Fetal Growth Restriction

Current Evidence and Clinical Practice

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Foreword

Fetal growth restriction remains as one of the most common pregnancy complications which can have devastating consequences for both mother and fetus or neonate. Growth restricted fetuses suffer increased risks for stillbirth, neonatal death, preterm birth, neonatal morbidity, and abnormal neurodevelopment. Long-term risks include adult chronic disorders such as obesity, diabetes, metabolic syndrome, and cardiovascular disease. One of the most recent fascinating observations is that the diagnosis of fetal growth restriction also carries a significant risk for the mother including recurrent ischemic placental disease: preeclampsia and placental abruption in the pregnancies to follow, and increased risk for ischemic cardiac disease and premature death following the birth of the growth restricted neonate.

Given the huge impact of fetal growth restriction on both maternal and fetal/neonatal health, this book is an extremely significant and timely contribution. The book is unique because of its international scope written by world-renowned experts that represent seven countries and span four continents! Given the short- and long-term health consequences for both mother and baby, it remains vital for the international community to be familiar with cutting-edge information regarding the prenatal and postnatal diagnosis of fetal growth restriction as well as its pathophysiology, management, prognosis, neurological sequalae, and maternal cardiovascular involvement. This book covers everything!

The book, "Fetal Growth Restriction: Current Evidence and Clinical Practice," is the result of a combined effort of four distinguished editors, Drs. Edward Araujo Júnior, Luciano Marcondes Machado Nardozza, Giuseppe Rizzo, and Russell Lee Deter. These individuals are well-recognized authorities who dedicated their careers to the field of fetal medicine and specifically in the area of fetal growth restriction. These editors have undertaken a successful task of recruiting individuals known for their innovative research and technologies to contribute to the various chapters of the book.

The book presents the most current thinking about fetal growth restriction including: the concept of fetal growth potential which is an individualized approach for each fetus to be used as its own control; the early detection of growth restriction and transition from adaption to fetal growth pathology; the pathophysiology and causes of fetal growth restriction; the genomic factors regulating the process of fetal-placental vasculogenesis; early and late onset fetal growth restriction; the value of current biochemical, biophysical, ultrasound, and Doppler markers in the

prenatal diagnosis and prognosis; current and future treatment; obstetrical management and interventions; and evaluation, treatment, and follow-up after birth including neurodevelopmental complications. The book concludes with the maternal cardiovascular long-term consequences for the woman after the birth of a growth restricted infant.

In my view, this book, "Fetal Growth Restriction: Current Evidence and Clinical Practice," covers every aspect of the topic of fetal growth restriction and provides up-to-date information like no other text or monograph before. This book will serve as *the* source for valuable information for clinicians and investigators and also as the basis for future research. I remain confident that this comprehensive book will come to stay as a classic reference in the area of fetal growth restriction and I strongly recommend its reading by all those health-care providers who are involved in the care of pregnant women and their fetuses.

Anthony M. Vintzileos, MD
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Preface

Fetal Growth Restriction: Current Evidence and Clinical Practice was conceived as a means for keeping the health professional up to date on a subject of great relevance to Obstetrics. It was written in clear and objective language, reflecting the experience of the authors in their respective fields. The book addresses aspects of normal intrauterine growth, as well as placental function, etiopathogenesis, and pathophysiology of this disease process. Clinical evaluation of fetal growth restriction (FGR) is described through its classification, diagnosis, and management. Long-term consequences of growth restriction are considered from the neurological and cardiovascular points of view.

We address recent knowledge about the new definition and recent classification of FGR, merging with the still important clinical evaluation. The presented proposal of pathology management appears as a consensus in the world literature.

This is a book for all professionals involved in Perinatology. It is the result of teamwork between professionals from different countries. However, this is not an exhaustive presentation of the subject but rather an update of the most important aspects of this topic.

We would like to thank all the professionals and friends from different countries who participated in this important work, especially the group that studies restriction of fetal growth at the Federal University of São Paulo, which encouraged us to undertake this important project.

São Paulo, SP, Brazil — Edward Araujo Júnior
São Paulo, SP, Brazil — Luciano Marcondes Machado Nardozza
Rome, Italy — Giuseppe Rizzo
Houston, TX, USA — Russell Lee Deter

Acknowledgment

I dedicate this book to my group of the Fetal Medicine Discipline, Federal University of São Paulo, and to my mother Antonia and my wife Renata who are with me in all moments.

