NeoReviews™
AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF THE PEDIATRICS

The Small-for-Gestational Age Infant

Patti J. Thureen, Marianne S. Anderson and William W. Hay, Jr

Neoreviews 2001;2;e139
DOI: 10.1542/neo.2-6-e139

The Small-for-Gestational Age Infant

Patti J. Thureen, MD,*
Marianne S. Anderson, MD,* William W. Hay, Jr, MD*

Objectives

After completing this article, readers should be able to:

1. Compare and contrast symmetric and asymmetric growth in small-for-gestational age (SGA) infants.
2. Describe common physical characteristics of the SGA infant.
3. Describe common problems encountered in SGA infants and their management.
4. Characterize postnatal growth and neurodevelopmental outcomes of SGA infants.

Introduction

More than 50 years ago, pediatricians and early "neonatologists" observed that newborns who had birthweights that were statistically less than the 10th percentile or 2 standard deviations below the mean weight for their gestational age experienced unique medical problems. These infants, termed small for gestational age (SGA), had more frequent problems with perinatal depression ("asphyxia"), hypothermia, hypoglycemia, polycythemia, long-term deficits in growth, and neurodevelopmental handicaps and higher rates of fetal and neonatal mortality (Fig. 1). Despite improvements in perinatal diagnosis and treatment, SGA infants are still born regularly (more frequently in underdeveloped countries, but also in the United States and other developed areas), and their perinatal morbidity and mortality rates continue to exceed those of normal fetuses and infants.

As the specific morbidities associated with SGA infants were recognized, relatively standardized approaches to their evaluation and clinical management were established. However, there always have been conflicting data in the literature regarding differences between SGA and appropriate-for-gestational age (AGA) infants in areas such as long-term outcome, nutrient metabolism, and growth potential. Recent literature suggest that adults who experienced severe growth restriction in utero have a significantly increased incidence of hypertension, insulin resistance, and type 2 diabetes. Additionally, new evidence suggests that untoward metabolic events in utero that produce fetal growth restriction also may produce lifelong alterations in growth and development.

Two distinct groups of infants are "undergrown" at birth. SGA infants, as determined by having a birthweight less than 2 standard deviations below the mean for infants of the same gestational age, have the capacity to grow normally. At birth, this population of infants may demonstrate a number of the clinical problems associated with being SGA that will be discussed later in this article. The second group of infants experience intrauterine growth restriction (IUGR) for a variety of reasons and have a decreased capacity for normal growth. The decreased fetal growth rate associated with IUGR is an adaptation to an unfavorable intrauterine environment and may result in permanent alterations in metabolism, growth, and development. The conflicting data regarding long-term outcome and metabolic differences between SGA and AGA infants may be due in part to most studies of SGA infants including a heterogeneous mixture of neonates who are grouped according to weight relative to a population mean without recognition of their metabolic diversity. Only recently have SGA infants begun to be differentiated and classified according to short- and long-term metabolic and problem-specific behavioral outcomes. Most of the information in this article focuses on issues directed toward the common and current concept of SGA infants. However, where data are available, specific reference will be made to information in IUGR versus SGA infants.

*Section of Neonatology, Neonatal Clinical Research Center, and the Division of Perinatal Medicine, Department of Pediatrics, University of Colorado School of Medicine, Denver, CO.

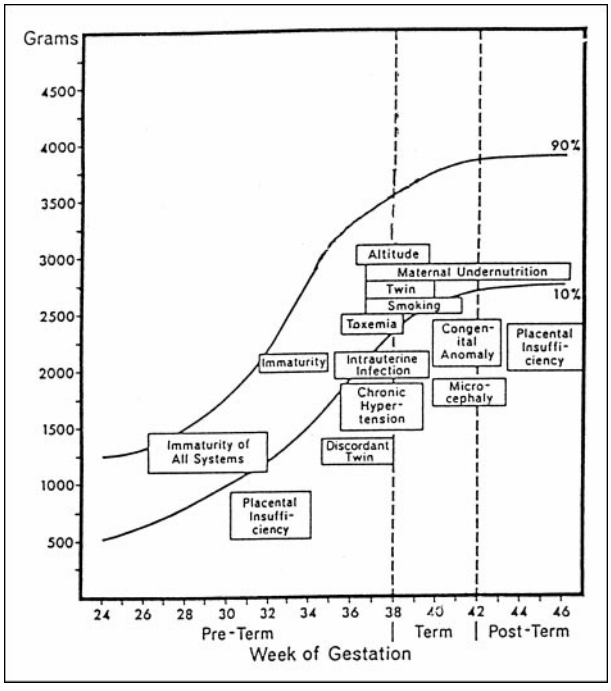

Figure 1. Morbidities specific to SGA infants. Adapted from Lubchenco LO. *The High Risk Infant.* Vol. XIV. In: Schaffer AJ, Markowitz M, eds. *Major Problems in Clinical Pediatrics.* Philadelphia, Pa: WB Saunders; 1976.

