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INDIVIDUALIZED FETAL GROWTH ASSESSMENT: CRITICAL EVALUATION OF KEY CONCEPTS IN THE SPECIFICATION OF THIRD TRIMESTER GROWTH TRAJECTORIES

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Abstract

Objectives—To characterize 2nd and 3rd trimester fetal growth using Individualized Growth Assessment in a large cohort of fetuses with normal growth outcomes.

Methods—A prospective longitudinal study of 119 pregnancies was carried out from 18 weeks, MA, to delivery. Measurements of eleven fetal growth parameters were obtained from 3D scans 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 model specification functions were re-established. These functions were used to generate individual growth models and determine predicted s and s-residual [s = pred s + s-resid] values. Actual measurements were compared to predicted growth trajectories obtained from the growth models and Percent Deviations [% Dev = {{actual − predicted}/predicted} × 100] calculated. Age-specific reference standards for this statistic were defined using 2-level statistical modeling for the nine directly measured parameters and estimated weight.

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 a much smaller cohort. The c values were strongly related to the 2nd trimester slope [R^2: 97%] as was predicted s to estimated c [R^2: 95%]. The latter was negative for skeletal parameters and positive for soft tissue parameters. The s-residuals were unrelated to estimated c's [R^2: 0%], and had mean values of zero. Rossavik models predicted 3rd trimester growth with systematic errors close to 0% and random errors [95% range] of 5.7 – 10.9% and 20.0 – 24.3% for one and three dimensional parameters, respectively. Moderate changes in age-specific variability were seen in the 3rd trimester..

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Conclusions—IGA procedures for evaluating 2nd and 3rd trimester growth are now established based on a large cohort [4–6 fold larger than those used previously], thus permitting more reliable growth assessment with each fetus acting as its own control. New, more rigorously defined, age-specific standards for the evaluation of 3rd trimester growth deviations are now available for 10 anatomical parameters. Our results are also consistent with the predicted s and s-residual being representatives of growth controllers operating through the insulin-like growth factor [IGF] axis.

Keywords

fetal growth; individualized growth assessment; Rossavik model; IGF

INTRODUCTION

Evaluation of fetal growth and neonatal growth status is an important part of obstetrical care because of links between growth abnormalities and perinatal morbidity/mortality, developmental abnormalities and subsequent adult disease (1–4). This evaluation process is confounded by differences in growth potential [growth specified by genetic and placental factors as manifest in 2nd trimester growth velocities in normally growing fetuses], age at time of evaluation and the way that growth abnormalities are expressed in different individuals (5). Currently, the most widely used methods focus primarily on estimated fetal weight [EWT] although other parameters are used less commonly (6). As previously emphasized, EWT is a measure of size, not growth (5). The effect of age is usually addressed by serial size assessments, using age-specific size standards, rather than *changes* in size, which are true growth measures. Such conventional methods make no corrections for differences in growth potential and only infrequently address the issue of different manifestations of growth abnormalities in different individuals.

An alternative approach to growth assessment that does not the problems listed above is called Individualized Growth Assessment [IGA] (5). This procedure is based on direct measurements of 2nd trimester growth rates [measures of the combined effects of both known and unknown factors determining growth in a given individual]. In normally growing fetuses [i.e. fetuses with normal neonatal growth outcomes], these measurements can be considered to reflect individual ‘growth potentials’. Slope measurements are used to specify Rossavik growth models that determine 3rd trimester growth trajectories and predict birth characteristics. If second trimester growth is normal, these trajectories and predicted birth characteristics represent Individualized Growth Standards against which actual measurements can be compared (7). The parameters generated in these comparisons [Percent Deviations {% Dev} in the 3rd trimester and Growth Potential Realization Index {GPRI} values at birth] are proportional to differences between the expected average growth rates and the actual average growth rates, thus are accurate measures of ‘growth’ (5). Predicted values also correct for differences in age at assessment since they are evaluated using age-specific standards or are determined by age. IGA has been applied to 15 different one- two-, and three- dimensional anatomical parameters from which sets of anatomical parameters can be defined. Five member sets have been used in the development of composite Scores [e.g. Prenatal Growth Assessment Score {PGAS}, Neonatal Growth

Assessment Score {NGAS}] that allow detection of growth abnormalities that variably manifest themselves among different individuals (5).

The IGA methods developed in Houston, Texas have given comparable results with samples from other populations in the United States, the Netherlands, Japan and Italy although the data was acquired from longitudinal studies of relatively small samples [20 or less] (5). Hence, there are legitimate questions concerning the representativeness of the original samples and the applicability of these methods to other populations that deserve further investigation. As a first examination of these questions, the current study of IGA procedures was carried out using 11 anatomical parameters in a new singleton population with a sample that was 4 – 6 fold larger than those used previously. Data from such a large sample can be considered more reliable than those obtained with smaller samples. Such data also permit a more detailed study of model coefficients with use of more sophisticated statistical analyses.

