NEONATAL NUTRITION AND METABOLISM

WILLIAM W. HAY, JR.

Neonatal Nutrition and Metabolism

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FOREWORD

Neonatal nutrition has been a major concern of pediatricians as growth is the province of pediatrics. Indeed, the beginnings of pediatrics as a specialty occurred with the development of foods to supplement or replace breast milk in the late 19th century. The host of formulas and books that were published competes in number and effectiveness with the number of articles and books published now on weight-reducing regimens.

For the next 100 years, pediatricians made numerous trials and experiments first to lower mortality, then to lower morbidity, then to improve long-term effects. With the development of hi-tech devices within the past third of a century nutrition as an area of study of the newborn was displaced as an area of research and practical interest. Pediatricians became more involved not only with mechanical devices but also with sophisticated metabolic studies and outcome studies of low-birth-weight and full-term infants.

As survival of infants improved in the past two decades infant nutrition has again become an added concern to both neonatologists and all those caring for children. As a result, major advances have occurred in the understanding of metabolic processes—an understanding that is applied not only to infants, but to children and adults as well. As a result, a host of informative articles and a number of books on infant nutrition have been published.

A need was recognized to collate knowledge in the diverse areas of nutrition and metabolism of the neonate. The result is the current volume, which summarizes in a delightfully readable form the bases for present clinical management. The road from basic science to applicability proceeds without detours. The considerations of practical methods of feeding and the avoidance of feeding problems and their treatment when they occur are detailed in a lucid manner. Complicated nutritional problems are not bypassed. Even some of the social problems are handled with finesse.

Feeding prematurely born and low-birth-weight infants properly requires familiarity with embryology and knowledge of physiological and biochemical development, as well as dietary requirements and limitations of the present information. All of these are addressed. A chapter on methods of feeding provides advice and empathy. The impact, limitations, and complications of tests and procedures are compared and contrasted with nutritional needs.

The interweaving of metabolic processes, nutritional demands, and social developments are presented, just as they occur in the growing and thriving neonate.

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PREFACE

Somewhere between what we feed to babies and the molecular biology of cellular biochemistry lies the interaction of nutrient substrate supply and the metabolism, for energy and for growth, of these substrates. This is the subject of this book. It is intended to provide a detailed examination of the general phenomena of neonatal growth and energy balance, and specific aspects of how different supplies of selected nutrients and various developmental and clinically significant conditions in the newborn infant (particularly those born prematurely and with altered fetal growth patterns) interact to produce special requirements for the use of nutrients for growth and for energy balance in these infants. All of this has grown out of my concern that at bedside teaching rounds in the newborn and intensive care nurseries, it has made much more sense (to me) to encourage students (of all kinds) to think of why different nutrient supplies might be important because of how they are used rather than according to a more traditional "intake and output" balance. This approach has proven useful for medical students, nursing students, nurse "specialist" trainees, residents in pediatrics and neonatology, and colleagues in basic science and clinical disciplines. This joint interest of clinicians and scientists also has shaped this book to include an important mixture of practical clinical material and more detailed accounts of metabolic phenomena. Central to all of these issues is my major concern that babies and their nutrition, growth, and health will benefit from clinicians and scientists thinking and working together, just as nutrient substrates and their metabolic interactions combine to successfully produce normal growth and the energy to thrive.

William W. Hay, Jr., M.D.

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WILLIAM W. HAY, JR., M.D.

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PART I

Growth and Energy

Chapter 1

Intrauterine Growth

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INTRAUTERINE GROWTH

Human intrauterine growth has received considerable attention in recent years. In obstetrics, intrauterine growth remains a most important sign of fetal well-being; in neonatal care, many therapeutic strategies are directed at matching rates of intrauterine growth.[1] Moreover, treatment of infants whose growth has been restricted by a process of intrauterine growth retardation presents clinical challenges in both acute management and long-term follow-up. Expanded clinical capabilities in both obstetrics and neonatology, better understanding of the physiology and pathophysiology of the fetus and premature infant, and changing attitudes, among other factors, have led to dramatic reductions in morbidity and mortality rates in small premature infants.[2, 3]

It is almost paradoxical, then, in an era of rapidly expanding clinical technology as well as rapid scientific advances at the molecular level, that clinicians and scientists alike are increasingly interested in reexamining a relatively old literature employing classic technologies to describe human intrauterine growth and nutrient accretion. Many cited observations of physical and chemical growth considerably predate modern analytic techniques, accurate assessment of gestational age, or modern statistical analysis.