Definitions

Symmetric and Asymmetric Growth Restriction

SGA infants traditionally have been defined as those whose birthweights are more than 2 standard deviations below the mean or less than the 10th percentile of population-based weight data obtained from infants at the same gestational age. In addition to weight, other defining criteria have included anthropometric indices, such as length and head circumference. Using these measurements, SGA infants generally have been categorized as "asymmetrically" (weight proportionately less than length and head circumference) or "symmetrically" (all growth indices proportionately small) SGA. Infants whose weight is greater than the 10th percentile but who are thin relative to their length and head circumference measurements also should be considered SGA. For example, an infant is considered "relatively" SGA if the weight is at the 25th percentile, but the length and head circumference are at the 75th percentile. The weight/length ratio (or the ponderal index = [weight, g] / [length, cm]^3) is less than normal for such an infant, suggesting that growth rates of adipose tissue and skeletal muscle, the principal determinants of weight, are less than normal, although bone and probably brain growth are not (Fig. 2).

Symmetric growth implies that both brain and body growth are about equally less than normal; asymmetric growth implies that body growth (primarily weight, but may also include length) is restricted more than growth of the head and, thus, the brain. However, asymmetric growth in SGA infants affects other organs beyond the brain. Even moderately SGA infants have growth restrictions of both brain and body, but to varying degrees that depend on the duration and severity of the growth-restricting influences. Asymmetric and symmetric growth restriction are the extremes of a continuum of growth patterns.

Classification of Size by Birthweight

A rather complex classification of size based on birthweight has evolved over the past 20 years because of the increasing survival rates among neonates and the recognition that neonates of different birthweights have rather unique sets of physiology and pathophysiology at the same chronologic age. Thus, newborns are referred to as having normal birthweight (>2,500 g), low birthweight (LBW) (<2,500 g), very low birthweight (VLBW) (<1,500 g), and extremely low birthweight (ELBW) (<1,000 g). Recently, the less formal term "micropremie" has been used by some to identify ELBW infants who weigh less than 750 g at birth. Classification only by weight, however, does not indicate the cause of low birthweight or the rate of fetal growth rate because most infants who have less-than-normal birthweights simply have shorter-than-normal gestations (ie, they were born preterm). It also is inappropriate to classify newborns as preterm or term only on the basis of birthweight, as was the practice of the World Health Organization and many pediatric authorities for many years, because many infants who have IUGR are SGA at any gestational age.

Etiology

Normal human fetal birthweights at term vary almost two-fold, depending on the reference population. For example, the mean birthweight of neonates born in New Guinea is only 2,400 g compared with normal birthweights in some European populations that often exceed 4,000 g. These and other normal anthropometric variations are determined by differences in genetic and environmental factors, but must be considered in relation to the diagnosis of SGA within each relatively unique population.

Factors intrinsic to the fetus generally cause symmetric growth restriction and tend to develop early during fetal life. These can include chromosomal anomalies, congenital infections, dwarf syndromes, various inborn

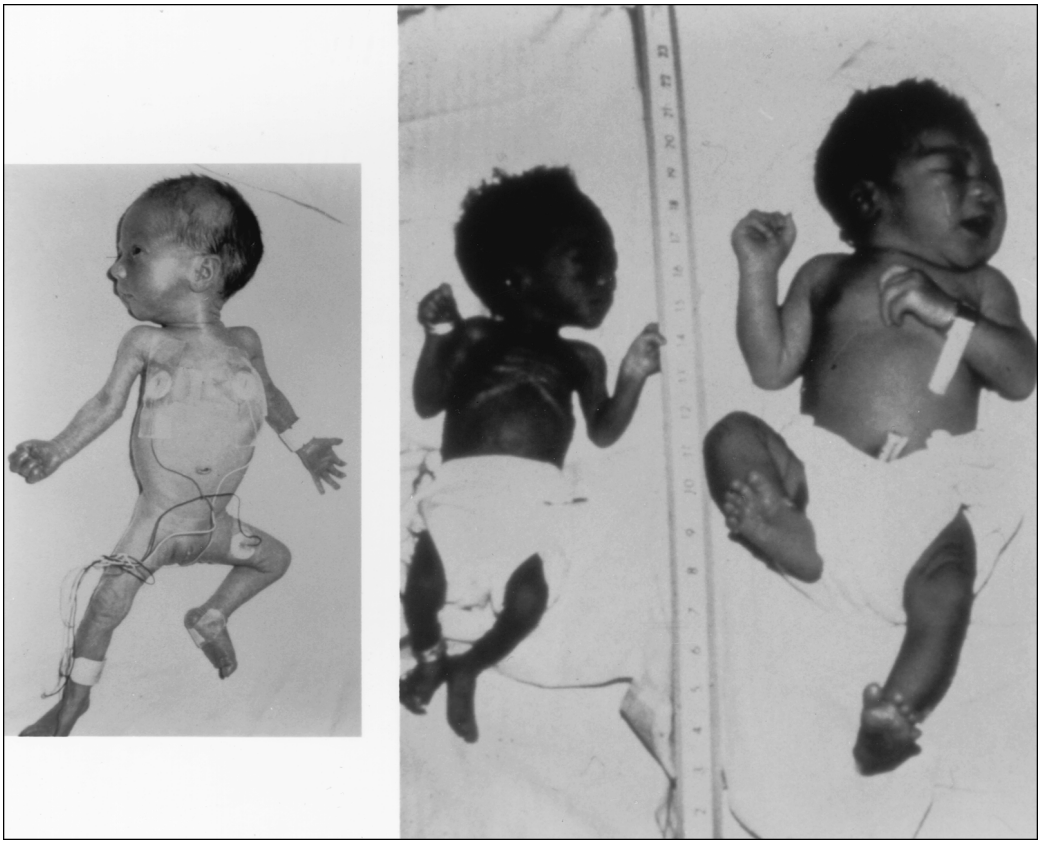

Figure 2. Preterm SGA infant at 34 weeks' gestation (left), severely SGA infant at 39 weeks' gestation (middle), and AGA infant at 40 weeks' gestation (right). From Anderson MS, Hay WW Jr. Intrauterine growth restriction and the small-for-gestational-age infant. In: Avery GB, Fletcher MA, MacDonald MG, eds. *Neonatology*. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 1999:411–444.

