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Small for Gestational Age: Short Stature and Beyond

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Depending on the definitions used, up to 10% of all live-born neonates are small for gestational age (SGA). Although the vast majority of these children show catch-up growth by 2 yr of age, one in 10 does not. It is increasingly recognized that those who are born SGA are at risk of developing metabolic disease later in life. Reduced fetal growth has been shown to be associated with an increased risk of insulin resistance, obesity, cardiovascular disease, and type 2 diabetes mellitus. The majority of pathology is seen in adults who show spontaneous catch-up growth as children. There is evidence to suggest that some of the metabolic consequences of intrauterine growth retardation in children born SGA can be mitigated by ensuring early appropriate catch-up growth, while avoiding excessive weight gain. Implicitly, this argument questions current infant formula feeding practices. The risk is less clear for individuals who do not show catch-up growth and who are treated with GH for short stature. Recent data, however, suggest that long-term treatment with GH does not increase the risk of type 2 diabetes mellitus and the metabolic syndrome in young adults born SGA. (*Endocrine Reviews* 28: 219–251, 2007)

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Abbreviations: AGA, Appropriate for gestational age; ALS, acid labile subunit; BMI, body mass index; 11β-HSD 2, 11β-hydroxysteroid dehydrogenase 2; IGFBP, IGF-binding protein; IGF-IR, IGF type I receptor; IUGR, intrauterine growth retardation; PCOS, polycystic ovarian syndrome; QUICKI, quantitative insulin sensitivity check index; SDS, SD score; SGA, small for gestational age; TDS, testis dysgenesis syndrome; UPD, uniparental disomy; VNTR, variable number of tandem repeats.

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I. Introduction

IT IS ESTIMATED THAT, depending on geographical region, between 8 and 26% of all infants born worldwide are of low birth weight (1). The World Health Organization has defined low birth weight as a weight of less than 2500 g (2), but this is an all-encompassing classification for international comparison of neonatal and public health, which includes premature infants, who though small, have a weight and length that is appropriate for their gestational age (AGA). The term "small for gestational age" (SGA) is used to describe fetuses or newborn infants whose weight and/or crown-heel length is less than expected for their gestational age and sex (3, 4). This is a basic description of the term, but an accurate definition of SGA that takes into account physiological variation (enabling the exclusion of constitutional smallness, which is not pathological) is under continued development and should eventually lead to individually customized fetal growth curves and birth weight percentiles (5).

There is a lack of data on the incidence of SGA births in many countries because birth length and gestational age are rarely recorded in national databases; however, based on available data, it has been estimated that between 2.3 and 10% of all infants are born SGA (4, 6, 7), although this may still be a gross underestimate in global terms (8). Of those born SGA, most go on to achieve appropriate catch-up growth by 2 yr of age, but approximately 15% do not (9, 10)

and most of these children continue to experience poor growth throughout childhood.

It is becoming increasingly recognized that being born SGA carries an elevated risk of developing metabolic disease in later life, particularly obesity, insulin resistance, carbohydrate intolerance, and dyslipidemia. Studies of individuals exposed *in utero* to famine during the Dutch Hunger Winter of 1944 have revealed that poor maternal nutrition, especially during the last trimester of pregnancy, can lead to growth restriction of the fetus and is associated with poor glucose tolerance and insulin resistance (11, 12). In addition, developmental sequelae affecting the GH-IGF axis, and adrenal and gonadal function are seen, particularly in individuals with abnormal weight gain in infancy and childhood. The tempo of postnatal weight gain is emerging as particularly important in the relationship between birth weight and adult disease. For example, recent evidence from Barker *et al.* (11) shows that excessive weight gain during childhood and adolescence in individuals whose weight was low at birth presents a particularly poor prognosis for the development of coronary heart disease in later life.

It now appears that the role of early postnatal growth, from birth to 2 yr of age, is even more critical than growth beyond the age of 2 yr. Unlike the findings of Barker *et al.* (11), observational studies of full-term infants and randomized trials of premature infants demonstrate that rapid weight gain in infancy—even within the first few weeks of life—can lead to hypertension, obesity, and related morbidities before the third decade of life (12–14). This is much sooner after being born SGA than identified by Barker *et al.* (11).

Being born SGA, therefore, confers a substantial risk of morbidity in adulthood. Moreover, insufficient catch-up growth in infancy is associated with continued short stature and an array of psychosocial and metabolic consequences. Attempts to promote catch-up growth in the perinatal period should, however, be tempered against the additional risk of subsequent metabolic disease, because rapid weight gain in early infancy is also associated with poor adult health. This review presents our current understanding of the SGA phenomenon, the possible mechanisms involved, the metabolic consequences, and the efficacy and safety of GH therapy. In addition, it summarizes recent studies that may challenge some of the hypotheses of fetal programming proposed originally by Barker and colleagues.

II. Definition of SGA

Traditionally, the term SGA has been used to describe a neonate whose weight and/or crown-heel length at birth is at least 2 SD below the mean for the infant's gestational age, equivalent to the 2.3 percentile, based on data derived from an appropriate reference population (4, 15). Some publications define SGA as a birth weight or length below the 3rd, 5th, or 10th percentiles for gestational age (16–18); however, −2 SD is likely to capture the majority of infants with impaired fetal growth. Certainly, numerous studies defining growth patterns and patients' response to GH therapy have used −2 SD as the cutoff for SGA (6, 15, 19, 20).

This broad description of SGA includes individuals with a low birth weight but normal birth length or, conversely, individuals who may have been born short in length with a normal birth weight. Indeed, some children born SGA are both short in length and low in weight. Consequently, infants born SGA may be classified as SGA with a low birth weight, SGA with a low birth length, or SGA with a low birth weight and length (21). In practice, it is important to use these classifications, because the prognosis and response to GH therapy may be different for different SGA subtypes.

The term "intrauterine growth retardation" (IUGR) is often used synonymously with the term SGA. However, because IUGR implies an underlying pathological process that prevents the fetus from achieving its growth potential, its use should be restricted to describing infants whose small size can be attributed to a specific cause and whose prenatal growth has been confirmed by several anomalous intrauterine growth assessments. Being born SGA does not necessarily mean that IUGR has occurred. Similarly, infants who are short after confirmed IUGR are not inevitably SGA. The designation SGA calls for the availability of birth weight and length reference data, specific to the ethnicity and geographic location of the population. In the United States, population-specific birth weight and length data derived by Usher *et al.* (22) are in common use; however, similar data are rarely available in other countries, making accurate definition of SGA problematic. Perhaps, even more important than reference data is the need for accuracy in gestational dating and in measurement of length and weight at birth. Birth weight is commonly recorded in developed countries; however, birth length is still not routinely, or accurately, recorded in many situations. Consequently, it can sometimes be difficult to distinguish an SGA neonate from one that is AGA, especially where gestational age data or appropriate birth measurements are lacking.

Despite the availability of normal growth curves in some countries, there are certain circumstances where they are not the most appropriate reference model. For example, some extremely premature infants born AGA at less than 30 wk may experience some postnatal growth restriction and their subsequent growth may actually be similar to that of SGA infants. Furthermore, there are currently no standard data for multiple births, and it is widely acknowledged that multiple gestation *per se* may be a cause of low birth weight; however, normal standards for catch-up in growth and height should, nevertheless, apply to individuals from multiple births. A new definition of SGA based on fetal growth potential has recently been developed (5) and is discussed in further detail in the diagnosis section of this review.

III. Epidemiology

According to recent estimates, 4,115,590 infants were born in the United States in 2004 (23). This means that, at 2.3% of the population, there were approximately 95,000 infants born SGA. By contrast, the incidence of GH deficiency is estimated at 1 in 3500 (24) and would have been diagnosed in almost 1200 infants in the same interval. Achondroplasia, the most common form of skeletal dysplasia, with an estimated incidence of between 1 in 10, 000 and 1 in 25,000 (25–27), would

have occurred in 160–400 infants in the same cohort. At one in 43, therefore, the incidence of SGA births is relatively high, compared with other growth disorders. Thus, those individuals born SGA who fail to show catch-up growth (approximately 10%) constitute a relatively high proportion of children and adults with short stature.

IV. Diagnosis

It is widely accepted that the most accurate methods for estimating gestational age are ultrasonography and the date of the last menstrual period (28, 29). In order for an infant to be identified as SGA, gestational ultrasonographic data must be supplemented by precise measurement of length at birth. Nevertheless, the validity of ultrasonographic indices, such as crown-rump length and biparietal diameter, in determining gestational age is dependent on accurate recordings being made throughout gestation (30). Moreover, anomalies in fetal growth can invalidate any predictions based on these measurements, leaving the date of the last menstrual period as a chief predictor of gestational age.