Edward Araujo Júnior

I would like to thank all my family, especially my wife, daughter, and son for their wonderful collaboration and for always being by my side.

Luciano Marcondes Machado Nardozza

I would like to dedicate this book to Wes Lee for his help and support over the last 20 years, to Roberto Romero for his critical thinking that significantly improved IGA, to Ivar Rossavik whose insight made IGA possible, and to my beautiful wife, Susan, who has always been the first to appreciate what I have done.

Russell Lee Deter

I dedicate this book to my research team.

Giuseppe Rizzo

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Standards for Fetal Growth and Neonatal Growth Outcomes

1

Russell L. Deter

Introduction

While the focus of this book is on *fetal growth restriction*, this condition cannot be discussed without defining normal growth in more general terms. The purpose of this chapter is to review how growth in both the fetus and neonate is assessed, and it will examine various ways of defining what is normal. With normal growth defined, growth restriction can be identified.

Growth Assessment

There are several fundamental aspects of growth assessment that are common to all methods now in use.

Choice of Growth Parameters

Fetal growth and development is a process by which a single cell evolves into an organism with 7500 named structures of different sizes [1, 2]. However, before the advent of obstetrical ultrasonography, this process could only be monitored noninvasively by measuring birth weight [3]. With ultrasound, the main components of the fetus can be visualized and measured [4]. For historical reasons [5], considerable effort has also been made to estimate fetal weight, a parameter that cannot be directly measured with ultrasound [6].

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Table 1.1 Prenatal and neonatal growth profiles

Prenatal growth profile	
Growth variable	*Measured parameter*
Head size	Head circumference (HC)
Trunk size	Abdominal circumference (AC)
Soft tissue	Partial thigh volume (TVol) [ThC included]
Length	Femur diaphysis length (FDL)
Weight	Estimated weight (EWT)
Neonatal growth profile	
Growth outcome variable	*Measured parameter*
Head size	Head circumference (HC)
Trunk size	Abdominal circumference (AC)
Soft tissue	Thigh circumference (THC), arm circumference (ArmC), percent body fat
Length	Crown-heel length
Weight	(WT)

This table presents the anatomical variables that provide a comprehensive evaluation of prenatal growth and neonatal growth outcomes

Studies of growth abnormalities in both fetuses and neonates suggest that a comprehensive assessment of growth is needed as these abnormalities manifest themselves in different anatomical parameters in individual fetuses/neonates [7–10]. These observations have led to the development of a prenatal growth profile and a neonatal growth profile (Table 1.1) [11]. The prenatal growth profile provides a comprehensive evaluation of the major anatomical components of the fetus and can detect most, but not all, growth abnormalities [8].

All components of the prenatal growth profile can be measured directly with ultrasound except weight. Fetal weight estimations are obtained from functions relating sets of measureable anatomical parameters [obtained within 1–3 days of delivery] to birth weight [12, 13]. The weight estimation functions are obtained by multiple regression analysis and may have increased systematic errors if not sample specific [14, 15].

Choice of Measurement Parameters

A quantitative description of anatomical parameter growth during pregnancy requires the use of dimensional measurements [length, surface area, volume]. Since assessment is primarily with ultrasound, direct measurements of length are used primarily. However, profile area [16, 17] and volumes [18, 19] can be measured. Weight is estimated from sets of length and volume measurements [14].

Selecting the appropriate measure for an anatomical parameter involves the use of latent and observable variables [20, 21], the former having multiple definitions while the latter precisely defined (Table 1.2). This process involves having a clear concept of the information needed and establishing (through a chain of latent variables) that the observable variable contains this information. The observable variable chosen for each anatomical parameter needs to be specifically justified.