errors of metabolism, and some drugs. Approximately 30% to 50% of extremely preterm neonates (<1,000 g birthweight and generally <27 weeks' gestation) are SGA, probably reflecting pathology that both produced growth restriction and led to preterm birth. Asymmetric growth restriction more commonly develops later in gestation, when limitations of external factors such as nutrients restrict fetal growth. More extreme limitations of nutrient substrates for longer periods of gestation affect both growth and energy storage. If nutrient supply is decreased early in gestation, growth of all body organs is restricted; decreased fetal nutrient supply later in gestation primarily restricts growth of glycogen content, adipose tissue, and skeletal muscle. Although the most common etiology of SGA at birth is "placental insufficiency" from a variety of causes, there are numerous etiologies of both asymmetric and symmetric growth retardation, some of which are listed in Table 1.

Physical Findings of the SGA Infant

Most mild-to-moderately SGA infants appear smaller than normal and somewhat thin. More severe SGA is characterized by relatively large heads for the size of the body, a small or scaphoid appearing abdomen, "scrawny" arms and legs, decreased subcutaneous tissue, dry and loose-appearing skin, and often a thin umbilical cord. In term and post-term severely affected infants, the face appears shrunken or "wizened," the anterior fontanelle may be large from diminished membranous bone formation, fingernails may be long, and the hands and feet tend to look large for the size of the body. Because of frequent meconium passage in utero, the umbilical cord and nails may be stained green or yellow.

Gestational age is difficult to determine and often inaccurate when based on physical criteria alone because processes that affect fetal growth also affect physical appearance. Vernix caseosa often is reduced or absent

Table 1. Etiologies of Small Size for Gestational Age at Birth

Maternal Factors

- Both young and advanced maternal age
- Maternal prepregnancy short stature and thinness
- Poor maternal weight gain during the latter third of pregnancy
- Maternal illness during pregnancy (diabetes, preeclampsia)
- Nulliparity
- Failure to obtain normal medical care during pregnancy
- Cigarette smoking, cocaine use, other substance abuse
- Lower socioeconomic status
- African-American ethnicity (in the United States)
- Uterine and placental anomalies (see below)
- Polyhydramnios
- Intrauterine infections

Fetal Factors

- Chromosomal abnormalities (eg, trisomies) and syndromes
- Metabolic disorders
- Congenital infections (eg, toxoplasmosis, rubella, cytomegalovirus)
- Metabolic disorders

Medications

- Amphetamines
- Antimetabolites (eg, aminopterin, busulfan, methotrexate)
- Bromides
- Cocaine
- Ethanol
- Heroin and other narcotics (eg, morphine, methadone)
- Hydantoin
- Isotretinoin
- Metals (eg, mercury, lead)
- Phencyclidine
- Polychlorinated biphenyls (PCBs)
- Propranolol
- Steroids
- Tobacco (carbon monoxide, nicotine, thiocyante)
- Toluene
- Trimethadione
- Warfarin

Placental and Uterine Abnormalities

- Avascular villi
- Decidual or spiral artery arteritis
- Infectious villitis (as with TORCH infections)
- Multiple gestation (limited endometrial surface area, vascular anastomoses)
- Multiple infarctions
- Partial molar pregnancy
- Placenta previa and abruption
- Single umbilical artery, umbilical thrombosis, abnormal umbilical vascular insertions
- Syncytial knots
- Tumors, including chorioangioma and hemangiomas

due to diminished skin perfusion during periods of fetal distress or depressed synthesis of estriol, which normally enhances vernix production. Without vernix, skin that is exposed continuously to amniotic fluid desquamates. This also affects the sole creases, which appear deeper, wider, and in a more mature pattern. Breast tissue formation also depends on peripheral blood flow and estriol levels and will be reduced in SGA infants. Generalized decreased subcutaneous tissue makes the female external genitalia appear less mature because of decreased perineal adipose tissue covering the labia. Even ear cartilage may be underdeveloped, producing a less mature-appearing ear structure.

SGA infants often appear to have advanced neurologic maturity, although this observation is derived primarily from comparisons with infants of similar birthweight rather than similar gestational age. Active and passive tone and posture are usually normal in SGA infants and are reliable guides to gestational age unless significant central nervous system or metabolic disorders are present. Mild-to-moderately SGA infants often appear "hyperalert" and somewhat anxious, and they frequently are jittery and hypertonic, even without simultaneous hypoglycemia. Tone can vary considerably from hypertonia to hypotonia. The Moro response is increased. More severely affected infants appear apathetic. They tend to show abnormal sleep cycles and a more consistent picture of diminished muscle tone, deep tendon and facial tactile reflexes, general physical activity, and excitability; overall, they appear floppy and are easily exhausted with handling. These more severe changes imply that central nervous system (CNS) function is impaired.

