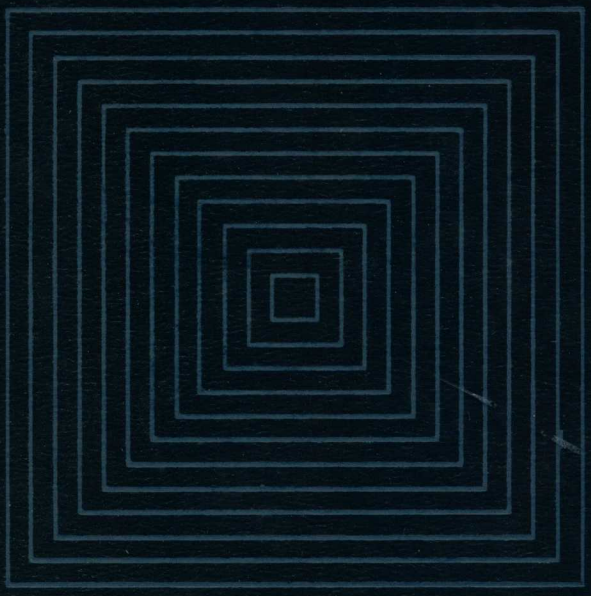
INTRAUTERINE GROWTH RETARDATION



A PRACTICAL APPROACH

Thomas L. Gross
Robert J. Sokol

INTRAUTERINE GROWTH RETARDATION
A Practical Approach

Thomas L. Gross, M.D.
Associate Professor and Chairman
Department of Obstetrics and Gynecology
University of Illinois College of Medicine at Peoria
Director of Maternal-Fetal Medicine
St. Francis Medical Center
Peoria, Illinois

Robert J. Sokol, M.D.
Professor and Chairman
Department of Obstetrics and Gynecology
Wayne State University School of Medicine
Chief, Department of Obstetrics and Gynecology
Hutzel Hospital
Detroit, Michigan

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To our parents,
Gilbert and Anna
Eli and Mildred

CONTRIBUTORS

José M. Belizán, M.D., Ph.D
Centro Rosarino de Estudios Perinatales
Rosario, Argentina

Richard A. Bronsteen, M.D.
Assistant Professor
Division of Maternal-Fetal Medicine
Wayne State University School of Medicine
Grace Hospital
Detroit, Michigan

Mitchell P. Dombrowski, M.D.
Assistant Professor
Division of Maternal-Fetal Medicine
Wayne State University School of Medicine
Hutzel Hospital
Detroit, Michigan

Mark I. Evans, M.D.
Director, Division of Reproductive Genetics
Wayne State University School of Medicine
Hutzel Hospital
Detroit, Michigan

Avroy A. Fanaroff, M.B., F.R.C.P.E.
Professor and Vice Chairman
Department of Pediatrics
Case Western Reserve University School of Medicine
Director of Neonatal Nurseries
Rainbow Babies and Childrens Hospital of University Hospitals of Cleveland
Cleveland, Ohio

Steven H. Golde, M.D.
Perinatologist, St. Joseph Medical Center
Burbank, California

Peter A. T. Grannum, M.D.
Associate Professor
Director of Medical Studies
Department of Obstetrics and Gynecology
Yale University School of Medicine
Director of High Risk Obstetrics
Yale-New Haven Hospital
New Haven, Connecticut

Thomas L. Gross, M.D.
Associate Professor and Chairman
Department of Obstetrics and Gynecology
University of Illinois College of Medicine at Peoria
Director of Maternal-Fetal Medicine
St. Francis Medical Center
Peoria, Illinois

Maureen Hack, M.B., Ch.B.
Associate Professor of Pediatrics
Case Western Reserve University School of Medicine
Neonatologist, Rainbow Babies and Childrens Hospital of University Hospitals of Cleveland
Cleveland, Ohio

Nadya J. Kazzi, M.D.
Assistant Professor of Pediatrics
Wayne State University School of Medicine
Associate Neonatologist
Hutzel Hospital
Detroit, Michigan