Table 1.2 Procedure for selecting a fetal growth parameter

Selection of an observable variable (accessible to ultrasound measurement) that can be used to quantify fetal growth requires a logical process involving latent variables. Given below is an example of such a process:
Latent variable 1 (definition of "growth assessment"): size or change in size with change in age
Size: Change in size with age is more appropriate but cannot be carried out if only one measurement is available
Latent variable 2 (anatomical parameter): head, abdomen, thigh, or femur
Head: All would be more appropriate since they represent different aspects of fetal growth, but *head* was chosen to simplify this example
Latent variable 3 (measure of size): profile circumference, profile area, volume
Profile circumference: Head volume would be more appropriate as it is not affected by shape changes, but complex technology is required for measurement. A head profile with unique anatomy can be defined
Latent variable 4 (method of measurement): tracing of perimeter of head profile or use of elliptical tool
Elliptical tool: *It has been* shown to give similar results as tracing, is less operator dependent and much faster
Latent variable 5 (standard to which measurement is compared): reference range, local prescriptive standard, national prescriptive standard, or international prescriptive standard
The observable variable in this example is the HC measured on the BPD plane with the elliptical tool and compared to the appropriate prescriptive standard

This table gives an example of the procedure used for selecting a growth parameter based on latent variables. Such a procedure provides a well-defined observable variable with the characteristics needed for a specific evaluation of a growth process

Choice of Age Estimate

As standards are age-specific, it is essential that the chosen fetal age be biologically justifiable and be determined as accurately as possible.

Types of Age Estimates

Menstrual age (MA) is the most widely used age estimate. It is measured from the first day of the last menstrual cycle [22]. This age includes a 2-week (on average) period *before* there is a fertilized zygote [22].

Conceptual age (CA) is measured from the date of either ovulation or fertilization and is synonymous with biological age [22].

Gestational age (GA) is synonymous with menstrual age even though its name suggests conceptual age. Because of this name discrepancy, it is not recommended as an age designation even though widely used.

Determining Age Estimates

Menstrual age is primarily determined from the patient's history. Estimates can also be obtained by ultrasound [4]. The most accurate estimates are provided by crown-rump length [CRL] measurements, followed by sets of biometric measurements made in the early 2nd trimester [22].

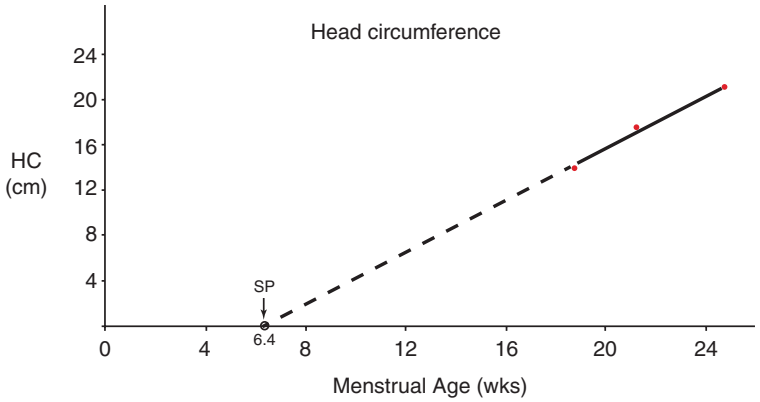

Fig. 1.1 Determination of start point. This figure gives an example of how the start point [SP] used to generate the time variable [t] of individualized growth assessment [IGA] is obtained [t = MA-SP]. A linear function [solid line] is fitted to three second trimester measurements of HC [red dots] and then extrapolated [broken line] back to where it crosses the menstrual age [MA] line. The crossing point [6.4 weeks in this example] is the start point for HC in this example. (HC head circumference)

Conceptional age can be determined by direct observation (IVF) and the LH surge or from basal body temperature and intercourse records [22].

Duration of growth $\{t\}$ involves both menstrual age and a start point [t = MA − SP]. Start point values can be obtained by extrapolating a line fit to 2nd trimester measurements back to where it crosses the MA axis (Fig. 1.1) [10]. On average, SP values are in good agreement with the embryological appearance ages for various anatomical structures [10]. However, because of variation among individuals, better results are obtained when individual SP values are used [23].

Processing Fetal Measurements Related to Growth

Group Approach

Conventionally, the primary means for defining normal growth involves comparing an individual to the group to which he/she can reasonably be considered a member. Past studies have defined these groups on a local, regional, national, or international basis. The issue of which group should be used in these comparisons is currently a major topic of discussion among investigators [24–26], and no consensus has been reached.

Types of Reference Samples

Descriptive In past studies, biometric data has been collected on unselected samples from a given race, ethnic group, geographical location, or economic class [24–28]. Such samples provide a simple description of the distribution of measurements within the group. Adequate sample size to assure representativeness is the main requirement for such sampling.