Physical examination of the SGA infant must include a detailed search for abnormalities that may provide clues to the etiology of small size. Dysmorphic features, "funny-looking" facies, abnormal

Table 2. **Clinical Problems of the Small-for-Gestational Age Neonate**

Problem	Pathogenesis/Pathophysiology	Prevention/Treatment
Intrauterine death	Chronic hypoxia Placental insufficiency Malformation Infection Infarction/abruption Preeclampsia	Antenatal surveillance Fetal growth by ultrasonography Biophysical profile Doppler velocimetry Maternal treatment: ? bed rest, ? O_2 Delivery for severe/worsening fetal distress
Asphyxia	Acute hypoxia/abruption Chronic hypoxia Placental insufficiency/preeclampsia Acidosis Glycogen depletion	Antepartum/intrapartum Adequate neonatal resuscitation
Meconium aspiration	Hypoxia	Resuscitation, including tracheal suctioning for definite, severe aspiration
Hypothermia	Cold stress Hypoxia Hypoglycemia Decreased fat stores Decreased subcutaneous insulation Increased surface area Catecholamine depletion	Protect against increased heat loss Dry infant Radiant warmer Hat Thermoneutral environment Nutritional support
Persistent pulmonary hypertension	Chronic hypoxia	Cardiovascular support Mechanical ventilation, nitric oxide
Hypoglycemia	Decreased hepatic/muscle glycogen Decreased alternative energy sources Heat loss Hypoxia Decreased gluconeogenesis Decreased counterregulatory hormones Increased insulin sensitivity	Frequent measurement of blood glucose Early intravenous glucose support
Hyperglycemia	Low insulin secretion rate Excessive glucose delivery Increased catecholamine and glucagon effects	Glucose monitoring Glucose infusion <10 mg/min/kg Insulin administration
Polycythemia/hyperviscosity	Chronic hypoxia Maternal-fetal transfusion Increased erythropoiesis	Glucose, oxygen Partial volume exchange
Gastrointestinal perforation	Focal ischemia Hypoperistalsis	Cautious enteral feeding
Acute renal failure Immunodeficiency	Hypoxia/ischemia Malnutrition Congenital infection	Cardiovascular support Early, optimal nutrition Specific antibiotic and immune therapy

Adapted from Anderson MS, Hay WW Jr. Intrauterine growth restriction and the small-for-gestational-age infant. In: Avery GB, Fletcher MA, MacDonald MG, eds. *Neonatology.* 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 1999:411–444.

hands and feet, and the presence of palmar creases, in addition to gross anomalies, suggest congenital malformation syndromes, chromosomal defects, or teratogens. Ocular disorders, such as chorioretinitis, cataracts, glaucoma, and cloudy cornea, in addition to hepatosplenomegaly, jaundice, and a blueberry-muffin rash, suggest a congenital infection.

Management of Clinical Problems (Table 2)

Management Issues At Delivery

SGA infants have a large surface area relative to bodyweight and, therefore, are prone to rapid heat loss. They should be placed promptly under an open warmer, dried, and covered with blankets. Infants who have severe SGA, particularly in conjunction with fetal distress, may have

cardiopulmonary difficulties at birth that require immediate evaluation and treatment, including meconium aspiration syndrome, hypoxemia, hypotension, mixed metabolic and respiratory acidosis, and persistent pulmonary hypertension.

Temperature Regulation

Compared with term infants, SGA infants have a narrow thermoneutral range. Heat production cannot match the rate of heat loss associated with continued environmental cold stress after birth. The rapid heat loss is due to the large head-to-body ratio, the exaggerated greater surface area, and the paucity of subcutaneous fat. SGA infants older than 30 weeks' gestation may have increased skin maturity and less evaporative heat loss than AGA infants of comparable weight, indicating that thermoneutral environments should be based on gestational age and not simply weight. Heat production may be impaired by concurrent hypoglycemia and hypoxia, which are common among these patients, because any associated CNS depression may prevent the increased muscular activity and catecholamine release seen with normal response to cold. Brain oxygen requirements in the SGA infant are high because brain tissue represents a large proportion of body weight. However, during the first few hours of life, oxygen consumption and heat production may be less than anticipated due to decreased available substrate. It is critical, therefore, that the SGA infant be resuscitated and nursed in a thermoneutral environment, especially until adequate substrate delivery can be provided.

Asphyxia

Perinatal hypoxia occurs with increased frequency among SGA infants, particularly those who have severe IUGR. In such cases, the already stressed, chronically hypoxic infant is exposed to the acute stress of diminished blood flow during uterine contractions. Cord blood lactate concentrations often are increased despite overall normal cord blood pH. The acute fetal hypoxia, acidosis, and cerebral depression may result in fetal death or neonatal asphyxia. Such conditions likely underlie the two-fold higher cesarean section rate in preterm SGA infants compared to preterm AGA infants, the increased incidence of low Apgar scores of SGA infants at all gestational ages, and the frequent need for resuscitation. Sequelae of perinatal asphyxia in both AGA and SGA infants can include hypoxic-ischemic encephalopathy, ischemic heart failure, glycogen depletion, meconium aspiration syndrome, persistent pulmonary hypertension, gastrointestinal hypoperistalsis and ischemia-induced necrosis leading to focal perforation, and acute renal tubular necrosis and renal failure.