It should be noted that the original data published by Barker and colleagues, relating low birth weight to metabolic and cardiovascular disease in later life, are marred by the fact that the epidemiological data frequently did not contain birth weight data but contained only weight at 1 yr of age. Moreover, there was no ultrasonographic assessment, which could mean that many of the individuals in Barker's cohorts may have been prematurely born infants, rather than SGA neonates. Indeed, later studies by Huxley *et al*. (31, 32) have suggested that the strength of associations between birth weight and adult disease may have been overestimated due to selective emphasis on specific measures from particular studies and may have been confounded by inappropriate adjustment for current weight and other variables. Although the "Barker hypothesis" is intriguing, data from Huxley *et al*. (31, 32) and others (33–36) have failed to confirm that birth weight is of relevance to blood pressure in later life. Further epidemiological studies should, therefore, critically appraise the available evidence and, most importantly, devise critical tests of the fetal programming hypothesis, rather than merely replicate its predicted associations (35, 36). As an alternative explanation to intrauterine programming, Neel (37) and Hattersley and Tooke (38) have proposed that insulin resistance is genetically mediated. This insulin-resistant genotype could result in low birth weight, glucose intolerance, insulin resistance, diabetes, and hypertension (Fig. 1).

Gestational age determination is entirely dependent on the accuracy of dating, and it is now well-recognized that accurate gestational dating is essential for the development of any reliable growth standard. Errors in such dating can invalidate any estimation of gestational age, particularly in the preterm range (5); therefore, ultrasonographic dating is the preferred method, because it is widely deemed to be more accurate than menstrual dating. It is also increasingly recognized that growth standards need to take into account physiological factors known to affect birth weight and postnatal growth, including ethnicity, parity, maternal height and weight in early pregnancy, and the sex of the baby (39, 40). By taking into account variables such as these, customized growth curves and birth weight percentiles can be constructed for individuals both pre- and postnatally. Such individualized growth curves offer better discrimination between pathological and physiological smallness than do standard growth curves based on mean values from large populations (41). Another approach to identify newborns with fetal growth restriction in weight and/or length based on the constitutional growth potential has recently been proposed by Mamelle *et al.* (42). This novel approach may also identify "at risk" infants. These investigators are currently tracking more than 600 infants.

Customized growth curves and birth weight percentiles have been shown to be better correlated with Apgar scores (40), neonatal morphometry indices (43, 44), and adverse gestational events (45, 46) than standard charts. A recent study from New Zealand revealed the superiority of customized charts over standard population-based charts in defining SGA. It showed that infants designated SGA by individually customized data were significantly at risk of several adverse events, including cesarean section for fetal

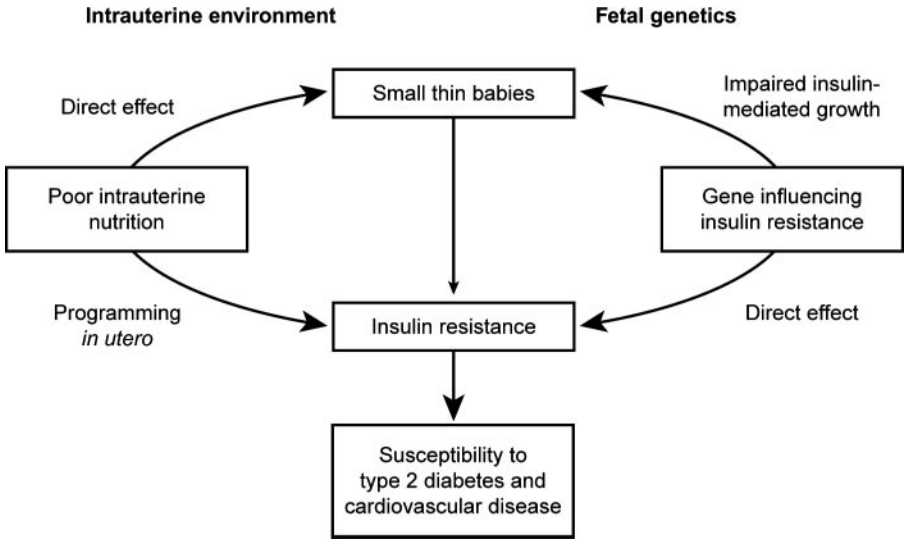

FIG. 1. Two possible explanations for the association of being born SGA with insulin resistance, type 2 diabetes, and ischemic heart disease: intrauterine environment and fetal genetics. [Adapted with permission from Hattersley and Tooke (38).]

distress, abnormal uterine and umbilical artery Doppler analysis, low ponderal index, hypoglycemia, and overall perinatal mortality, whereas infants designated SGA by the regular population standards alone were not at increased risk of any of the same outcomes (47). These and other studies suggest that infants defined as SGA by customized growth charts have probably suffered IUGR and are at risk of associated morbidities and mortality, whereas small-normal infants are at no greater risk than normal-sized infants (5).

V. Intrauterine Growth

Size at birth is determined by two important factors: placental function and duration of pregnancy. Although low birth weight is associated with a variety of peri- and postnatal diseases, fetal overgrowth is also associated with significant neonatal and subsequent morbidity. Prevention of poor intrauterine growth and preterm labor relies upon problems being detected through routine antenatal assessments; however, such observations are only as reliable as the methods used to make them. Although ultrasonography is considered to be the most reliable method for assessing fetal growth and gestational age, it does suffer from some intrinsic limitations. For example, among the measurements routinely made at 18–20 wk gestation is femur length; however, ultrasonography detects only ossification and not cartilaginous mass at the end of the bone, which could introduce errors. Another problem with determining fetal growth and age is that the values obtained are used to assign the fetus to a particular percentile to predict birth outcome. Although this is desirable, in practice adherence to a particular height percentile is only evident beyond the age of 2 yr. Before this age, "percentile crossing" is common, including *in utero* (48).

Traditionally, it has been believed that intrauterine growth disruption in the first and early second trimesters of pregnancy results in infants that are proportionately small in weight and length, that is, subject to symmetric growth restriction. Intrauterine growth anomalies in late pregnancy are thought to result in disproportionately small, thin infants; that is, these infants are said to have suffered from asymmetric growth restriction. Several studies suggest that asymmetric growth in fetuses predisposes to worse perinatal outcomes than symmetric growth (49, 50) and that both proportionate and disproportionate growth restriction may occur from early in the second trimester (51, 52). These observations suggest that popular thinking about symmetry and asymmetry in fetal growth may be somewhat misguided, particularly in the "fetal origins of disease" hypothesis, which places great emphasis on the stage at which IUGR occurs and, hence, assumes symmetric or asymmetric growth restriction to be important in determining the risk of adult disease (53).

The UCL (University College of London) Fetal Growth Study by Hindmarsh *et al.* (51) looked at the determinants of shape at birth. Among all normal full-term pregnancies that were free of complications in their study, they found that the major determinant of shape at birth was the proportionality between anthropometric measures of size at birth. Interestingly, they found that classic concepts of disproportionate growth did not contribute significantly to shape at birth, suggesting that in this low-risk, normal population, clinically important disproportionality was not present. Shape at birth was also significantly affected by gender, with male infants exhibiting greater birth weight and head circumference and lower skinfold thickness than females.

It is commonly assumed that intrauterine growth follows a predictable pattern, but in practice this is not the case. In the UCL Fetal Growth Study, anthropometric measures at 20 wk gestation, 30 wk gestation, and birth were compared. Correlations between parameters at all dates were poor, and the predictive value of any of these measures for size at birth was weak. The authors ascribe the poor predictive power of these measurements to percentile crossing *in utero*, as is also seen in the first 2 yr of life. It is not known what the mechanism for percentile crossing is; however, it has been suggested that changes in placental nutrient delivery or inherent fluctuations in growth *in utero* may be responsible (48).

VI. Factors Influencing Intrauterine Growth

Normal fetal growth is dependent on an optimal intrauterine environment, particularly in relation to the delivery of oxygen and nutrients via the placenta (54). Some of the many factors known to cause IUGR are listed in Table 1.

TABLE 1. Factors associated with IUGR

Medical complications
Preeclampsia
Acute or chronic hypertension
Antepartum hemorrhage
Severe chronic disease
Severe chronic infections
Systemic lupus erythematosus
Antiphospholipid syndrome
Anemia
Malignancy
Abnormalities of the uterus
Uterine fibroids
Maternal social conditions
Malnutrition
Low pregnancy BMI
Low maternal weight gain
Delivery at age <16 or >35 yr
Low socioeconomic status
Drug use
Smoking
Alcohol
Illicit drugs
Fetal problems
Multiple births
Malformation
Chromosomal abnormalities
Inborn errors of metabolism
Intrauterine infections
Environmental problems
High altitude
Toxic substances
Abnormalities of the placenta
Reduced blood flow
Reduced area for exchange
Infarcts
Hematomas
Partial abruption

Adapted from Bryan and Hindmarsh (48).