Robert M. Kliegman, M.D.
Associate Professor of Pediatrics
Case Western Reserve University School of Medicine
Associate Director of Neonatal Intensive Care Unit
Rainbow Babies and Childrens Hospital of University Hospitals of Cleveland
Cleveland, Ohio

Donald L. Levy, M.D.
Professor and Director
Division of Maternal-Fetal Medicine
Eastern Virginia Medical School
Santara Norfolk General Hospital
Norfolk, Virginia

Federico E. Mariona, M.D.
Clinical Professor of Obstetrics and Gynecology
Wayne State University School of Medicine
Oakwood Hospital
Dearborn, Michigan

Ronald L. Poland, M.D.
Professor of Pediatrics
Wayne State University School of Medicine
Director of Neonatal Services
Detroit Medical Center Affiliated Hospitals
Detroit, Michigan

Robert Resnik, M.D.
Professor and Chairman
Department of Reproductive Medicine
University of California at San Diego School of Medicine
San Diego, California

Vincent L. Smeriglio, Ph.D.
Associate Professor
Department of Maternal and Child Health
The Johns Hopkins University School of Hygiene and Public Health
Baltimore, Maryland

Robert J. Sokol, M.D.
Professor and Chairman
Department of Obstetrics and Gynecology
Wayne State University School of Medicine
Chief, Department of Obstetrics and Gynecology
Hutzel Hospital
Detroit, Michigan

José Villar, M.D., M.P.H., M.Sc.
Associate Professor
Department of Obstetrics and Gynecology
The Johns Hopkins University School of Medicine
Epidemiologist, Prevention Research Program
National Institute of Child Health and Human Development
Baltimore, Maryland

Steven L. Warsof, M.D.
Assistant Professor
Division of Maternal-Fetal Medicine
Eastern Virginia Medical School
Santara Norfolk General Hospital
Norfolk, Virginia

Robert A. Welch, M.D.
Assistant Professor
Department of Obstetrics and Gynecology
Wayne State University School of Medicine
Hutzel Hospital
Detroit, Michigan

Honor M. Wolfe, M.D.
Assistant Professor
Division of Maternal-Fetal Medicine
Wayne State University School of Medicine
Hutzel Hospital
Detroit, Michigan

FOREWORD

Despite our enhanced understanding of fetal physiology and the pathogenesis of many diseases complicating pregnancy, a common problem, intrauterine growth retardation (IUGR), has remained somewhat of an enigma. One of the reasons that the condition is so difficult to characterize is that the definition of IUGR is based on mean weight for gestation. Even if a uniform definition of the fifth percentile (or below) were agreed upon, those fetuses/infants falling below this threshold would include 5% of the normal population. The abnormal infants in this group have a very high perinatal mortality rate and are at increased risk of perinatal asphyxia and neonatal morbidity. Earlier studies also suggest that many growth retarded babies will ultimately be neurologically compromised.

In order to circumvent this inherent mortality and morbidity, the diagnosis must be made early in pregnancy and those fetuses that need increased attention must be identified. Today, it is not difficult to diagnose the undergrown fetus. In fact, with ultrasound it is not only possible to estimate fetal weight with reasonable accuracy, but to determine, by analysis of biometric data, whether the fetus is symmetrically or asymmetrically small. Since the small-for-dates fetuses that contribute most to perinatal mortality are those who are either anomalous, suffering from congenital infection, or are simply deprived, the thrust of today's diagnostic endeavors has been to identify these fetuses.

Improvement in ultrasound technology has allowed us to better diagnose fetal anomalies. Better understanding of congenital infections has enabled investigators to better identify the fetus whose primary growth curtailment is due to infection. Doppler ultrasound investigation has shown promise in singling out the small-for-dates fetus suffering from a faulty supply line. In addition, since many growth-retarded fetuses are hypoxic, it is hoped that percutaneous fetal blood sampling will provide a way to identify and treat the hypoxic fetus, often by timely delivery.