Respiratory Distress

Surfactant deficiency respiratory distress syndrome is not increased in more mature SGA infants closer to term, despite the increased incidence of other forms of respiratory distress.

Hypoglycemia

Hypoglycemia is extremely common among SGA infants, increasing with the severity of IUGR. The risk of hypoglycemia is greatest during the first 3 days of life, but fasting hypoglycemia, with or without ketonemia, can occur repeatedly up to weeks after birth. Early hypoglycemia usually is due to diminished hepatic and skeletal muscle glycogen contents and is aggravated by diminished alternative energy substrates, including reduced concentrations of fatty acids from the scant adipose tissue and decreased concentrations of lactate from the hypoglycemia.

Deficient counterregulatory hormones also contribute to the pathogenesis of hypoglycemia in SGA infants. Catecholamine release is deficient during periods of hypoglycemia. Although basal glucagon levels may be elevated, exogenous administration of glucagon fails to increase glucose concentrations because of the decreased hepatic glycogen stores. Hyperinsulinemia, increased sensitivity to insulin, or both may contribute to a greater incidence of hypoglycemia, although there are few data available to prove this. SGA infants also demonstrate decreased gluconeogenesis and resolution of persistent hypoglycemia that is coincident with improved capacity for and rates of gluconeogenesis.

Blood or plasma glucose concentrations should be measured early and frequently for all SGA infants. Blood glucose concentrations should be maintained at greater than 2.5 mmol/L (45 mg/dL). Early enteral feeding usually can prevent hypoglycemia. In less mature infants or those who have other clinical problems, intravenous glucose should be administered at 4 to 8 mg/min per kilogram as soon after birth as possible. This initial infusion rate should be adjusted in response to frequent (every 30 to 60 minutes) measurements of blood glucose until the values are consistently greater than 2.5 mmol/L (45 mg/dL). Less frequent measurements should be continued until the infant tolerates reasonably full enteral feedings. Infants who have severe hypoglycemia (<2.22 mmol/L [20 mg/dL]) that persists for more than 10 to 30 minutes, coma, and seizures should be treated immediately with an intravenous "mini-bolus" of

10% dextrose in water at 200 mg/kg (2 mL/kg) followed by a glucose infusion of 10% dextrose in water at 4 to 8 mg/min per kilogram. Glucose concentrations should be measured at least every 30 minutes until they are consistently greater than 2.5 mmol/L (45 mg/dL). Infants at greatest risk of having severe hypoglycemia are those who have been asphyxiated and those who are the thinnest according to the ponderal index, indicating the least amount of body glycogen content.

Hyperglycemia

Very preterm SGA infants have developmentally low insulin secretion rates and plasma insulin concentrations, which may underlie the relatively common problem of hyperglycemia in ELBW SGA infants. Higher concentrations of counterregulatory hormones, such as epinephrine, glucagon, and cortisol, also may contribute, although only limited evidence supports this commonly held assumption. In contrast, administration of insulin to even preterm SGA infants usually produces prompt decreases in glucose concentration, indicating at least normal, and probably greater than normal, insulin sensitivity.

Polycythemia–Hyperviscosity Syndrome

SGA infants manifest an increased incidence of polycythemia that probably is related to chronic in utero hypoxia leading to increased erythropoiesis. Even when not polycythemic (venous hematocrit >0.60 [60%]), SGA infants have higher-than-normal hematocrit measurements. Approximately 50% of all SGA term infants have a central hematocrit greater than 0.60 (60%). Viscosity is related directly to venous hematocrit, and increased viscosity interferes with normal tissue perfusion. Although the incidence of hyperviscosity is about 5% in the general population, it is seen much more frequently (18%) in SGA infants in whom polycythemia is the most likely etiology. Most polycythemic infants remain asymptomatic, but SGA infants, particularly males, are at greater risk of symptoms and clinical consequences. Polycythemia may contribute to hypoglycemia, hypoxia, and an increased risk of necrotizing enterocolitis. Partial volume exchange transfusion should be considered for the symptomatic infant or asymptomatic infant who has a high hematocrit.

Specific Nutrient Metabolism

One of the major drawbacks to drawing conclusions about the nutrient metabolism of SGA infants from existing studies is the previously noted inclusion of heterogeneous groups of infants. Some studies compare AGA and SGA groups of infants who are of comparable gestational age and, therefore, presumably of comparable metabolic maturity; others compare groups of similar weight. Feeding schedules and the composition of nutrients in the feedings have not always been comparable. The definition of SGA infants has varied among studies, with some including infants who might be considered mildly SGA with infants demonstrating severe growth retardation. For all of these reasons, many aspects of nutrient metabolism in SGA infants are not well understood.