A. Maternal nutrition

Several adverse factors are known to influence the growth of the developing fetus. For example, calorie restriction and insufficient maternal weight gain during gestation can result in the birth of infants of normal length but reduced weight (55). The influence of maternal nutrition in fetal development is complex, and the timing of adverse nutritional status has an important impact on the shape or weight of the infant. In the Dutch Hunger Winter famine of 1944–45, for example, extreme malnutrition in mothers in their last trimesters of pregnancy gave rise to infants with a low ponderal index at birth (56). There is limited evidence to suggest that nutritional supplementation during gestation can improve birth weight and reduce the fetal mortality rate (8, 48, 57, 58).

During the first two trimesters of pregnancy, maternal metabolism, mediated by placental and pituitary hormones, is directed toward energy storage and uteroplacental development. In addition to increased maternal food intake, first-stage insulin secretion typically increases by approximately 60%, whereas sensitivity to insulin and fasting glucose concentrations remains relatively normal (59). The etiology of weight gain during early to midgestation is multifactorial but is likely to include a consequence of the ever-decreasing levels of pituitary GH, which normally inhibits adipogenesis, and the increasing levels of progesterone, prolactin, and placental lactogen, which stimulate food intake, fat storage, and insulin production (59). The hyperinsulinemic state of early and midpregnancy promotes lipogenesis and the storage of fat and is associated with a rise in plasma leptin concentrations and a concomitant decrease in plasma lipid and IGF-I levels (59).

In the later stages of pregnancy, although food intake and fat deposition continue to rise, changes in insulin production and action mean that maternal metabolism is redirected toward supporting fetal, placental, and mammary growth. Maternal insulin resistance is typical of this stage of gestation. Insulin-mediated glucose utilization by skeletal muscle can drop by 40% or more in the third trimester of gestation, whereas a more modest reduction in insulin-stimulated glucose uptake by cardiac and adipose tissue is normal. Total body insulin sensitivity at this stage of pregnancy can be up to 70% lower than in nonpregnant women (59). These changes in insulin activity during late gestation facilitate efficient storage of energy during times of nutritional abundance, while permitting rapid nutrient mobilization during periods of fasting.

B. Placental size and function

Throughout pregnancy, the size of the placenta changes and remains highly correlated with birth weight; small placentae generally give rise to small babies (60). At approximately midgestation, the fetus and placenta are of similar weights, but from 32 wk, fetal growth exceeds that of the placenta and the fetal/placental weight ratio increases. It is unlikely that the size of the placenta causes fetal growth restriction (48), because the placenta is able to withstand functional inactivation of up to 40% of its villous population without affecting fetal growth (61) and is, in any case, capable of compensatory growth (62).

C. Parity and maternal age

Parity and maternal age have unavoidable consequences on birth weight. For example, infant birth weight in primagravidae is frequently lower than subsequent births (63), and pregnancy in girls under 16 yr of age is commonly associated with suboptimal fetal growth (64). Fetal growth restraint is particularly evident in first pregnancies, whereupon infants tend to be thinner and lighter than subsequent siblings, although they have similar lengths and head circumferences.

Figure 2 illustrates the interaction between birth order and genotype in terms of fetal head circumference (65), and Fig. 3 illustrates the effects of multiple births on birth weight (66).

D. Smoking

Smoking during pregnancy is one of the most avoidable causes of fetal growth retardation. Evidence shows that smoking reduces birth weight by 13 g per cigarette smoked per day (67). Infants born to mothers who smoke during pregnancy generally have a lower birth weight, length, and head circumference than infants born to nonsmoking mothers (67–71). The adverse effects of smoking are not limited to maternal smoking habit; passive smoking has also been shown to carry substantial risks to both pregnant mothers and their fetuses (72).

E. Genetic factors

Infant birth weight is strongly associated with maternal birth weight (73), suggesting that weight at birth is an inherited trait through the maternal line (74, 75). It is likely that variation in the mitochondrial genome plays an important role in determining infant birth weight, because it is exclusively transmitted through the maternal line. Mitochondrial DNA 16189 variant, for example, is associated with thinness at birth (76). Additionally, the maternally expressed gene *H19*, responsible for the imprinting of *IGF-II*, is associated with size at birth (77). Maternal glucose levels may also

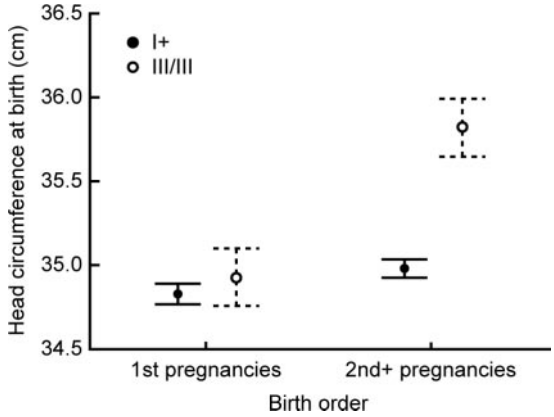

FIG. 2. Interaction between birth order and genotype on head circumference. Both the insulin gene VNTR (class I+ or class III alleles) and birth order (first *vs.* second or later pregnancies) were associated with head circumference at birth (interaction, $P = 0.02$), such that the genotype association was apparent only in offspring of second and subsequent pregnancies ($P = 0.0003$). The mean BMI was identical in I/I and I/III subjects. Data are means ± SEM. [Reproduced with permission from Ong *et al.* (65).]

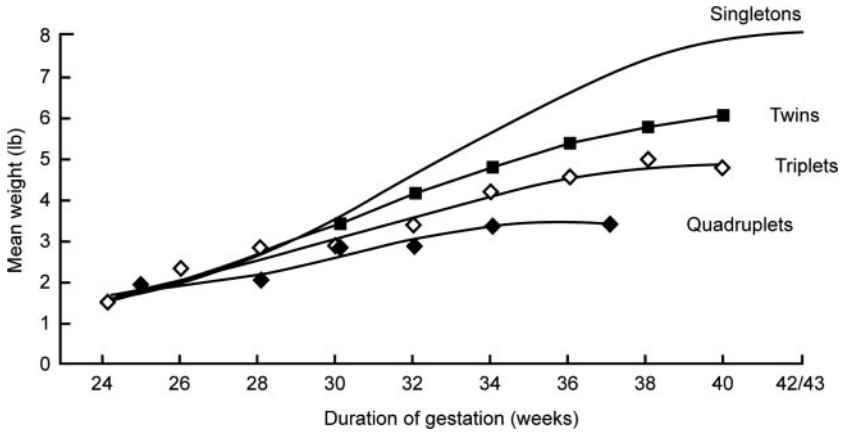

FIG. 3. Mean birth weights decrease progressively with multiple births. [Reproduced with permission from McKeown and Record (66).]

contribute to birth weight or size. This may or may not be a genetic trait. Certainly, pregnancy in diabetic mothers generally results in infants with greater adiposity than the offspring of nondiabetic mothers, and the risk of gestational diabetes appears to be correlated with low maternal birth weight (78). In addition to these factors, several genetic conditions are associated with reduced size at birth. They include the chromosomal abnormalities of Turner syndrome and Down syndrome. Confirmed placental mosaicism and uniparental disomy (UPD) are increasingly recognized as influencing fetal growth and development.

It is noteworthy that a minisatellite DNA polymorphism comprising a variable number of tandem repeats (VNTR) upstream of the human insulin gene (*INS*) promoter is associated with size at birth (79). The effects of this polymorphism, which is thought to influence transcription of *INS* and *IGF-II* (80, 81), are more evident in second and subsequent pregnancies, suggesting that fetal genes, especially those expressed by the father, may have considerable influence on fetal growth when maternal restraint on fetal growth is less marked (82).

Genetic determinants of fetal growth restraint, through programming or epigenetic effects on the fetus, and genes that determine postnatal catch-up in weight, may be the important links between size at birth and disease in adulthood (82).

1. Imprinting. Although imprinted genes account for no more than 0.5% of the genome, they have a disproportionately large effect on early fetoplacental development, affecting the growth, morphology, and nutrient transfer capacity of the placenta and thus delivery of nutrients to the fetus (83). The imprinted *IGF-II* and *H19* genes, for example, are heavily involved in fetoplacental development, acting as a single epigenetic regulatory unit through coordinated action of their differentially methylated regions (84). Expression of *Igf2* is sensitive to nutritional and endocrine signals, particularly glucocorticoids (85, 86); the ovine *Igf2* gene has a glucocorticoid response element and is transcriptionally down-regulated by cortisol (87). The sensitivity and the complexity of the *IGF-II* imprinting mechanisms may have a significant impact on developmental programming and might explain the poor prognosis of the child born SGA and the wide spectrum of adult-onset diseases originating *in utero* (84–89).