This comprehensive text chronicles the advances made in the last few years in our understanding of the various processes responsible for IUGR and provides an up-to-date version of the diagnosis and treatment of this potentially devastating problem.

John Hobbins, M.D.
Department of Obstetrics and Gynecology
Yale University
New Haven, Connecticut

PREFACE

This textbook is for clinicians only. It is intended to serve as a handbook for students and residents and as an update for the practicing physician on current standard management for intrauterine growth retardation. The scope of the book is broad, and readers with primary obstetric and pediatric interest will find it of value. The manuscript was written and edited to emphasize the clinical aspects and present an outline of the state-of-the-art management for the mother, the growth retarded fetus, and the small-for-gestational-age neonate and infant.

The book is divided into four parts: (1) why fetal growth retardation is important, (2) etiology and mechanisms, (3) diagnostic approaches, and (4) management. Part I defines fetal growth, normal and abnormal. Part II includes chapters reviewing the increased risk to the growth retarded fetus and neonate and, in addition, reviews the conflicting data regarding the long-term risk for abnormal neurodevelopmental outcome in the infant. Part III deals with etiology and includes chapters regarding maternal and placental causes and those associated with intrinsic fetal disease. In Part IV the diagnosis of fetal growth retardation is initially introduced from the standpoint of the clinical history and physical. The major diagnostic tool, i.e., prenatal ultrasound, is covered in detail in Chapter 10. Chapter 10 and its accompanying appendices include all of the information and growth tables needed for the physician to perform Level I ultrasound. A chapter on Doppler blood flow (Chapter 11) is included because of the rapidly expanding knowledge regarding fetal and umbilical blood flow and its relationship to growth retardation. Part V covers the approach to the management of intrauterine growth retardation: the maternal and fetal aspects in Chapters 12 and 13 and the neonatal in Chapter 14.

Chapter 14 gives the clinician caring for high risk newborns a standard approach to reduce morbidity in the small-for-gestational-age neonate from the delivery room to the intensive care nursery. Finally, as the book was being prepared two chapters were added to keep readers current on new concepts. Chapter 15 examines new ideas in invasive fetal therapy, and Chapter 17 reviews the ever present malpractice risk as it relates to the management of intrauterine growth retardation.

The rapid increase in our knowledge regarding antepartum, intrapartum, and neonatal risk in the growth retarded fetus and neonate has raised clinical suspicion to a high level so that ultrasound diagnosis can now allow us to

recognize most cases of fetal growth retardation prior to delivery. Of course, once the diagnosis of growth retardation is suspected, we need to search for an etiology. Even if it is not found, we now know that the general application of an intensive care approach both prior to labor and around the time of delivery can allow us to optimize outcome. This book has been edited to help the practicing clinician understand how to perform this intensive care management so that the fetal and neonatal outcome can be raised to the highest possible level.

Thomas L. Gross, M.D.

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Thomas L. Gross, M.D.

CONTENTS

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Definition of Fetal Growth: Normal and Abnormal

Steven H. Golde, M.D.

> Growth is the only evidence of life. . . John Henry Cardinal Newman, Apologia pro Vita Sua, 1864.

Growth is a basic fundamental of life. DNA replicates, cells enlarge and divide, tissues increase in mass, and organisms increase in size and weight. This constant drive to grow is no more evident than in the developing mammalian fetus. Structures form during embryogenesis in a strict sequence encoded by genes and guided by the physical and biochemical environment that surrounds them. Cellular change occurs and is balanced by the generation of new cells, each process keenly dependent on complex interactions between nature and nurture. The identification of growth disturbance would seem a field fully matured, with definitions that are concise and rigorously laid out. Such is not the case. As late as 1966 a major textbook in obstetrics declared that "healthy full-term children frequently weigh less than 3200 g and sometimes as little as 2300 g (5 pounds), although when the weight falls below 2500 g the child is premature *by definition.*"[1] The definition of gestational age in terms of neonatal weight stemmed from the recommendation of the American Academy of Pediatrics in 1935 and was designed to allow data comparisons between urban and impoverished rural areas. Growth, the underlying truth of biology, has been poorly studied in the human.