Table 1.3 Criteria for selecting prescriptive samples

Criterion	Villar et al. [30]	Kiserud et al. [29]
Maternal age (years)	≥18 to ≤35	≥18 to ≤40
Maternal BMI (kg/m^2)	≥18.5 to ≤30	≥18 to ≤30
Maternal height (cm)	≥153	–
Singleton pregnancy	Yes	Yes
Fetal age	Known, normal MA	CRL confirmed MA
Type of pregnancy	Natural	Not stated
Medical history	No previous problems	No previous problems
Socioeconomic constraints	None	None
Tobacco/drug use	None in this pregnancy	None in this pregnancy
Alcohol use	<50 ml/week	Not stated
Recurrent miscarriage	None	None
Premature/LBW delivery	None	None
Congenital disease	None	Not in this pregnancy
Vascular disease of pregnancy	None	Not stated
Rh disease	None	Not stated
Urinalysis	Negative	Not stated
Blood pressure (mm Hg)	<140, <90	Not stated
Anemia	None	Not stated
Sexually transmitted disease	None	Not stated
Environment/physical work	Not adverse to pregnancy	Not adverse to pregnancy

This table lists the criteria used in two recent studies for selecting a patient sample which optimizes fetal growth and minimizes growth abnormalities

Prescriptive More recent studies have specified conditions that maximize normal growth and minimize factors causing growth pathology (Table 1.3) [29, 30]. Fetal growth in pregnancies meeting these criteria has been presented as how fetuses *should* grow. Results obtained using these samples have been proposed as international *standards* for normal growth since similar growth was found in different countries, at least for skeletal parameters [31].

A second type of prescriptive sample is chosen on the basis of a particular desirable neonatal characteristic [e.g., normal neonatal growth outcome as determined with the modified neonatal growth assessment score and a sample-specific reference range] [32]. Fetuses having this desired characteristic were assumed to have grown normally so were used to define size and growth reference ranges.

A third precriptive approach has been applied only to birth weight. The relationships between birth weight and known size determinants [maternal height, weight in early pregnancy, parity and ethnic group, as well as fetal sex] were established in a large, unselected sample using regression analysis [33, 34]. A function containing these variables was then used to determine the "term optimal weight" for any neonate at 280 days.

Classification of Size

With selection of a specific measurement, a fetal age parameter, and an appropriate sample, regression analysis is used to create cross-sectional, *population* size charts (Fig. 1.2) [29]. These charts usually present a set of continuous lines that represent *group percentile lines.* Comparison of individual biometric measurements to such a

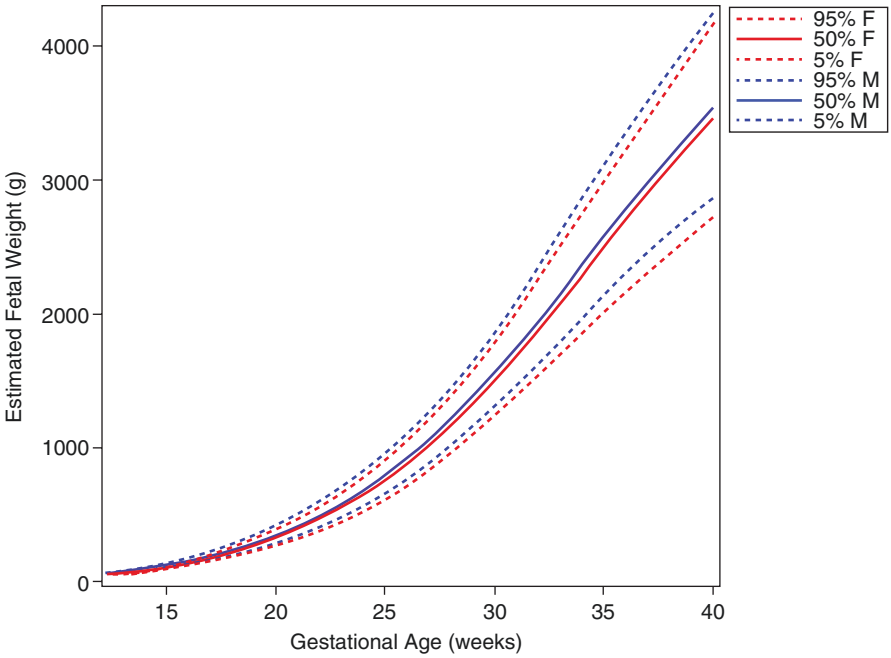

Fig. 1.2 Example of size standard for a specified group. This figure shows the conventional size [estimated weight] reference range used in comparing an individual measurement to the group. In this example, the 5th, 50th, and 95th percentile lines are plotted for both males (blue lines) and females (red lines). (These curves were obtained from the prescriptive sample of Kiserud T, et al. PLOS Med. 2017;14:1–36. [Figure used with permission])