While perinatologists have developed enormously their abilities to evaluate and treat neonates—and to an increasing extent, the fetus—this technology does not intrinsically supply "yardsticks" for understanding the newer technologies. Reassessment of older approaches may be increasingly important in providing a foundàtion for integration of concepts relating to intrauterine growth.

Definitions

Several important concepts and definitions underlie considerations of intrauterine growth. First, one should note the many terms in common usage to describe variations in fetal growth (Table 1–1). *Low-birth-weight (LBW)* and *very low birth weight (VLBW)* describe infants with birth weights less than 2,500 g and 1,500 g, respectively. These terms do not incorporate a concept of gestational age. In contrast, *small-for-gestational age (SGA)* or *small-for-dates* refers to those infants below the 10th percentile in growth,

TABLE 1–1.
Terminology Basic to Intrauterine Growth Studies

Term	Definition
Low birth weight (LBW)	Birth weight < 2,500 g
Very low birth weight (VLBW)	Birth weight < 1,500 g
Macrosomic	Birth weight > 4,000 g
Premature	Gestational age < 38 wk
Postmature	Gestational age > 42 wk
Large-for-gestational age (LGA)	Percentile > 90%
Appropriate-for-gestational age (AGA)	Percentile between 10% and 90%
Small-for-Gestational age (SGA)	Percentile < 10%
Intrauterine growth retarded (IUGR)	Process of growth restriction

adjusted for gestational age; *large-for-gestational age (LGA)* or *large-for-dates* refers to infants above the 90th percentile, adjusted for gestational age. Those between 10th and 90th percentile in growth are termed *appropriate-for-gestational age (AGA).*

Second, in common usage, *intrauterine growth retarded (IUGR)* is often used synonymously with SGA. However, within this chapter, IUGR will be used to denote a pathophysiologic process resulting in restriction of fetal growth, whereas SGA will refer to a statistical grouping of infants below the 10th percentile. From a practical standpoint, there may be considerable overlap of the two groups; however, at a conceptual level, the distinction may be important. Statistically, 10% of infants should be below the 10th percentile regardless of medical intervention, and this group may reflect biologic diversity as well as restriction of growth. In contrast, a fetus who by clinical or ultrasound criteria has stopped growing, but is delivered before the 10th percentile crosses the estimated weight, may be considered as subject to a process that restricts growth, even if AGA. If the processes restricting growth result in other long-term consequences, then it would be reasonable to regard such infants as at risk, even if above an arbitrary percentile.

Third, estimations of the duration of pregnancy present recurrent problems. The importance of dating gestation is a historically modern concept, and many earlier studies relate development to weight, length, foot length, or other indices of fetal size. Gestational duration may be dated from the last menstrual period, conception, or implantation. Alternatively, gestation may be staged by the developmental stage of the fetus, as is commonly referenced in early embryology.

Clinically, events are generally dated in terms of *gestational age,* which estimates age from the first day of the last normal menstrual period (LMP). The *estimated date of confinement* (EDC) is the projected date of delivery, measured from the LMP. Näegele's rule calculates the EDC as the date of the first day of the last menstrual period, less 3 months, plus 1 week. Dated from the time of the LMP, the average duration of pregnancy is 279 ± 17 days.[4] Embryologic *postconceptional age* is measured from the time of conception. Since the time of conception is generally not known accurately, the clinical use of LMP dating is reasonable. However, gestational age differs from postconceptional age by the time from LMP to conception, typically about 2 weeks. Estimation of gestational age becomes difficult in the presence of irregular or abnormal menstruation.

Other terms have also been used, including *fetal age* or *developmental age,* measuring from the time of implantation. Additionally, in literature on the newborn, *corrected age,* dating actual postnatal age from the EDC, is frequently used in newborn follow-up to adjust for differences in prematurity. Thus, an infant 6 months post delivery at 32 weeks might be considered as 4 months corrected age.

The accuracy of gestational dating poses some serious conceptual problems. In clinical practice, LMP data is not infrequently unavailable or unreliable, and estimations must be made from other clinical criteria of actual gestational age. In obstetric practice, physical examination and ultrasound assessment of growth and development provide assessment of gestation. Similarly, in the neonatal period, assessments proposed by Dubowitz et al.,[5] Ballard et al., [6] and Lubchenco,[7, 8] which are based on both neurologic and physical findings, are used to estimate gestational age in neonates. Each of these examinations ultimately calibrated its estimate of gestational age on maternal dates, and each has an error of about ± 1 to 2 weeks. Both the obstetric and neonatal examinations provide useful estimates of gestational age where LMP data are unavailable or obviously incorrect. However, "correction" of gestational age by these examinations invites circularity in reasoning and complexity in interpretation of abnormal growth patterns. Infants may not infrequently be categorized differently, depending on which gestational age (e.g., LMP, neonatal examination, fetal ultrasound) is used.

