefficients *c* (−58.3% to −94.1%) and Coefficient *s* (−44.0% to −73.8%) were seen with all anatomical parameters.

Coefficients *c** and *s**

Table 4 summarizes the data on Rossavik size model coefficients obtained using fixed values of *k* (*c** and *s**). Coefficient *c** values were all positive with a marked difference in magnitude between 1D anatomical parameters (BPD, HC, AC, FDL, ThC, HDL, ArmC) and 3D anatomical parameters (AVol, TVol). Normal distributions were noted in five cases (BPD, HC, AC, ThC, ArmC) and were normalized by natural log transformation in two additional cases (HDL, AVol). In the other two cases (FDL, TVol), several simple transformations did not normalize the distributions.

Table 3. Rossavik model coefficients – coefficient *k*.

Parameter	*n*	Mean ± SD	CV (%)
Biparietal diameter	118	1.3672 ± 0.1849	13.5
Head circumference	118	1.4047 ± 0.1853	13.2
Abdominal circumference	119	1.0430 ± 0.1882	18.0
Humerus diaphysis length	119	1.3545 ± 0.2158	15.9
Mid-arm circumference	119	0.8441 ± 0.2678	31.7
Fractional arm volume	119	2.9266 ± 0.7163	24.5
Femur diaphysis length	118	1.2581 ± 0.1827	14.5
Mid-thigh circumference	114	0.8778 ± 0.1939	22.1
Fractional thigh volume	119	3.0355 ± 0.3797	12.5

SD = standard deviation; CV = coefficient of variation; *n* = number of fetuses.

For skeletal parameters (BPD, HC, FDL, HDL), Coefficient *s** values were strongly negative while for the soft tissue parameters, they were weakly negative (AC, TVol) or positive (ThC, ArmC, AVol). All distributions were Normal except those for FDL and HDL. No simple transformations could normalize these two distributions.

Coefficient predicted *s** values, derived from second trimester model specification functions, were very similar to Coefficient *s** values for all anatomical parameters with respect to means and SD's (Table 5). Two distributions (AVol, TVol) were different for Coefficients *s** and Coefficients predicted *s**. Of the nine parameters, five of the Coefficients predicted *s** distributions (BPD, HC, AC, ThC, ArmC) were Normal and two (FDL, HDL) could be normalized by natural log transformation after the individual values were made positive by multiplication by −1. No simple transformation normalized the other two distributions (AVol, TVol). Individual Coefficients predicted *s** values were 100% negative for BPD, HC, FDL and HDL but 100% positive for ThC and ArmC. AC, AVol and TVol had intermediate values (23.7%–80.3% positive). Coefficients predicted *s** values were strongly related to estimated Coefficients *c** (93.5–98.6%).

Coefficients *s**-residual (difference between Coefficient *s** and Coefficient predicted *s**) had different characteristics. The means for all anatomical parameters were not different from zero (*t*-test) and the standard deviations were quite low, being somewhat higher for 3D anatomical parameters (AVol, TVol). All distributions were Normal except those for ArmC and AVol. These last distributions were symmetrical around zero but with tails. They could not be normalized by using simple transformations. No evidence of relationships between the Coefficients *s**-residual and the estimated Coefficients *c** was found (adjusted $R^2 = 0\%$).

Rossavik size model specification functions

Table 6 presents functions relating Coefficients *c** to the slopes of the 2nd trimester growth curve and those for those relating Coefficients *s** to Coefficients *c** in Table 7. These functions permit completion of second trimester specification of Rossavik growth models [5]. As can be seen, the relationships between *c** and *slope* were very strong (R^2's above 95%) for all anatomical parameters. The relationships

Table 4. Rossavik model coefficients – coefficient *c** and coefficient *s**.