METHODS

Sample Selection—This prospective longitudinal study was carried out in a sample of 142 pregnant women from the Detroit metropolitan area using a protocol 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. Modified Neonatal Growth Assessment Scores [m_3NGAS_{51}], determined using IGA methods independently developed in Houston (8), were obtained for all 142 neonates and the 119 [83.8%] with values within a sample-specific normal range were selected for further study. Several preliminary studies were necessary to establish this reference range [see below].

Growth Potential Realization Index [GPRI] Normal Ranges for ThC, AC, and EWT—As described previously (5), mNGAS values are calculated from Growth Potential Realization Index [GPRI] values for weight [WT], mid-thigh circumference [ThC], abdominal circumference [AC], crown-heel length [CHL] and head circumference [HC]. GPRI values are defined as ratios of actual birth characteristic values to their predicted values, the latter corrected for systematic prediction errors [due to sample differences and modeling errors] if necessary, multiplied by 100. In our previous work with Detroit-area neonates (9), we found that the correction factor [cf = 1.0 − (% sys error/100)] for ThC in this population [0.911], and the subsequent $GPRI_{ThC}$ normal range [88 – 118], differed from those found previously in Texas (10). Therefore, re-evaluations of the other two parameters frequently requiring correction factors [AC and WT] were carried out in Detroit-area neonates.

From our longitudinal data set, we identified 22 neonates with normal values for $GPRI_{ThC}$ (9) and $GPRI_{WT}$ (10) based on previous standards. Using predicted AC values derived from 2nd trimester Rossavik growth models [assuming growth cessation at 38 weeks, MA] (11) and AC measurements at birth, we calculated the Percent Difference [% Diff = {predicted AC − birth AC}/birth AC × 100] for each neonate. The mean Percent Difference was 9.4%, giving a correction factor of 0.906. Using this correction factor, the GPRI's for AC were calculated. The mean value was 101% with a 95% range of 90–110 %. A similar study using predicted WT, derived from predicted head cubes [Hcube] and abdominal cubes [Acube]

(12), and birth weight was carried out in 53 neonates with normal $GPRI_{ThC}$ and $GPRI_{AC}$ values, based on sample-specific normal ranges. The mean Percent Difference was found to be 0.007%. As this value was not significantly different from zero [t-test], no correction factor was needed. The normal range for $GPRI_{WT}$ was found to be 85 – 125%.

mNGAS Normal Range—In the longitudinal data set there were 40 neonates with normal GPRI values for WT, ThC, AC, HC and CHL and thus considered to have normal neonatal growth outcomes. Using the weighting factors previously determined for m_3NGAS_{51} (8), m_3NGAS_{51} values were calculated from the GPRI values for each fetus. The mean value was 197.7 +/− 10.2 SD % and the values were normally distributed [Anderson-Darling Normality Test: p-value = 0.559). These results gave a sample-specific 95% normal range of 177 – 218 %.

Since all fetuses in pregnancies with risk factors for growth abnormalities do not grow abnormally and all fetuses in pregnancies without such risk factors do not have normal growth, our ‘normal growth’ group was selected based on neonatal growth outcome. The m_3NGAS_{51} is a comprehensive five-parameter measure of neonatal growth status that corrects for differences due to age at delivery, growth potential, growth cessation after 38 weeks, and systematic prediction errors (13). This composite variable weighs the individual parameters with respect to their importance in identifying different growth outcomes and effectively separates IUGR and Macrosomic neonates from Normal neonates (8). In the sample studied in this investigation, all neonates had m_3NGAS_{51} values within the sample-specific normal range [177–218]. Additionally, all included fetuses had well defined ages, at least 3 scans between 17 and 28 weeks, MA, 2 to 4 scans after 28 weeks, MA, and a complete set of neonatal measurements [WT, ThC, AC, CHL, HC]. Pregnancies with multiple gestations and fetuses with anomalies were excluded. Of the 119 selected, 22 [18.5%] had been used previously in IGA studies of arm parameters (14) and TVol (15). 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 1st trimester CRL measurements (16), 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 2nd 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 (17–20) 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 two weeks were added to give an equivalent menstrual age (21).

Sonographic Evaluation—Ultrasound scans were performed 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 the majority of cases. The number of scans per fetus averaged 6.8 +/− 0.8 SD and the last-scan-to-delivery interval was 1.7 +/− 1.1 SD weeks.

The study protocol called for measurement of 6 standard parameters [BPD, HC, AC, FDL, Hcube, Acube] (22), three arm parameters [HDL, ArmC, fractional arm volume (AVol)] (14) and fractional thigh volume (TVol) (15). The HC and AC parameters were calculated from their profile short and long axes (22). Fetal weight was estimated from Hcube and Acube measurements using the method of Deter et al (12). These measurements were made using 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]. 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 [see Results].

Neonatal Evaluation—Within 48 hours of delivery, 5 anatomical measurements [WT, CHL, HC, AC, ThC, ArmC] were made on each fetus as previously described (11). These measurements were used in the evaluation of neonatal growth status.