Since the abandonment of the concept that weight determines age, a host of terms have evolved to describe infants who demonstrate altered growth. Such terms as "small for gestational age" (SGA), "large for gestational age"

(LGA), and "intrauterine growth retardation" (IUGR) have served to focus attention on the special problems of infants with growth disturbance. Such shorthand terms, while focusing attention on a group at risk, may hide significant facts from analysis. Terminology is a double-edged sword serving first to categorize, then to explain a phenomenon. It is the purpose of this chapter to explore the definition of growth and its disturbance, point out current limitations in categorization, and offer some guidelines to categorization that may serve a broader diagnostic and therapeutic purpose.

CELLULAR GROWTH

Tissue growth is characterized by the processes of cell hyperplasia and hypertrophy. Both processes may occur in isolation or in concert. DNA content reaches a maximum before organ weight, suggesting that cell division stops within organs before growth stops.[2] Hyperplasia is a function of the rate of cell division. The higher the rate the greater the amount of tissue generated; hence the larger the animal. Studies conducted in rabbits showed that embryos of larger strains had greater cell numbers at any given point in development than did embryos of smaller strains, and also demonstrated higher rates of mitosis.[3,4]

Hyperplasia and hypertrophy are orchestrated by genetic and environmental influences throughout development and act in three distinct phases. During early fetal growth organ DNA content increases at the same rate as organ protein content. Growth thus is achieved by hyperplasia alone, because the ratio of DNA (a measure of cell number) to protein (a measure of cell size) remains constant. DNA synthesis then slows, but protein production continues at its previous rate. During this period hyperplasia and hypertrophy occur together. Finally, DNA synthesis stops, but net protein synthesis continues, an index of growth by hypertrophy alone.[5]

Insults occurring during these different growth phases are likely to have differing results. Malnourishment, hypoxia, chemical interaction, or all three, if present during the phase of hypertrophic growth, yield smaller offspring in rats, which then are capable of catch-up growth because their cell number remains undisturbed, but cell size is reduced. The cells "fatten" when nutrition is restored.[6,7] These same factors, if present during a period of hyperplastic growth, result in a decreased cell population that is unable to catch up if nutrients are supplied later.[8,9]

RATE OF HUMAN FETAL GROWTH

The rate of organism growth is determined by the sequence of organ system development and varies throughout gestation. Total growth is slow

while organs are forming during the first 2 months of fetal life. Growth accelerates sharply by the eighth week, and reaches maximum between 4 and 6 months. Slowing of growth occurs after this time, and remains fairly constant until 3 months of postnatal life.[10]

The mechanisms directing growth are not well understood. Genetics plays a large role. By 1889 Sir Frances Galton recognized that there was a constancy in the stature of populations, independent of differences in upbringing and correlating with mid-parental height.[11] It is currently believed that genetic regulation of stature is polygenic, with at least some of the genes located on both the X and Y chromosomes. Females are smaller than males, weighing on average 150 gm less at term than their male counterparts,[12] and their growth is ultimately more constrained.[13,14]

Though important in determining ultimate size, genetic growth potential is not especially critical in influencing size at birth. Infant birth weight correlates well with maternal weight but only poorly with weight of the father.[15] This was made obvious by the studies of Walton and Hammond[16] on cross-breeding of Shetland ponies and shire horses. Shire mares bred to Shetland stallions gave birth to foals three times larger than foals delivered from Shetland mares bred to shire stallions.