	Coefficient *c** (cm/week)			Coefficient *s** (1/week)	
Parameter	*n*	Mean ± SD	Dist	Mean ± SD	Dist
Biparietal diameter	118	0.14757 ± 0.02485	N	−0.00527 ± 0.00121	N
Head circumference	118	0.49560 ± 0.06501	N	−0.00586 ± 0.00098	N
Abdominal circumference	119	1.05000 ± 0.15100	N	−0.00077 ± 0.00106	N
Humerus diaphysis length	119	0.11151 ± 0.02500	nN	−0.00576 ± 0.00171	nN
Mid-arm circumference	119	0.50680 ± 0.09608	N	0.00302 ± 0.00110	N
Fractional arm volume	119	0.00122 ± 0.00059	nN	0.00144 ± 0.00314	N
Femur diaphysis length	118	0.16593 ± 0.02944	nN	−0.00480 ± 0.00140	nN
Mid-thigh circumference	114	0.71465 ± 0.10507	N	0.00257 ± 0.00100	N
Fractional thigh volume	119	0.00308 ± 0.00114	nN	−0.00100 ± 0.00258	N

*c** and *s** are Rossavik size model coefficients that are obtained using a fixed coefficient *k*.
n = number of fetuses; SD = 1 standard deviation; N = Normal distribution; nN = non-Normal Distribution.

Table 5. Rossavik model coefficients – coefficient predicted *s** and coefficient *s**-residual.

		Coefficient predicted *s** (1/week)		Coefficient *s**-residual (1/week)	
Parameter	*n*	Mean ± SD	Dist	Mean ± SD	Dist
Biparietal diameter	118	−0.00527 ± 0.00011	N	0.00000 ± 0.00037	N
Head circumference	117	−0.00586 ± 0.00092	N	0.00001 ± 0.00043	N
Abdominal circumference	118	−0.00076 ± 0.00096	N	0.00002 ± 0.00066	N
Humerus diaphysis length	118	−0.00576 ± 0.00168	nN	0.00001 ± 0.00058	N
Mid-arm circumference	118	0.00303 ± 0.00082	N	−0.00001 ± 0.00089	nN
Fractional arm volume	118	0.00146 ± 0.00278	nN	0.00005 ± 0.00206	nN
Femur diaphysis length	117	−0.00480 ± 0.00133	nN	0.00000 ± 0.00064	N
Mid-thigh circumference	113	0.00259 ± 0.00071	N	−0.00002 ± 0.00083	N
Fractional thigh volume	118	−0.00104 ± 0.00281	nN	−0.00002 ± 0.00171	N

Predicted *s** and *s**-residual are Rossavik size model coefficients that are obtained using a fixed coefficient *k*.
n = number of fetuses; SD = 1 standard deviation; N = Normal distribution; nN = non-Normal Distribution.

Table 6. Rossavik size model specification functions – coefficient *c**.

Parameter	Coefficient *c**			
	$\text{Log}_e\ (c^*) = b_0 + b_1\ \text{log}_e$ (slope)			
	n	b_0	b_1	R^2 (%)
Biparietal diameter	118	−0.220670	1.48803	97.9
Head circumference	118	−0.932629	1.49788	97.2
Abdominal circumference	119	−0.130612	1.33812	97.1
Femur diaphysis length	118	−0.022250	1.36650	97.7
Mid-thigh circumference	114	0.295160	1.13400	96.2
Humerus diaphysis length	119	−0.019590	1.47663	98.4
Mid-arm circumference	119	0.462700	1.17788	96.2
Fractional arm volume	119	2.007900	3.81873	97.1
Fractional thigh volume	119	1.225700	3.67054	97.5

*c** is a Rossavik size model coefficient that is obtained using fixed coefficient *k*.
R^2 = coefficient of determination.

Table 7. Rossavik size model specification functions – coefficient *s**.

Parameter	Coefficient *s**			
	$s^* = c_0 + c_1\ (c^*)$			
	n	c_0	c_1	R^2 (%)
Biparietal diameter	118	0.0015705	−0.0463800	90.5
Head circumference	118	0.0012558	−0.0143648	91.3
Abdominal circumference	119	0.0059617	−0.0064066	83.1
Femur diaphysis length	118	0.0026321	−0.0447860	88.7
Mid-thigh circumference	114	0.0075645	−0.0069906	53.9
Humerus diaphysis length	119	0.0016460	−0.0664250	94.7
Mid-arm circumference	119	0.0072949	−0.0084344	53.9
Fractional arm volume	119	0.0070512	−4.5928000	75.3
Fractional thigh volume	119	0.0046800	−1.8970000	69.5

*s** is a Rossavik size model coefficient that is obtained using fixed coefficient *k*.
R^2 = coefficient of determination.

of *s** to *c** were very strong for skeletal parameters (BPD, HC, FDL, HDL), strong for parameters having several significant tissue components (AC, AVol, TVol) and moderate for 1D soft tissue parameters (ThC, ArmC).