Data Analysis

Second Trimester Growth Model Specification—As described previously (5), specification of 2nd trimester Rossavik Growth models [$P = c(t)^{k+st}$] requires determination of individual Start Points and model coefficients. Logically, growth of specific anatomical parameters cannot begin until they exist embryologically, which occurs considerably after the zero time point for menstrual age (5). Therefore, Start Points were estimated for each anatomical parameter in each fetus by fitting a linear function [$P = a_0 + a_1MA$] to conventional one-dimensional measurements [or the cube roots of volume measurements] made before 28 weeks, MA. Individual Start Points were calculated using the following expression: $SP = -a_0/a_1$ (7). The time variable (5) was then defined as $t = MA - SP$.

Model coefficients were determined by the anatomical parameter studied [k] or estimated from the slope [a_1] of the 2nd trimester growth curve [c, s] (5). Rossavik functions were fit to complete data sets for each anatomical parameter in each fetus using regression analysis and the average values and SD's of the R^2's and the model Coefficients $\underline{k}$, $\underline{c}$, and $\underline{s}$ for each anatomical parameters determined. In a second set of regression analyses using complete data sets, the values of Coefficient $\underline{k}$ were fixed at their respective mean values [to re-evaluate the concept that $\underline{k}$ represents the anatomical characteristics of what is being measured and therefore is constant between individuals(5)] and the individual values of R^2, Coefficients $\underline{c}$ and Coefficient $\underline{s}$ determined again. The means and SD's for the R^2 and the model coefficients were re-calculated from these data. Sets of $\underline{a_1}$ and $\underline{c}$ [from regressions with fixed values of $\underline{k}$] values were used to define relationships between $\underline{c}$ and $\underline{a_1}$ [$\log_e c = d_0 + d_1 \log_e a_1$] for each anatomical parameter using regression analysis. Similarly, sets of $\underline{s}$ and $\underline{c}$ values were used to define relationships between $\underline{s}$ and $\underline{c}$ [$s = e_0 + e_1 c$] for each anatomical parameter. The '$\underline{s}$' predicted using the latter functions are called predicted $\underline{s}$ [pred $\underline{s}$] values. The difference between $\underline{s}$ and pred $\underline{s}$ is called the $\underline{s}$-residual [$\underline{s}$-residual = $\underline{s}$ − pred $\underline{s}$] (23). Coefficient distributions were evaluated using the Anderson-Darling test for normality while relationships between the predicted $\underline{s}$ values or the $\underline{s}$-residuals and the

coefficients c estimates were assessed using linear regression analysis. As coefficient distributions were obtained from normally growing fetuses, they represent appropriate reference ranges for these parameters.

Growth Model Predictions of Third Trimester Measurements—To determine the degree of agreement between predicted growth trajectories and actual measurements, predicted values at time points after 28 weeks, MA, were obtained using appropriate individual Rossavik growth models specified in the 2nd trimester as described above. Actual parameter measurements made in 3rd trimester scans were then compared to predicted values and the Percent Deviations [% Dev] determined [% Dev = {{actual measurement − predicted measurement}/predicted measurement} × 100]. The set of Percent Deviation values for each anatomical parameter contained multiple measurements from the same fetus as well as different numbers of measurements from different fetuses. The times of measurement were also variable between fetuses.

Percent Deviations provide a means for calculating 3rd trimester prediction errors. Expected values are measures of the systematic prediction error and their variances are measures of the random prediction error. Determining these errors as a function of fetal age is challenging but can be accomplished using multi-level statistical modeling [longitudinal data nested in fetuses] as described by Royston and Altman (24). This technique was used to determine the expected values and their associated variability at weekly intervals between 28 and 38 weeks, MA, using MLwiN software [University of Bristol, Bristol, UK]. As these sets of Percent Deviations values came from normally growing fetuses, the results obtained also define the age-specific reference ranges for Percent Deviations in the 3rd trimester.

RESULTS

Maternal and Neonatal Characteristics

Table 1 presents the maternal and neonatal characteristics of the women and neonates in this sample. Our patients were primarily Caucasian, in the 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 sample.

Second Trimester Rossavik Growth Model Specification

Table 2 presents comparisons of Start Points and Coefficient k values for 11 anatomical parameters obtained in the current study, with those from previous publications (5,8,14,15,25). The mean Start Points did not differ significantly for those parameters evaluated only in the current population [ThC, HDL, ArmC, AVol, TVol] but were significantly different for those parameters studied independently in the Houston and Detroit area populations [BPD, HC, AC, FDL, Hcube, Acube]. However, for the latter parameters, the age order was the same in both populations and consistent with the appearances of the structures in embryological studies (26,27). Increasing the sample size 4–5 fold did not cause a marked increase in Start Point variability for any parameter.

