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Intrauterine Growth Restriction and the Small for Gestational Age Infant

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▪ INTRODUCTION

The interest in studying intrauterine growth restriction (IUGR) that produces small for gestational age (SGA) infants began with the observation that newborn infants who were classified according to birth weight as small, average, or large for gestational age (SGA, AGA, and LGA, respectively) showed specific morbidities and rates of death that were unique to each of these birth weight-gestational age classifications (1). IUGR/SGA infants were recognized as having more frequent problems with perinatal depression (“asphyxia”), hypothermia, hypoglycemia, polycythemia, long-term deficits in growth, neurodevelopmental handicaps, and higher rates of fetal and neonatal mortality (**Fig. 23.1**). In addition, epidemiologic studies have consistently shown strong associations between IUGR/SGA birth and increased risk of developing heart disease, diabetes, and obesity later in life (2). Although there have been tremendous improvements in perinatal diagnosis and treatment, severe IUGR and the birth of markedly SGA infants continue to be frequent problems, and the perinatal morbidity and mortality rates of IUGR fetuses and SGA infants continue to exceed those of normal fetuses and infants.

▪ DEFINITIONS

Small for Gestational Age

SGA infants are defined as having a birth weight that is more than two standard deviations below the mean or less than the 10th percentile of a population-specific birth weight versus gestational age plot. Broader definitions include less than normal anthropometric indices, such as length and head circumference, and marked differences between growth parameters, even when they are within the normal range. For example, an infant can be considered “relatively” SGA when its weight is at the 25th percentile, but its length and head circumference are at the 75th percentile. In this case, the weight/length ratio (or the ponderal index = [weight (g)]/[length (cm)]^3) is less than normal, indicating that growth rates of internal organs, adipose tissue, and skeletal muscle, the principal determinants of weight, were less than normal.

Intrauterine Growth Restriction

IUGR is defined as a rate of fetal growth that is less than normal for the population and for the growth potential of a specific infant. IUGR therefore produces infants who are SGA, but also infants who are AGA who experienced reduced fetal growth rates *in utero*. SGA infants can be the result of normal but slower than average rates of fetal growth, such as those constitutionally small (1). Thus, small size at birth can be either a normal outcome or one that is a result of intrinsic or extrinsic factors that limit fetal growth potential. This distinction is important, because diagnosis by antenatal findings of IUGR such as Doppler velocimetry and fetal heart rate

abnormalities are more predictive of need for hospitalization and mortality than is classification of SGA or AGA according to standard neonatal growth curves (1).

Birth Weight Classification of Growth

Many terms are used to describe variations in fetal growth (see **Table 23.1** for the standard classification of fetal growth). Classification by weight alone says little about fetal growth rate, however, as most infants with less than normal birth weights are the result of a shorter than normal gestation, that is, they are preterm. Similarly, classifying newborns as preterm or term on the basis of birth weight is erroneous, as infants with IUGR are smaller than normal at any gestational age.

Normal Variations and the Assessment of Fetal Growth

Normal fetal growth varies almost twofold. For example, mean birth weight for neonates born in New Guinea is 2,400 g, whereas normal birth weights in other populations can exceed 4,000 g. Such variations are related to genetic and environmental factors, including local diets. Birth weight does not always represent differences in body composition, either, as intrauterine growth patterns contribute to the relative balance of fat versus lean mass. For example, infants born in India compared to infants born in the United Kingdom are lighter, shorter, and thinner, but have similar subscapular skin fold thicknesses, indicating smaller muscle mass but preserved fat mass (3). These and other normal anthropometric variations must be considered in relation to the diagnosis of IUGR in fetuses and SGA status of newborns.

Symmetric and Asymmetric Growth Restriction

SGA infants have been classified as having symmetric or asymmetric IUGR (**Figs. 23.2 and 23.3**). Symmetric IUGR implies that both brain and body growth are limited relatively equally. Asymmetric growth indicates that body growth is restricted to a much greater extent than head (and thus, brain) growth (1). In asymmetric cases, brain growth is considered "spared." Even though brain growth is spared relative to overall fetal growth, head circumference is frequently below the 10th percentile for gestational age (4), and there is reduced brain volume (5). The heart also is larger for body weight and "spared" in these infants, whereas the liver and thymus are smaller for body weight.

Mechanisms that allow brain growth to continue at a faster rate than peripheral tissues are not completely known. Contributing factors may include an increased rate of cerebral blood flow relative to the umbilical and systemic circulations (6). In some experimental models, cerebral glucose transporter concentrations are preserved despite fetal hypoglycemia, supporting cerebral glucose uptake capacity (7).

In general, factors intrinsic to the fetus cause symmetric growth restriction, whereas external factors cause asymmetric growth. Intrinsic factors that limit the growth of both the fetal brain and body include chromosomal anomalies (e.g., particularly trisomy conditions), congenital infections (toxoplasmosis, rubella, cytomegalovirus), dwarf syndromes, some inborn errors of metabolism, and some drugs. Due to their intrinsic nature, patterns of symmetric growth restriction develop early during fetal life.

Asymmetric growth restriction classically develops during the late second and third trimesters. This is due to reductions in energy substrate supply to the fetus, limiting fat and glycogen storage and the growth of skeletal muscle, but allowing for continued bone and brain growth. Indeed, extremely preterm neonates are often SGA and have asymmetric growth, probably reflecting common underlying pathology, like placental insufficiency, that produced growth restriction and preterm birth. More extreme limitations of nutrients for longer periods affect both growth and energy storage, producing reductions in length and head circumference as well as body weight and soft tissue mass. Timing is important; with decreased nutrient supply early in gestation,

growth of all body organs is restricted, whereas decreased fetal nutrient supply later in gestation primarily restricts growth of adipose tissue and skeletal muscle.

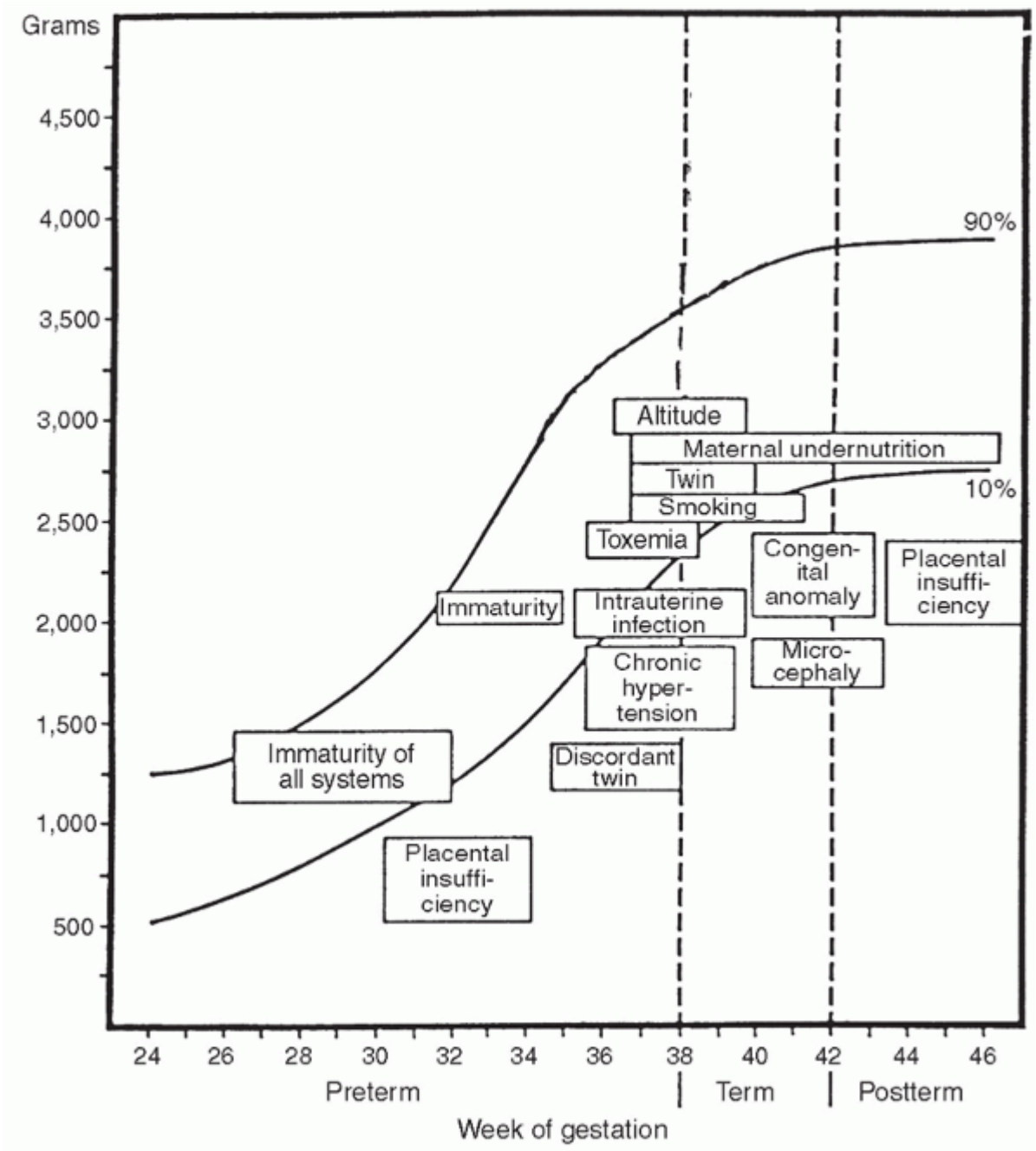


FIGURE 23.1 Morbidities specific to SGA infants. Adapted from Lubchenco LO. The high risk infant. In: Schaffer AJ, Markowitz M, eds. *Major problems in clinical pediatrics*, Vol. XIV. Philadelphia, PA: WB Saunders, 1976:6.

▪ INTERPRETATION OF FETAL GROWTH CURVES

Growth Curves Based on Neonatal Measurements

Cross-sectional growth curves have been developed from anthropometric data in populations of infants born at different gestational ages (8,9). Such curves have been used to demonstrate whether an infant's weight is within the normal range for a given gestational age and thus to estimate whether that infant's *in utero* growth was greater or less than normal.

Each curve is based on populations with variable composition of maternal age, parity, socioeconomic status, race, ethnic background, body size, degree of obesity or thinness, health, pregnancy-related problems, and nutrition. Estimating gestational age, in particular, has considerable error. Such error is derived from variability in dating conception because of maternal postimplantation bleeding and irregular menses, wide variability in the development of physical features of maturation in the infant, and interobserver variability in assessing an infant's developmental stage.

TABLE 23.1 Classification of Fetal Growth

SGA: Small for gestational age (birth weight <10th percentile for gestational age)
AGA: Average for gestational age (birth weight between 10th and 90th percentiles for gestational age)
LGA: Large for gestational age (birth weight >90th percentile for gestational age)
Normal birth weight: >2,500 g at term gestation
Low birth weight (LBW): birth weight <2,500 g
Very low birth weight (VLBW): birth weight <1,500 g
Extremely low birth weight (ELBW): birth weight <1,000 g

Adapted from Philip AGS, Stevenson DK, Hay WW Jr. Intrauterine growth restriction. In: Stevenson DK, Benitz W, Sunshine P, et al., eds. *Fetal and neonatal brain injury*, 4th ed. Cambridge UK: Cambridge University Press, 2009:75-95.

While the growth curves shown in Figure 23.2 from Lubchenco et al. (10) in Denver, Colorado, published in 1966 are biased to slightly lower birth weights compared with many other growth curves, they are unique in showing the weight/length ratio. This ratio is important for demonstrating failure of weight gain relative to length and head circumference growth as evidence of undernutrition, while an increased ratio would be strong evidence for excessive caloric intake, an increasing problem today in populations with greater frequency of obesity and diabetes among pregnant women. Growth curves similar to those from the original studies by Lubchenco et al. (10) have been produced at sea level among similar socioeconomic and racial groups. Several of these are shown in **Figure 23.4**, along with the updated Fenton Growth Curve that was derived from six developed countries. Regardless of the population studied or growth curves derived, the key feature that is common in all is the rapid rate of fetal growth from the onset of postnatal viability around 24 weeks of gestation through term.

Growth Curves Based on Fetal Measurements

Fetal growth curves also have been developed from serial ultrasound measurements of fetuses that subsequently were born at term in healthy condition and with normal anthropometric measurements, providing continuous rather than cross-sectional indices of fetal growth. These curves correlate better with the expected rate of normal fetal growth than do cross-sectional, population-based growth curves of infants born at different gestational ages, since the intrauterine growth of those infants was likely affected by the same pathologic factors that led to their preterm birth.

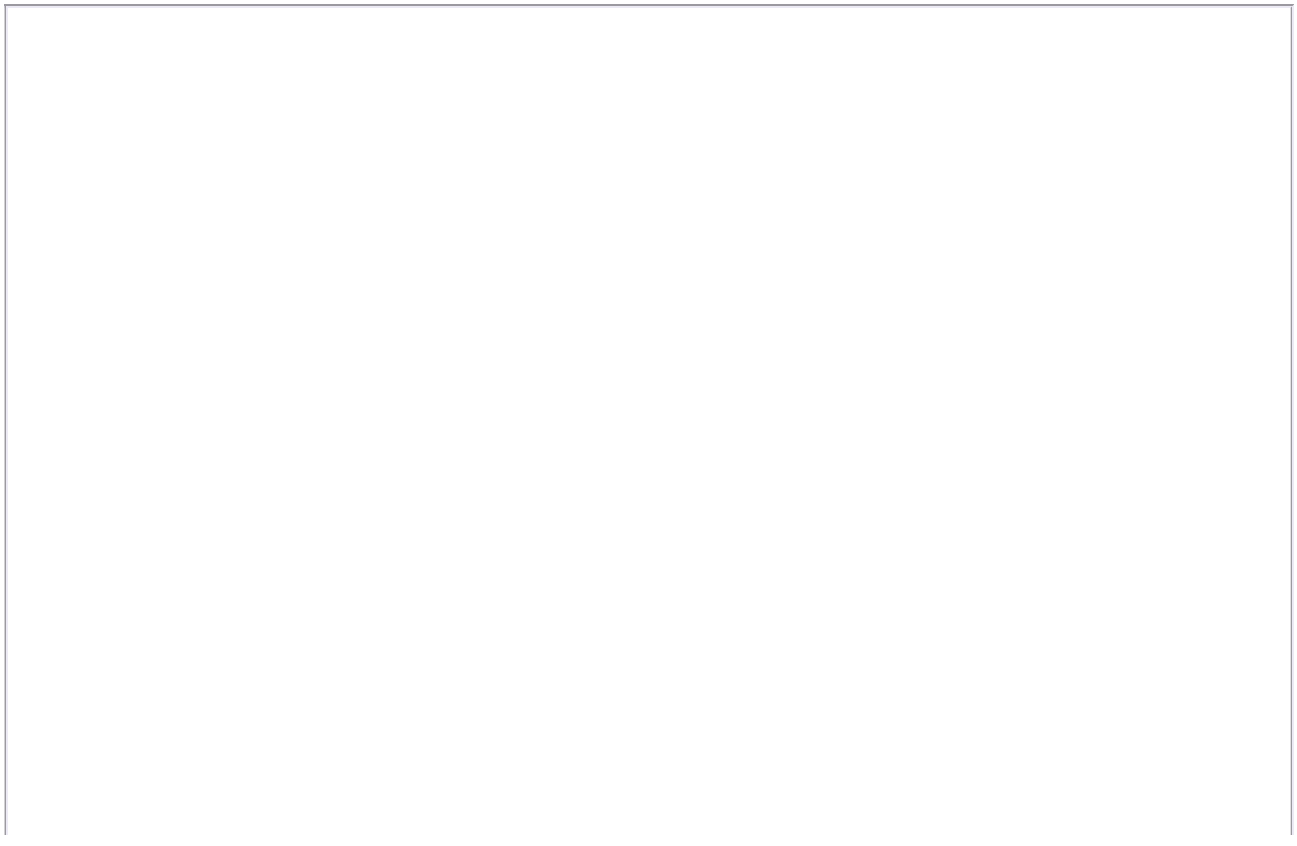
Thus, there probably is no ideal fetal growth curve derived from postbirth, cross-sectional measurements. Serial ultrasound measurements of fetal growth also more accurately determine how environmental factors, such as acute, severe maternal illness and undernutrition, can inhibit fetal growth and how improved nutrition can rescue such acute growth restriction. Future growth curves to assess *in utero* growth of a specific newborn should be based on more thoroughly and accurately determined fetal growth parameters from ultrasound measurements in pregnancies with definitely known dates of conception and birth at term of normally grown and developed infants.