PROTEIN

SGA infants are particularly deficient in muscle mass, but information from a limited number of studies differ about how well such infants tolerate aggressive amino acid and protein nutrition. In general, nitrogen balance studies have not shown significant differences in protein digestion between AGA and SGA infants. More recent and informative studies have used stable isotopes, a technique that provides much more information about the dynamic aspects of protein metabolism. One such study concluded that SGA infants have a 20% to 30% increase in protein turnover rate, catabolism, and synthesis compared with AGA infants; another demonstrated a 20% decrease in protein turnover rate, catabolism, and synthesis. In the latter study, AGA and SGA infants had equal weight gain and composition of weight gain, prompting the researchers to conclude that the lower protein synthetic rate in SGA infants resulted in a more efficient protein gain/protein synthesis ratio. Two other studies concluded that AGA and SGA infants had equal protein turnover rates, although only one investigation noted increased nitrogen balance in SGA infants. Another study found decreased protein oxidation in SGA infants. It also has been suggested that protein turnover, synthesis, catabolism, and oxidation should be normalized to fat-free mass, the metabolically active component of the body, and not to total body mass, as generally is reported.

LIPID

SGA infants have lower plasma free fatty acid concentrations than normally grown infants. Fasting blood glucose levels in SGA infants directly correlate with plasma free fatty acid and ketone body levels. In addition, once fed, many SGA infants have deficient utilization of intravenous triglycerides. After the intravenous administration of triglyceride emulsion, SGA infants have high free fatty acid and triglyceride levels, but ketone body formation is attenuated. These observations indicate that the utiliza-

tion and oxidation of free fatty acids and triglycerides are diminished in SGA neonates. However, the duration of these postnatal alterations in lipid metabolism has not been well defined.

ENERGY

Because metabolic rate and oxygen consumption are related more to gestational age than birthweight, SGA infants have higher rates of oxygen consumption and total energy expenditure than less mature neonates of the same weight. For AGA and SGA infants studied at the same gestational age, data conflict regarding differences in the components of energy expenditure. However, most studies demonstrate an increase in resting energy expenditure per kilogram in SGA infants, probably due to a larger body weight percentage of metabolically active organs. Although some nutritional balance studies of preterm SGA infants have demonstrated an increase of fecal fat and protein loss, more recent investigations indicate adequate digestion of nutrients and percent nutrient retention of metabolizable nutrient intake. Thus, the majority of SGA infants can achieve normal energy intake rates on a per-kilogram basis. Anecdotally, many clinicians have observed SGA infants who take in large volumes of enteral nutrition compared to typical AGA infants and demonstrate significant "catch-up" growth.

Nutrition Management

Most SGA infants are deficient in both fat and muscle mass (see "Intrauterine Growth Restriction" in this issue). Thus, it seems logical that nutrition strategies in SGA infants, particularly for "catch-up" growth, should involve supplementation with extra protein and energy. Clinically, many SGA infants respond to this strategy. However, animal studies of significant fetal IUGR due to maternal protein restriction have demonstrated a shortened life span, particularly in males, when a "catch-up" strategy of markedly increased protein intake was administered postnatally. These findings, as well as the observation that fetuses who are IUGR due to in utero nutrient deprivation are prone to type 2 diabetes and other disorders, suggest that additional postnatal nutrient delivery to the subset of SGA infants that is severely IUGR may be "toxic" to a metabolism that has been permanently altered to ensure fetal survival. To date, large-scale rigorous trials of different rates and amounts of nutrition to such infants have not been conducted. Such trials are needed to determine whether these infants will tolerate more aggressive feeding safely and whether this will result in improved nutritional rehabilitation, growth, and perhaps, neurodevelopmental outcome.

Miscellaneous Problems

Immunologic function of SGA infants may be depressed at birth and may persist into childhood, as in older infants who have postnatal onset of malnutrition. Immunologic abnormalities have included decreased lymphocyte number and function, lower immunoglobulin levels during infancy, and an attenuated antibody response to oral polio vaccine. At birth, cord prealbumin and bone mineral content are low in term SGA infants. Calcium and iron stores may be low due to chronic decreased placental blood flow and insufficient nutrient supply. Significant hypocalcemia can occur after stressful birth complicated by acidosis. Thrombocyopenia, neutropenia, prolonged thrombin and partial thromboplastin times, and elevated fibrin degradation products may also be seen in SGA infants. Inguinal hernias are common among preterm SGA infants. The incidence of sudden infant death syndrome may be higher.

Mortality

The consequences of SGA depend on the etiology, severity, and duration of growth restriction. Considerable debate continues on this subject. Most studies have included heterogeneous groups of infants with respect to the degree and cause of IUGR, the degree of prematurity, and the severity of clinical problems in the early neonatal period. On balance, there is little evidence to support the concept of improved survival after "perinatal stress" in SGA infants, and the perinatal mortality rate for SGA infants with relatively severe IUGR is 5 to 20 times that of AGA infants of the same gestational age. Particularly when adjusted for maternal neonatal risk factors of IUGR, including birthweight percentile, gestational age at birth, maternal height, prepregnancy weight, gestational weight gain, race, and parity, a subgroup of SGA infants is defined that has consistently and markedly higher perinatal mortality and morbidity rates than normally grown infants.