Finally, it is important to recognize that measurements of fetal growth depend both on the timing of the measurements and the techniques used to make such measurements. Each neonatal gestational age assessment has an optimal time of performance to achieve accuracy and precision. With increasingly short neonatal hospital stays, the examinations may be performed outside this optimal period.

Widely used curves of "intrauterine growth" typically span the last trimester with either serial or cross-sectional measurements. Many standard "growth curves," including those of Lubchenco et al.,[9] Usher and McLean,[10] and Gruenwald[11] are in fact cross-sectional measurements collected near the time of birth, and do not represent serial measurements in the same subject over time. While limitations of this approach will be discussed in detail later, it is important to note that these types of somatic measurements are subject to both measurement errors and conceptual concerns.

Ultrasound has more recently provided serial estimates of fetal growth in individual subjects during pregnancy. This technology has advanced rapidly, with greatly increased precision and accuracy of fetal measurement. Nonetheless, in many studies, the measurement error is large relative to fetal size, complicating interpretation of such curves.

Stages of Intrauterine Growth

From a conceptual point of view, three periods appear important for intrauterine growth. The *preconceptional period* includes the time leading up to conception. The *embryonic period* includes time from conception through embryogenesis and the development of all major organ systems. For the human, this includes the first 8 weeks of development. The *fetal period* spans from the end of the embryonic period through delivery. Each of these intervals may impact on development and growth; however, the issues are somewhat different for each period.

Periconceptional Issues

There is evidence that alterations in the maternal milieu may impact subsequent development of the conceptus. The mechanisms of such effects are generally poorly understood, but may include genetic, nutritional, biologic, and environmental factors.

Biologically, maternal weight and nutritional status may affect the environment in which conception is to occur. Body fat appears to be related to normal reproductive function. Loss of body fat through undernutrition or intensive exercise may lead to loss of reproductive function; refeeding may restore it. Early in human pregnancy, women ordinarily begin to store fat; they continue to do so through the second trimester. A rapid rate of maternal fat deposition is shared by many species.[15]

An interesting epidemiologic literature also describes the impact of maternal events on fetal growth. For example, early menarche,[16] low prepregnancy weight [17, 18] and low prepregnancy height,[19] and short interpregnancy interval[20, 21] have each been associated with shifts in growth curves or increased risk of delivering a small baby. Of perhaps more concern are epidemiologic data suggesting that a history of delivery of a prior growth-retarded infant predisposes to an increased risk of growth retardation in subsequent pregnancies.[17, 22] Indeed, there is evidence that growth retardation may span generations. Careful review of maternal birth weight and infant birth weight suggests that mothers who were themselves of low birthweight are more likely to produce LBW infants.[23]

It is also likely that maternal genetic variations affect fetal growth. There are differences in growth curves in different geographic regions and among different racial and ethnic groups within the United States. For example, evidence has been presented that blacks have several-fold higher rates of fetal death or delivering premature and SGA infants, after statistical correction for social and demographic factors.[24, 25] However, it is extremely difficult to factor environmental factors from true genetic differences, and such data should be interpreted cautiously.

Embryogenesis and Differentiation

During early growth and differentiation, teratogenesis is a major consideration, and there is also evidence that maternal periconceptional status may impact on embryogenesis and development. Major concerns have been expressed regarding teratogenicity of uncontrolled maternal diabetes, with the recommendation that good control be established before conception.[26, 27] More recently, evidence is accumulating that suggests a relationship between maternal vitamin status, particularly with regard to folic acid, and the frequency of neural tube defects.[28, 29] Similarly, there is evidence that some forms of vitamin A may be associated with a teratogenic syndrome.[30, 31] While mechanisms may be poorly understood, a variety of teratogenic factors may impact on differentiation, with an effect on fetal growth.

Fetal Growth

Many factors may impact on the rate of growth during fetal life. Such effects may be mediated by many mechanisms, including nutrition, hypoxia, environment, and genetic factors.[16–18] These will be discussed in detail later in the chapter.

Standards of Intrauterine Growth

Graphical standards for percentiles of birth weight, length, and head circumference of infants at increasing gestational age have become traditional tools in perinatal medicine. The curves of Lubchenco and associates (Fig 1–1),[7, 9] among others, are widely disseminated on clinical perinatal services, and the assessment of appropriateness for gestational age based on such standards has proved usefulness in projecting neonatal risks for mortality[2, 3, 9] as well as many morbidities, such as hypoglycemia.[32]