Reference standards for third trimester percent deviations

Mean values for Expected Percent Deviations were very close to zero for all nine anatomical parameters and EWT (Table 8). However, 2-level statistical modeling indicated that the

Table 8. Third trimester percent deviations (28–38 weeks, menstrual age).

			Expected Value (%)		2 SD (%)	
Parameter	No. Fetuses	*n*	Mean	Range	Mean	Range
BPD	117	399	0.5	−0.7 to 1.7	6.9	6.5 to 7.7
HC	117	400	0.1	−0.3 to 0.5	5.6	5.1 to 6.7
AC	118	403	0.0	−0.3 to 0.4	7.4	6.9 to 8.4
FDL	117	403	0.1	0.0 to 0.2	8.0	7.4 to 8.7
ThC	113	388	0.0	−0.1 to 0.0	9.9	9.3 to 10.9
EFW	117	400	0.5	0.2 to 0.8	13.0	10.7 to 16.4
HDL	118	402	0.1	−0.1 to 0.2	6.8	6.1 to 8.2
ArmC	118	402	0.0	−0.5 to 0.5	10.8	10.2 to 12.4
AVol	118	402	0.5	−0.8 to 1.7	24.4	22.7 to 29.1
TVol	118	403	−0.1	−2.2 to 1.9	20.9	18.0 to 25.8

Expected Value (%) refers to age-specific value derived from function relating % Deviation to fetal age: 2 standard deviations (2SD) refers to third trimester age-specific variability. The mean and range (minimum and maximum values) of 11 weekly variability measures are given for each anatomical parameter. BPD = biparietal diameter; HC = head circumference; AC = abdominal circumference; FDL = femur diaphysis length; ThC = mid-thigh circumference; EFW = estimated weight; HDL = humerus diaphysis length; ArmC = mid-arm circumference; AVol = fractional arm volume; TVol = fractional thigh volume; SD = standard deviation; *n* = number of % deviation value.

Expected Values (EV) changed somewhat with fetal age (Table 8, EV ranges), with higher values found at the ends of the 28–38 week age-period. These differences were small, particularly when compared to their respective 2 SD reference ranges.

Table 8 presents age-specific Percent Deviation reference ranges (2 SD) for the nine anatomical parameters and EWT. Two-level statistical modeling showed that these ranges changed with fetal age between 28 and 38 weeks, MA. Observed maximum differences were relatively small for 1D anatomical parameters (<2%) but, as high as 5% for 3D anatomical parameters. The magnitudes of such differences indicate that age-specific normal ranges should be used for all nine anatomical parameters and EWT when evaluating individual Percent Deviations (Appendix).

Discussion

Comparison of IGA results between studies

The principal difference in the current investigation compared to those published previously is sample size. This cohort is

4–6 times larger than any sample previously used in IGA procedural studies. Earlier results for BPD, HC, AC and FDL were from a Houston sample, while those for ThC, HDL, ArmC, AVol and TVol were from a Detroit area cohort. Estimated weight, derived from BPD, AC and TVol measurements [19], has not been studied previously using IGA techniques. Normal neonatal outcomes in Houston were determined from a detailed neonatal examination by an experienced neonatologist (R. Hill) and from comparisons using cross-sectional size standards [24]. Previous Michigan studies used the m_3NGAS_{51} values of Deter and Spence [8] with a normal range of 182.5–210%; in this investigation, a sample-specific m_3NGAS_{51} normal range of 177.4–218% was used. Sample overlap (same fetuses included in current and previous samples) was 0% for BPD, HC, AC, FDL and EFW; 18.5% for HDL, ArmC, AVol and TVol and 25.2% for ThC.

Results for anatomical parameters studied in Houston were obtained using Rossavik models derived from 4 to 5 second trimester measurements and fetal age variables based on known dates of conception [6,7,25]. Previous and current IGA studies from Michigan were based on Rossavik models derived from three 2nd trimester measurements and fetal age variables calculated from the LMP, confirmed by early ultrasound measurements [9–11]. The interpretation of all earlier third-trimester IGA studies, based on Percent Deviations, did not previously consider the potential effect of autocorrelation between repeated measurements or differences in the number/timing of the data contributed by different fetuses. Corrections for differences in all these variables were made by using 2-level statistical modeling in the current study [26]. Differences in patient sample characteristics, growth curve sampling, standards for defining normal growth outcome and analytical techniques may have contributed to discrepancies in the results obtained in different studies.