Outcomes of SGA infants

Hospitalization

At term, SGA infants are admitted more frequently to the intensive care unit and have longer hospital stays than their AGA counterparts, and their incidence of readmission to hospital during the first year is significantly increased. Neurologic disorders and other morbidities requiring follow-up and hospitalization are more frequent among IUGR infants, occurring 5 to 10 times more

often than among AGA infants. SGA infants also are more likely to be hospitalized for serious respiratory infections.

Growth and Developmental Outcome

As noted previously, because most studies of SGA infants have involved a heterogeneous group of babies with the potential for a variety of outcomes, it is difficult to predict outcomes in SGA infants. Some affected infants are small from familial predisposition to small size and, therefore, may be expected to achieve their full growth potential and have normal neurodevelopment. Infants who have specific chromosomal errors or significant congenital infections are likely to experience severe and unrecoverable failure of growth and development. Most infants have a less defined reason for abnormal in utero growth. The infant who has symmetric growth restriction may have little chance for postnatal catch-up growth after an early, global disruption of growth. However, a neonate who had normal growth in early gestation, but developed growth restriction from limited nutrient availability in later gestation, likely has a reasonable potential for catch-up growth and normal development. Additionally, socioeconomic status and environment are among the most important, but difficult to control, variables affecting the growth and development of SGA infants.

Most studies of normal and restricted fetal growth and development support the concept of critical windows of time in human development during which normal growth of certain tissues (eg, fat, muscle, bone) or organs (eg, pancreas, brain) must occur. Insults at such times that limit growth can program persistent, even lifelong failures in growth and development. In rats, for example, undernutrition at a vulnerable period of brain development permanently decreases brain size, brain cell number, normal behavioral development, learning, and memory. Only relatively recently have studies of outcomes of IUGR and SGA infants included in the study design the recognition that the etiology of small size at birth carries great prognostic value. Because head size correlates with brain size, volume, weight, and cellularity, head growth at the time of birth and the degree of catch-up growth thereafter are prognostic of future neurodevelopment. Deficient fetal head growth, evidenced by relative microcephaly at birth, whether at term or preterm, is felt to be a poor prognostic indicator because it reflects the severity and duration of in utero growth failure. A lack of head sparing and small head circumference is associated with poor neurologic and psychological outcome. If catch-up head growth has not occurred by 8 months of age, head size is a predictor of lower intelligence test scores at 3 years of age. This correlation seems to be independent of environmental or other risks. Decreased head size when compared with siblings carries significant risks of deficient mental and motor function.

Postnatal Physical Growth of SGA Infants

As with developmental outcome, long-term growth probably depends most on the etiology and severity of fetal growth restriction. Many SGA infants continue to be smaller and relatively underweight for age as they grow older, even through adolescence and early adulthood. These infants more commonly have short stature as teenagers and young adults, indicating lifelong growth deficit.

Differences in patterns of early growth have been observed in SGA infants. Normal infants experience a period of rapid growth during the first 3 years of life. Adult size correlates with the individual growth curve after this time. Moderately affected SGA infants whose reduction in weight occurred primarily in the third trimester of gestation follow the same pattern of normal neonatal and infant growth, but tend to have an accelerated velocity of growth during the first 6 months of life. This catch-up growth occurs mostly from birth to 6 months of age, with some infants continuing an accelerated rate of growth for the first year. A few of these infants achieve a normal growth percentile and thereafter have a growth rate similar to appropriately grown children. Head circumference parallels growth in length during catch-up and sustained growth periods. After the first year, no difference in the rate of growth has been noted.

Ultimate weight and height are less in SGA children compared with their normal siblings. Interestingly, a subgroup of severely growth-restricted infants (<40% of expected birthweight) showed no difference in weight or height at 6 months of age compared with less-affected SGA peers, adding concern for the growth outcome of even modest degrees of IUGR. Former SGA infants had no delay in bone age, puberty, or sexual maturation at adolescence, although they were shorter, lighter, and had smaller heads. Muscle mass between the two groups was similar, but adipose tissue development was less in the SGA group.

Postnatal Neurodevelopmental Outcome of Term SGA Infants

Neurologic disorders and other morbidities are generally more frequent in SGA infants, occurring 5 to 10 times more often than in AGA infants. However, IUGR may have little impact on behavior or mental ability in adoles-

cence or adulthood among term, mild-to-moderately SGA infants who have normal brain growth, no hypoxic-ischemic injury, and good environmental support. The incidence of major handicap and risk of severe neurologic morbidity in term infants born SGA is not increased; cerebral palsy is infrequent. Findings on routine neurologic examination are usually normal. Although the absence of gross neurologic outcome in the term SGA infant is reassuring, evidence of minimal brain dysfunction continues to be of concern. Many studies have revealed signs of minor brain damage, including hyperactivity, short attention span, learning problems, poor fine motor coordination, and hyperreflexia.

Former term SGA infants more frequently have substandard school performance and display subtle neurologic and behavioral problems despite normal intelligence quotients. Sensorimotor abilities often are affected. Overall, poor early brain growth in infancy is associated with more problems. Measures of cognition at 4 to 6 years correlate well with test results at adolescence, which suggests that cognitive potential is reached early. It seems likely that environmental and socioeconomic factors play a significant role in the learning deficiencies seen in these children. At adolescence, trends toward lower test scores, especially in mathematics, and an increased incidence of learning disabilities have been noted. Most believe, however, that the cognitive and academic differences are small and do not significantly affect school performance or ultimate intellectual ability.