group standard requires calculation of the appropriate *percentiles*. The percentile for a given measurement involves determining the number of standard deviation (SD) units between the measurement value and its expected, or 50th percentile, value in a normal distribution. The difference between the measurement and its expected value is calculated (deviation), and this difference is divided by the SD value (z-score [21]). The z-score value can be converted to a percentile, assuming a normal distribution, using a look-up table [35]. Obtaining expected and SD values for percentile calculation requires mathematical techniques found in the regression analysis literature and is age-specific [36].

Obtaining Expected and SD Values for Percentile Calculation

Cross-Sectional Data If all measurements are independent (one measurement per fetus), ordinary least squares regression analysis can be used to generate the expected value function with respect to fetal age and calculate the variability. If the variability is uniform with respect to age, a single SD value can be obtained and used at any age in the percentile calculation [37]. If there is a change in variability with respect to age, regression analysis has to be used to generate a function relating variability to age [38].

Longitudinal Data The use of longitudinal data to generate expected values and SDs is a relatively recent development but has the advantages of being more efficient and providing knowledge of growth outcomes which can be used to select a more appropriate reference sample. However, in addition to variability variation with age, the repeated measurements in each fetus are correlated with each other [autocorrelation] [39]. This results in biased estimates of the variability [40].

These statistical problems can be solved by using two-level, hierarchical linear modeling (first level, characteristics of the group; second level, characteristics of the individuals in the group) and generalized least squares regression analysis [41]. These procedures generate expected value and total variance functions that are age-dependent. With these functions, the expected value and SD at any age can be obtained.

Customized Percentiles In this procedure, the term optimal weight, based on known, physiological size determinants, is taken as the expected value at 40 weeks [33, 34]. The 40-week standard deviation of the birth weight sample used for specifying the term optimal weight function (expressed as a percent of the 40-week mean value) is taken as the variability parameter. These statistics are used to determine the percentile of the measured birth weight if delivery is at 40 weeks. In deliveries before 40 weeks, the term optimal weight is adjusted using a "proportionality curve" obtained by comparing 50th percentile *estimated weights* at ages before 40 weeks to the 50th percentile estimated weight value at 40 weeks [34]. The SD, as a proportion of the adjusted term optimal weight, is considered to be the same as that determined at term [34].

Distribution-Free Percentile Values A new technique, called *quantile regression*, is now available for obtaining age-specific percentile values directly from the data [42, 43]. This method makes no distributional assumptions and is more robust against the influence of outliers than conventional methods.

Criteria for Classifying Percentiles

The traditional, though still arbitrary, definition of a group of values is the 95% range because there are usually outliers due to errors of different kinds. This definition is independent of any distributional assumptions. For a normal distribution (usually assumed by most reference range studies), this is equivalent to the 2.5–97.5 percentile range. However, beginning in 1967 with birth weight [44], many clinical studies have used the <10th, 10–90th, and >90th percentiles to define abnormally low, normal, and abnormally high values for biometric parameters. More recently [45–47], below the 5th or the 3rd percentile has been used to define abnormally low values.

However, as pointed out by Deter and Harrist [11], what actually needs to be done is to find boundaries *empirically* that optimally separate normal and abnormal cases (Fig. 1.3). The objective of this approach is to choose a boundary that minimizes misclassification. However, this approach has the disadvantages of giving boundaries that change with different types of abnormalities and even with the same