The importance of genetic imprinting for fetal growth is illustrated by UPD in humans and mice. Growth appears to be promoted by paternal disomies, whereas it is inhibited by maternal disomies (90). Among the imprinted genes determining fetal growth, several are involved in the IGF system. For example, *Igf2* is paternally expressed, whereas *Igf2r* is maternally expressed, at least in the mouse; expression of this gene in humans, however, has been shown to be largely biallelic (91, 92). The IGF type 2 receptor is implicated in the degradation of extracellular IGF-II and therefore depletes circulating levels of the growth factor. This illustrates the conflicting paternal and maternal priorities in the regulation of fetal growth and development (93). Table 2 lists several growth disorders that have been associated with imprinting effects in humans and ruminants (94).

It is entirely possible that imprinted genes also play a role in the regulation of placental blood vessel development and the control of nutrient transporter expression. In this way, they may also indirectly control fetal growth and development (95).

TABLE 2. Growth disorders caused by imprinting effects

Chromosome	Parental origin	Disease	Growth type
Human			
7	Maternal	Silver-Russell syndrome	IUGR
11	Maternal	Silver-Russell syndrome	IUGR
11	Paternal	Beckwith-Wiedemann syndrome	Overgrowth
14	Maternal	mUPD14	IUGR
16	Maternal	mUPD16	IUGR
Ruminant			
7	Maternal	Large offspring syndrome	Overgrowth

Adapted from Gicquel and Le Bouc (94). mUPD, Maternal UPD.

Beckwith-Wiedemann syndrome, characterized by prenatal and/or postnatal overgrowth, several anatomical abnormalities, and an increased risk of cancer in childhood, is a good example of an imprinting disorder. The syndrome results from derangement of the imprinting of the 11p15 region, which contains a cluster of imprinted genes belonging to two separately controlled domains (93). Studies in mice show that this region is prominent in fetal growth. The changes to the 11p15 region in Beckwith-Wiedemann syndrome result in down-regulation of maternally expressed genes and/or the up-regulation of paternally expressed genes.

The level of involvement of imprinted genes in IUGR is still unclear; however, IUGR has been shown to be associated with a number of maternal UPDs of chromosomes 7, 14, 16, and 20. For example, about one in 10 patients with Silver-Russell syndrome (a condition characterized by IUGR, reduced postnatal growth, and dysmorphic facial features and body asymmetry) has evidence of maternal disomy for chromosome 7; however, the precise role of the genes involved is poorly understood (90).

Because they are determinants of fetal growth, genes imprinted within the 11p15 region may also influence the link between IUGR and adult disease. Duplications in chromosome 11p15 of maternal origin have been found in patients with phenotypes suggestive of Silver-Russell syndrome (96, 97). Gicquel *et al.* (98) have recently shown that epigenetic defects in 11p15, resulting in the silencing of *IGF-II*, are found in 50% of patients with Silver-Russell syndrome. The epimutation consists of partial loss of paternal methylation at three different loci in the telomeric imprinted domain. It results in decreased expression of the gene for IGF-II and reduced fetal growth (98). Interestingly, recent studies have suggested that assisted reproductive technology may predispose to imprinting disorders (98), such as Beckwith-Wiedemann syndrome. Fetuses conceived using assisted reproductive technology are also known to be at increased risk of IUGR (99), although the mechanism is not yet understood.

F. Sex of the fetus

Shape and size of the fetus and neonate are influenced by gender. At birth, males tend to be heavier, with a greater head circumference than females. They also tend to be leaner, with a lower skinfold thickness, than females. These differences were discernable *in utero* at 20 wk gestation (48). Abdominal circumference was greater in males, whereas there was no difference in femur length at 20 wk. The differences in abdominal circumference may reflect different rates of maturation of abdominal structures, such as the liver, whereas differences in femur lengths would not be expected at 20 wk, given that peak length velocity *in utero* occurs at approximately 26–28 wk gestation.

G. Endocrine factors

1. The GH-IGF axis. The insulin resistance characteristics of late gestation may be caused by the increasing concentration of placental GH, which progressively replaces pituitary GH. Placental GH differs from pituitary GH in 13 of the 191 constituent amino acids. It is thought that this change in structure significantly diminishes the affinity of placental GH for lactogenic receptors, leading to insulin resistance and an increase in IGF-I concentration in late gestation (100).

Placental GH is detectable in the maternal but not the fetal compartment. Several studies have found lower maternal levels of circulating placental GH and IGF-I in the third trimester of pregnancies complicated by IUGR than in normal controls (101–103). The mechanisms by which maternal placental GH and/or IGF-I regulate fetal growth are still not well understood (104–107). In pregnancies with IUGR, the concentration of IGF-I in cord blood is reduced compared with that in fetuses with normal growth (108–114). At birth, the importance of IGF-II is surpassed by IGF-I, and IGF production becomes dependent on infantile GH, resetting the regulatory feedback cycles.

IGF-II plays an important role in regulating fetoplacental growth. The mature IGF-II results from posttranslational processing of the biologically inactive pro-IGF-II peptide. Qiu *et al.* (115) provide evidence that aberrant processing of IGF-II may also be a cause of SGA. They found that proprotein convertase 4, expressed in the placenta, normally cleaves pro-IGF-II to generate intermediate processed forms and mature IGF-II. Pregnant woman carrying SGA fetuses had higher levels of pro-IGF-II, compared with controls, suggesting that processing by proprotein convertase 4 in these women was abnormal. Whether this is a primary cause of SGA birth or whether it is secondary to placental dysfunction is unclear at this stage, but elevated pro-IGF-II in the maternal circulation may be a useful marker for an SGA fetus. Specific knockout of IGF-II in the placentae of mice has been shown to cause reduced fetal and placental growth (116). Furthermore, the placenta can respond to fetal demand signals through regulation of the expression of specific placental transport systems, such as *GLUT1* and *GLUT2* transporter genes. In mice that lack IGF-II, the placenta is small. Through increases in transporter genes, the transfer of glucose and amino acids can be regulated to meet fetal demand (117).

Over the past 10 yr, a series of elegant animal knockout experiments have identified the importance of IGF-I, IGF-II, insulin, and their respective receptors in regulating fetal growth and size at birth (53, 65, 118). Furthermore, several studies have shown the correlation between umbilical cord levels of IGF-I and IGF-II to birth weight (112, 119–122). The importance of insulin in fetal growth is demonstrated by the larger-than-normal birth weight of infants born to diabetic mothers and in the correspondingly low birth weight in infants with mutations of the insulin receptor (123). Variations in insulin metabolism may also be responsible for the differences in birth weight within the normal population, as suggested by studies of the insulin variable nucleotide repeat sequence proximal to the insulin gene (65). At present, it is unclear whether this reflects a change in insulin production or an indirect effect on other genes in the same genetic locus.

Expression of IGF-I and IGF-II is present in all fetal tissue from preimplantation to the final stages of maturation before birth. IGF-II is the principal growth factor supporting early embryonic growth, whereas IGF-I becomes more of a prominent influence in the later stages of gestation. IGF-I concentrations are decreased *in utero* and at birth in infants and

fetuses displaying IUGR and are correspondingly raised in infants born large for gestational age (124, 125). Nutrient restriction produces a decrease in serum concentrations of IGF-I and IGF-II; however, the *Igf1* gene appears to be eminently more sensitive to changes in nutritional status than the *Igf2* gene (125, 126). IGF-I levels are positively regulated by insulin, possibly by increasing the availability of cellular glucose through increased uptake, whereas tissue-specific expression of both the *Igf1* and *Igf2* genes is under the control of glucocorticoids (127).

Expression of IGF-binding proteins (IGFBPs) is developmentally regulated (125), and all six of the recognized IGFBPs have been found in fetal plasma and tissues. IGFBP-I may be the most important of the binding proteins *in utero*. Babies with IUGR have elevated levels of IGFBP-1, which are negatively correlated with birth weight. Such elevated levels of IGFBP-1 in the fetus would decrease the amount of IGF available for fetal growth.