▪ INTRAUTERINE GROWTH RESTRICTION AND PRETERM BIRTH

In cases of severe IUGR, the pathophysiologic processes causing the IUGR also can lead to preterm labor and preterm delivery. Thus, IUGR frequently occurs with a variety of maternal conditions that are associated with preterm delivery (**Table 23.2**).

Insufficient endometrial surface area for placental invasion and growth, plus abnormal placental perfusion, may combine to restrict nutrient delivery to the fetus, leading to IUGR. Poor placental growth and function limit placental supply of growth-promoting hormones to the fetus, for example, human placental lactogen (hPL), steroid hormones, and insulin-like growth factor-I (IGF-I) (11,12), and limit effective maternal-fetal nutrient exchange. IUGR sometimes occurs in conditions such as fetal infection, anemia, cardiac failure, and neuromuscular disorders. Intrauterine fetal infections can limit fetal growth by damaging the fetal brain and the neuroendocrine axis that support fetal growth via insulin-like growth factors (IGFs) and insulin. Intrauterine infections also can damage the fetal heart, leading to diminished cardiac output, poor placental

perfusion, and inadequate nutrient substrate uptake. Preeclamptic women have poor endometrial vascular support for growth of the placenta, leading to placental growth failure, fetal nutrient deficit, and IUGR (13). Fetal hypoglycemia, hypoxemia, and acidosis usually are present in such cases of poor placental development and perfusion. These factors lead to increased production of prostaglandins and the activation of labor-promoting cytokines, leading to preterm delivery (14). Women at the age limits of childbearing produce IUGR infants who often are born prematurely. Nutritional, uterine, and vascular mechanisms may be common in these situations. Young, still-growing adolescent girls appear less capable of mobilizing fat reserves in late pregnancy, apparently reserving them instead for their own continued development (15). IUGR in cases of maternal smoking and substance abuse may result from reduced placental blood flow, inhibition of uteroplacental vascular development, or direct fetal toxicity.



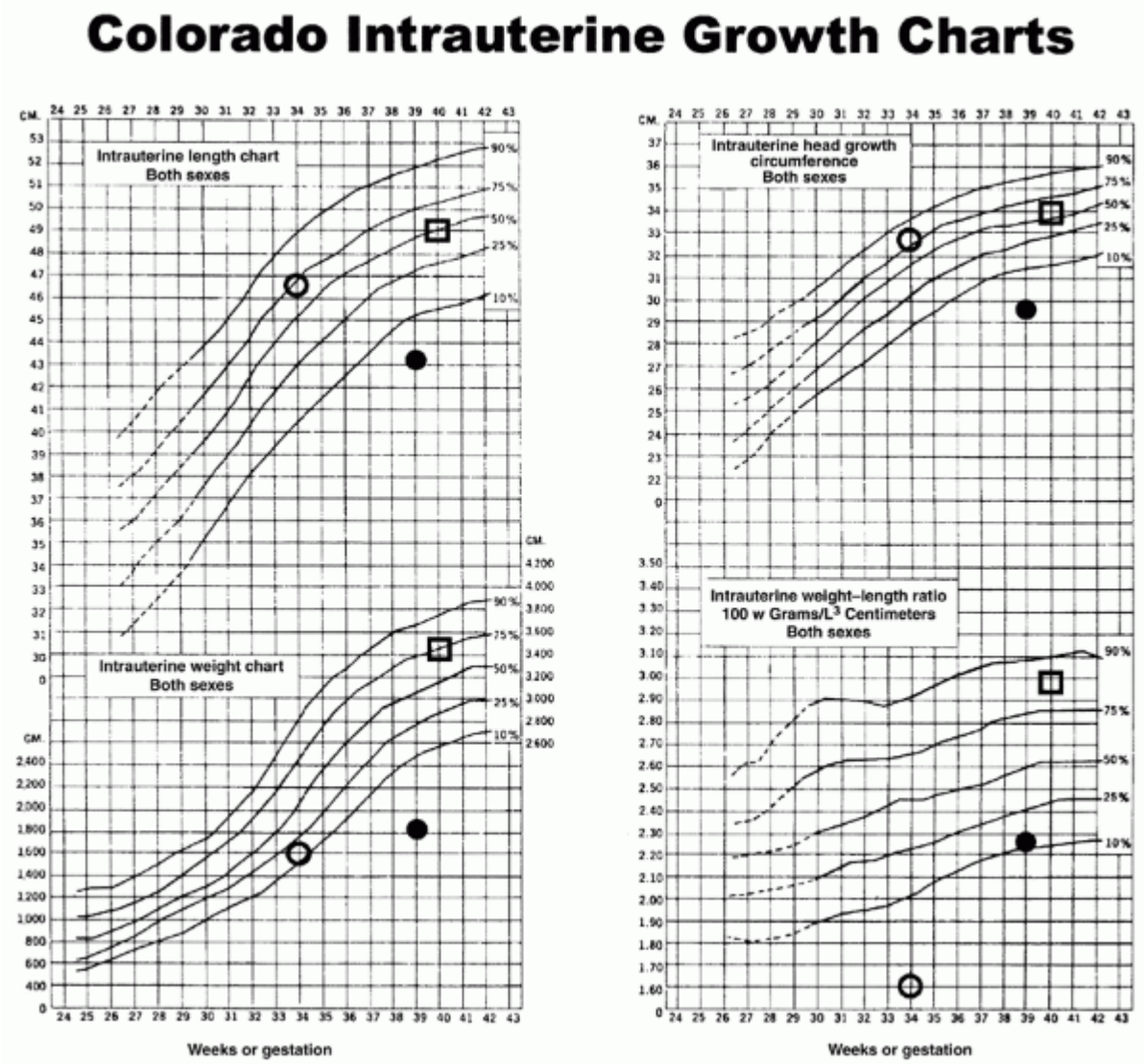


FIGURE 23.2 Intrauterine growth charts with symbols that define the anthropometric measurements for the three infants shown in Figure 23.3. (○) Preterm infant at 34 weeks of gestation, showing asymmetry of weight (15th percentile) versus length and head circumference (75th percentile), producing a weight-to-length ratio less than 10th percentile; (•) severely but symmetrically SGA infant at 39 weeks, showing weight, length, and head circumference all about equally and markedly less than 10th percentile; and (□) symmetric AGA infant at 40 weeks, showing weight, length, head circumference, and weight-to-length ratio about the 65th to 75th percentile. Growth charts adapted from Lubchenco LO, Hansman C, Boyd E. Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. *Pediatrics* 1966;37:403.

Iatrogenic preterm delivery is performed in the context of suspected fetal acidosis and heart rate abnormalities in severely affected IUGR pregnancies. Many of these cases are delivered preterm to protect the mother from eclampsia. Doppler assessment of the umbilical artery is the recommended method of fetal surveillance once an IUGR pregnancy is suspected (see also Chapter 12). During conditions of placental insufficiency, blood flow in the umbilical artery decreases during diastole, progressing from increased pulsatility of blood flow, to absent blood flow, and then reversed blood flow (see Fig. 12.17). Doppler velocimetry

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abnormalities have been shown to develop in a sequential fashion as placental insufficiency progressively worsens, and

may predict risk of acidosis and perinatal mortality as well as help to predict optimal timing of delivery (16).

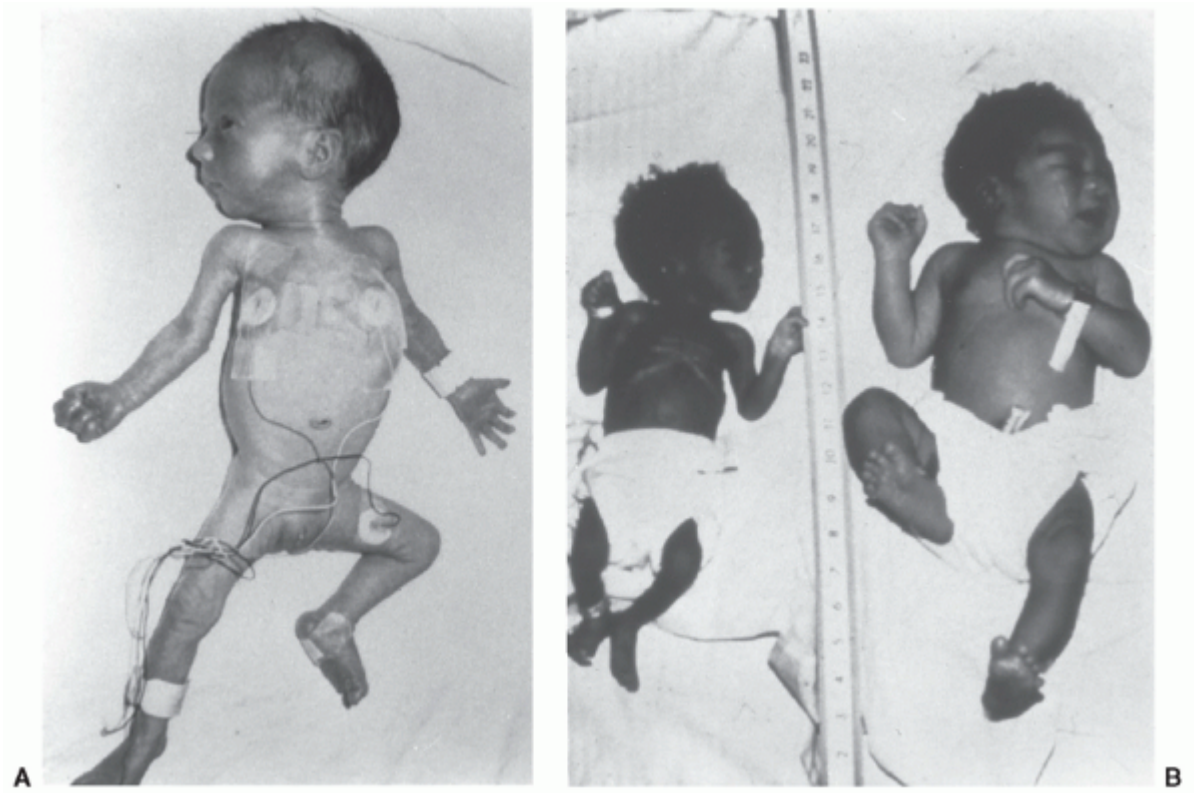

FIGURE 23.3 Preterm, SGA infant at 34 weeks of gestation **(left)**, severely SGA infant at 39 weeks **(middle)**, and AGA infant at 40 weeks **(right).**

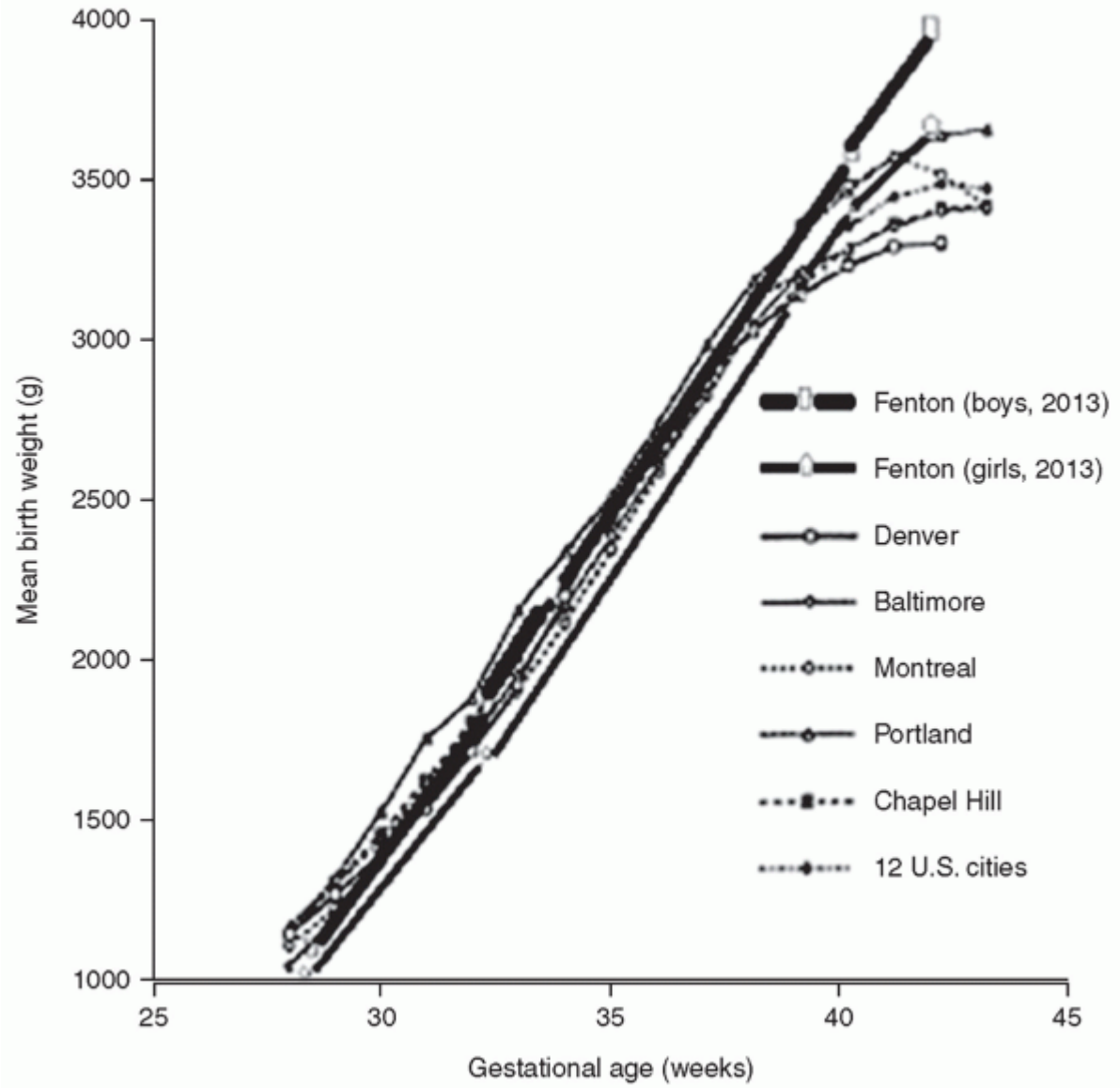

FIGURE 23.4 Mean birth weights by gestational age from six early sources. Adapted from Naeye R, Dixon J. Distortions in fetal growth standards. *Pediatr Res* 1978;12:987 and from the most recent Fenton growth chart for preterm infants for boys and girls in Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr* 2013;13:59.