Postnatal Neurodevelopmental Outcome in Preterm SGA Infants

The prognosis for preterm SGA infants is less clear and is confounded easily by other problems of preterm birth. In general, subnormal intellectual outcomes are more common among preterm SGA infants than term SGA infants. Some authors have shown that infants who suffer the dual insults of preterm birth and growth restriction are at higher risk of neurodevelopmental deficit. Among extremely preterm infants, gestational age (not growth status) has been the most significant predictor of intellectual outcome. Socioeconomic status is independently associated with learning disabilities in these children.

ACKNOWLEDGMENTS

Supported in part by NIH Grant MO1 RR00069.

Suggested Reading

Allen MC. Developmental outcome and follow up of the small for gestational age infant. *Semin Perinatol*. 1984;8:123–156.

Barker DJP. Fetal and infant origins of adult disease [editorial]. *BMJ*. 1990;301:111

Fitzharding PM, Steven EM. The small-for-date infant. I. Later growth patterns. *Pediatrics*. 1972;49:671–681.

Fitzharding PM, Steven EM. The small-for-date infant. II. Neurologic and intellectual sequelae. *Pediatrics*. 1972;50:50–57.

Hack M. Effects of intrauterine growth retardation on mental performance and behavior outcomes during adolescence and adulthood. *Eur J Clin Nutr*. 1998;52:S65–S71.

Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. *N Engl J Med*. 1991;325:231–237.

Hawdon JM, Platt MPW. Metabolic adaptation in small for gestational age infants. *Arch Dis Child*. 1993;68:262–268.

Hutton JL, Pharoah POD, Cooke RWI, Stevenson RC. Differential effects of preterm birth and small gestational age on cognitive and motor development. *Arch Dis Child*. 1997;76:F75–F81.

Kok JH, den Ouden AL, Verloove-Vanhorick SP, Brand R. Outcome of very preterm small for gestational age infants: the first nine years of life. *Br J Obstet Gynaecol*. 1998;105:162–168.

Low JA, Handley-Derry MH, Burke SO, et al. Association of intrauterine fetal growth retardation and learning deficits at age 9 to 11 years. *Am J Obstet Gynecol*. 1992;167:1499–1505.

McCarton CM, Wallace IF, Divon M, Vaughn HG Jr. Cognitive and neurologic development of the premature, small for gestational age infant through age 6: comparison by birth weight and gestational age. *Pediatrics*. 1996;98:1167–1178.

Pena IC, Teberg AJ, Finello KM. The premature small-for-gestational-age infant during the first year of life: comparison by birth weight and gestational age. *J Pediatr*. 1988;113:1066–1073.

Sinclair J. Heat production and thermoregulation in the small for date infant. *Pediatr Clin North Am*. 1970;17:147–158.

Smart J. Undernutrition, learning and memory: review of experimental studies. In: Taylor TG, Jenkins NK, eds. *Proceedings of XII International Congress of Nutrition*. London, England: John Libbey; 1986:74–78.

Strauss RS, Dietz WH. Growth and development of term children born with low birth weight: effects of genetic and environmental factors. *J Pediatr*. 1998;133:67–72.

Sung I, Vohr B, Oh W. Growth and neurodevelopmental outcome of very low birth weight infants with intrauterine growth retardation: comparison with control subjects matched by birth weight and gestational age. *J Pediatr*. 1993;123:618–624.

Veelken N, Stollhoff K, Claussen M. Development and perinatal risk factors of very low-birth-weight infants. Small versus appropriate for gestational age. *Neuropediatrics*. 1992;23:102–107.

Westwood M, Kramer MS, Munz D, Lovett JM, Watters GV. Growth and development of full-term nonasphyxiated small-for-gestational-age newborns: follow-up through adolescence. *Pediatrics*. 1983;71:376–382.

NeoReviews Quiz

7. A newborn infant, whose estimated gestational age is 34 weeks, weighs 1,100 g (below the 10th percentile of the population mean), has a crown-heel length of 39 cm (10th percentile), and has a head circumference of 31.5 cm (50th percentile). Of the following, the *most* likely cause for this infant's growth pattern is:

   A. Chromosomal anomaly.
   B. Congenital infection.
   C. Inborn error of metabolism.
   D. Maternal drug exposure.
   E. Placental insufficiency.

8. You are examining a newborn who is small for gestational age. Maternal history is remarkable for late-onset hypertension and proteinuria. Of the following, the *most* likely finding on physical examination of this infant would be:

   A. Anxious facies.
   B. Cloudy cornea.
   C. Decreased Moro reflex.
   D. Microcephaly.
   E. Protuberant abdomen.

9. Metabolic adaptation at birth often is impaired in newborns who are small for gestational age (SGA). Of the following, the *most* common metabolic feature in an SGA infant is:

   A. Attenuation of ketone body formation.
   B. Decreased sensitivity to insulin.
   C. Deficient production of surfactant.
   D. Enhanced release of catecholamines.
   E. Reduced rate of oxygen consumption.

The Small-for-Gestational Age Infant

Patti J. Thureen, Marianne S. Anderson and William W. Hay, Jr

Neoreviews 2001;2;e139
DOI: 10.1542/neo.2-6-e139