The results for Coefficient k values were similar to those for the Start Points but there were even fewer significant differences. The Coefficient k values for only 4 parameters [BPD, HC, FDL, Hcube] differed significantly and all except 2 [Hcube: 13.8%, AVol: 11.8%] of these differences were less than 10%. There was some increase in k variability but only for those parameters studied in Detroit and Houston [exception: Acube]

As found previously (7), fixing the Coefficient k's at their mean values did not affect the quality of the fit [variable k R^2's: all means above 99% with SD's of 0.3–0.7 %; fixed k R^2's: all means above 99% with SD's of 0.3–0.8%]. However, decreased variabilities for both Coefficient c [−58.3 % to −94.1 %] and Coefficient s [−44.0% to −73.8%] were seen with all anatomical parameters. Subsequent regression analyses utilized fixed values [i.e. means] of the Coefficients k.

Table 3 presents the functions relating Coefficients c to the slopes of the 2nd trimester growth curve and those for those relating Coefficients s to Coefficients c. These functions permit completion of 2nd 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 and similar to the results obtained previously (5,9,14,15,25). The relationships of s to c were strong for certain parameters [BPD, HC, FDL, Hcube, HDL], moderate for others [AC, Acube, AVol, TVol] and weak for two parameters [ThC, ArmC]. With smaller samples, the R^2 values in previous studies were smaller for most of the parameters studied in Houston [BPD, HC, AC, Hcube, Acube] but higher for most of the parameters studied in Detroit [ThC, ArmC, AVol, TVol]. These differences were relatively small except for BPD [69.8% vs. 90.5%] and ThC [53.9% vs. 85.6%], possibly due to sampling.

Rossavik Growth Model Coefficients

Table 4 summaries the data on Rossavik Growth Model coefficients in normally growing fetuses. Coefficients c were all positive with a marked difference in magnitude between 1-D parameters [BPD, HC, AC, FDL, ThC, HDL, ArmC] and 3D parameters [Hcube, Acube, AVol, TVol]. The distributions were Normal in 5 cases [BPD, HC, AC,ThC, ArmC] and could be normalized by natural log transformation in two additional cases [HDL, AVol]. In the other 4 cases [FDL, Hcube, Acube, TVol], several simple transformations did not normalize the distributions.

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

As shown in Table 4b, the Predicted Coefficient s values, derived from 2nd trimester model specification functions, were very similar to Coefficient s values for all parameters with respect to means and SD's. Four [Hcube, Acube, AVol, TVol] distributions were different for Coefficients s and Predicted Coefficients s. Of the 11 parameters, 5 of the Predicted Coefficient 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 4 distributions [Hcube, Acube, AVol, TVol]. Individual Predicted Coefficient s values were 100% negative for BPD, HC, FDL, Hcube and HDL but 100% positive for ThC and ArmC. AC, Acube AVol and TVol had intermediate values [23.7% – 80.3%]. As would be expected from the method of calculation, the Predicted Coefficient s values were strongly related to estimated Coefficients c [93.5% – 98.6%, exception: Hcube – 75.3%].

Coefficients s residual [difference between Coefficient s and Predicted Coefficient s] had unusual 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 parameters [Hcube, Acube, AVol, TVol]. All distributions were Normal except those for ArmC and AVol. These last distributions were quite symmetrical around zero but had tails. They could not be normalized by any simple transformation. No evidence of relationships between the Coefficients s-residual and the estimated Coefficients c was found [adjusted R^2 = 0%] except for the Hcube where the adjusted R^2 was 2.7%.

Reference Standards for Third Trimester Percent Deviations

Measurements of any anatomical parameter at a specified time point vary for two reasons, differences in the biological factors that determine their true values and much smaller variations around the true values due to different types of errors [e.g. measurement errors]. Percent deviations contain only the latter, along with modeling errors that affect predicted values. They were collected from all appropriate members of this sample and used, together with 2-level statistical modeling, to determine age-specific standards (Appendix). These standards indicate how much a single measurement can deviate from its expected value [given by its Rossavik growth model] if the fetus has a normal growth outcome. Clearly, the ideal value for a Percent Deviation is zero. As can be seen in Table 5, the mean values in the current study and those published previously were very close to this value for all 10 anatomical parameters. However, the 2-level statistical modeling used in this investigation showed that the Expected Values [EV] changed somewhat with fetal age [Table 5: 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 values [i.e. reference ranges].

The two standard deviation [2 SD] values presented in Table 5 represent Percent Deviation age-specific, normal ranges for the 10 anatomical parameters. Average values were similar to the previously published 95% ranges although somewhat larger (exceptions: BPD, HC). This was particularly true for the true 3D parameters, AVol and TVol. Again, 2-level statistical modeling showed that these normal ranges [2 SD ranges] changed with fetal age between 28 and 38 weeks, MA. The maximum differences found were relatively small for 1D parameters [less than 2 percentage points], intermediate for the quasi-3D parameter EWT [around 3 percentage points] and up to 5 percentage points for the true 3D parameters. The sizes of these differences indicate that in evaluating individual Percent Deviations, age-specific normal ranges should be used for all 10 anatomical parameters.