TABLE 23.2 Maternal Conditions Associated with Intrauterine Growth Restriction and Preterm Delivery

Both very 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
Nulliparity in very young adolescent girls
Failure to obtain normal medical care during pregnancy
Lower socioeconomic status
Black race (in the United States)
Multiple gestation
Uterine and placental anomalies
Polyhydramnios
Preeclampsia
Hypertension, both chronic and pregnancy induced
Chronic, severe diabetes
Intrauterine infections
Cigarette smoking, cocaine use, and other substance abuse

▪ GROWTH OF BODY COMPONENTS IN THE FETUS

Water and Minerals in IUGR, Small for Gestational Age Infants

Fetal body water content, expressed as a fraction of body weight, decreases over gestation as a result of relative increases in protein and mineral accretion and the development of relatively large amounts of adipose tissue in the third trimester (17). Thus, fetuses with marked IUGR and SGA neonates who have decreased body fat content have slightly higher fractional contents of body water. Measurements of extracellular space in SGA infants usually are normal for gestational age, as adipose tissue, skeletal muscle, and mineral accretion all are decreased to about the same extent (18).

Fetal calcium content in SGA and AGA fetuses increases exponentially with a linear increase in length, because bone density, area, and circumference increase exponentially in relation to linear growth. Accretion of other minerals varies more directly with body weight and according to the distribution of the minerals into extracellular (e.g., sodium) or intracellular (e.g., potassium) spaces.

Nitrogen and Protein Accretion in IUGR, Small for Gestational Age Infants

Among SGA infants, nitrogen and protein contents are reduced for body weight, primarily as a result of deficient production of muscle mass. Skeletal muscle growth is particularly vulnerable because blood flow and nutrient supplies are preferentially shunted to vital organs in response to decreasing fetal oxygenation (19). In fact, skeletal muscle mass as well as fat mass are reduced in the IUGR fetus during late gestation when compared to AGA controls (20,21). Findings of reduced muscularity extend into the neonatal period as well as into childhood (22).

Glycogen Content in IUGR, Small for Gestational Age Infants

Many tissues in the fetus, including brain, liver, lung, heart, and skeletal muscle, produce glycogen over the second half of gestation. Liver glycogen content, which increases with gestation, is the most important store of carbohydrate for systemic glucose needs, because only the liver contains sufficient glucose-6-phosphatase for release of glucose into the circulation. Skeletal muscle glycogen content increases during late gestation and forms a ready source of glucose for glycolysis within the myocytes. Lung glycogen content decreases in late gestation with change in cell type, leading to loss of glycogen-containing alveolar epithelium, development of type II pneumocytes, and onset of surfactant production. Cardiac glycogen concentration decreases with gestation, owing to cellular hypertrophy, but cardiac glycogen appears essential for postnatal cardiac energy metabolism and contractile function.

Hepatic glycogen content in IUGR fetal sheep is similar or even increased compared to normal late-gestation fetal sheep (23). Human AGA and SGA infants have similar rates of glycogenolysis, suggesting similar hepatic glycogen stores (24). Previous estimates of lower glycogen content in such infants probably reflected studies done postnatally in preterm infants receiving intravenous nutrition with or without very limited enteral nutrition. In preterm infants, IUGR/SGA or not, gluconeogenesis accounts for nearly 70% of total glucose production rates, indicating a lesser role for glycogenolysis, which may reflect lower available hepatic glycogen stores after birth and in response to insufficient early postnatal nutrition.

Decreased Fat Content in Adipose Tissue in IUGR, Small for Gestational Age Infants

At term, fetal fat content, expressed as a fraction of fetal weight, varies markedly among species. The fat content of the newborn of almost all land mammals at term is 1% to 3%, which is considerably less than the 15% to 20% fat content of human term infants. Between 26 and 30 weeks of gestation, nonfat and fat components contribute equally to the carbon content of the fetal body (25). After that period, fat accumulation exceeds that of the nonfat components. By term, the deposition of fat accounts for more than 90% of the carbon accumulated by the fetus.

Human infants born IUGR have lower total body fat contents than AGA infants, often less than 10% of body weight (26). In these cases, the smaller placenta limits fetal fatty acid and triglyceride supply. Similarly, the smaller placenta decreases fetal glucose supply, which reduces glycerol production and triglyceride synthesis. Decreased production of insulin and lower plasma insulin concentrations in IUGR/SGA infants, a result of decreased glucose and amino acid supply to the fetus, also limit lipid synthesis and peripheral lipoprotein lipase activity, which is necessary to release fatty acids from circulating lipoproteins for adipocyte uptake and triglyceride synthesis. As a result of decreased insulin and decreased adipose tissue mass, IUGR/SGA fetuses and infants also have decreased leptin and other adipocytokine concentrations, which may underlie mechanisms for increased adiposity later in life (27).

Caloric Accretion Deficiency in Small for Gestational Age Infants

Growth of fat and nonfat (protein plus other) tissues is metabolically linked through energy supply that is used for protein synthesis and the production of anabolic hormones. These promote positive protein, fat, and carbohydrate growth. Thus, restriction of nutrient supply produces growth deficits of all tissues, including muscle, glycogen, and fat. For example, chronic selective caloric (glucose) restriction in the experimental fetal sheep model leads to increased protein breakdown and lower rates of fetal growth and lipid content (28). Recent data in a fetal sheep model of IUGR demonstrate that the combined net fetal uptake of glucose, lactate, and amino acids, expressed as nutrient:oxygen quotients, was reduced to nearly 1.0 compared to 1.3 in normally grown fetuses. This demonstrates that net carbon supply to the IUGR fetus is only sufficient to sustain oxidative metabolism, with no additional carbon available for fetal growth (29).

▪ REGULATION OF FETAL GROWTH

Fetal growth is regulated by maternal, placental, and fetal factors, representing a mix of genetic mechanisms and environmental influences through which genetic growth potential is expressed and modulated.

Epidemiologic Considerations

The incidence of IUGR is difficult to ascertain, since actual measurements of fetal growth versus their growth potential are not available. Maternal risk factors for IUGR include maternal nutritional status, maternal BMI, maternal genetics, maternal substance abuse, social determinants, and environmental pollutants.

Genetic Factors

Many genes contribute to fetal growth (**Table 23.3**). Maternal genotype is more important than is fetal genotype in the overall regulation of fetal growth. However, the paternal genotype is essential for trophoblast development, which secondarily regulates fetal growth by placental provision of nutrients.

Chromosomal abnormalities commonly restrict fetal growth, particularly noted in infants with trisomy 21, 13, and 18, but also among infants with triploidy, various deletion syndromes, and those with multiple or “super” X syndromes (XXY, XXXY, XXXX). As few as 2% to 5% of infants with IUGR have chromosomal abnormalities; the incidence increases when both IUGR and mental retardation are present. Many fetuses with growth restriction have congenital malformations and/or dysmorphic syndromes such as thanatophoric dwarfing; leprechaunism; Potter, Cornelia de Lange, Smith-Lemli-Opitz, Seckel, Silver, or Williams syndromes; or VATER or VACTERL (vertebral, anal, cardiovascular, tracheoesophageal, renal, radial, and limb) associations. Infants with various types of cardiovascular disorders, such as congenital heart disease, particularly hypopolastic left heart syndrome, and those with single umbilical arteries, often have IUGR. Monozygotic twins usually have some degree of IUGR that exceeds that of dizygotic twins; all multiple gestation fetuses are prone to IUGR. Donor fetuses in twin-to-twin transfusion syndrome tend to be growth restricted. These disorders are not common, accounting for less than 2% of infants with IUGR. Certain genetic, metabolic, and endocrine disorders are associated with IUGR. Examples include infants with transient neonatal diabetes mellitus, neonatal thyrotoxicosis, Menkes syndrome, hypophosphatasia, I-cell disease, and iron overload disease.

TABLE 23.3 Factors Determining Variance in Birth Weight

		Percent of Total Variance
Fetal		
	Genotype	16
	Sex	2
	Total	18
Maternal		
	Genotype	20

Maternal environment	24
Maternal age	1
Parity	7
Total	52
Unknown	30

From Penrose LS. Proceedings of the Ninth International Congress of Genetics, Part 1, 520, 1954, with permission.

From Milner RDG, Gluckman PD. Regulation of intrauterine growth. In: Gluckman PD, Heymann MA, eds. *Pediatrics & perinatology: the scientific basis*, 2nd ed. London, UK: Arnold, 1993:284, with permission.

Infectious Diseases

A causal relationship for IUGR primarily involves rubella, cytomegaloviral infection, and toxoplasmosis. These infections directly inhibit cell division and/or cell death (including apoptosis), leading to a decreased number of fetal cells. Intrauterine infections with other organisms, including syphilis, varicella-zoster, human immunodeficiency virus (HIV), *Trypanosoma*, and malaria have also been associated with IUGR, but it is unclear in these cases whether it is the infectious agent itself or the poor maternal health and nutrition that are causal. Congenital infections account for very few cases of IUGR, perhaps as little as 3%.

Nongenetic Maternal Factors

Under usual conditions, fetal growth follows its genetic potential, unless the mother is unusually small and limits fetal growth by a variety of factors considered collectively as “maternal constraint.” Maternal constraint represents a relatively limited uterine size, including placental implantation surface area and uterine circulation, and thus, the capacity to support placental growth and nutrient supply to the fetus. A clear example of maternal constraint is the reduced rate of fetal growth of multiple fetuses in a species—human—that optimally supports only one fetus (1) (**Fig. 23.5**). Obviously, small fetuses of small parents do not reflect fetal growth restriction; in fact, their rates of growth are normal for their genome and for the size of the mother. Unless maternal constraint is particularly prominent, such fetuses would not grow faster or to a larger size if more nutrients were provided, although they might grow somewhat larger if the maternal uterine endometrial surface area, and thus placental implantation and growth area, were increased.

Maternal stress of many kinds, but particularly noted for hard work, perhaps via increased cortisol secretion, may restrict fetal growth. A study from Thailand, for example, indicated that the risk of delivering an SGA infant was increased for pregnant women working more than 50 hours per week, especially in those women whose work involved protracted squatting and for those having high psychological job demands (30).

Maternal Nutrition

The single most important environmental influence that affects fetal growth is the availability of nutrition for the fetus. Normal variations in maternal nutrition, however, have relatively little

impact on fetal growth and the severity of IUGR. This is because changes in maternal nutrition, unless extreme and prolonged, do not markedly alter maternal plasma concentrations of nutrient substrates or the rate of uterine blood flow, the principal determinants of nutrient substrate delivery and transport to the fetus by the placenta. Human epidemiologic data from conditions of prolonged starvation, and nutritional deprivation in experimental animals, indicate that even severe limitations in maternal nutrition limit fetal growth only by 10% to 20%. Epidemiologic data from the Dutch during the Hunger Winter of 1944 showed an average reduction in fetal weight at term of 300 g (31). In animal models, experimental restriction of calorie and protein intakes to less than 50% of normal for a considerable portion of gestation are needed before marked reductions in fetal growth are observed. Such severe conditions often result in fetal loss before the impact of fetal growth rate in late gestation and fetal size at birth are manifested. Attempts to increase fetal weight gain with maternal nutritional supplements have produced mixed results. Higher caloric feeding increases fetal adiposity, not growth of muscle mass or gain in length or head circumference (32). In contrast, high protein supplements tend to produce delayed fetal growth (32). Mechanisms responsible for these disparate outcomes are not known, though insights resulting from experimental amino acid infusions into pregnant sheep have been proposed, including competitive inhibition among coinfused amino acids for common transporters across the placenta, as well as a possible mismatch between amino acid supply and fetal growth factor availability (i.e., insulin and IGF-1, which also are reduced in IUGR fetuses), limiting anabolic capacity even when amino acid supply might be increased (33).

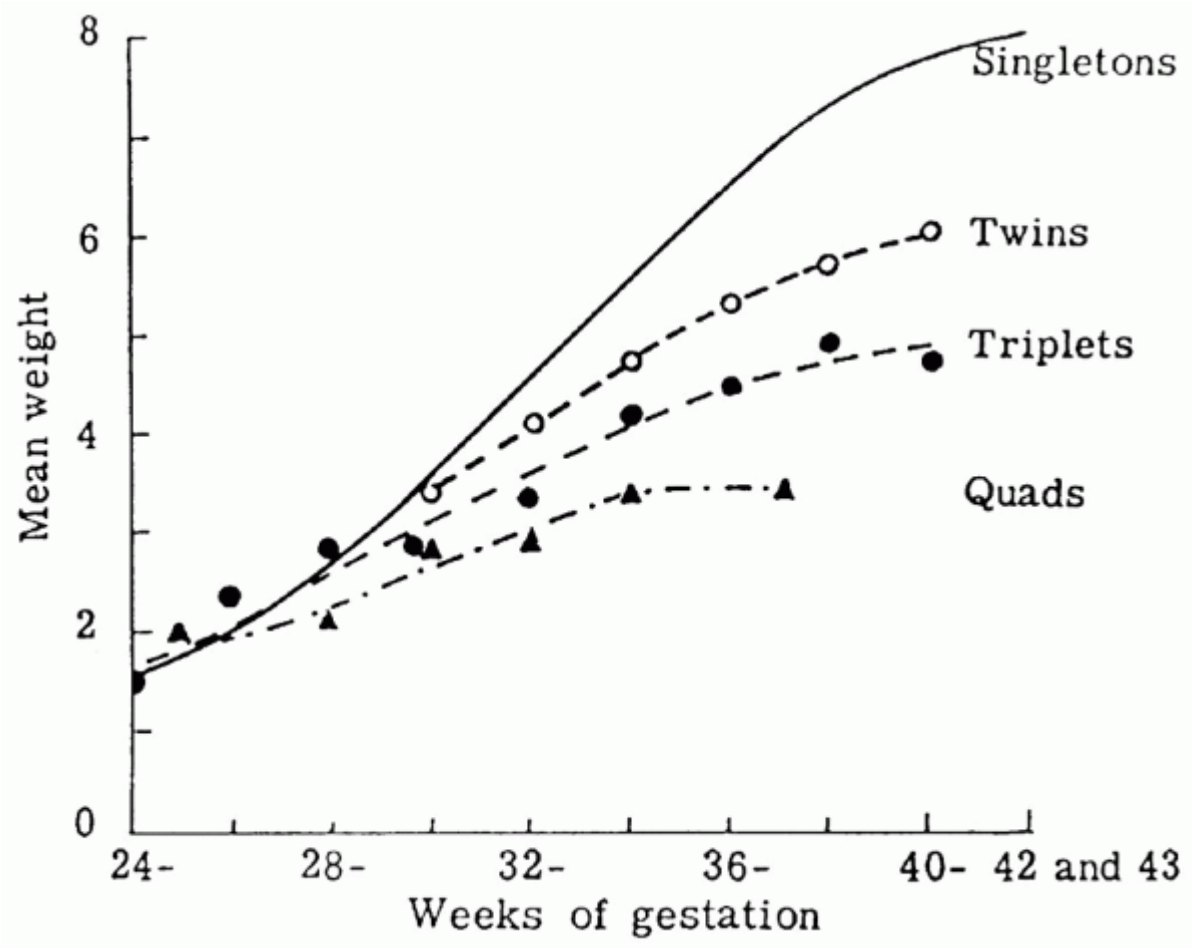

FIGURE 23.5 Mean birth weight of single and multiple human fetuses related to duration of gestation. Adapted from McKeown T, Record RG. Observation on foetal growth in multiple pregnancy in man. *J Endocrinol* 1952;8:386, with permission.