Second trimester growth rates

This is the first comprehensive presentation of second trimester growth rates used in IGA studies of nine fetal anatomical parameters. Since these growth rates were obtained when fetal growth demands were small, and thus easily satisfied, they represent an empirical measure of known and unknown constituent growth controllers. The latter is of particular importance since a recent study of 16 demographic, obstetrical and physiological factors thought to be related to birth weight has shown that only 36.3% of birth weight variability could be accounted for [27]. This strongly suggests that the nature of most growth controllers is unknown. Since these growth rates were empirically determined in individual fetuses with normal neonatal growth outcomes, they can be considered representative reference standards for normal second trimester growth. Optimal use of Rossavik size models requires that second trimester growth rates should be within these normal ranges.

Start points

Our results clearly indicate linear growth in the second trimester (Table 2). The degree of agreement between Start Points and embryological events related to the first appearance of anatomical structures suggests that their growth is approximately linear during the first trimester as well. These two concepts are the basis for valid Start Point calculations [2]. Although the order was embryologically correct (22.23) for the six anatomical parameters (BPD, HC, AC, FDL, Hcube, Acube) studied in both Houston and Detroit, the mean Start Points in the current study were somewhat earlier although their variability ranges were quite similar [2]. The original Houston data were derived from a larger number of second trimester measurements and are based on known dates of conception. They also are in better agreement with embryological data. The effect of sample size on Start Point estimates is shown by comparing their means $\pm$ SD for ThC, HDL, ArmC, AVol and TVol in the current versus previous Detroit studies, which both used the same methods. With an exception of AVol (slight increase), all other mean values decreased with minimal changes in variability after increasing the sample size by 4–6 times. Hence, the SP values obtained from smaller samples appear to have been representative of the results found in the current study.

Rossavik modeling of fetal growth

The current study of Rossavik size models, using a much larger sample, confirms all the fundamental IGA characteristics that were previously reported using smaller samples [2,6]. Rossavik models fit complete data sets very well for all nine parameters (mean R^2 values above 99%). Fixing the Coefficients k at their mean values did not affect the fits but significantly reduced the variabilities of Coefficients c and s. The Coefficient k values were very similar to those obtained previously (less than 10% difference in most cases). Again, it appears that the small samples [20–30] used in previously published studies were fairly representative of normally growing fetuses.

Second trimester size model specification

Significant correlations between the slopes of the second trimester growth curve and Coefficients c^* were confirmed for all nine anatomical parameters (Table 6). Accordingly, Coefficient c^* can be taken as a measure of the growth controllers in an individual if growth is normal in the second trimester. The relationship between the Coefficient s^* and the Coefficient c^* (Table 7) is more complicated. This larger sample demonstrated a stronger, or similar, relationship for the anatomical parameters studied previously in Houston (BPD, HC, AC, FDL) [7], probably due to the increase in sample size. However, the anatomical parameters studied in Detroit (ThC, HDL, ArmC, AVol, TVol) using similar methods had weaker relationships (exception: HDL, similar) [9–11]. This was particularly true for ThC where, interestingly, the relationship was the same as that for ArmC, both the most direct 1D soft tissue measures. For soft tissue parameters, the Coefficient s^* appears to be less strongly controlled by the Coefficient c^* and this characteristic manifests itself more definitively when larger samples are studied, probably because such samples are more representative.

Could the components of coefficient *s* have biological meaning?

Coefficient *s* has been considered to represent an unknown regulator of fetal growth for many years [28]. Coefficients *s*, which have their major effects toward the end of the third trimester, have two components with very different properties [28]. First, Coefficients predicted *s** are strongly related to fetal growth controllers through the coefficient *c** for all nine anatomical parameters. This component appears to be inhibitory for skeletal parameters and stimulatory to soft tissue parameters; these are properties that would permit soft tissue accretion without allowing mechanical size changes that could have prevented successful delivery before the advent of modern obstetrical intervention. In contrast, the Coefficients *s**-residual component of the nine anatomical parameters have no relationships with their Coefficients *c** and their distributions are narrow, symmetrical and have zero means (characteristics of random processes) in these normally growing fetuses. Substituting these two components of the Coefficient *s* in the Rossavik function provides an alternative means to calculate a growth parameter $\{P\}$:

$$P = c\{t\}^{k+t\,s} = c\{t\}^{k+t(\text{predicted } s+t\,s-\text{residual})}$$
$$= c\{t\}^{k}\{t\}^{t(\text{predicted } s)}\{t\}^{t(s-\text{residual})}.$$

As is seen in this form of the Rossavik model, the Coefficient predicted *s* can either stimulate or inhibit growth, particularly in the last part of the 3rd trimester. A zero Coefficient *s*-residual has no effect on growth while a negative Coefficient *s*-residual slows growth and a positive one stimulates growth. In normally growing fetuses, the Coefficients *s*-residual have values very close to zero for all anatomical parameters, which are their set points.