DISCUSSION

Comparison of IGA Results

A major objective of this investigation was a comparison of current data with those obtained previously. It is important to point out that virtually all previous studies of the basic IGA characteristics for the anatomical parameters studied in this investigation have been carried out by Deter and colleagues in Houston and Lee and colleagues in the Detroit metropolitan area. This is an important limitation of the current study. However, it indicates that the differences and similarities between the current investigation and studies in these two locations are important in comparing published results with those reported here.

As indicated previously, the principal difference in results for all parameters is sample size. This sample is 4–6 times larger than any sample used in previous IGA procedure studies. Moreover, for BPD, HC, AC, FDL and EWT, previous data are from the Houston population but those for ThC, HDL, ArmC, AVol and TVol, are from the Detroit area cohort. 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 (28). Previous Michigan studies used the m_3NGAS_{51} of Deter and Spence (8) having a normal range of 182.5 – 210 % while 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 EWT, 18.5% for HDL, ArmC, AVol and TVol and 25.2% for ThC.

In addition, results for parameters studied in Houston were obtained using Rossavik models derived from 4 – 6 measurements in the 2nd trimester and fetal age variables utilizing known dates of conception (7). Those in Detroit [previous and current studies] were based on Rossavik models derived from three 2nd trimester measurements and fetal age variables were calculated from the LMP, confirmed by early ultrasound measurements (9,14,15). Previous 3rd trimester Percent Deviation studies did not take into account the autocorrelation between repeated measurements or differences in the number and timing of the values contributed by different fetuses. All these variables were corrected for in the present study through use of 2-level statistical modeling (24).

Start Points

The results of this much larger study [Table 2a} clearly indicate approximate linear growth in the 1st and 2nd trimesters, the concept underlying Start Point calculation (5). Although the order was embryologically correct (26,27) for the six parameters (BPD, HC, AC, FDL, Hcube, Acube) studied in both Houston and Detroit, the mean Start Points in the current study were somewhat earlier than those found previously(5) even though the SD's were similar. The original Houston data were derived from a larger number of 2nd trimester measurements and are based on known dates of conception. They also are in better agreement with embryological data., For these reasons, they are probably more accurate. The effect of sample size on Start Point estimates is shown by comparing the means +/−SD of Start Points for ThC, HDL, ArmC, AVol and TVol in the current and previous Detroit studies that use the same methods. Increasing the sample size by 4 to 6 times slightly

decreased the mean values [exception: AVol, slight increase], but only small changes in the variability were seen.

Rossavik Modeling of Fetal Growth

This study of Rossavik growth models (5) with a much larger sample confirms all the IGA characteristics reported previously with small samples. Rossavik models fit complete data sets very well for all 10 parameters (mean R^2's above 99%) and fixing the Coefficients k at their mean values did not affect the fits but significantly reduced the variabilities of the Coefficients c and s. The Coefficient k values were very similar to those obtained previously [less than 10% difference in most cases]. Thus it appears that the small samples [20–30] used in previously published studies were fairly representative of normally growing fetuses.

Second Trimester Growth Model Specification

The results of this investigation [Table 3a] indicate a very strong relationship between the slope of the 2nd trimester growth curve [an empirical measure of known and unknown controllers of growth] and the Coefficient c for all 10 anatomical parameters. This means that the Coefficient c can be taken as a measure of the growth controllers in an individual if growth is normal in the 2nd trimester. The relationship between the Coefficient s and the Coefficient c is more complicated. This larger sample demonstrated a stronger, or similar, relationship for the anatomical parameters studied previously in Houston [BPD, HC, AC, FDL, Hcube, Acube], probably due to the increase in sample size. However, the parameters studied in Detroit [ThC, HDL, ArmC, AVol, TVol] using similar methods had weaker relationships [exception: HDL, similar]. This was particularly true for ThC where, interestingly, the relationship was the same as that for ArmC, both the most direct soft tissue measures. It appears that with soft tissue parameters, the Coefficient s is 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.

Coefficient s and the Insulin-like Growth Factor System

The Insulin-like Growth Factor [IGF] system is known to play an important role in the regulation of normal and abnormal fetal growth. It is composed of IGF-I, IGF-II and their binding proteins (29–32). As it is the free form of the hormone that has a biological effect (31), changes in both hormone levels and/or their binding proteins determine the biological activity of these hormones. 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 (30,31,32). Experimental studies involving exogenous administration, drug treatment and genetic manipulation, as well as clinical studies of gene abnormalities, have shown that both IGF's have important tissue-specific effects on growth and differentiation that manifest themselves in anatomical parameters (31,32). IGF-II also regulates placental size and function (29,31,32). IGF deficiencies are associated with IUGR and IGF-II over-production with Macrosomia (29,31,32). Fowden and Forhead (32) concluded 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 to fetal mass accumulation".