Studies in transgenic mouse models have offered valuable insights into the role of the fetal IGF system in fetal growth and development. For example, using standard gene targeting techniques, Efstratiadis and colleagues created murine cell lines lacking the genes for *Igf1*, *Igf2*, *Igf1r*, and *Igf2r* (128). Knockout of the *Igf1*, *Igf2*, or *Igf1r* gene in isolation leads to fetal growth retardation, which becomes more severe if additional genes are deleted (Fig. 4). Deletion of the *Igf1* or *Igf2* gene produces a similar degree of growth retardation, resulting in pups weighing 40% less than their wild-type littermates. Deletion of the *Igf1r* gene results in more severe growth retardation, producing offspring with a birth weight that is 55% less than normal, suggesting that both IGF-I and IGF-II act through the IGF type I receptor (IGF-IR). This is supported by the observation that mice lacking a functional IGF-IR do not survive beyond the perinatal period due to poor muscle development and respiratory failure. The combined deletion of *Igf1r* and *Igf2* or *Igf1* and *Igf2* results in very severe growth retardation, generating offspring with birth weights that are 70% less than normal. Thus, it appears that a different receptor may mediate some of the fetal growth effects of IGF-II. A possible candidate for this receptor is a splice variant of the insulin receptor (129). Mutations in *Igf1*and *Igf1r* do not affect placental weight, unlike mutations in the *Igf2* gene. Moreover, deletion of the placenta-specific *Igf2* transcript leads to restriction of placental and, subsequently, fetal growth, due to decreased nutrient supply from the mother to the fetus (130). Interestingly, disruption of the *Igf2r* gene, causing overexpression of IGF-II, results in fetal overgrowth (Fig. 4). A similar effect is seen where there is transactivation of the *Igf2* gene or biallelic expression of IGF-II after disruption of the *H19* gene (125).

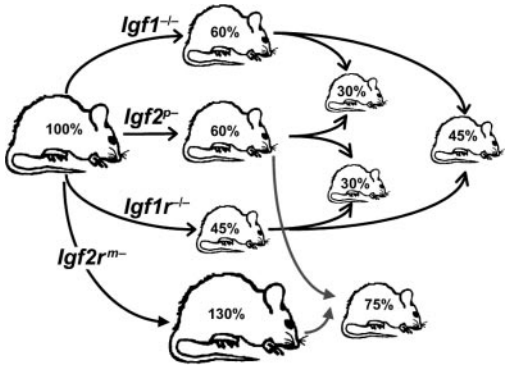

FIG. 4. Effects of the disruption of one or more genes of the IGF system on fetal growth in mice. Figures represent percentage of normal body weight. m−, Maternally disrupted allele; p−, paternally disrupted allele; −/−, both maternal and paternal alleles disrupted. [Reproduced with permission from Gicquel and Le Bouc (94).]

Whereas deletion of genes encoding the IGFs and their receptors causes obvious disruption of fetal growth, disruption of the genes encoding the IGFBPs or the acid labile subunit (ALS) has little effect on fetal growth. However, modest postnatal growth restriction has been documented in transgenic models of mice overexpressing IGFBP-1, -2, or -3 (131, 132). Naturally occurring mutations in the human IGF system are exceptionally rare. Nevertheless, polymorphisms in the gene encoding IGF-I have been reported to be associated with low birth weight and low serum IGF-I levels (133, 134); however, to date, only three patients with severe pre- and postnatal growth retardation have demonstrated deletions or mutations in the *IGF-I* gene (135–137). Mutations of the *IGF-IR* gene are similarly rare, and very few patients with IUGR have exhibited a defect in this gene (138, 139). To date, no mutations in the genes encoding the IGFBPs or IGF-II have been identified in IUGR; however, a defect in the *ALS* gene has recently been shown to have mild effects on fetal growth (140).

2. Glucocorticoids. Glucocorticoids are also thought to have a role in the fetal origins of adult disease. Animal data have implicated lower levels of 11β-hydroxysteroid dehydrogenase 2 (11β-HSD 2) activity in fetal programming leading to SGA (141). Placental 11β-HSD 2, which converts physiologically active glucocorticoids to inactive products, is an important modulator of fetal glucocorticoid exposure and is regulated by many placental hormones and factors associated with pregnancy, including estradiol, progesterone, and prostaglandins (141). Benediktsson *et al.* (142) showed a potential correlation between placental 11β-HSD 2 activity and term fetal weight and a correlation with placental weight. These investigators proposed that the relationship between low birth weight, high placental weight, and increased adult blood pressure may be mediated by glucocorticoid exposure *in utero* (142). Inhibition of placental 11β-HSD 2 by carbenoxolone gave similar results, producing smaller offspring with impaired glucose tolerance in later life and reduced hepatic 11β-HSD 1 and reduced renal 11β-HSD 2 gene expression (143–145).

3. Other endocrine factors. Progesterone also plays a part in the development of insulin resistance in late gestation, because at high concentrations it interferes with insulin binding and glucose transport in skeletal muscle and adipose tissue (146). A further cause of maternal insulin resistance in the third trimester is the rise in plasma concentrations of TNF-α and free cortisol, which inhibit glucose uptake in skeletal muscle and stimulate lipolysis in adipocytes. Furthermore, TNF-α inhibits expression of adiponectin in preadipocytes, which, together with an excess of free cortisol, exacerbates the insulin resistance caused by other hormones.

VII. Postnatal Growth

In addition to poor maternal nutrition during pregnancy, the quality of perinatal nutrition has been shown to influence the subsequent development of the newborn. Widdowson and McCance (147) reported that undernourishment of rat pups during the 3-wk period of lactation led to slower weight gain throughout their lifetime, compared with control pups, despite the fact that all pups had *ad libitum* access to food after weaning. On the other hand, 3 wk of similar energy deficiency in rats between 9 and 12 wk of age resulted in only short-term effects on weight gain. These studies show that nutritional or environmental insults in perinatal life can cause irreversible, long-term outcomes. Importantly, the timing of such insults is significant in determining the extent of later adverse consequences to health, such that there is evidently a critical period in development when unfavorable events have the potential to exert their maximal effects.

A. Hormonal regulation of growth in children born SGA

The endocrine mechanisms governing catch-up growth are still poorly understood, although Baron *et al.* (148) proposed that they reside within the growth plate and are based on a delay in normal growth plate senescence.

1. GH. The growth response of infants in the first months of postnatal life appears to be fundamental to the future health and stature of individuals born SGA. Most catch-up growth occurs in this relatively brief period, yet the rate and extent of this growth has profound long-term consequences that may or may not be favorable.

Infants born SGA frequently exhibit increased concentrations of GH (114, 149, 150) and have low levels of IGF-I and IGFBP-3, suggesting that SGA neonates are GH insensitive. However, normalization of the GH-IGF axis occurs early in postnatal life (113), and most children born SGA go on to show a normal response to GH stimulation testing and have normal levels of IGF-I and IGFBP-3 (151).

In studies measuring spontaneous daily GH secretion in short children born SGA, several investigators have found high pulse frequency, attenuated pulse amplitude, and relatively elevated interpulse concentrations of serum GH, accompanied by reduced concentrations of IGF-I (152–154). This is similar to what is seen in adults with long-term critical illness (155), and it has been suggested that altered GH secretion at birth may represent a consequence of extended critical illness *in utero* (156).

2. The IGF system. In addition to GH, IGF-I and IGF-II play a key role in the regulation of postnatal growth. Within the circulation, they are bound to high-affinity binding proteins that control the availability of the IGFs. Around 75% of the IGFs circulate in a ternary complex, consisting of IGF, IGFBP-3, and ALS. Approximately 20–25% of the remaining IGFs are associated with one of the other IGFBPs in a binary complex, and less than 1% exists in the free form. Decreased levels of IGF-I have been detected in fetuses and infants deemed to be SGA, indicating that dysfunction of IGF-I or its metabolism may be involved in IUGR (113, 157). Indeed, polymorphisms of IGF-I have been associated with pre- and postnatal growth retardation (134, 158), and homozygous partial deletion of the gene encoding IGF-I in humans results in severe impairment of growth pre- and postnatally (136).

The importance of IGF-I is further underlined by the association of pre- and postnatal growth restriction with mutations of the *IGF-IR* gene (138). Moreover, infants born SGA demonstrate reduced levels of IGFBP-3, with concomitantly higher levels of IGFBP-1 and IGFBP-2 (157).

Despite substantial evidence of abnormal IGF levels in infants born SGA, there does not appear to be a firm link between IGF-related variables at birth and postnatal growth (113, 114). Cianfarani *et al.* (159) have reported a correlation between catch-up growth and the IGF-I/IGFBP-3 molar ratio in infancy. They suggested that the affinity of IGFBPs for IGFs may be modulated by cation-dependent proteolytic enzymes that degrade the IGFBPs, thereby increasing the level and bioavailabilty of IGF-I. Postnatally, the IGF system is switched on, allowing catch-up growth in the majority of infants born SGA (159). Furthermore, the alterations in IGF-I levels observed in neonates born SGA appear to be transient, because abnormal levels of IGF-I and IGFBP-3 have not been detected in older children who were born SGA (160).