Specific micronutrient deficiencies also can restrict fetal growth even in the presence of adequate caloric and protein intakes. Zinc deficiency in pregnant women has been associated with increased rates of preterm delivery and fetal IUGR (34), which can be ameliorated by maternal zinc supplementation. Thiamine deficiency in pregnant women also has been associated with IUGR, though difficult to distinguish from simultaneous inadequate nutritional intake, hyperemesis, alcohol abuse, and various infections, including HIV (35). Severe maternal undernutrition/malnutrition is common in underdeveloped countries and exists in subpopulation areas in developed countries where appropriate nutrition, nutritional supplementation, or nutritional consultation is lacking. It also is seen in pregnant women with severe gastrointestinal disease, such as Crohn disease or ulcerative colitis, and women with chronic, unrelenting hyperemesis. Both animal and human studies have shown that undernutrition in the immediate months prior to pregnancy increases the risk for IUGR (36).

Maternal Chronic Diseases (See also Chapter 13)

Chronic hypertension, pregnancy-induced hypertension, and preeclampsia, as well as other vascular disorders including severe and long-standing diabetes mellitus and serious autoimmune disease associated with the lupus anticoagulant (antiphospholipid antibodies with systemic lupus erythematosus [SLE]), have a common effect of limiting trophoblast invasion, placental growth and development, uteroplacental blood flow, and fetal oxygen and nutrient delivery (1,37). Maternal cyanotic congenital heart disease can limit fetal oxygen supply, which can limit fetal growth (38). Severe sickle cell crises can damage uterine vasculature, leading to decreased placental growth and transport capacities (1). Women with chronic anemias, such as sickle cell disease, sickle-C disease, and thalassemia, more frequently produce IUGR/SGA infants. It also is well recognized that women with a history of poor outcome in pregnancy have an increased risk of IUGR in subsequent pregnancies, doubling after one infant with IUGR and quadrupling after two such outcomes (39). These authors urged that women who have growth-restricted infants should undergo comprehensive testing to search for an underlying maternal disorder if the reason for the IUGR is otherwise not apparent.

Maternal hypoxia that produces fetal hypoxia also significantly reduces fetal growth. The most common example is high-altitude hypoxia, but usually this is only clinically significant for nonindigenous women who move to altitudes above 10,000 ft (40). Infants born to mothers who live at 10,000 ft (3,000 m) or greater above sea level weigh approximately 250 g less at birth than do infants born to mothers who live at sea level (41), increasing to weight reductions of up to 15% at altitudes greater than 15,000 ft (4,500 m). Interestingly, the placentas of these IUGR infants weighed more than those near sea level, indicating compensatory development of mechanisms for nutrient delivery (42). More recent studies have shown that long-term adaptation, involving increased uterine blood flow, to higher altitude increases birth weight, while smaller infants generally come from recent immigrants to high altitude (43). Indigenous high-altitude ancestry also protects against hypoxia-associated fetal growth reduction in a dose-dependent fashion consistent with the involvement of genetic factors. Further, some of the genes involved appear to be influenced by parent-of-origin effects, as maternal transmission restricts and paternal transmission enhances fetal growth via growth effects on the placenta (44).

Maternal Drugs (See also Chapters 14 *and* 54)

Specific effects of drugs on fetal growth (**Table 23.4**) are often difficult to sort out clinically, as many women who abuse drugs do so with many drugs taken intermittently, at different doses, and at different periods of fetal vulnerability. These women also frequently suffer from other disorders that could lead to poor fetal growth, such as poor nutrition, recurrent acute illnesses, and chronic diseases. Fetal growth restriction is a major part of the fetal alcohol syndrome. It is not clear when during gestation the specific effects of alcohol on fetal growth rate occur. Alcohol may exert its nonteratogenic effects by limiting placental-to-fetal amino acid transport (45). Cocaine probably exerts its primary effects on producing fetal growth restriction by causing uterine and perhaps umbilical vasoconstriction and reduced placental perfusion (46). There also is evidence that marijuana can reduce fetal growth, though the mechanisms are not clear; this potential problem deserves urgent study as legalization of marijuana is expanding in the United States, and there currently is no legal restriction for its use during pregnancy (47).

TABLE 23.4 Drugs Associated with Intrauterine Growth Restriction

Amphetamines
Antimetabolites (e.g., aminopterin, busulfan, methotrexate)
Bromides
Cocaine
Ethanol
Heroin and other narcotics, such as morphine and methadone
Hydantoin
Isotretinoin
Metals such as mercury and lead
Phencyclidine
Polychlorinated biphenyls (PCBs)
Propranolol
Steroids
Tobacco (carbon monoxide, nicotine, thiocyanate)
Toluene
Trimethadione
Warfarin

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The drug most consistently producing fetal growth restriction is nicotine from cigarette smoking (48). Deficits of at least 300 g (about 10% of normal term weight) are not uncommon. A likely mechanism is the constricting effect of nicotine, and of catecholamines released in response, on the uterine and perhaps the umbilical vasculature, reducing placental perfusion. Carbon monoxide, cyanide, and other cellular toxins may limit oxygen transport to fetal tissues and cellular respiration. Caffeine, particularly when consumed in amounts greater than 300 mg/d, has been associated

with IUGR, though effects of caffeine are often difficult to separate from those of concurrent smoking (49). Mercury toxicity causing growth restriction was observed during the 1950s to the 1970s in epidemics of mercury poisoning in Japan and Iraq. Methyl mercury has the greatest toxicity, as it crosses the placenta readily, producing both teratogenic and adverse growth effects in the fetus (48). Radiation exposure, common agricultural toxins (e.g., bisphenol A, atrazine), and contaminated food or water, over long periods of time, or at critical stages of fetal development, appear to increase risk for IUGR. The incidence and severity of growth restriction due to these factors are not known at present.

Placenta (See also Chapter 11)

The size of the placenta and its nutrient transport functions are the principal regulators of nutrient supply to the fetus and fetal growth. Nearly all cases of IUGR are associated with a smaller-thannormal placenta. **Figure 23.6** shows a direct relationship between fetal weight and placental weight in humans, demonstrating that LGA, AGA, and SGA infants are directly associated with LGA, AGA, and SGA placentas (50). Placental growth normally precedes fetal growth, and failure of placental growth is directly associated with decreased fetal growth, although there is considerable redundancy in placental functional capacity, such that up to 30% loss of placental function can still allow for normal fetal growth. Variable limitations in placental nutrient transfer capacity modulate this primary effect of placental size on fetal growth. In some cases of experimentally reduced placental size, for example, fetal weight is not reduced proportionately (50). This indicates that either the capacity of the smaller placenta to transport nutrients to the fetus increases adaptively or the fetus develops increased capacity to grow. More characteristically, though, fetal growth fails first, or in direct relation to decreased nutrient supply. With primary fetal growth failure, placental growth can increase disproportionately, resulting in a larger-than-normal placental-to-fetal weight ratio for gestational age. This is characteristically seen under chronic hypoxic conditions of high-altitude exposure or maternal anemia and has been seen in certain experimental situations of maternal undernutrition in early gestation (51). A variety of placental pathologic conditions are associated with IUGR (**Table 23.5**). In most of these cases, the placenta is simply smaller than normal. In many, there also is abnormal trophoblast development, including abnormal vascular growth in the trophoblast villi, frequently associated with limited uterine vascular perfusion of the intervillous spaces.

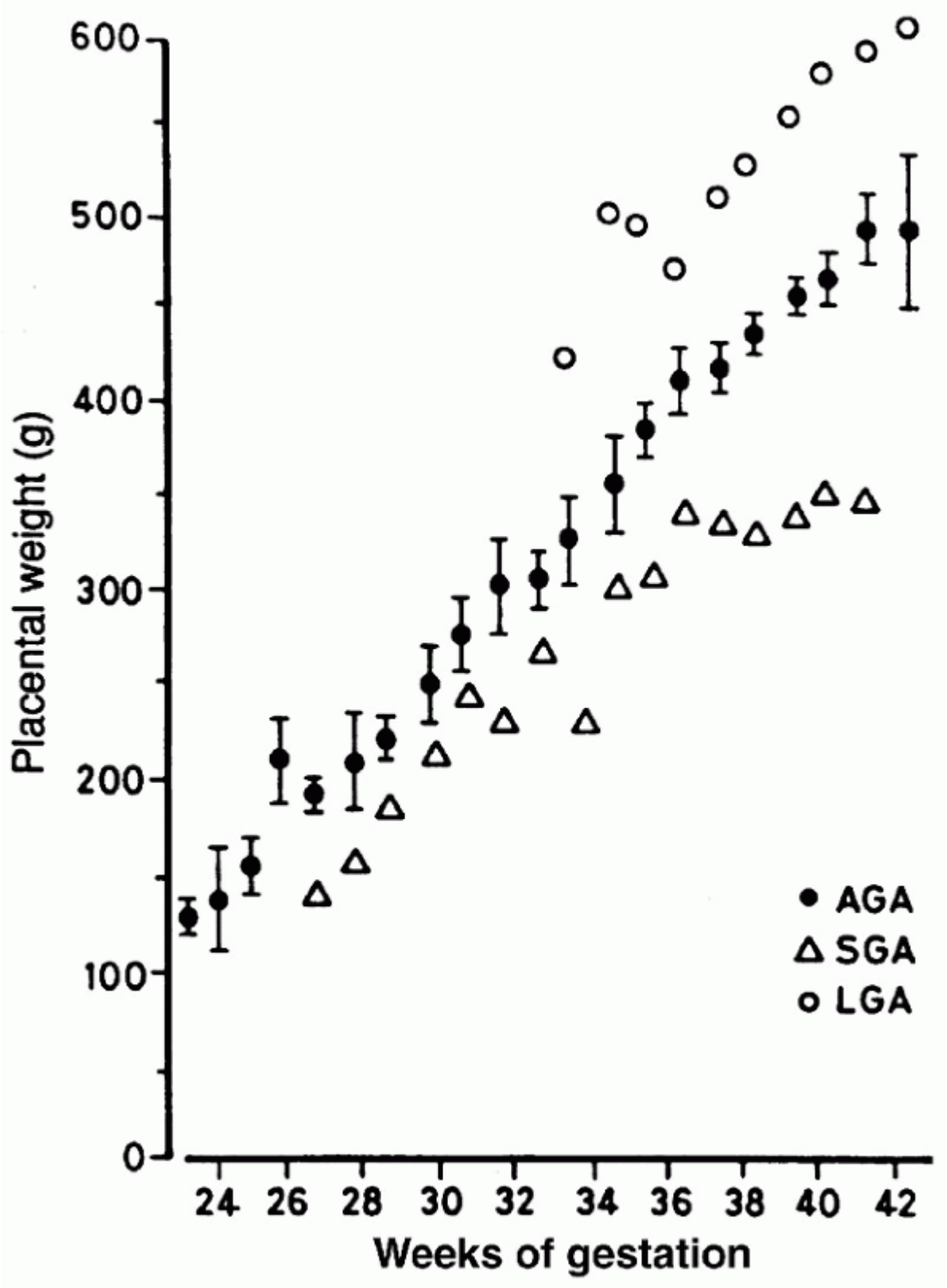

FIGURE 23.6 Mean placental weights for LGA (○), AGA (•), and SGA (Δ) human infants at each gestational age. ± SEM given for AGA infants alone. From Molteni RA, Stys SJ, Battaglia FC. Relationship of fetal and placental weight in human beings: fetal/placental weight ratios at various gestational ages and birth weight distributions. *J Reprod Med* 1978;21:327, with permission.

TABLE 23.5 Placental Growth Disorders that Lead to or Are Associated with Intrauterine Growth Restriction

Abnormal umbilical vascular insertions (circumvallate, velamentous)
Abruption (chronic, partial)
Avascular villi
Decidual arteritis
Fibrinosis, atheromatous changes, cytotrophoblast hyperplasia, basement membrane thickening
Infectious villitis (as with TORCH infections)
Ischemic villous necrosis and umbilical vascular thromboses
Multiple gestation (limited endometrial surface area, vascular anastomoses)
Multiple infarcts
Partial molar pregnancy
Placenta previa
Single umbilical artery
Spiral artery vasculitis, failed or limited erosion into intervillous space
Syncytial knots
Tumors, including chorioangioma and hemangiomas

Placental and fetal growth both depend on an adequate supply of maternal blood to the placenta. IUGR is associated with inadequate development of the uteroplacental circulation, and radioisotope studies have demonstrated more than a twofold blood flow reduction in comparison with normal pregnancies (52). IUGR in the second half of gestation is due primarily to a failure of the normal villous vascular tree, mainly in the phase of nonbranching angiogenesis, because terminal villi are critical for oxygen and nutrient transport to the fetus (53). This angiogenesis in turn depends on cytotrophoblast invasion of the uterus and its arterioles. Cytotrophoblast invasion is actually a differentiation

process whereby the cells lose the ability to proliferate and modulate their expression of state-specific antigens. These antigens include members of the integrin family of cell-extracellular matrix receptors that are required for migration and invasion of the endometrium and decidua of the uterus (54).

The most common maternal condition with restricted placental growth and function is preeclampsia. Preeclamptic placentas have decreased growth of terminal villi, which limits oxygen, glucose, and amino acid transport to the fetus. Preeclampsia begins with shallow cytotrophoblast invasion (55). Abnormal cytotrophoblast differentiation also occurs, evidenced by the cells' inability to switch on their integrin repertoire (56). The same observations have been made on cultured normal cytotrophoblast cells in a hypoxic environment (57). These *in vitro* results indicate that whatever leads to hypoxia of the invading cytotrophoblast cells

increases cytotrophoblast proliferation over differentiation and invasion, thus setting the stage for deficient placental development that can result in deficient nutrient and growth factor supply to the fetus, producing fetal growth restriction.

At more advanced stages of placental development, placental production of growth factors and growth-regulating hormones develops, leading to significant autocrine regulation of placental growth and placental regulation of fetal growth processes. Human placental lactogen (hPl) is synthesized and secreted by the syncytiotrophoblast cells of the placenta (58). Fetal growth-promoting actions of placental lactogen are mediated by stimulation of IGF production in the fetus and by increasing the availability of nutrients to fetal tissues (59). Obviously, placental growth failure and/or nutrient deficit to the placenta can result in decreased placental production of growth factors that then would lead to fetal growth failure.