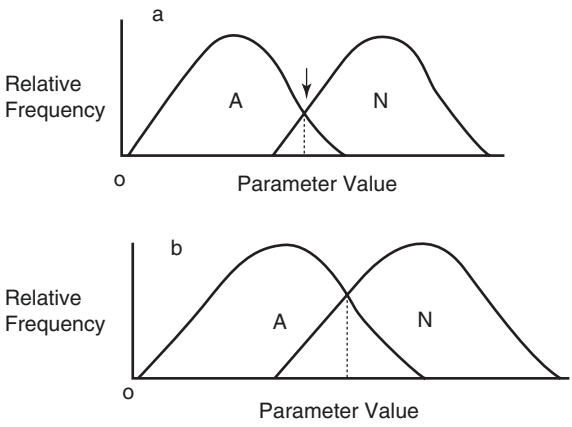

Fig. 1.3 Overlap of normal and abnormal size distributions. (**a**) shows an acceptable degree of overlap between the distributions of normal [N] and abnormal [A] values for a specific size parameter. This degree of overlap gives reasonable numbers for false positives and false negatives. (**b**) shows an unacceptable degree of overlap because the number of false positives and false negatives would be too high

abnormality, in different samples. Such boundaries are also subject to change with sample size until representativeness has been reached. However, such boundaries provide the most definitive information on the quality of the separation boundary in any given sample.

Finally, it must be pointed out that most symmetric distributions have theoretical limits of plus and minus infinity, so no matter what boundary is chosen, there will be some normal values below the boundary and some abnormal values above the boundary. The best that can be done is to minimize misclassification.

Problems with Conventional Classification

Descriptive Reference Ranges Reference ranges from unselected samples may contain individuals with growth abnormalities since growth outcome is not evaluated. They also may or may not be representative, and as they do not take differences in growth potential into account, this source of variation is included in the "normal variability." Group percentile lines cannot be considered individualized size trajectories [5].

Prescriptive Standards Because of the strict and comprehensive inclusion criteria, growth abnormalities are likely to be rare but still possible unless sample selection includes neonatal growth outcome information. Differences in growth potential are not taken into account so are again part of "normal variability." Again, group percentile lines cannot be considered individualized size trajectories [5].

There is also controversy over which biometric parameters to include in international standards [24–26]. Only skeletal parameters [more invariant between countries] have been proposed by one group [31], while other groups also include soft

tissue measures and estimated weight (more sensitive to socioeconomic factors [31]) [28, 29]. This difference in approach appears to be due to what the standards are designed to do. The former would provide a means for evaluating overall obstetrical performance of different *groups* [e.g., countries]. The latter would be most useful in determining the growth status of *individuals* in different groups.

Customized Percentiles These percentiles are limited by their availability only for birth weight. Previous studies have shown that birth weight may not be affected in neonates with clear evidence of growth restriction [9, 47, 48]. The demographic parameters in the "term optimal weight" function only account for <10% of the birth weight variability [49–51], and including sex and birth age increases the percentage to around 25% [49, 50]. Adding pathological variables [50] or using a more comprehensive set of size determinants [52] increased the percentage to no more than 36% of the variability. These results indicate that the "term optimal weight" is being derived from only a fraction of the birth weight determinants and thus is very unlikely to be "optimal."

The "proportionality curve" used to adjust for delivery before 40 weeks may or may not be valid as it is based on weight *estimates*, not actual weight measurements, that are derived from a parameter set that does not include a measure of fat/muscle [12]. Its use also assumes that *group percentile lines* are the actual growth trajectories of individual fetuses. This assumption has been tested against individualized growth trajectories generated from empirical estimates of individual growth potential in fetuses with normal neonatal growth outcomes [53]. The use of percentile lines as individual trajectories resulted in significantly larger systematic and random prediction errors, indicating that an *individual*'s growth does not follow *group* percentile lines.

Individualized Approach

An alternative to the group approach described above is called individualized growth assessment [IGA] [10]. This procedure uses each fetus as its own control, generating individual- and parameter-specific size trajectories and predicted birth characteristics from empirical estimates of growth potential. A detailed presentation of IGA and its implementation (individualized growth assessment program [iGAP]) has recently been published [5].

Estimating Growth Potential and Start Points

Growth in the 2nd trimester has been shown to be quite linear in fetuses with normal growth outcomes and those with growth restriction for one-dimensional measurements [54]. This has also been found for two-dimensional and three-dimensional parameters after linearization with the appropriate mathematical manipulation [2D, square root;

3D, cube root] [10]. Linear functions fit to 2nd trimester measurements can be used for two purposes: estimating growth potential and determining start points for all anatomical parameters in each fetus.