In infants with IUGR, low cord levels of IGF-I normalize rapidly after birth (Fig. 5). However, serum levels of IGF-I remain significantly reduced in infants who fail to show catch-up growth (height below −2 SD) by 2 yr of age (114, 161). Furthermore, the mean IGF-I levels of older children born SGA of both short and normal stature have been shown to be lower than in healthy children born AGA (162). This was also confirmed in a prospective study by Chellakooty *et al.* (163). Because low IGF-I levels in adulthood have been associated with an increased risk of ischemic heart disease (164) and because it is established that individuals born SGA are predisposed to cardiovascular disease, it is important to investigate the IGF-I/IGFBP-3 axis in adults born SGA. In an observational case-control study, Verkauskiene *et al.* (162) analyzed the dynamics of IGF-I and IGFBP-3 in a cohort of young adults born SGA (defined as birth weight below the 10th percentile for gestational age and gender) and a cohort born AGA. They found that serum IGF-I concentrations and the IGF-I/IGFBP-3 ratio were lower in adults born SGA than in those born AGA. This suggests that long-term abnormality of IGF-I metabolism may be implicated in the association between IUGR and cardiovascular and metabolic diseases in later life.

3. Hypothalamic-pituitary-adrenal axis. Functioning of the hypothalamic-pituitary-adrenal axis may be permanently programmed during development (165). Cianfarani *et al.* (166) have reported that children born SGA who do not show catch-up growth have significantly higher fasting levels of plasma cortisol than children born SGA who achieve catch-up growth (Fig. 6). In addition, cortisol may act by limiting IGFBP-3 proteolysis in the perinatal period, thereby minimizing the availability of circulating IGFs and imposing early growth restriction.

Reduced concentrations of circulating free T_4 and free T_3, together with a discreet rise in concentrations of thyotropin, have been recorded in fetuses with IUGR (167). Furthermore, a significant decrease in the expression of thyroid receptor

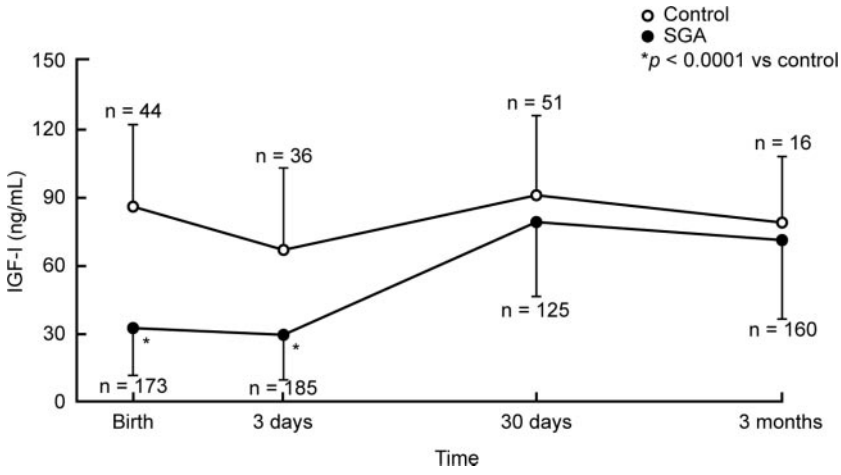

FIG. 5. Mean (±SD) serum levels of IGF-I in children born SGA and controls from birth (cord blood measurements) to 3 months of age. Levels of IGF-I were significantly reduced in the cord blood of infants born SGA, but serum IGF-I levels normalized rapidly after birth. [Data from Leger *et al.* (114).]

isoforms in the human fetal nervous system has been documented in IUGR (168).

B. Postnatal growth in preterm infants

So far, we have discussed postnatal growth regulation in the full-term infant. Wit *et al.* (169) have recently provided evidence for catch-up growth in preterm infants. The majority of preterm infants show evidence of growth retardation in the postnatal period. In addition to preterm growth restraint, there is also substantial postnatal growth impairment, which is largely due to inadequate nutrient intake. Embleton *et al.* (170) found that this nutrient intake accounts for 45% of the variation in weight SD score (SDS). Preterm infants thus accumulate a considerable nutrient deficit that cannot be replaced by feeding to current recommended daily intakes. With appropriate feeding protocols, however, catch-up growth can be achieved in preterm infants. Despite this, the prevalence of short stature in 5 yr olds who were born preterm (less than 32 wk gestation) is comparable to that seen in children born SGA and amounts to approximately 10% of the respective populations (169). The growth responses of these children were followed into adulthood, and the authors conclude that childhood growth and adult height are similar in preterm individuals born SGA, in preterm individuals born AGA with evidence of prenatal growth restraint, and in individuals with very low birth weight.

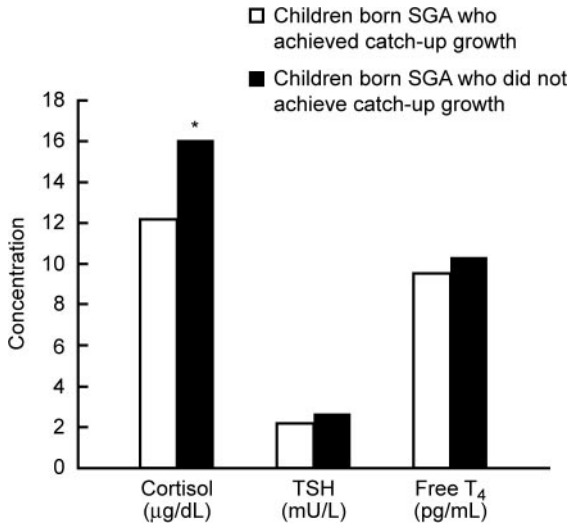

FIG. 6. Cortisol, TSH, and free T_4 concentrations in a case-control study of 20 children born SGA who achieved catch-up growth and 20 who did not, matched for age, gender, pubertal status, and BMI. *, $P = 0.04$ compared with those who achieved catch-up growth. [Reproduced with permission from Cianfarani *et al.* (166).]

Evidence is accumulating to show that postnatal growth failure is extremely common in preterm infants. Some of this evidence suggests that growth impairment is not restricted to the early postnatal period. For example, Gibson *et al.* (171) investigated 200 preterm infants and 50 randomly selected healthy term infants from the same population from birth to 7 yr of age. They found early growth impairment in all preterm infants, which improved rapidly in the more mature preterm infants. In very preterm infants (born at 23–28 wk gestation), however, growth impairment continued for up to 4 yr, after which time some improvement in growth was seen, although these children never fully achieved a normal size, particularly with respect to head circumference. Similarly, in a study of 280 children born before 32 wk gestation and 210 term infants, median centiles for weight, height, head circumference, and body mass index (BMI) at 7 yr of age were 25, 25, 9, and 50 for boys and 50, 25, 9, and 50 for girls, respectively, compared with 50, 50, 50, and 75, respectively, for the controls born at term (172). The same study revealed a link between prematurity and poor cognitive behavior, with short stature and small head circumference being the strongest predictors of poor performance. One further study demonstrated an increased incidence of neurodevelopmental problems at 30 months in infants born at 25 wk gestation or less (173).

C. Definition of catch-up growth

A general definition of catch-up growth is a growth velocity (centimeters per year) greater than the median for chronological age and gender. Definitions based on the normal height range for the population (for example, catch-up growth is considered to be achieved when the patient's height is above the third percentile) do not incorporate the patient's expected adult height, based on parental stature. This is an important distinction, because the target height, *i.e.*

an estimate of the genetic potential in stature, is a strong predictor of response to GH therapy. Target height is commonly estimated by midparental height corrected for gender (174, 175).

Most children who are born SGA experience catch-up growth and will achieve a height above −2 SD. Catch-up growth is typically an early postnatal process that, in most SGA infants, is completed by the age of 2 yr. Within this 2-yr period, premature SGA infants (less than 37 wk gestation) may take longer to catch-up than full-term infants (10, 176, 177). In more than 80% of infants born SGA, catch-up growth occurs during the first 6 months of life. For this reason, growth monitoring during the early postnatal period provides useful information, and different growth patterns may be identified in infants as young as 3 months of age.

The situation is different for infants born SGA who have short parents. Volkl *et al.* (178) observed catch-down growth to the lower familial range, as defined by their parental heights, during the first 2 yr of life.

VIII. Consequences of Being Born SGA

Being born SGA carries an increased risk of morbidity and mortality both in the perinatal period and in later life. In the perinatal period, these manifestations include respiratory complications, hypotension, hypoglycemia, necrotizing enterocolitis, and neonatal death (179, 180). Subsequently, infants and children born SGA are prone to neurological impairment, delayed cognitive development, and poor academic achievement (181–184). Adolescents and adults born SGA are at increased risk of developing additional morbidities, such as cardiovascular complications, obstructive pulmonary disease, type 2 diabetes mellitus, renal insufficiency, and impaired reproductive function (185–189). Failure to achieve appropriate catch-up growth after SGA birth results in persistent short stature and is associated with greater health risks and psychosocial impairment, compared with patients born SGA who achieve their growth potential (190–193).