▪ FETAL NUTRIENT UPTAKE AND METABOLISM AND REGULATION OF FETAL GROWTH

IUGR that results from decreased nutrient supply can be interpreted as a successful, if not perfect, adaptation to maintain fetal survival.

Glucose Uptake, Metabolism, and Regulation of Fetal Growth

Nearly all IUGR fetuses, whether studied experimentally in animal models or in women by cordocentesis (direct umbilical blood sampling), have relatively lower plasma glucose concentrations compared with normally grown fetuses (60,61). Fetal “hypoglycemia” has several consequences important to fetal adaptation and survival when maternal glucose supply is limited. First, relative fetal hypoglycemia is an important and natural compensatory mechanism that helps to maintain the maternal-to-fetal glucose concentration gradient and thus the transport of glucose across the placenta to the fetus. Despite this compensation, fetal hypoglycemia limits tissue glucose uptake directly by diminished mass action and indirectly by limiting fetal insulin secretion and thus the effect of insulin to promote tissue glucose uptake by skeletal muscle, heart, adipose tissue, and liver. Reduced glucose supply alone decreases fetal growth rate and oxygen consumption rate (metabolic rate) proportionally, showing the tight linkage of energy supply and growth during periods of rapid growth such as occurs in the fetus (62). Insulin also normally suppresses hepatic glucose production and release, and it acts as an anabolic hormone that increases net protein balance by inhibiting protein breakdown. Thus, a decrease in fetal plasma insulin concentration initially may allow fetal glucose production to take place (63), thereby providing glucose for both fetal and placental needs, but subsequently, combined with hypoglycemia, results in increased protein breakdown and decreased protein accretion (64). Interestingly, animal studies have demonstrated increased insulin sensitivity for glucose disposal in IUGR fetuses and postnatal offspring (63).

Circulating concentrations and tissue-specific expression of growth factors such as IGF-I (see “Fetal Amino Acid Metabolism”) also are decreased during fetal hypoglycemia (65), which may contribute to increased fetal protein breakdown and decreased rates of fetal growth. Thus, fetal hypoglycemia in response to a decrease in maternal glucose supply acts to maintain fetal glucose supply, but it also leads to lower anabolic hormone concentrations, which limit the rate of fetal growth, thereby decreasing fetal nutrient needs.

Fetal Amino Acid Metabolism

The placenta contains a large variety of amino acid transporters that use energy to actively concentrate amino acids in the trophoblast, which, followed by diffusion into the fetal plasma, produces higher concentrations than in the maternal plasma. With small placentas, fetal amino acid supply is reduced, as are fetal amino acid concentrations, fetal protein synthesis, fetal protein and nitrogen balance, and, ultimately, fetal growth rate. A consistent feature in human IUGR pregnancies is reduced placental transfer of certain essential amino acids. Furthermore, the severity of IUGR correlates with the severity of decreased amino acid transfer (66).

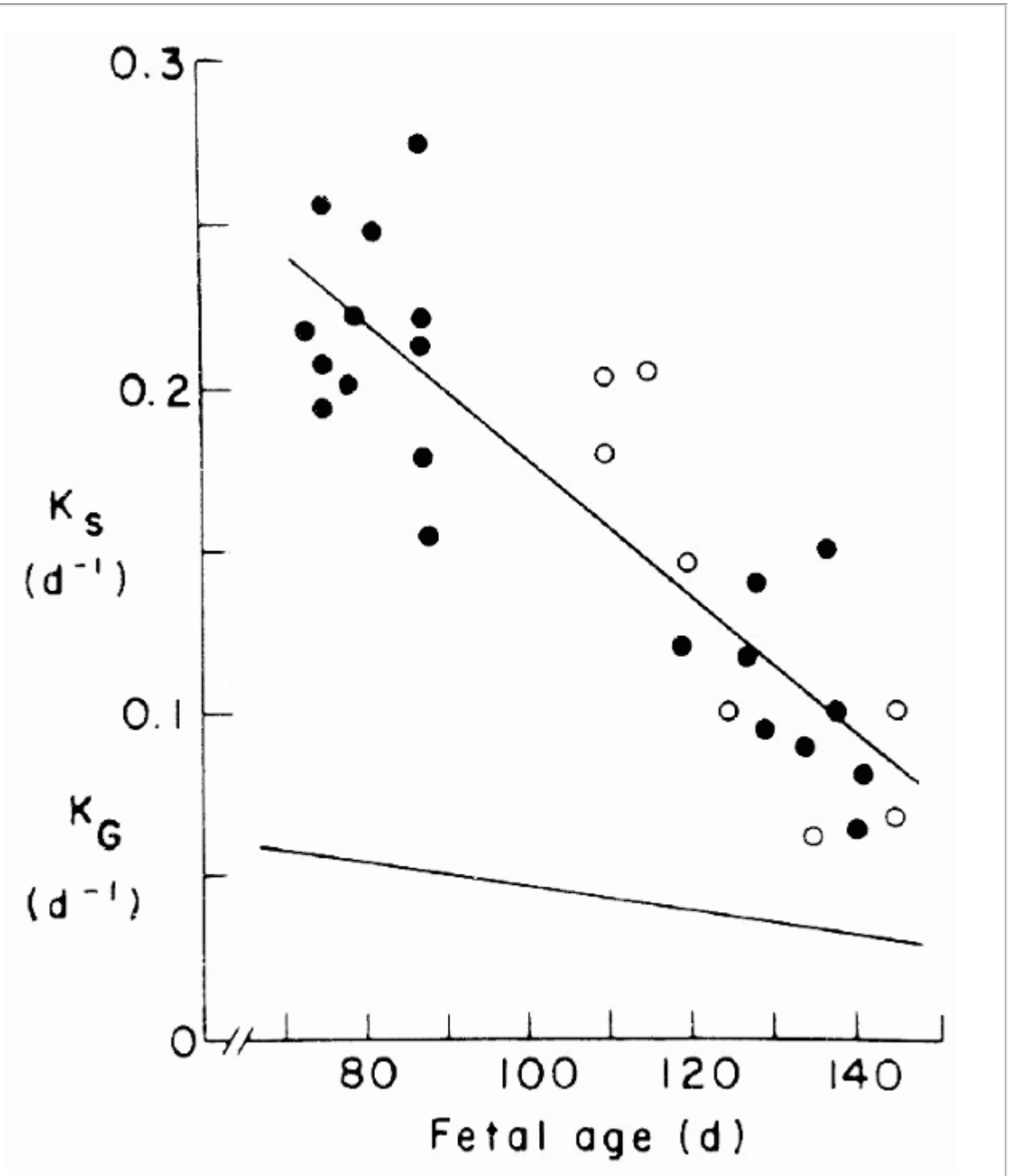

FIGURE 23.7 Fractional rate of protein synthesis (K_s) over gestation in fetal sheep studied with leucine (•) and lysine (○) radioactive tracers compared with the fractional rate of growth (K_G) in the lower portion of the figure (——). From Meier PR, Peterson RG, Bonds DR, et al. Rates of protein synthesis and turnover in fetal life. *Am J Physiol* 1981;240:E320.

Reduced energy supply to the placenta also reduces amino acid transport to the fetus. This is especially the case for oxygen deficit, either from primary hypoxemia or from reduced uteroplacental blood flow, and glucose deficit from chronic maternal and fetal hypoglycemia (67,68). Of course, hypoxemia and hypoglycemia could reduce fetal growth independently of reduced amino acid transport, for example, by limiting anabolic hormone and growth factor production or by decreasing energy supply, both of which are necessary to produce protein synthesis and to limit protein breakdown in fetal tissues.

The importance of amino acid and energy supplies for fetal protein and nitrogen balance and for fetal growth is illustrated in **Figure 23.7**. This figure shows results of experiments in fetal sheep over the second half of gestation, comparing fractional protein synthesis rates derived from tracer amino acid data and fractional body growth rates derived from carcass analysis data. The fractional rate of protein turnover per unit wet weight of fetus is several fold higher at 50% to 60% of term gestation (equivalent to about 20 to 24 weeks of human gestation). Such high rates of protein turnover require a much greater rate of amino acid supply and energy than at term, when fetal protein turnover rate is much lower. Indeed, in midgestation fetal sheep, glucose utilization rates per whole fetal weight and oxygen consumption rates per dry fetal weight are much higher in the early fetus than at term (69). These conditions result in a 50% higher rate of net protein accretion and fractional rate of fetal growth at midgestation than at term. Clearly, amino acid and energy deficits will affect the growth rate of the fetus at earlier stages of gestation, when fetal growth normally is much more rapid than at term.

Fetal Endocrine and Autocrine/Paracrine-Acting Growth Factor Effects on Fetal Growth

Fetal hormones promote growth (and development) *in utero* by altering both the metabolism and gene expression of fetal tissues (11,12). These hormonal actions ensure that fetal growth rate is commensurate with nutrient supply. **Table 23.6** lists those hormones whose deficiency results in decreased fetal growth.

TABLE 23.6 Effects of Specific Endocrine Deficiencies on Body Weight and Crown-Rump Length, and Individual Tissues Adversely Affected by Treatment in Sheep Fetuses Delivered near Term (>95% Gestation)

Endocrine Deficiency	Procedure	Gestational Age at Onset (d)	Body Weight	Crown-Rump Length	Tissues with Specific Developmental Abnormalities
Insulin	Streptozotocin	70-80	↓50%	↓20%	None
	Pancreatectomy	115-120	↓30%	↓15%	None
Thyroid hormones	Thyroidectomy	80-96	↓30%	↓10%	Skeleton, skin, lungs, nervous system
		105-115	↓20%	↓10%	Skeleton, nervous system

Adrenal hormones	Adrenalectomy	110-120	↑10%-15%	No change	Liver, lungs, gut, pituitary
Pituitary hormones	Hypophysectomy	70-79	↓30%	↓8%	Bones, liver, lungs, placenta
		105-110	↓20%	↓10%	Bones, liver, lungs, placenta, adrenal, gonads
		110-125	No change to ↓15%	No change	Bones, gonads, adrenal, liver
	Pituitary stalk section	108-112	↓15%	No change	Adrenals, other tissues

From Fowden AL. Endocrine regulation of fetal growth. In: Harding R, Genkin G, Grant A, eds. Progress in perinatal physiology. *Reprod Fertil Dev* 1995;7:50, with permission.

Insulin

Insulin has direct mitogenic effects on cellular development and cell number. It also enhances glucose consumption and limits protein breakdown. The latter effects are associated with reduced fetal growth when insulin concentration is low. Fetal growth restriction has been produced directly by experimental surgical (70) and chemical (71) ablation of the pancreas and/or the function of the pancreatic beta cells to secrete insulin and has been observed clinically in infants who suffer pancreatic agenesis (72). Much of the growth reduction with hypoinsulinemia from pancreatectomy is caused by a release of insulin's normal inhibitory role on glucose production, resulting in fetal hyperglycemia, a secondary decrease in the maternal-fetal glucose concentration gradient, and thus a decrease in glucose transport to the fetus. Without this glucose, fetal growth decreases, as has been shown by experimental restriction of placental glucose supply to the fetus (65).

Fetal amino acid uptake decreases under the same circumstances. Thus, insulin deficiency, directly and indirectly, results in a decrease in fetal nutrient supply. Initially, fetal protein breakdown results in fetal amino acid release for energy (via direct amino acid oxidation in the tricarboxylic [citric] acid cycle) and glucose production. Later, the reduced rate of fetal growth during conditions of low insulin, glucose, and amino acid concentrations is sustained by increased protein breakdown (28); amino acids are used to maintain protein turnover rate and not for protein accretion, oxidation, or glucose production. Increased rates of glucose production and increased gluconeogenic gene expression have been found in sheep models of IUGR (63,73), and both are resistant to suppression with insulin, suggesting insulin resistance. However, peripheral tissues remain insulin sensitive in terms of glucose disposal in IUGR fetuses (63), supporting tissue-specific adaptations in IUGR.

Chronically reduced fetal glucose supply is sufficient to reduce pancreatic insulin secretion in response to glucose, primarily due to reduced pancreatic and ß-cell mass, and is not correctable with insulin (65). Interestingly, chronic hypoglycemia in fetal sheep induces hepatic gluconeogenesis and in contrast to IUGR, is suppressible with insulin (73).

Insulin-Like Growth Factor-I

Growth hormone, which is the major hormonal regulator of postnatal growth, has no demonstrable effect on fetal growth (12). Instead, IGF-1 is a major anabolic hormone in fetal development. IGF-I is positively regulated by glucose

supply in the fetus. Infusion of IGF-I into fetal sheep decreases protein breakdown, especially when protein breakdown is increased by fasting-induced hypoglycemia. Metabolic effects of a decreased plasma concentration of IGF-I have not been studied, although, as for insulin, such effects might be difficult to separate from simultaneous changes in nutrient substrate supply and concentration. Thus, IGF-I probably can regulate metabolic processes that affect fetal protein balance and growth, but these have been difficult to measure.

Plasma IGF-I concentrations are positively related to fetal size at birth. Indeed, human IUGR fetuses have decreased plasma IGF-I concentrations (74). Several animal models of maternal diet restriction and/or placental insufficiency also demonstrate decreased circulating fetal plasma concentrations of IGF-1 (75). Mutations in the *Igf1* and *Igf1r* genes in humans cause both intrauterine and postnatal growth restriction (76). Other transgenic models with increased expression of IGF-I have been associated with increased brain growth (77). IGF-I stimulates an increase in oligodendrocytes and neuronal number, and neuronal outgrowth with increased dendritic arborization and axon terminal fields (78). Because IGF-I is decreased directly by reduced nutrient supply, particularly glucose, and insulin-like growth factor binding protein-1 (IGFBP-1) is decreased under these circumstances, the smaller, more densely packed neuronal structure of the undernourished brain that is seen in some infants with severe IUGR may have been mediated by nutrient regulation of IGF-I and IGFBP-1 expression. Such developmental limitations might underlie the poorer neurodevelopmental outcome of severely SGA infants who have relative microcephaly.

Insulin-Like Growth Factor-II [IGF-II], Insulin-Like Growth Factor Binding Protein-2 [IGFBP-2], Insulin-Like Growth Factor Binding Protein-3 [IGFBP-3], and Vasoactive Intestinal Polypeptide

Although serum concentrations of IGF-II do not correlate with fetal size at birth in human infants, it has been shown conclusively that targeted mutation of the IGF-II gene reduces fetal size in mice (79). Furthermore, IGF-II is the predominant IGF expressed in the tissues of embryos and fetuses of all species. As with IGF-I and IGFBP-1, transgenic overexpression of IGF-II and IGFBP-2 shows that cellular growth is dependent on the balance between the binding protein and the IGF molecule itself. Vasoactive intestinal peptide (VIP) is another growth factor in the fetus that affects neuronal and whole body growth (80). Antagonists to VIP in pregnant mice produce smaller fetuses that are particularly microcephalic (81), with central nervous system neurons that show reduced mitosis and migration. These effects of VIP occur in the first half of gestation, coincident with transiently high VIP concentrations in the maternal plasma (82).

Thyroid Hormones

In all species, fetal thyroid hormone deficiency or reduced free thyroxine (T4) produces developmental abnormalities in certain tissues and reduced growth (11). Fetal hypothyroidism decreases oxygen consumption and oxidation of glucose, thereby potentially

decreasing fetal energy supply for growth. Hypothyroidism also can decrease circulating and tissue concentrations of IGF-I (11).