Start Points [SP] Fetal age is customarily determined from the first day of the last menstrual period [menstrual age {MA}] [22]. However, this is, on average, 2 weeks *before* there is a fertilized zygote and over a month before embryological development has produced the first structure [head] that will be measured as part of the prenatal growth profile [1, 22]. Since it is not logical to talk about the growth of an anatomical structure before it exists (at least microscopically), an estimate of the *start point* [5, 10] for each measured anatomical parameter is needed for all fetuses. Start point values can be obtained by extrapolating the line fit to 2nd trimester measurements back to where it crosses the MA axis (Fig. 1.1). On average, SP values are in good agreement with the embryological appearance ages for various anatomical structures [10]. The availability of SP values allows definition of a new time variable for IGA, the *duration of growth* [t = MA − SP] [5, 10].

Growth Potential Linear growth in the 2nd trimester implies that the nutritional requirements of these very small fetuses are easily satisfied in normal pregnancies and even those with future growth restriction [54]. Under these circumstances, growth of the fetus is being determined by other growth controllers, both known and unknown [5, 54]. This is one of the several characteristic of 2nd trimester growth velocities (Table 1.4) that has led to these empirical measurements being proposed as estimators of growth potentials [each biometric parameter has its own growth potential] [54]. Second trimester growth velocities can be calculated directly if only two measurements are available. With three or more, regression analysis can be used to fit a linear function. The slope of this linear function is

Table 1.4 Second trimester growth velocity estimates of fetal growth potentials

Characteristics of second trimester growth velocities
Measures of change in size with age, not size alone, so most appropriate *growth* measurements
Empirical measures reflecting the effects of both known and unknown growth determinants
Measured during pregnancy when fetal nutritional requirements are low, thus primarily reflecting intrinsic determinants of growth
Remain constant during the second trimester, consistent with intrinsic control of growth and adequate nutritional supply
Specify Rossavik size models that accurately predict third trimester size trajectories and birth characteristics in fetuses with normal neonatal growth outcomes
Similar second trimester growth in fetuses with normal growth, growth restriction, and macrosomia

This table gives the characteristics of second trimester growth velocities that support their use as estimators of the growth potential of different anatomical parameters

taken as an estimate of the growth potential for that parameter in the fetus being studied. At least two sets of measurements (anatomical measurement and menstrual age measurement) separated by 2–3 weeks must be available between 14 and 26–28 weeks, MA [5].

Rossavik Size Model Specification

Rossavik Model IGA utilizes the Rossavik size model [55, 56] to generate 3rd trimester size trajectories and predict anatomical birth characteristics:

$$P = c(t)^{k+st}$$

1. $P \equiv$ anatomical parameter value
2. $t \equiv$ time variable [t = MA−SP]
3. $c, k, s \equiv$ model coefficients

A Rossavik size model is completely specified when values for the start point and for coefficients c, k, and s are known. The method for determining SP values is given in Fig. 1.1. Values for coefficients c, k, and s have been determined for nine anatomical parameters [BPD, HC, AC, FDL, ThC, HDL, ArmC, AVol, and TVol] by regression analysis in 118 fetuses with normal neonatal growth outcomes [32]. Coefficient k was found to represent the anatomical characteristics of the measured parameters (Table 1.5). Since coefficient k reflects anatomical characteristics that do not change, it is held constant at its mean values (Table 1.5). Repeated regression analysis with a fixed k gave new sets of coefficients c and s [c*, s*], c* being linearly related to growth velocity (Fig. 1.4) and s* being linearly related to

Table 1.5 Coefficient k values for different anatomical parameters

Head measurements	Abdominal measurements
HC: 1.405 BPD, 1.367	AC: 1.043
HA: 2.624	AA: 2.180
HV: 4.056	AV: 5.206
Upper arm measurements	Thigh measurements
HDL: 1.355	FDL: 1.258
ArmC: 0.844	ThC: 0.878
AVol: 2.927	TVol: 3.030

This table presents the empirically determined mean values for the coefficient k of the Rossavik size model, obtained from fetal samples with normal neonatal growth outcomes. They illustrate how this coefficient is related to the anatomy of what is being measured
Deter et al. [32, 56]
HC head circumference, *HA* head profile area, *HV* head volume, *BPD* biparietal diameter, *AC* abdominal circumference, *AA* abdominal profile area, *AV* abdominal volume, *HDL* humerus diaphysis length, *ArmC* arm circumference, *AVol* partial arm volume, *FDL* femur diaphysis length, *ThC* thigh circumference, *TVol* partial thigh volume