IX. SGA and Metabolic Consequences in Adulthood

After the publication in 1989 of a paper linking size at birth to ischemic heart disease in later life (194), many researchers have investigated the possible links between fetal growth restriction and adult diseases. Early programming of such diseases has been the focus of much of this research, which has been performed in diverse ethnic groups and geographical settings. The independent effect of thinness at birth and its lack of association with gestational age strongly suggest that reduced fetal growth, rather than prematurity *per se*, is a major factor in defining long-term risk of metabolic disease.

The initial hypothesis of Barker and colleagues proposed that the type 2 diabetes commonly associated with low birth weight was a consequence of impaired β-cell function that may have resulted from undernutrition at a critical stage of fetal development. It was proposed that this nutritional insult may have caused dysfunction of the endocrine pancreas (195). In a later study, the same group found a correlation between low birth weight and defective insulin secretion in 21-yr-old adults (196). More recently, however, no evidence of a defect in insulin secretion in young adults born SGA was found, and furthermore, β-cell function appeared to be normal in these individuals (197, 198).

Additional confirmation that major β-cell dysfunction is not the primary defect associated with undernutrition *in utero* is provided by the work of Beringue *et al.* (199). They found that β-cell morphology, islet density, and the percentage of pancreatic area occupied by β-cells were identical in fetuses born SGA and those born AGA.

A. SGA and insulin resistance in children and adults

One of the first reports of small size at birth being associated with elevated insulin levels in adults was published in 1993 from retrospective birth data (200). Since then, insulin resistance has been reported in children and adults born SGA (196–198, 201, 202). Importantly, the decreased insulin sensitivity found in these individuals was independent of confounding factors, such as BMI and age.

A detailed prospective case-control study of birth weight and insulin resistance took place in the Alsatian town of Haguenau, France, and included more than 1500 young adults (190). The cohort comprised individuals who were selected according to birth data from the Maternity Register in Haguenau between 1971 and 1985. Individuals were assigned to the SGA group if they were singletons born between 32 and 42 wk gestation and had a birth weight below the 10th percentile for gender and gestational age according to local growth curves. The comparable AGA group consisted of singletons born between 32 and 42 wk gestation, with a birth weight between the 25th and 75th percentiles for the local population and who were the first babies in the register to be born immediately after an infant born SGA.

Both direct and indirect measurements revealed that insulin resistance was more prominent in the SGA group, compared with the AGA group (190, 197, 203). Fasting insulin/glucose concentrations were significantly higher, and values for the quantitative insulin sensitivity check index (QUICKI) were significantly lower in the SGA group compared with the AGA group (Fig. 7) (204). Moreover, insulin sensitivity was 20% lower in 30% of the individuals born SGA than it was in individuals born AGA when assessed by the hyperinsulinemic euglycemic clamp method. This insulin resistance was independent of confounding factors, such as BMI, age, family history of diabetes or dyslipidemia, oral contractive use, and smoking.

In addition to insulin resistance in adulthood, individuals born SGA show moderate insulin resistance in infancy, typically in the catch-up growth period from 0 to 2 yr of age (18, 205). It is interesting to note that in the study of Soto *et al.* (18), insulin resistance was found only in infants born SGA who achieved catch-up growth and not in infants born SGA who did not achieve catch-up growth or who were born AGA, suggesting yet again that rapid catch-up growth can give rise to adverse metabolic outcomes. This phenomenon is further supported by a study in prepubertal children born SGA, where significant insulin resistance was found only in chil-

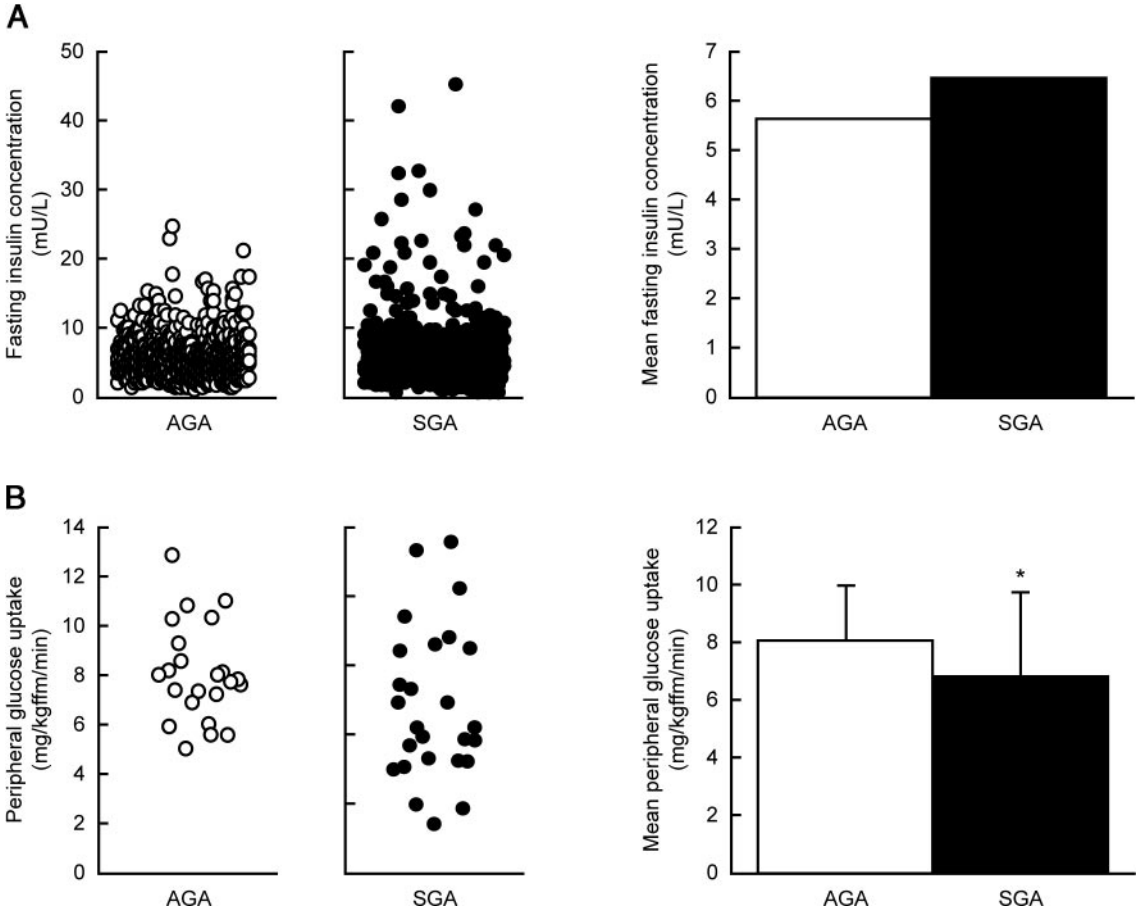

FIG. 7. Insulin resistance in the Haguenau study of individuals born small for gestational age. A, Fasting insulin concentrations in 734 adults born SGA and 689 born AGA. B, Peripheral glucose uptake during hyperinsulinemic clamps in 26 individuals born SGA and 25 born AGA. The *left-hand graphs* represent individual values, and the *right-hand graphs* represent the mean values observed in the two groups. *Black circles and bars*, SGA; *open circles and bars*, AGA. kgffm, Kilograms fat-free mass. *, $P = 0.05$ compared with individuals born AGA. [Reproduced with permission from Lévy-Marchal and Czernichow (204).]

dren with catch-up growth resulting in a current BMI of 17 kg/m^2 or greater (201).

B. SGA and the metabolic syndrome

Low birth weight has been linked to development of the metabolic syndrome (206), a constellation of metabolic abnormalities, including abdominal adiposity, dyslipidemia, hypertension, and raised fasting plasma glucose concentrations. In the 1993 study of Barker *et al.* (206), the risk of metabolic syndrome (referred to as insulin resistance syndrome by the authors) at the age of 50 yr was 10-fold greater in individuals with a birth weight less than 2.5 kg than in those whose birth weight exceeded 4.5 kg. Similarly, in a Caucasian cohort aged 30 yr or older, each tertile drop in birth weight was associated with almost twice the relative risk of developing insulin resistance (191).

In the Haguenau study, there were statistically significant differences in all components of the metabolic syndrome at 22 yr of age between the SGA and the AGA groups (203). According to the criteria laid out in the third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of Adults (Adult Treatment Panel III) (207), 2.3% of individuals born SGA in the Haguenau cohort had metabolic syndrome, compared with only 0.3% of individuals born AGA. Furthermore, insulin resistance was significantly associated with other indicators of the metabolic syndrome, such as a high waist-to-hip ratio, hypertension, hypertriglyceridemia, and hyperglycemia (Fig. 8).