Cortisol

Increasing fetal concentrations of cortisol near the end of gestation cause a switch in fetal tissues from accretion to differentiation and are important in the maturation of tissue-specific enzymatic pathways (11). These include glycogen deposition, gluconeogenesis, fatty acid oxidation, induction of surfactant production and release, structural maturation of alveoli, structural maturation of the gastrointestinal tract, increased expression of digestive enzymes, increased adrenal function, switch from fetal to adult hemoglobin synthesis, and others. Many IUGR fetuses have increased cortisol concentrations that appear to result from intermittent hypoxic stress. Increased fetal cortisol concentrations may induce organ differentiation prematurely, which may account for much of the apparent increased maturation of IUGR fetuses, even when born preterm (11). Cortisol also increases catabolic pathways in tissues, including protein breakdown in skeletal muscle and glycogenolysis in the liver, and can restrict placental growth and nutrient transport, which can result in reduced overall fetal growth rates (11).

▪ ANTENATAL CARE OF THE INTRAUTERINE GROWTH-RESTRICTED FETUS

Diagnosis of Intrauterine Growth Restriction

Antenatal diagnosis of IUGR is difficult and often inaccurate. Despite careful attention to gestational dating by maternal history and early and serial fetal ultrasound evaluation, frequent maternal physical examinations, and repeated assessment of risks for IUGR, many infants with IUGR may not be identified before birth (1).

Serial ultrasound evaluation of fetal growth rate and fetal body proportions and Doppler velocimetry of the uterine, placental, and fetal circulations are now the standard diagnostic approaches to determining the severity of IUGR (1). Chronic fetal distress resulting from placental insufficiency, hypoxia, and ischemia (with or without acidosis) is associated with increased Doppler arterial waveform amplitudes that indicate increased vascular resistance and reduced systemic flow in the fetal descending aorta and umbilical artery. Various ratios of systolic-to-diastolic flow velocity (amplitude) waveforms are also used, including the systolic-to-diastolic ratio, systolic-diastolic/systolic ratio (resistance index), and systolic-diastolic/mean ratio (pulsatility index). Ratios or indexes greater than two standard deviations from the mean are associated with IUGR, whereas reversed or absent diastolic waveforms represent severe fetal hypoxia and increased risk of fetal death. The most severely affected IUGR fetuses with the greatest risk of death demonstrate absent or reversed diastolic flow in systemic fetal arteries, along with increased dilation and shunting through the ductus venosus (83). Interestingly, these same fetuses often have decreased cerebral (internal carotid artery) pulsatility index, indicating increased cerebral blood flow (6,84). This flow pattern has been interpreted as one way in which brain growth is spared, as body growth rate slows as a result of placental ischemia and/or placental growth failure. Doppler velocimetry abnormalities have been shown to develop in a sequential fashion as placental insufficiency progressively worsens and may predict risk of acidosis and perinatal mortality, as well as help to predict optimal timing of delivery (16). However, more studies are needed to evaluate the effects of perinatal surveillance by umbilical and fetal Doppler velocimetry on perinatal, neonatal, and long-term outcomes.

The fetus also should be examined by ultrasound for anatomic abnormalities that indicate congenital malformations, genetic syndromes, and deformations. Amniotic fluid index also is useful to identify oligohydramnios. The latter is a risk factor for congenital anomalies, severe IUGR with reduced urine production, pulmonary hypoplasia, variable decelerations from cord compression, and intrauterine death in as many a 5% to 10% of affected fetuses.

Future Diagnosis and Treatment of Intrauterine Growth Restriction

Reduced fetal growth rate, and pathophysiology associated with IUGR, usually develop insidiously, such that once these conditions are clinically obvious, injury has already taken place. It is important, therefore, to develop and apply diagnostic techniques to the fetus that would establish accurately even minimal changes in growth rate and physiologic function. Currently, Doppler ultrasound measurements of fetal cardiac output, systemic blood flow, and organ blood supply are close to achieving this goal, particularly with respect to the placental circulation.

It also is important that diagnostic techniques are developed to assess what damage is being done in the more extreme cases of IUGR. Current techniques include magnetic resonance imaging, Doppler measurements of blood flow to specific organs, and cordocentesis (85). Based on such advances in fetal diagnosis, it soon may be possible to assess whether detected changes in fetal growth rate and measured fetal pathophysiology associated with IUGR are, in fact, as serious and indicative of future handicap as current postnatal follow-up studies have indicated.

Considerably more research is necessary to determine when and how damage to the fetus can be reversed or ameliorated. Some efforts have been made in humans and animal models to improve maternal and fetal nutrition, enhance fetal growth by manipulating fetal anabolic hormone concentrations (33,86), and increase uterine blood flow and nutrient delivery (87). Continued work is necessary to assess the effects of such treatments on long-term growth and development of all affected organs, especially the brain to improve neurodevelopmental outcomes. Intervening in a fetus that has already adapted to a decreased nutrient supply may result in more harm than good, emphasizing the need for continued preclinical trials (88,89).

Antenatal Management

There are few, if any, proven treatments of IUGR. Bed rest and treatment of acute and chronic illnesses appear beneficial. Having the mother breathe supplemental oxygen improves fetal oxygenation, and in a few studies of severe

IUGR fetuses with signs of chronic distress, this has been associated with improved rates of fetal growth and reduced fetal aortic blood flow velocity (increased flow) (90).

Trials of low-dose aspirin therapy initiated early in pregnancy, aimed primarily at preventing preeclampsia, may show some benefit for improving fetal growth (91). Correction of maternal nutritional deficiencies also is useful, particularly when the mother is markedly undernourished. Maternal dietary zinc supplements have improved fetal growth when zinc deficiency was prominent. High protein intakes have not helped and, in fact, have been associated with worse IUGR and perinatal morbidity and mortality (32).

Fetal surveillance techniques should be instituted to determine whether the fetal condition is beginning to fail and if delivery would be more likely to result in a successful pregnancy outcome, as discussed above. Traditional fetal surveillance techniques have included fetal activity recordings, the oxytocin challenge test, which measures fetal heart rate changes after oxytocin-induced uterine contractions, and the nonstress test, which measures the acceleration and beat-to-beat variability of the fetal heart rate after spontaneous fetal movement. These tests, although still done, have been replaced by Doppler velocimetry and the biophysical profile (see also Chapter 12), which combine analyses of fetal breathing movements, gross body movements, fetal heart rate, fetal heart rate reactivity to movement, and estimated amniotic fluid volume. The combined use of Doppler velocimetry and the biophysical profile has improved the antenatal management of IUGR. A low biophysical profile correlates with fetal hypoxia, determined by absent or reversed diastolic flow in the umbilical artery, and fetal blood gas and acid-base measurements obtained by cordocentesis, and with impending fetal demise.

Most obstetricians avoid labor when combined fetal surveillance techniques show severe fetal growth restriction and evidence of

severe chronic distress, including absent or reversed diastolic flow in the fetal aorta, increased pulsations and/or reversed flow in the umbilical arteries, and a low biophysical profile score. Fetuses with these conditions also usually have a nonreactive nonstress test result and a flat baseline fetal heart rate variability pattern. Such fetuses tolerate labor poorly and readily develop signs of acute distress. In all severe cases, the delivery should be coordinated with the neonatology service to provide prompt postnatal evaluation and care and to prepare for resuscitation of a depressed or asphyxiated neonate.

In the absence of repeated observations of severe or progressively worsening IUGR and signs of fetal distress, the moderately affected IUGR fetus should be left *in utero*, while providing good nutrition, perhaps bed rest, and optimal health care to the mother, and continuing fetal surveillance. Decisions to deliver these fetuses prematurely to prevent fetal death should be tempered by the difficulties of accurately diagnosing the worsening of fetal condition and successfully managing all potential neonatal problems of a preterm infant. Although lung maturity may be present, the many other problems associated with preterm delivery should add caution to a decision for early delivery, especially before 31 to 32 weeks of gestation.

▪ CLINICAL EVALUATION AND TREATMENT OF THE SMALL FOR GESTATIONAL AGE INFANT

General Evaluation in the Delivery Room (see also Chapter 18)

SGA infants often present a variety of clinical problems immediately after birth in the delivery room. Because of their large surface area relative to body weight, SGA infants lose heat rapidly. To prevent hypothermia, immediate attention should be given to providing a thermoneutral environment. Severely SGA infants who suffered marked oxygen and substrate deprivation *in utero* may have cardiopulmonary difficulties at birth. Closer to term they may pass meconium and present with meconium aspiration syndrome and show signs of asphyxia, including hypoxemia, hypotension, mixed metabolic and respiratory acidosis, and persistent pulmonary hypertension. Immediately after birth, these infants need prompt and careful attention to their airway, breathing, and oxygen needs.

Brief Physical Examination in the Delivery Room

SGA infants have several characteristic features, even when those infants with obvious anomalies and syndromes and those born to mothers with severe illness or malnutrition are excluded (92). Severely SGA infants who had marked

IUGR have relatively large heads for their undergrown trunks and extremities. The abdomen often appears shrunken or "scaphoid" and must be distinguished from infants with diaphragmatic hernias. The extremities appear scrawny with thin skin folds, and there is evidence of decreased subcutaneous fat and skeletal muscle. The skin is loose and often rough, dry, and peeling. In term and postterm SGA infants, the fingernails may be long, and the hands and feet tend to look large for the size of the body. The face appears shrunken or "wizened." Cranial sutures may be widened or overriding, and the anterior fontanelle may be larger than expected, representing diminished membranous bone formation. The umbilical cord often is thinner than usual. When meconium has been passed *in utero*, the cord is yellow-green stained, as are the nails and skin.

Gestational Age Assessment of the Small for Gestational Age Infant

Gestational age assessment based on physical criteria often is erroneous (92). Vernix caseosa frequently is reduced or absent as a result of diminished skin perfusion during periods of fetal distress or because of depressed synthesis of estriol, which normally enhances vernix production. In the absence of this protective covering, the skin is continuously exposed to amniotic fluid and will begin to desquamate. Sole and palmar creases appear more mature as a result of increased wrinkling from exposure to amniotic fluid. Breast tissue formation also depends on peripheral blood flow and estriol levels and is reduced in SGA infants. The female external genitalia appears less mature because of the absence of perineal adipose tissue covering the labia. Ear cartilage also may be diminished. Specific organ maturity continues at normal developmental rates despite diminished somatic growth in most IUGR infants.

Neurologic Examination of the Small for Gestational Age Infant

Neurologic examination for gestational age assessment may be little affected by IUGR (92). These infants often appear to have advanced neurologic maturity, although this observation is derived mostly from comparisons with infants of similar birth weight, not similar gestational age. Peripheral nerve conduction velocity and visual- or auditory-evoked responses correlate well with gestational age and are not impaired as a result of IUGR. These aspects of neurologic maturity are not sensitive to nutritional deprivation. Active and passive tone and posture are usually normal in SGA infants and are reliable guides to gestational age, assuming that infants with significant central nervous system and metabolic disorders are excluded.

Behavioral Observations

SGA infants often demonstrate specific abnormal behaviors. They may have a "hyperalert" or "starved and hungry" appearance, and they often are described as being jittery and hypertonic, even without simultaneous hypoglycemia. They may be hyperexcitable, showing aberrations in tone from hypertonia to hypotonia and, in many cases, apathy. The Moro response is increased, with exaggerated extension and abduction of the arms, windmill motions, and prolongation of the tonic neck posture (93). When IUGR is particularly severe, SGA infants 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 responsiveness. Such severely SGA infants often appear floppy and develop exhaustion more easily after handling (94). The behavioral disorders occur even in the absence of significant central nervous system disease. Hypoexcitability indicates an adverse effect on polysynaptic reflex propagation and implies that central nervous system functional maturity does not necessarily proceed independently of the intrauterine events that result in IUGR.

Deferred Physical Examination to be Done in the Neonatal Intensive Care Unit

Careful evaluation is important as there is an increased incidence of severe malformation, chromosomal abnormality, and congenital infection among SGA infants (92). Dysmorphic features, "funny-looking facies," abnormal 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. Maternal infections, such as toxoplasmosis, syphilis, hepatitis, zoster, rubella, cytomegalovirus, and herpes simplex, resulting in IUGR are unusual in the absence of other clinical signs of chronic congenital infection; screening cord blood for antibodies and antigens specific to certain infections (which can be augmented by polymerase chain reaction

techniques) and a urine culture for cytomegalovirus may be indicated. Radiographic examination of the long bones, looking for possible anomalies and for the quality of mineralization, may be useful. Examination of the head with ultrasonography to establish the presence of congenital anatomic abnormalities or evidence of congenital infection also may be helpful in making a diagnosis.

▪ CLINICAL PROBLEMS OF THE SMALL-FOR-GESTATIONAL-AGE NEONATE

Morbidity and Mortality

The consequences of small size for gestational age depend on the etiology, severity, and duration of growth restriction. There continues to

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be much debate on this subject. Previous studies included heterogeneous groups of infants, SGA, IUGR, premature, and syndromic, who would be expected to have substantially different clinical problems and outcomes. Additionally, studies have been conducted over extended periods of changing perinatal management and increasing survival of smaller, more preterm infants, normally and abnormally grown. For example, some studies have suggested that the fetus responds to the “stress” of growth restriction with an acceleration of maturity. There is evidence that extremely preterm SGA infants have decreased incidence of respiratory distress syndrome and surfactant deficiency when compared to gestational age-matched AGA controls, perhaps related to stress-induced cortisol secretion at the time of birth (95). However, the same population of SGA preterm infants had longer mechanical ventilation requirements and increased need for postnatal steroid administration, potentially indicating a higher incidence of chronic lung disease despite less early evidence of classic respiratory distress syndrome (95). This possibility is supported by decreased alveolarization shown in IUGR fetal sheep (96). SGA status has consistently been shown to be an independent predictor of increased fetal, perinatal, and neonatal death (95). In fact, when a cohort of SGA neonates was compared to both birth weight-matched and gestational age-matched AGA cohorts, mortality as well as several other morbidities such as ventilator days, patent ductus arteriosus, days to reach full enteral feeds, and total oxygen days were greater in the IUGR cohort compared to the gestational age-matched cohort. Furthermore, morbidities such as hypoglycemia, direct hyperbilirubinemia, necrotizing enterocolitis (NEC), thrombocytopenia, chronic lung disease, and feeding difficulties were higher in the SGA cohort than either of the two comparison groups (97). On balance, there is little evidence to support the concept of improved clinical course or survival after perinatal stress in SGA infants (**Table 23.7**).