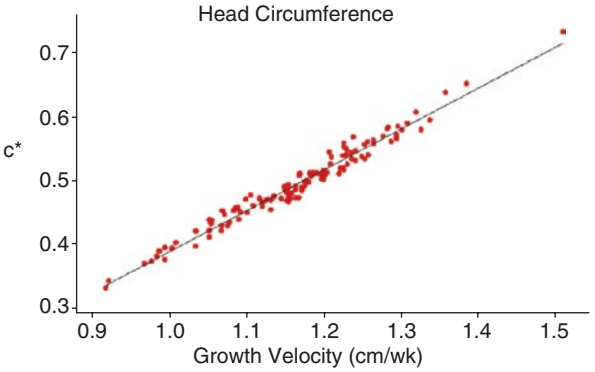

Fig. 1.4 Relationship of coefficient c^* to second trimester growth velocity. This figure demonstrates the strong linear relationship between coefficient c^* and the second trimester growth velocity of the head circumference in a sample of 119 fetuses with normal neonatal growth outcomes. The R^2 for this linear regression was 97.2% (see Table 1.6)

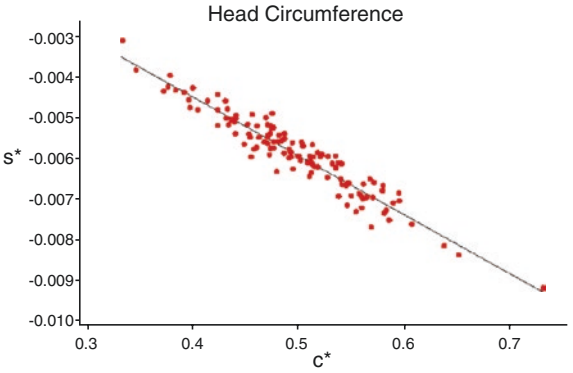

Fig. 1.5 Relationship of coefficient s^* to coefficient c^*. This figure demonstrates the strong linear relationship between coefficient s^* and c^* of the head circumference in a sample of 119 fetuses with normal neonatal growth outcomes. The R^2 for this linear regression was 91.3% (see Table 1.6)

Table 1.6 Mathematical functions used to obtain estimates of Rossavik size model coefficients

		$\log_e(c^*) = b_0 + b_1 \log_e(\text{slope})$			$s^* = c_0 - c_1(c^*)$		
Measurement	k	b_0	b_1	R^2	c_0	c_1	R^2
HC	1.405	−0.9326	1.4979	97.2	0.0013	0.0144	91.3
AC	1.043	−0.1306	1.3381	97.1	0.0060	0.0064	83.1
FDL	1.258	−0.0223	1.3665	97.7	0.0026	0.0448	88.7
HDL	1.355	−0.0196	1.4766	98.4	0.0016	0.0664	94.7
ThC	0.878	0.2952	1.1340	96.2	0.0076	0.0070	53.9
ArmC	0.844	0.4627	1.1779	96.2	0.0073	0.0084	53.9
AVol	2.927	2.0079	3.8187	97.1	0.0071	4.5928	75.3
TVol	3.036	1.2257	3.6705	97.5	0.0047	1.8970	69.5
BPD	1.367	−0.2207	1.4880	97.9	0.0016	0.0464	90.5

This table provides the functions needed to calculate estimates of the coefficient c^* from the slope of the linear function fit to second trimester measurements (growth velocity). It also gives the functions used to calculate estimates of coefficient s^* from coefficient c^*. Values for the coefficients k, c^*, and s^* specify a Rossavik size model in the second trimester

Deter et al. [32]

Note: *HC* head circumference, *AC* abdominal circumference, *FDL* femoral diaphysis length, *HDL* humeral diaphysis length, *ArmC* mid-arm circumference, *ThC* thigh circumference at level of mid-femoral diaphysis, *Hcube* head cube, *Acube* abdominal cube, *AVol* and *TVol* fractional arm and thigh volume, *BPD* biparietal diameter. HC and AC determined from short- and long-axis diameters