Women who are nutritionally deprived and thus small deliver infants who are also small.[17] There is also good correlation between maternal weight gain and birth weight.[18] The size of the placenta itself may serve to restrict fetal growth. If the fetal-placental weight ratio is compared, the growth-retarded fetus tends to be heavier in relation to the weight of the placenta,[19–21] suggesting that placental growth is impaired first. In contrast to growth-retarded fetuses, twin fetuses are lighter in relation to their placentas than would be expected.[22,23] Growth restriction in these cases may more relate to spatial constraints than to nutrient restriction.[24] Such spatial restriction may also account for the smaller size of firstborn infants.[25]

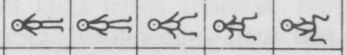
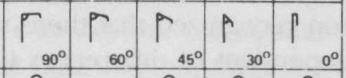
DEFINITIONS OF HUMAN FETAL GROWTH RETARDATION

Numerous attempts have been made to define populations at risk for adverse outcome due to measured growth disturbances. An early attempt by Battaglia and Lubchenco[26] demonstrated that birth weight and gestational age assessment at birth could be combined to demarcate infants at increased risk. This technique has been used to describe abnormal intrauterine growth and is carried out as follows. The neonate undergoes a physical and neurologic examination in which the factors examined are given points. The scoring has been empirically correlated with a gestational age. The gestational age obtained is then plotted on a nomogram along with the birth weight. Various levels have been used to define fetal growth retardation, including less than the 2.5th, 5th, or 10th birth weight percentile. The definitions most frequently

ESTIMATION OF GESTATIONAL AGE BY MATURITY RATING

Symbols: X · 1st Exam O · 2nd Exam

NEUROMUSCULAR MATURITY

	0	1	2	3	4	5
Posture						
Square Window (Wrist)	 90°	60°	45°	30°	0°	
Arm Recoil	 180°		100° 180°	90° 100°	< 90°	
Popliteal Angle	 180°	160°	130°	110°	90°	< 90°
Scarf Sign						
Heel to Ear						

PHYSICAL MATURITY

	0	1	2	3	4	5
SKIN	gelatinous red, trans-parent	smooth pink, visible veins	superficial peeling &/or rash, few veins	cracking pale area, rare veins	parchment, deep cracking, no vessels	leathery, cracked, wrinkled
LANUGO	none	abundant	thinning	bald areas	mostly bald	
PLANTAR CREASES	no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases cover entire sole	
BREAST	barely percept.	flat areola, no bud	stippled areola, 1–2 mm bud	raised areola, 3–4 mm bud	full areola, 5–10 mm bud	
EAR	pinna flat, stays folded	sl. curved pinna, soft with slow recoil	well-curv. pinna, soft but ready recoil	formed & firm with instant recoil	thick cartilage, ear stiff	
GENITALS Male	scrotum empty, no rugae		testes descend-ing, few rugae	testes down, good rugae	testes pendulous, deep rugae	
GENITALS Female	prominent clitoris & labia minora		majora & minora equally prominent	majora large, minora small	clitoris & minora completely covered	

Gestation by Dates _____ wks

Birth Date _____ Hour _____ am pm

APGAR _____ 1 min _____ 5 min

MATURITY RATING

Score	Wks
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

SCORING SECTION

	1st Exam=X	2nd Exam=O
Estimating Gest Age by Maturity Rating	_____ Weeks	_____ Weeks
Time of Exam	Date _____ Hour _____ am pm	Date _____ Hour _____ am pm
Age at Exam	_____ Hours	_____ Hours
Signature of Examiner	_____ M.D.	_____ M.D.

FIG 1–1.

Modified Dubowitz examination scoring sheet for determining pediatric estimate of gestational age. (Courtesy of Bristol Myers USPNG, Evansville, Indiana.)

used clinically are SGA—less than or equal to the 10th birth weight percentile—and LGA—equal to or higher than the 90th birth weight percentile (Fig 1–1). Although this is a very useful scheme and the most frequently used clinical method for defining fetal growth retardation, there are major sources of potential error. The data used to define the original growth curves were generated in a population at high altitude, an environment that may produce slower fetal growth. Other investigators have since redefined SGA neonates in their own populations near sea level, and these studies find that the data from the high altitudes often exclude 30% to 50% of neonates defined as SGA at sea level. Another major problem is that constitutionally small infants such as those normally born to small parents are classified as SGA by