TABLE 23.7 Clinical Problems of the SGA Neonate

Problem	Pathogenesis/Pathophysiology	Prevention/Treatment
Intrauterine death	Chronic hypoxia	Antenatal surveillance
	Placental insufficiency	Fetal growth by ultrasound
	Growth failure	Biophysical profile
	Malformation	Doppler velocimetry
	Infection	Maternal treatment: possibly bed rest, possibly O_2
	Infarction/abruption	Delivery for severe/worsening

		fetal distress
	Preeclampsia	
Asphyxia	Acute hypoxia/abruption	Antepartum/intrapartum monitoring
	Chronic hypoxia	Adequate neonatal resuscitation
	Placental insufficiency/preeclampsia	
	Acidosis	
	Glycogen depletion	
Meconium aspiration definite, severe	Hypoxia	Resuscitation including tracheal suctioning for aspiration
Hypothermia	Cold stress	Protect against increased heat loss
	Hypoxia	Dry infant
	Hypoglycemia	Radiant warmer
	Decreased fat stores	Hat
	Decreased subcutaneous insulation	Thermoneutral environment
	Increased surface area	Nutritional support
	Catecholamine depletion	
Persistent pulmonary hypertension	Chronic hypoxia	Cardiovascular support
		Mechanical ventilation, Nitric oxide
Hypoglycemia	Decreased alternative energy	Frequent measurement of blood

	sources	glucose
	Heat loss	Early intravenous glucose support
	Hypoxia	
	Decreased gluconeogenesis	
	Decreased counterregulatory hormones	
	Increased insulin sensitivity	
Hyperglycemia	Low insulin secretion rate	Glucose monitoring
	Excessive glucose delivery	Glucose infusion <10 mg/min/kg
	Increased catecholamines and glucagon	Insulin administration glucagon effects
Polycythemia/hyperviscosity	Chronic hypoxia	Glucose, oxygen
	Maternal-fetal transfusion	Partial volume exchange transfusion
	Increased erythropoiesis	
Gastrointestinal perforation	Focal ischemia	Cautious enteral feeding
	Hypoperistalsis	
Acute renal failure	Hypoxia/ischemia	Cardiovascular support
Immunodeficiency	Malnutrition	Early, optimal nutrition
	Congenital infection	Specific antibiotic and immune therapy

Intrauterine Growth Restriction/Small for Gestational Age Status versus Preterm Birth: Effects on Morbidity and Mortality

Infants born preterm as well as full term can be affected by IUGR. As discussed previously, progressive fetal compromise as a result of worsening placental insufficiency and IUGR is often an indication for preterm delivery. When evaluating the effect of IUGR on both perinatal and long-term morbidity and mortality, it is important to recognize that preterm and IUGR infants have independent and overlapping problems. As gestational age decreases, the problems of prematurity have a larger role in the outcome of both SGA and AGA infants. However, when SGA and AGA preterm infants are compared, SGA infants have higher risk for perinatal mortality and poor long-term neurodevelopmental outcomes (95,98). When IUGR has been prolonged and severe, infants have a higher neonatal morbidity and mortality rate than their AGA counterparts, or those IUGR infants who have been more mildly affected (99). Fetal hypoxia, perinatal depression, multisystem organ failure, NEC, coagulation disorders, immune compromise, and lethal congenital anomalies are the main contributing factors to the high mortality rate for IUGR fetuses and neonates. Improved survival depends on achieving an optimal balance between the consequences of elective preterm delivery and the risks of continued IUGR.

Perinatal Depression

Perinatal depression (“asphyxia”), although uncommon, occurs at increased frequency in SGA infants and complicates the immediate neonatal course of severely growth-restricted infants. SGA infants frequently do not tolerate labor and vaginal delivery, and signs of fetal distress are common. In such cases, the already compromised, chronically hypoxic fetus is exposed to the acute stress of diminished blood flow during uterine contractions. Cord blood lactate concentrations are often increased, especially in the most severely affected IUGR fetuses (100). Preterm SGA infants are delivered by cesarean section twice as often as preterm AGA infants (101). SGA infants have an increased incidence of low Apgar scores at all gestational ages (101), frequently need resuscitation, and are more likely to require postnatal vasopressor support (102).

The need for neonatal resuscitation may compound *in utero* insults. Sequelae of perinatal depression may include multiple organ system dysfunction, such as hypoxic-ischemic encephalopathy, heart failure from hypoxia-ischemia and glycogen depletion, meconium aspiration syndrome, persistent pulmonary hypertension, gastrointestinal hypoperistalsis and ischemia-induced necrosis with focal perforation or NEC, hypocalcemia, acute renal tubular necrosis, or renal failure.

Neonatal Metabolism

Hypoglycemia (See also Chapters 20 and 34)

Hypoglycemia is extremely common in SGA infants, increasing with the severity of IUGR (**Fig. 23.8**) (103). The risk of hypoglycemia is greatest during the first 3 days of life, but fasting hypoglycemia, with or without ketonemia, can persist or occur repeatedly up to weeks after birth. Early hypoglycemia is aggravated by diminished alternative energy substrates, including reduced concentrations of fatty acids and lactate. Hyperinsulinism, impaired gluconeogenesis, or deficient counterregulatory hormones may also contribute to neonatal hypoglycemia. Resolution of persistent hypoglycemia is coincident with improved capacity for, and rates of, gluconeogenesis (104,105,106,107).

Fasting hypoglycemia is becoming less common in SGA infants as standard nutritional support includes early intravenous glucose and protein and enteral feeding. All SGA infants should have early and frequent measurements of blood or plasma glucose concentrations. In the first few days of life, blood glucose concentrations greater than 50 mg/dL are considered optimal. For mature neonates, early enteral feeding, sometimes with formula supplementation, may prevent hypoglycemia. In less mature infants or those who have other clinical problems, intravenous glucose infusion should be started at 4 to 8 mg/min/kg as soon after birth as possible, preferably by 30 minutes of age. As the brain is relatively large in many infants with IUGR (especially if asymmetrical) and relies almost completely on glucose for energy metabolism, estimated glucose requirements should be based on what the weight would be for a symmetric head circumference/body weight ratio (e.g., based on a weight consistent with the size of the head rather than the actual body weight).

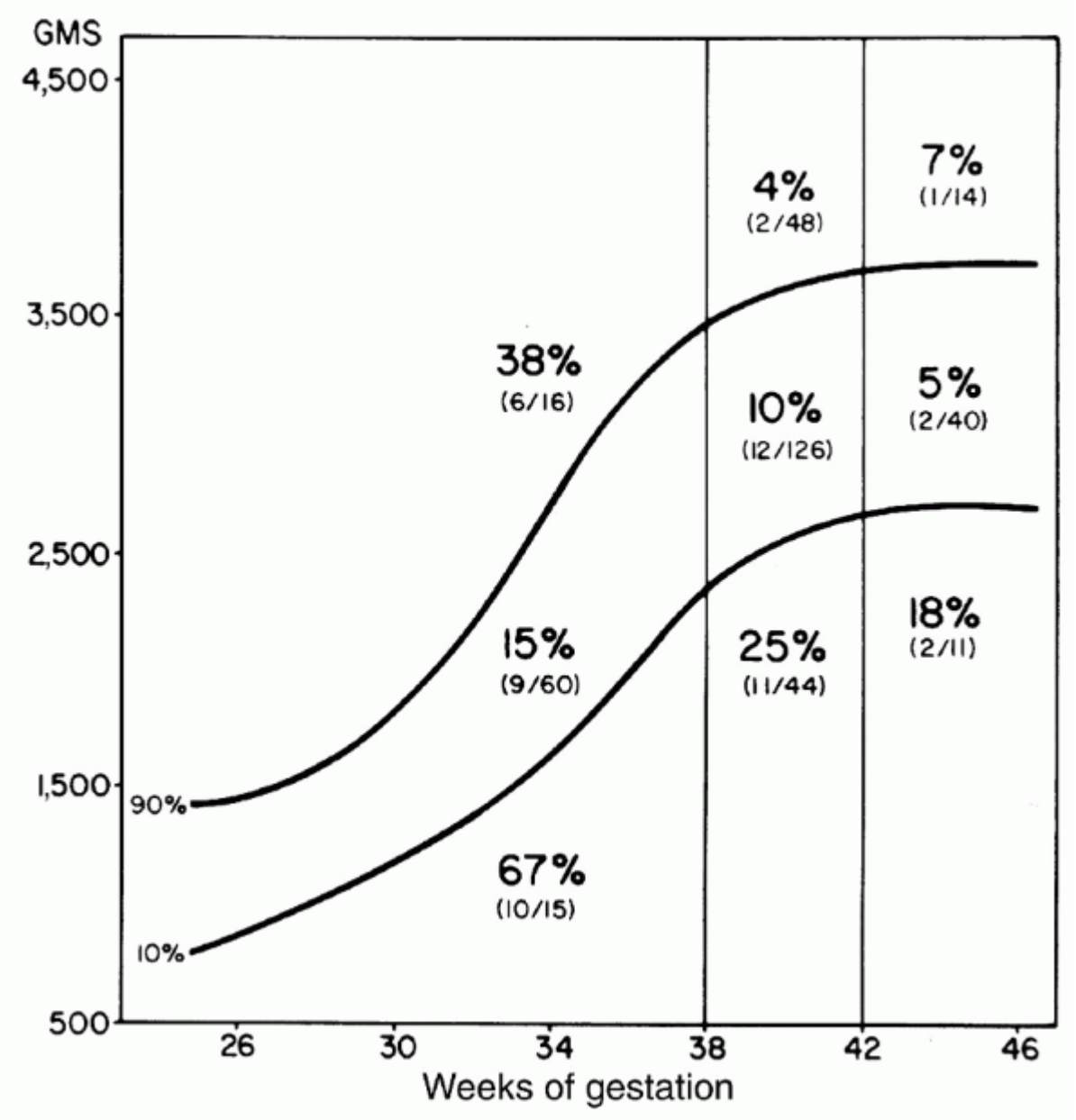

FIGURE 23.8 Incidence of hypoglycemia prior to first feeding (blood glucose <30 mg/dL) among LGA, AGA, and SGA infants, demonstrating the much greater incidence of early hypoglycemia among SGA infants at all gestational ages. From Lubchenco LO, Bard H. Incidence of hypoglycemia in newborn infants classified by birth weight and gestational age. *Pediatrics* 1971;47:831, with permission.

The initial glucose infusion rate should be adjusted in response to measurements of blood glucose concentration every 30 to 60 minutes until values are consistently greater than 50 mg/dL. Less frequent measurements should be continued until the infant is tolerating full enteral feedings. Infants with severe hypoglycemia (<20 mg/dL) should be treated immediately with an intravenous "minibolus" of 10% dextrose in water at 200 mg/kg (2 mL/kg), followed by a glucose infusion starting at 4 to 8 mg/min/kg. Glucose concentrations should be measured at least every 30 minutes until blood glucose concentrations are consistently above 50 mg/dL. Infants at greatest risk of having severe hypoglycemia are those who have had perinatal compromise and those who are the thinnest according to the ponderal index, representing those infants with the least amount of nutritional reserves.

Hyperglycemia

Insulin concentrations that are lower than in AGA infants of the same gestation, or unnecessarily high rates of glucose infusion (>11 to 14 mg/min/kg), may contribute to the hyperglycemia sometimes seen in SGA infants (105,108). High concentrations of counterregulatory hormones, such as epinephrine, glucagon, and cortisol, may also contribute, although there is only limited evidence to support this commonly held assumption (109). 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 (110).

Lipid Metabolism

SGA infants have lower plasma free fatty acid concentrations than normally grown infants. Fasting blood glucose concentrations in SGA infants directly correlate with plasma free fatty acid and ketone body concentrations. Additionally, SGA infants have a deficient utilization of intravenous triglycerides. After the intravenous administration of triglyceride emulsion, SGA infants have high free fatty acid and triglyceride concentrations, but ketone body formation is attenuated (111,112). These observations indicate that the utilization and oxidation of free fatty acids and triglycerides are diminished in SGA neonates. Free fatty acid oxidation is important because it spares peripheral tissue use of glucose, whereas the hepatic oxidation of free fatty acids may contribute the reducing equivalents and energy required for hepatic gluconeogenesis. Deficient provision or oxidation of fatty acids may be partly responsible for the development of fasting hypoglycemia in these infants.

Energy Metabolism

When nursed in a neutral thermal environment, SGA infants demonstrate the usual decline of the respiratory quotient after birth, representing a shift toward free fatty acid oxidation. During the first 12 hours after birth, basal oxygen consumption may be diminished in SGA neonates. Similar observations have been recorded *in utero* among spontaneously SGA fetal lambs, indicating a deficiency of potentially oxidizable substrates in both situations. Supporting this hypothesis is the marked increment of oxygen consumption that occurs in well-fed SGA infants (113), similar to the increase in energy production after nutritional rehabilitation of infants with marasmic kwashiorkor. The increment of oxygen consumption after fetal or infantile malnutrition represents the energy cost of growth. Partly because of enhanced caloric intake, and because metabolic rate and oxygen consumption are related more to gestational age than birth weight, SGA infants have a higher oxygen consumption rate and a higher rate of total energy expenditure (primarily as a result of increased resting energy expenditure) than less mature neonates (112,114). Although some nutritional balance studies of preterm SGA infants have demonstrated an increase of fecal fat and protein loss, more recent studies indicate adequate digestion of nutrients and percent nutrient retention of metabolizable nutrient intake. Thus, these infants can achieve normal, and occasionally faster, rates of growth compared with preterm AGA infants of similar weight (115).

Amino Acid and Protein Metabolism

SGA infants are particularly deficient in muscle mass (22). Improving growth of skeletal muscle and increasing total body protein are priorities in these infants. There is conflicting information from a limited number of studies, however, about how well SGA infants tolerate aggressive amino acid and protein nutrition. Extremely-low-birth-weight and VLBW SGA infants have higher rates of protein loss in stools, and of lipids (112), with 11% to 14% lower rates of absorption. This may be partly compensated for by higher intakes, which can normalize metabolizable protein intakes. Further, although growth rate may be increased in SGA infants by increased intake of protein and nonprotein calories, specific evidence for this comes largely from preterm infants, some of whom were AGA and some SGA. Also, animal studies show more limited fetal and neonatal pancreatic development (116) and intestinal size in SGA offspring (117), which may limit feeding tolerance, protein digestion, and the production of insulin. In fact, there is evidence that SGA infants have higher alpha-amino-nitrogen in the serum and urine as well as total bile acid concentrations in the serum, compared to AGA infants, when administered higher protein intakes, suggesting that SGA infants are more sensitive to an excessive protein intake than AGA infants (118).

Some studies, however, have shown that amino acid turnover rates are higher in SGA LBW infants (119), but other studies show no difference (120). SGA infants may be more energy efficient in protein synthesis (120). Thus, SGA infants possibly may tolerate higher protein intake, but the benefit of increased intake is not clear. Further studies are

critically needed to determine optimal protein delivery for SGA and IUGR neonates in order to maximize lean mass and linear growth.

Nutritional Problems and Management

In fetal sheep that are acutely glucose deficient, amino acids are used for oxidation and for glucose production (121). It is not clear if human infants born following similar patterns of IUGR and nutrient deficiency will have similar patterns of metabolism after birth, nor is it known what types and amounts of nutrients are best fed to such infants to restore normal metabolism and to reestablish normal rates of growth as quickly as possible. A rapid rate of glucose supply can lead to marked hyperglycemia, especially in the ELBW preterm SGA infant. If insulin and IGF-I are deficient in these infants, one would also expect lower anabolic rates until glucose and amino acid supplies and concentrations, and production rates of these growth factors, are restored. Similar issues may apply to lipid tolerance. Such considerations have prompted some reluctance to feed the SGA infant as aggressively as their deprived nutritional state would indicate, but 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 nutritional support and whether this will result, safely, in improved nutritional rehabilitation, growth, and perhaps, neurodevelopmental outcome.