The Coefficient s has been considered to represent an unknown regulator of fetal growth for many years (23). More recently, Deter (5) has proposed that the Coefficient s may be related to the IGF system. The results of our investigation further supports this hypothesis. The Coefficients s, which have their major effects toward the end of the 3rd trimester, have two components with very different properties (23). The Coefficients Predicted s are strongly related to fetal growth controllers through the Coefficient c for all 11 anatomical parameters. This component appears to be inhibitory for skeletal parameters and stimulatory to soft tissue parameters, properties that allow for tissue accretion without allowing mechanical size changes that would prevent successful delivery before the advent of modern obstetrics. In contrast, the Coefficients s-residual of the 11 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 gives:

$$P=c(t)^{k+t\,s}=c(t)^{k+t\,\mathrm{pred}\,s+t\,s-\mathrm{resid}}=c(t)^{k}\,(t)^{t\,\mathrm{pred}\,s}\,(t)^{t\,s-\mathrm{resid}}$$

As is seen in this form of the Rossavik model, a 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. The characteristics exhibited by these two components of the Coefficient s are consistent with what would be expected of indicators of IGF-I [s-residual], IGF-II [predicted s] and/or their binding proteins. Comparisons of changes in the IGF system with those of the Coefficient s components are required to determine if these components are true mathematical representatives of the IGF system. If so, they would provide a means for non-invasive characterization of the 3rd trimester behavior of certain aspects of the IGF system.

Predicting Third Trimester Growth

As shown in Table 5, the results of this study confirm the ability of Rossavik Growth Models [specified in the 2nd trimester] to predict actual 3rd trimester measurements. No systematic prediction errors were found for any of the 10 anatomical parameters and the random prediction errors varied with fetal age and anatomical parameter. The average of the mean random errors for the 6 one-dimensional parameters was 8.1%, which implies errors of 16% for two dimensional parameters and 24% for three dimensional parameters if the precisions were similar. The EWT, which is calculated from the products of two diameters raised to the 1.5 power [quasi- 3D parameters: Hcube, Acube], was 20% while that for true 3D parameters [AVol, TVol] was 24.3% and 20.8%, respectively. These random prediction errors were somewhat larger than those found previously (5,14,15). This is most likely due to the larger sample being more representative and because the sample-specific normal range for mNGAS used to identify normal neonatal growth outcomes was larger than those used previously (8). The detection of changes in random prediction error with fetal age was another result of the availability of a larger sample but also due to the use of 2-level statistical modeling that takes into account more diverse sources of variability (24).

Conclusions

This investigation confirms the previously established 2nd and 3rd trimester characteristics of IGA in fetuses with normal neonatal growth outcomes using a sample that was 4 to 6 times larger than those used before. It also provides additional evidence supporting the hypothesis that the Coefficient s of the Rossavik growth model represents the Insulin-like Growth Factor system. New, more rigorously defined, age-specific standards for the evaluation of deviations from predicted 3rd trimester growth trajectories are now available for 10 anatomical parameters (BPD, HC, AC, FDL, ThC, HDL, ArmC, EWT, AVol, TVol). These results support the clinical application of IGA for evaluating fetal growth on an individualized basis in the majority of fetuses [>90%] not manifesting evidence of first trimester growth abnormalities (33,34).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

BPD (cm)	biparietal diameter
HC (cm)	head circumference
AC (cm)	abdominal circumference
FDL (cm)	femur diaphysis length
ThC (cm)	mid-thigh circumference
EWT (g)	estimated weight
HDL (cm)	humerus diaphysis length
ArmC (cm)	mid-arm circumference
AVol (mL)	fractional arm volume
TVol (mL)	fractional thigh volume

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APPENDIX

Calculation of Age-Specific Reference Ranges for Percent Deviations

As shown by Royston (35), age-specific reference ranges for fetal anatomical parameters require data on the coefficients [B_0,B_1] of the linear functions fit to measurements from each individual fetus, their variances [varB_0, varB_1], covariance [varB_0B_1] and the random error [varError]. These data are used to calculate the expected value [EV_i] of the parameter at any given age [Age_i] and its associated variance [Var_i] using the following two equations:

$$\mathrm{EV}_i = B_0 + B_1\,[\mathrm{Age}_i] \quad \{1\}$$

$$\mathrm{Var}_i = \mathrm{varB}_0 + \mathrm{varB}_1[\mathrm{Age}_i]^2 + 2\mathrm{varB}_0 B_1[\mathrm{Age}_i] + \mathrm{varError} \quad (2)$$

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

The Royston procedure was adopted for calculation of the age-specific Reference Ranges for the 3rd trimester Percent Deviations [% Dev]. As no more that four Percent Deviation measurements were available for each fetus, a linear function was the only reasonable model for these data. The needed statistical parameters can be obtained using 2-level modeling [longitudinal data nested within fetuses] and the MLwiN 2.16 software [University of Bristol, Bristol, UK]. The statistical parameters used to obtain the reference ranges at weekly intervals between 28 and 38 weeks, MA, for 9 anatomical parameters are given below:

Parameter	B_0.	B_1.	varB_0.	varB_1.	varB_0B_1.	varError
BPD	8.277	−0.237	111.15	0.104	−3.287	3.237
HC	2.729	−0.080	105.25	0.104	−3.244	2.822
AC	1.330	−0.052	84.65	0.084	−2.534	4.244
FDL	−1.336	0.042	217.58	0.211	−6.634	4.770
ThC	0.200	−0.007	74.54	0.081	−2.277	10.325
EWT	−5.824	0.172	354.39	0.434	−11.554	32.367
HDL	−1.009	0.032	130.81	0.135	−4.115	4.330
ArmC	3.305	−0.099	193.40	0.197	−5.899	9.253
AVol	−7.600	0.244	1218.68	1.280	−38.096	38.048
TVol	−13.590	0.408	722.57	0.856	−24.013	31.660

Table 1

MATERNAL CHARACTERISTICS

Age	Race				Gravida.			
	White	Black	Asian	Hispanic	1	2	3	4+
yrs.	%	%	%	%	%	%	%	%
30.9 ± 5.2	88.2	7.6	3.4	0.8	40.3	25.2	18.5	16.0

NEONATAL CHARACTERISTICS

	BA,	WT	CHL	HC	AC	ThC	ArmC	Sex.	
								Male	Female
	wks	g	cm	cm	cm	cm	cm	%	%
Mean	39.0	3293	49.6	34.2	31.8	15.6	10.6	47.1	52.9
SD	1.4	354	1.9	1.4	1.7	1.4	1.0		

Table 2a

START POINTS

Parameter	Current Study.			Previous Studies[1].			Difference
	n.	Mean.	SD.	n.	Mean.	SD.	p-value[2]
		wk	wk		wk	wk	
BPD	118	4.9	1.9	20	5.5	1.0	0.05
HC	118	4.7	1.4	20	5.8	0.9	0.001
AC	119	6.5	1.5	20	7.4	1.4	0.01
FDL	118	7.7	1.7	20	9.7	1.5	0.001
ThC	114	8.9	1.6	30	8.3	2.1	ns
Hcube	118	3.7	2.0	20	5.6	1.1	0.001
Acube	119	6.1	1.7	20	7.2	1.3	0.001
HDL	119	5.8	2.3	22	5.7	1.9	ns
ArmC	119	7.3	2.7	22	7.6	2.9	ns
AVol	119	6.3	2.0	22	6.1	2.0	ns
TVol	119	8.5	1.4	22	9.0	1.4	ns

[1] References 5, 9,14,15,28

[2] two sample t-test

Table 2b

COEFFICIENT k

Parameter	Current Study.			Previous Studies[1].			Difference
	n.	Mean.	SD.	n.	Mean.	SD.	p-value[2]
BPD	118	1.3672	0.1849	20	1.2500	0.0850	0.001
HC	118	1.4047	0.1853	20	1.3000	0.1040	0.001
AC	119	1.0430	0.1882	20	1.0480	0.1100	ns
FDL	118	1.2581	0.1827	20	1.1560	0.0790	0.001
ThC	114	0.8778	0.1939	30	0.8651	0.1916	ns
Hcube	118	4.3869	0.6726	20	3.8450	0.2460	0.001
Acube	119	3.0673	0.6205	20	3.2526	0.7120	ns
HDL	119	1.3545	0.2158	22	1.2990	0.1700	ns
ArmC	119	0.8441	0.2678	22	0.8980	0.2690	ns
AVol	119	2.9266	0.7163	22	2.6170	0.7650	ns
TVol	119	3.0290	0.3845	22	2.9760	0.3140	ns

[1] References 9,14,15,25,28

[2] two sample t-test

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Table 3a

ROSSAVIK GROWTH MODEL SPECIFICATION FUNCTIONS

	Coefficient c				
	$\log_e(c) = d_0 + d_1 \log_e(\text{slope})$.				
Parameter	**n.**	**d_0,**	**d_1.**	**R^2**	**pR^2.**
				%	**%**
BPD	118	−.0.220670	1.48803	97.9	97.6
HC	118	−0.932629	1.49788	97.2	96.1
AC	119	−0.130612	1.33812	97.1	96.3
FDL	118	−0.022250	1.36650	97.7	98.4
ThC	114	0.295160	1.13400	96.2	98.6
Hcube	118	−1.227070	4.66046	98.0	96.6
Acube	119	0.724050	3.81959	95.5	96.2
HDL	119	−0.019590	1.47663	98.4	98.7
ArmC	119	0.462700	1.17788	96.2	97.7
AVol	119	2.007900	3.81873	97.1	98.2
TVol	119	1.225700	3.67054	97.5	98.5

p: previously published data in References 9,14,15,25,28,36

Table 3b

ROSSAVIK GROWTH MODEL SPECIFICATION FUNCTIONS

		Coefficient s			
		$s = e_0 + e_1 (c)$.			
Parameter	**n**	**e_0.**	**e_1.**	**R^2.**	**pR^2.**
				%	**%.**
BPD	118	0.0015705	−0.0463800	90.5	69.8
HC	118	0.0012558	−0.0143648	91.3	81.1
AC	119	0.0059617	−0.0064066	83.1	64.9
FDL	118	0.0026321	−0.0447860	88.7	90.3
ThC	114	0.0075645	−0.0069906	53.9	85.6
Hcube	118	−0.0124016	−3.0377600	90.2	81.2
Acube	119	0.0047773	−0.1489920	70.3	69.7
HDL	119	0.0016460	−0.0664250	94.7	93.4
ArmC	119	0.0072949	−0.0084344	53.9	59.6
AVol	119	0.0070512	−4.5928000	75.3	84.9
TVol	119	0.0046800	−1.8970000	69.5	85.8