Although it is likely that a number of nutrient sensor systems exist, one with characteristics similar to those of Coefficient *s* is the Insulin-like Growth Factor (IGF) system. This system has two major components (IGF-I, IGF-II and their binding proteins) that play an important role in the regulation of normal and abnormal fetal growth [29–32]. Both IGF-I and IGF-II concentrations increase with fetal age and are associated with important tissue and hormonal effects at the end of pregnancy [30–32]. IGF deficiencies are associated with IUGR and IGF-II over-production with macrosomia [29,31,32]. Fowden and Forhead [32] have proposed that IGF-I may act as a nutrient sensor that insures fetal growth is commensurate with the nutrient supply while IGF-II provides the constitutive drive for fetal mass accumulation. The relationship of Coefficient *s* components to the IGF system warrants further investigation.

Predicting third trimester size and estimated fetal weight

No systematic prediction errors were found for any of the nine anatomical parameters studied and the random prediction errors varied with fetal age and anatomical parameter. The average of the mean random errors for the six 1D anatomical parameters was 8.1%, which implies errors of 16% for 2D anatomical parameters (not studied) and 24% for 3D anatomical parameters (AVol: 24.3%; TVol: 20.8%) if their precisions were similar. The random prediction errors were somewhat larger than those found previously [2,10,11]. This is most likely due to the larger sample being more representative and because the sample-specific normal range for m_3NGAS_{51} used to identify normal neonatal growth outcomes was larger than that used previously [8]. The detection of changes in random prediction error with fetal age was another result of the availability of a larger sample and the use of 2-level statistical modeling that accounts for more diverse sources of variability [26].

Our results confirm the ability of second trimester Rossavik size models to predict third trimester size trajectories (Table 8). Included for the first time are EFW predictions obtained using the weight estimation procedure of Lee et al. [19]. This weight estimation procedure utilizes 1D and 3D parameter measurements (BPD, AC, TVol) instead of calculated Hcube and Acube parameters [33]. The performance of this weight estimation procedure in the current longitudinal study and a previous cross-sectional study [19] was essentially the same (systematic error {mean}: 0.5% versus 0.1%; random error {2SD}: 13.0% versus 13.2%). These results represent a significant improvement over those obtained with the previous weight estimation procedure based on the head and abdominal cubes (mean random error: 20.3%, unpublished).

Strengths and limitations

Individualized Growth Assessment applies the results from an existing longitudinal dataset to make size predictions in new cases. This approach depends on a series of linear regression steps that are easily accessible to non-statisticians (refer to IGA analysis software materials (S3) by visiting http://iGAP.research.bcm.edu). Age-specific reference ranges for the Percent Deviations are derived from two-level hierarchical linear modeling that accounts for the within-subject correlation and differences in the number and timing of data points that each fetus contributes. Several strengths differentiate our investigation from other studies:

(1) The current investigation applied IGA to the largest sample of fetuses ($n = 119$).
(2) All fetuses had normal neonatal growth outcomes as defined by a multiple parameter modified Neonatal Growth Assessment Score that adjusts for differences in age at delivery, growth potential and the occurrence of growth cessation at term [34].
(3) Fetal age was primarily determined using first trimester scans.
(4) Anatomical parameter measurements were made over a relatively long time period (range approximately 18–37 weeks, MA), with the last- scan-to-delivery interval being 1.7 weeks on average.
(5) At almost all time points, seven 1D and two 3D anatomical parameters (as well as estimated weight) were measured in each fetus, more than in any previous longitudinal study of fetal growth.

These characteristics permit a comprehensive evaluation of fetal growth, the generation of robust reference standards and direct growth comparisons between different anatomical parameters.