Temperature Regulation

A normal increase in nonshivering thermogenesis is seen in SGA infants because some brown fat is available (122). *In utero* stress that depletes catecholamine stores can contribute to a failure of brown fat to produce heat. Compared with term infants, SGA infants have a narrow thermoneutral range. Heat production cannot match the rate of heat loss with continued cold stress. Rapid heat loss as a result of the large head-to-body ratio and increased surface area seen in all infants is exaggerated in the asymmetric SGA infant. Heat is also lost more quickly through a thin layer of subcutaneous fat insulation (122). However, SGA infants of more than 30 weeks of gestation may have increased skin maturity and less evaporative heat loss than preterm AGA infants of comparable weight, indicating that thermal neutral environments should be based on gestational age and not weight alone. Heat production may be impaired by concurrent conditions of hypoglycemia and hypoxia seen commonly in these patients. The normal response to cold involves increased muscular activity and catecholamine (norepinephrine) release. Central nervous system depression may prevent this response (122).

During the first few hours of life, oxygen consumption and heat production may be less than anticipated as a result of decreased available substrate. Fewer fatty acids are available for oxidation. Later, as nutritional support is provided, the infant may have higher than expected oxygen consumption. Brain oxygen requirements are high, and in the SGA infant, brain tissue represents a large proportion of body weight. Limited availability of glucose *in utero* limits metabolic rate. After delivery, as glucose substrate is provided, the brain increases its metabolic rate and oxygen consumption. Based on brain size, increased rates of oxygen consumption are appropriate in the SGA infant. It is critical, therefore, that the SGA infant be resuscitated and nursed in a thermoneutral environment. The newborn should be placed immediately under a radiant warmer, dried well, and protected from drafts with warmed blankets. Alternatively, very SGA infants may be placed wet into a plastic “bowel bag,” with the head then dried and capped. Chemical mattresses may also be used to prevent heat loss, but care must

be taken to prevent overheating. A prewarmed hat will minimize excessive heat loss from the head.

Polycythemia-Hyperviscosity Syndrome

SGA infants manifest an increased incidence of polycythemia and resulting hyperviscosity (123). Increased red blood cell volume is likely related to chronic *in utero* hypoxia leading to increased erythropoiesis (124). Even when not polycythemic (venous hematocrit >60%), SGA infants have higher than normal hematocrit (124). Approximately half of all term SGA infants have a central hematocrit above 60%, and about 17% of term SGA infants have a central hematocrit above 65% in contrast to only about 5% in AGA term infants (123). Viscosity is directly related to hematocrit, and increased viscosity interferes with normal tissue perfusion. Most polycythemic infants remain asymptomatic, but SGA infants are at greater risk of symptoms and clinical consequence (123). Interestingly, male SGA infants are at highest risk. Polycythemia contributes to hypoglycemia and hypoxia. Increased viscosity interferes with

neonatal hemodynamics and results in impaired postnatal cardiopulmonary and metabolic adaptation. There also is an increased risk of NEC. In addition to correcting hypoxia and hypoglycemia in these infants, partial volume exchange transfusion should be considered to lower hematocrit and minimize associated morbidities.

Necrotizing Enterocolitis

The exact etiology of NEC remains uncertain, but ischemia of the bowel and susceptibility to infection are generally considered part of the disorder. Based on the increased incidence of hypoxia, acidosis, and hyperviscosity in severe cases of IUGR, it is understandable how blood flow to the intestine of infants with IUGR could be compromised. Increased susceptibility to infection adds an additional risk. Not surprisingly, therefore, IUGR/SGA infants have an increased incidence of NEC (125), best predictable not as much based on the size of the infant but on the absence of end-diastolic flow on fetal Doppler studies (126). In such cases, delaying the onset of rapid advancement and/or large volumes of enteral feeding generally are recommended. Minimal enteral feedings, particularly with mother's milk, may, however, increase intestinal blood flow, improve GI integrity, and improve immunity.

Immune Function and Infectious Disease Risk

Immunologic function of SGA infants may be depressed at birth and may persist into childhood, as in older infants with postnatal onset of malnutrition (127). Though studies to evaluate risk of infection are limited, there is evidence that preterm SGA infants are at higher risk for infection episodes and culture-proven sepsis in the neonatal period (128).

Miscellaneous Problems

At birth, cord prealbumin and bone mineral content are low in term SGA infants (129). Calcium and iron stores may be low as a result of chronic decreased placental blood flow and insufficient nutrient supply. Significant hypocalcemia can occur after stressful birth complicated by acidosis. Thrombocytopenia, neutropenia, prolonged thrombin and partial thromboplastin times, and elevated fibrin degradation products are also problems among SGA infants. Sudden infant death syndrome may be more common after IUGR. Inguinal hernias also disproportionally follow preterm IUGR.

▪ OUTCOMES AND LONG-TERM CONSEQUENCES OF SMALL FOR GESTATIONAL AGE INFANTS

Hospitalization

As fetal compromise due to IUGR is an indication for preterm delivery, IUGR infants have extended hospital stays secondary to morbidities related to both prematurity and SGA status. But even when born at term, SGA infants are admitted more frequently to the intensive care unit and have longer hospital stays than their AGA counterparts. Similarly, SGA infants born late preterm (34 to 36 6/7 weeks gestation) have longer hospital stays and increased morbidity compared to AGA late-preterm neonates (130).

Growth and Developmental Outcome (See also Chapter 56)

Most studies of normal and restricted fetal growth and development support the concept that critical windows of time are present in human development during which normal growth of certain tissues (e.g., fat, muscle, bone) or organs (pancreas, brain) must occur. Insults at such times limit growth and 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, axonal length, dendritic arborization, and synapse formation, as well as later life behavioral development, learning, and memory (131). Permanent deficits may result if growth failure occurs during these critical periods (132). Not surprisingly, therefore, longer-term outcome studies have more often related worse neurodevelopmental outcome in those IUGR/SGA infants with smaller than normal head circumferences (133).

SGA infants are a heterogeneous group of babies with the potential for a variety of outcomes. Some are small from genetic or familial causes and therefore may be expected to achieve their full growth potential and have normal neurodevelopment. Others have specific chromosomal errors or injury from infections, which are likely to result in severe and unrecoverable failure of growth and development. Most have a less defined reason for abnormal *in utero*

growth. The infant with symmetric growth restriction may have little chance for postnatal catch-up growth after an early, global disruption of growth. Outcomes are even less well defined for the population of neonates who had normal growth in early gestation, but developed growth restriction from limited nutrient availability in later gestation with evidence of preserved brain growth. Studies of growth-restricted infants have been plagued by methodologic problems. Many early studies included all SGA infants without adequate distinction between those born at different gestational ages, with evidence of fetal growth restriction measured either by Doppler velocimetry or by serial measurements of fetal growth trajectory, or those with limited familial or genetic growth potential. Infants with obvious chromosomal abnormalities and evidence of congenital infection have also been included. Only relatively recently have studies differentiated IUGR and SGA infants from AGA infants, to show that the etiology of small size at birth carries great prognostic value. Even recent studies of this subject have been limited by uncontrolled confounding factors. An infant's perinatal morbidity, including degree of prematurity, inborn or outborn (requiring transport) status, presence of abnormal umbilical artery waveforms, and a variety of neonatal complications, such as asphyxia, hypoglycemia, polycythemia, and cold stress, can impact on ultimate outcome. Multiple gestation and even birth order can influence future growth potential.

Socioeconomic status and environment are among the most important, but difficult to measure, variables affecting the growth and development of SGA infants. There are strong associations between socioeconomic factors and the cognitive development and school performance of growth-restricted children (134).

Postnatal Physical Growth of Small for Gestational Age Infants

Although measurements of weight, length (or height), and head circumference are standardized and reproducible, many authors have given more attention to one measurement over another or have been more concerned with a specific interrelationship of measurements, such as the ponderal index. In general, SGA infants continue

to be smaller and relatively underweight for age as they grow older, even through adolescence and early adulthood (**Fig. 23.9**). These infants more commonly have short stature as teenagers and young adults, indicating lifelong growth deficit.

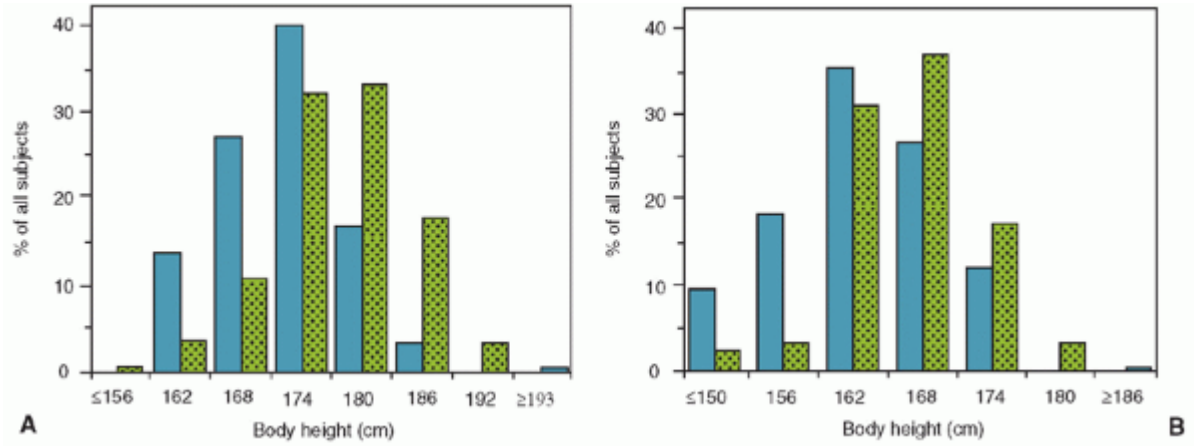

FIGURE 23.9 Distribution of height at age 17 years in 30 boys **(A)** and 34 girls **(B)** born SGA **(***solid bars***)** and their peers who were born appropriate for gestational age **(***shaded bars***).** From Paz I, Seidman DS, Danon YL, et al. Are children born SGA at increased risk of short stature? *AM J Dis Child* 1993;147:337, with permission.

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 who had primarily a reduction in weight 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. This catch-up growth occurs primarily from birth to 6 months of age, with some infants continuing an accelerated rate of growth for the 1st year. A few of these infants will 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, while postnatal growth of lean mass and muscularity remain restricted (22,135). 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 recognized by relative microcephaly at birth, whether at term or preterm, is felt to be a poor prognostic indicator, as it reflects the severity and duration of growth failure. A lack of head sparing and small occipital-frontal circumference (OFC) is associated with poor neurologic and psychological outcome (136). Head size, if catch-up head growth has not occurred by 8 months of age, is a predictor of lower intelligence test scores at 3 years of age (137). This correlation seems to be independent of environmental or other risks.

Postnatal Neurodevelopmental Outcome of Full-Term, Small for Gestational Age Infants

Neurologic disorders and other morbidities are more frequent in SGA infants as a group (138). For example, in one study of a large population of infants born greater than 35 weeks of gestation, fetal growth restriction was a significant contributor to increased risk of cerebral palsy and neonatal death (139). However, in full-term, mild-to-moderately SGA infants who have normal brain growth, no hypoxic-ischemic injury, and good environmental support, IUGR may have little impact on behavior or mental ability in adolescence or adulthood (132,136).

Although the absence of gross neurologic outcome in the term SGA infant is reassuring, evidence of mild brain dysfunction among these children 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. An increased number of diffuse abnormalities are seen on electroencephalogram (140). A large fraction of term SGA children have speech problems, including delayed onset of speech, immature vocabulary with persistent infantile articulation, and poor receptive and expressive abilities for age. In contrast, only 1.5% of the general population and about 5% of their siblings had speech difficulties. Delays in language development in this population have been further correlated with slower relative head growth (141). At adolescence, trends toward lower test scores, especially in mathematics, and an increased incidence of learning disabilities have been noted (142).

Postnatal Neurodevelopmental Outcome in Preterm, Small for Gestational Age Infants

The prognosis for preterm SGA infants is less clear and is easily confounded by other problems of preterm birth. In general, restricted growth for gestational age is associated with more cognitive disability in infants who were born preterm (143,144). There is increasing evidence showing that those infants suffering the dual insults of preterm birth and growth restriction are at higher risk of neurodevelopmental deficit (95,98).

Diffuse cerebral damage as a result of hypoxia and decreased intrauterine blood flow, especially to the brain, probably accounts for the differences in expression of brain damage seen in preterm AGA and SGA children (145). The need for special education is higher and becomes apparent at an earlier age in these preterm SGA infants when they reach school age (145).

Adult Disorders Resulting from Intrauterine Growth Restriction

Recent epidemiologic evidence indicates that obesity, insulin resistance, type 2 diabetes, and cardiovascular disease are more common among adults who were smaller than normal at birth and very likely SGA secondary to IUGR, particularly those who had a high placental-to-fetal-weight ratio (2,146). A variety of animal studies support this concept, including the greater incidence of obesity, glucose intolerance, plasma lipid abnormalities, and hypertension in offspring whose mothers were fed a low-protein diet during pregnancy. Those studies suggest that certain adult pathologies may be unavoidable consequences of environmentally imposed conditions, such as severe and prolonged fetal undernutrition, which lead to fetal growth restriction to ensure fetal survival. These conditions may represent an example of “programming,” in which an insult, when applied at a critical or sensitive stage in development, may

result in a lasting, even lifelong, effect on the structure or function of the organism (2). IUGR, therefore, is increasingly seen as an adaptive physiologic process, even though it can produce adverse fetal, neonatal, and potentially adult consequences (**Table 23.8**). Mechanisms responsible for these later-life morbidities in adults who were growth restricted *in utero* are not yet established. There is animal evidence of diminished pancreatic growth and development (116), which might present in later life as pancreatic insufficiency when the adult starts and then continues eating a diet rich in simple carbohydrates and lipids. Peripheral insulin resistance may develop in the same way, possibly due to persistent reductions in muscle mass after chronic placental insufficiency (147). Human epidemiologic data indicate that adults who were IUGR are at an increased risk of developing uncontrolled hepatic glucose production (148), with hepatic insulin resistance originating during fetal life (63). Cardiovascular disorders and hypertension in adulthood may be the result of altered adrenal and renal development in response to IUGR (149).

TABLE 23.8 Fetal, Neonatal/Infancy, and Adult Disorders that Might Result from Fetal Programming as a Consequence of Fetal Undernutrition at Different States of Gestation

	Trimester of Pregnancy		
	First	**Second**	**Third**
Consequences	Low growth trajectory	Disturbed fetal-placental relationships	Brain growth sustained, but not body
Fetal adaptation	Down-regulation of fetal growth	Insulin resistance	Growth factor(s) resistance/deficiency
Anthropometry	Symmetric	Mixed	Asymmetric
Infant growth	Reduced infant growth	Reduced infant growth	Catch-up growth possible
Adult life	Increased BP	Increased BP, type 2 diabetes	Increased BP, type 2 diabetes, ischemic heart disease hypercholesterolemia

BP, blood pressure; NIDDM, non-insulin-dependent diabetes mellitus.

From Barker D. *Mothers, babies, and diseases later in life*. London, UK: BMJ Books, 1994, with permission.

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