p: previously published data in References 9,14,15,25,28.36

Table 4a

MODEL COEFFICIENTS

		Coefficient c.			Coefficient s.		
Parameter	**n**	**Mean.**	**SD.**	**Dist.**	**Mean.**	**SD.**	**Dist.**
		cm/wk	**cm/wk**		**1/wk**	**1/wk**	
BPD	118	0.14757	0.02485	N	−0.00527	0.00121	N
HC	118	0.49560	0.06501	N	−0.00586	0.00098	N
AC	119	1.05000	0.15100	N	−0.00077	0.00106	N
FDL	118	0.16593	0.02944	nN	−0.00480	0.00140	nN
ThC	114	0.71465	0.10507	N	0.00257	0.00100	N
Hcube	118	0.00234	0.00120	nN	−0.01952	0.00382	N
Acube	119	0.03956	0.01885	nN	−0.00112	0.00335	N
HDL	119	0.11151	0.02500	nN	−0.00576	0.00171	nN
ArmC	119	0.50680	0.09608	N	0.00302	0.00110	N
AVol	119	0.00122	0.00059	nN	0.00144	0.00314	N
TVol	119	0.00308	0.00114	nN	−0.00100	0.00258	N

Dist: distribution; N: normal; nN: not normal

Table 4b

MODEL COEFFICIENTS

		Coefficient Predicted s.			Coefficient s Residual.		
Parameter	**n**	**Mean.**	**SD.**	**Dist.**	**Mean.**	**SD.**	**Dist.**
		1/wk	**1/wk**		**1/wk**	**1/wk**	
BPD	118	−0.00527	0.00011	N	0.00000	0.00037	N
HC	117	−0.00586	0.00092	N	0.00001	0.00043	N
AC	118	−0.00076	0.00096	N	0.00002	0.00066	N
FDL	117	−0.00480	0.00133	nN	0.00000	0.00064	N
ThC	113	0.00259	0.00071	N	−0.00002	0.00083	N
Hcube	117	−0.01953	0.00366	nN	−0.00002	0.00165	N
Acube	117	−0.00102	0.00267	nN	−0.00009	0.00225	N
HDL	118	−0.00576	0.00168	nN	0.00001	0.00058	N
ArmC	118	0.00303	0.00082	N	−0.00001	0.00089	n N
AVol	118	0.00146	0.00278	nN	0.00005	0.00206	nN
TVol	118	−0.00104	0.00218	nN	−0.00002	0.00171	N

Dist: distribution; N: normal; nN: not normal

Table 5

PERCENT DEVIATIONS

Parameter	Fetus N	% Deviations (28–38 wks, MA).					Fetus N	% Deviations (3rd trimester).		
	Number of Fetuses	N	Expected Value		2 SD			N	Percent Deviations[1]	
			mean	range	mean	range			p mean	p 95%
			%	%	%	%			%	%
BPD	117	400	0.5	0.6 to −0.7	6.8	7.7 to 6.5	20	97	0.3	+/− 7.0
HC	117	400	0.1	0.5 to −0.3	5.7	6.8 to 5.2	20	99	0.9	+/− 6.0
AC	118	404	−0.4	−0.1 to −0.7	7.5	8.4 to 7.1	20	99	−0.1	+/− 7.0
FDL	118	401	0.1	0.3 to −0.2	8.1	9.6 to 7.4	20	99	−0.1	+/− 7.0
ThC	113	388	− 0.0	0.0 to −0.1	9.7	10.7 to 9.1	30	116	−0.0	+/− 7.4
EWT	117	400	−0.2	0.7 to −0.1	20.0	23.3 to 17.8	20	99	0.6	+/− 15.0
HDL	118	402	0.1	0.2 to −0.1	6.9	8.3 to 6.2	22	72	−0.1	+/− 6.8
ArmC	118	402	0.0	0.5 to −0.5	10.9	12.5 to 10.2	22	72	0.5	+/− 9.2
Avol	118	402	0.5	1.7 to −0.8	24.3	29.0 to 22.2	22	72	0.4	+/− 17.0
Tvol	118	403	−0.1	1.9 to −2.2	20.8	25.7 to 18.0	22	72	−0.5	+/− 15.0

[1] Data previously published in References 9,10,14,15,25,28

n: number of % Deviation values;

Expected Value: age-specific value derived from function relating % Deviation to fetal age:

2 SD: age-specific variance;

m: mean of set of 11 weekly expected values:

range: maximum and minimum values for the set of 11 weekly variances;

pm: previously published mean value: p95%: previously published 95% range.