However, IGA is essentially a procedure that fits a mathematical model to longitudinal data and makes subject-specific predictions. These goals could also be achieved, theoretically, using mixed-effects linear modeling [35]. Unlike IGA, this standard modeling approach does not treat each fetus equally since (1) individual fetuses may contribute different numbers of data points and (2) the goodness of the fit of the regression model may not be similar in all cases. Although IGA does not account for these sources of variation, they had no effect on the results obtained in this study since variations in the number of data points and the quality of fits in individual fetuses were small. Work is currently in progress to evaluate the feasibility of using mixed-effects modeling for the same purpose as IGA and to compare these two approaches under a wide range of scenarios.

Finally, the patients studied were a sample of opportunity, not one designed to represent a specific population. Demographic characteristics of this sample are provided so the reader can determine if it is reasonable to use these results in his/her population.

Conclusion

This investigation confirms second and third trimester characteristics of IGA in fetuses having normal neonatal growth outcomes in a sample that is 4–6 times larger than those used previously. Second trimester growth velocity standards for individual parameters are now provided. New, more rigorously defined, age-specific standards for the evaluation of deviations from predicted third trimester size trajectories have also been defined for nine anatomical parameters (BPD, HC, AC, FDL, ThC, HDL, ArmC, AVol, TVol) and EFW. The results of this longitudinal study are consistent with an earlier cross-sectional investigation [23] that showed improved precision from adding a soft tissue component (TVol), to a sample-specific weight estimation procedure. Our results support the use of IGA in evaluating fetal growth on an individualized basis in the majority of fetuses (>90%) not manifesting evidence of early growth abnormalities [36,37].

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Declaration of interest

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Appendix

Calculation of age-specific reference ranges for percent deviations

As shown by Royston [26], age-specific reference ranges for fetal anatomical parameters require data on the Expected Value coefficients (B_0,B_1) of the linear functions fit to measurements from each individual fetus, their variances (varB_0, varB_1), covariance (covB_0B_1) and the random error (varError). These data are used to calculate the expected value (EV_{ij}) of the anatomical parameter (j) at any given age (Age_i) and its associated variance (Var_{ij}) using the following two equations:

(1) $EV_{ij} = B_{0j} + B_{1j}\ [Age_i]$

(2) $Var_{ij} = varB_{0j} + varB_{1j}[Age_i]^2 + 2\ covB_{0j}B_{1j}[Age_i] + varErrorj$

The square root of the variance at a given age is the standard deviation (SDj) and twice the standard deviation (2 SDj) includes 95% of the measurements at that age. A reference range is determined by adding and subtracting the 2 SD value from the Expected Value.

The Royston procedure was adopted for calculation of the age-specific Reference Ranges for 3rd trimester Percent Deviations (% Dev). As no more than four Percent Deviation measurements were available for each fetus, a linear function was the only reasonable model for these data [38]. Unbiased estimates of the needed statistical parameters can be obtained using 2-level modeling (longitudinal data nested within fetuses) using Restricted Iterative Generalized Least Squares (RIGLS) regression. The RIGLS method corrects for autocorrelation between measurements and differences in variances [39]. It can be performed using MLwiN 2.23 software (University of Bristol, Bristol, UK). The coefficients and variance components used to obtain the reference ranges at weekly intervals between 28 and 38 weeks, MA, for nine anatomical parameters and EWT are given below:

Parameter	B_0	B_1	varB_0	varB_1	varB_0B_1	varError
BPD	8.366	−0.239	114.48	0.107	−3.383	3.230
HC	2.726	−0.080	107.29	0.106	−3.306	2.820
AC	2.359	−0.070	101.68	0.100	−3.070	4.174
FDL	−0.563	0.020	0.00	0.008	0.000	7.263
ThC	0.200	−0.007	77.95	0.085	−2.378	10.330
EWT	2.585	−0.062	264.78	0.336	−9.151	12.675
HDL	−1.006	0.032	133.50	0.137	−4.196	4.327
ArmC	3.306	−0.099	197.69	0.201	−6.027	9.256
AVol	−7.601	0.245	1242.28	1.303	−38.811	38.047
TVol	−13.618	0.409	746.76	0.880	−24.770	31.601

BPD = biparietal diameter; HC = head circumference; AC = abdominal circumference; FDL = femur diaphysis length; ThC = mid-thigh circumference; EWT = estimated weight derived from BPD, AC and TVol; HDL = humerus diaphysis length; ArmC = mid-arm circumference; AVol = fractional arm volume; TVol = fractional thigh volume.