C. The origins of insulin resistance

1. Potential mechanisms. A number of mechanisms for the development of insulin resistance in individuals born SGA have been proposed. One of the first of these was the "small baby syndrome," suggested by Barker *et al.* (206), which stated that undernutrition during critical periods of fetal development could program diabetes and other components of the metabolic syndrome. It is a theory that highlights the role of the fetal environment in the etiology of disease in adult life; however, evidence from the Haguenau cohort reveals that individuals born SGA as a result of maternal smoking, for example, do not exhibit lower insulin sensitivity in adult life, compared with individuals born SGA as a result of other fetal or maternal factors.

Another mechanism that has been proposed is a modification of the "thrifty genotype" hypothesis originally suggested by Neel (37). This hypothesis speculates that genes

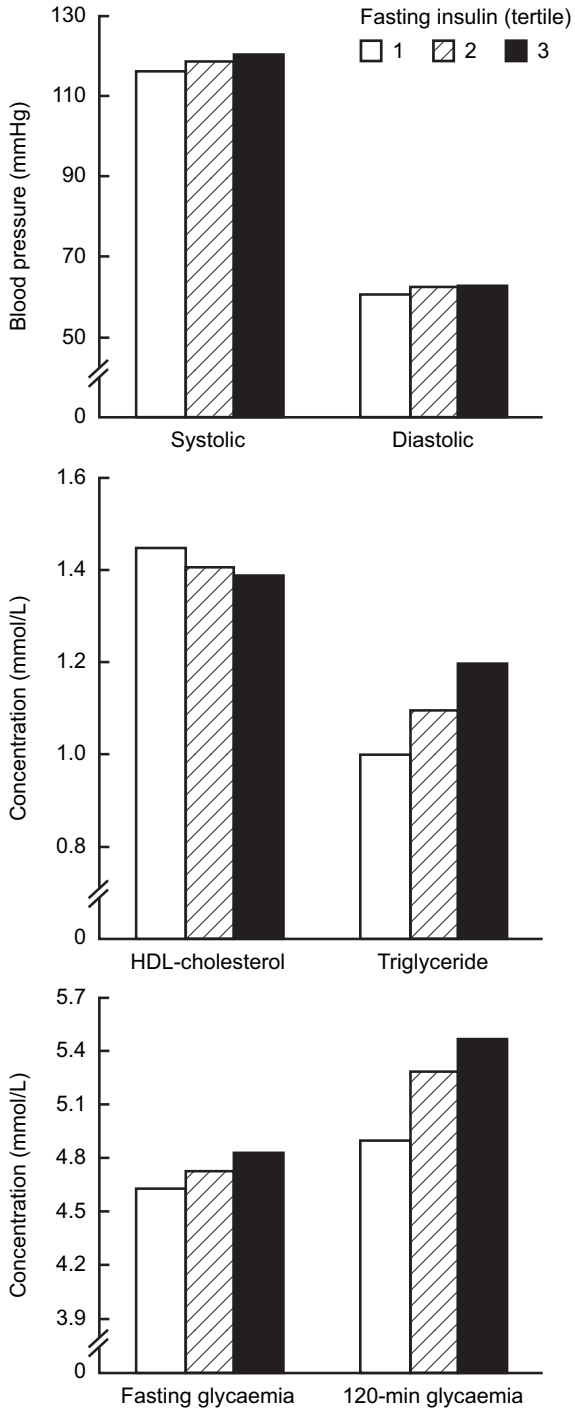

FIG. 8. Effect of insulin resistance on components of the metabolic syndrome in the Haguenau cohort. Insulin sensitivity was assessed by the QUICKI and subsequently divided into tertiles. The highest tertile represents the more insulin-resistant individuals. Comparisons were tested after adjustment for current age, gender, BMI, smoking, oral contraception in women, and a family history of metabolic and cardiovascular diseases. HDL, High-density lipoprotein. [Reproduced with permission from Lévy-Marchal and Czernichow (204).]

which promote survival and growth of the fetus in an unfavorable prenatal environment also promote the development of insulin resistance in a favorable postnatal environment. The most likely candidate genes in this regard are those that encode insulin and its VNTR. Two studies have found an association between the class III variant of the *INS* VNTR and low birth weight, which is amplified in individuals who fail to show catch-up growth (79, 208). These observations have not, however, been reproduced in studies of other Caucasian populations (209), and it would appear that the etiology of insulin resistance is eminently more complex than first thought. It is unlikely that a single gene is wholly responsible for the development of insulin resistance, but it is likely that several genetic factors interfacing with the fetal and postnatal environments are the cause.

Within the past decade, Poulsen *et al.* (210) reported that low birth weight in twins was associated with type 2 diabetes mellitus in adulthood. They studied 14 pairs of identical (monozygotic) twins and 14 pairs of nonidentical (dizygotic) twins, 63–69 yr of age. In each pair, one twin had type 2 diabetes mellitus and one did not, according to a standard oral glucose tolerance test. Most interestingly, they showed that diabetic monozygotic twins had significantly lower birth weights than their genetically identical nondiabetic twins. This finding denounces the theory that the association between low birth weight and risk of developing type 2 diabetes in adulthood is determined exclusively by a common genotype that predisposes to both.

The "thrifty phenotype" hypothesis, proposed by Hales and Barker (211) over a decade ago, suggests that the fetus adapts to an adverse intrauterine environment by diverting limited nutrients to essential organs, such as the brain, at the expense of less important organs, such as the pancreas, in so doing inhibiting overall fetal growth. This process gives rise to changes in insulin sensitivity and reduced β-cell mass that, although adequate to maintain glucose homeostasis in the short term, predisposes to type 2 diabetes in times of nutritional abundance in later life (14).

The "fetal salvage" model proposed by Hofman *et al.* (202) suggests that the malnourished fetus maintains a constant nutrient supply to essential organs by developing peripheral insulin resistance (14). The development of insulin resistance diverts glucose away from muscle and fat to essential organs, such as the brain, while maintaining some insulin secretion.

In addition to its role in carbohydrate metabolism, insulin plays a vital part in fetal homeostasis, such as in the regulation of the IGF-I axis (212). Cianfarani and colleagues suggest that growth retardation *in utero*, followed by immediate postnatal catch-up growth, programs high concentrations of IGF-I, which predispose to insulin resistance and type 2 diabetes mellitus in later life.

2. The role of adipose tissue and insulin resistance. That altered development of adipose tissue may be a root cause of IUGR is supported by absorptiometry studies, showing that the amount of adipose tissue in neonates born SGA is dramatically less than that present in neonates born AGA (213, 214). It is accepted that catch-up growth is likely to promote an increase in adiposity. This is supported by data from the Haguenau cohort, in which the BMI was similar in young adults born SGA and AGA, whereas fat mass was elevated in those born SGA (203).

Furthermore, data from the Haguenau study suggest that, in addition to altered fetal development of adipose tissue,

there is abnormal function of adipose tissue in individuals born SGA. Early insulin resistance in adipose tissue yet normal tolerance to glucose was found in individuals born SGA in the Haguenau cohort (197). Equally, the concentrations of circulating leptin and adiponectin in individuals born SGA were lower than those found in individuals born AGA, even after correction for BMI, gender, and hyperinsulinemia (215–217). It was also found that abdominal sc tissue was hyperresponsive to catecholamines (218) and that insulin resistance was altered by genetic polymorphisms of fundamental components of adipose tissue, such as β3-adrenoceptors and peroxisome proliferator-activated receptor γ (219).

Adipose tissue was traditionally considered to be an inert energy depot, but it is now increasingly recognized to be a highly active endocrine organ, secreting numerous bioactive substances, including those that modulate insulin sensitivity. Adiponectin, for example, which is produced exclusively by adipose tissue, exerts an important insulin-sensitizing effect (220–222). Jaquet *et al.* (223) demonstrated a negative correlation between insulin resistance and adiponectin levels in infants born AGA and significantly reduced serum adiponectin levels in infants born SGA. The observations made in individuals born SGA suggest that adipose tissue morphology or function is altered after a period of IUGR and highlight the critical contribution of adipose tissue in the metabolic complications associated with reduced fetal growth. Changes in adipose tissue also appear to occur postnatally in the SGA patient, with long-term metabolic consequences. Given the above information, it is plausible that early *in utero* or neonatal alterations in adipose tissue may program insulin resistance and related metabolic complications.

3. Catch-up growth and insulin resistance. In 1999 a study conducted in a Finnish cohort revealed a possible link between catch-up growth and insulin resistance. The study reported that individuals who were thin at birth, but who experienced catch-up growth resulting in average to above average body mass by 7 yr of age, had the highest mortality from coronary heart disease (224). Since then, many researchers have sought to elucidate further the role of catch-up growth in insulin resistance and associated metabolic disorders. The studies of Soto *et al.* (18) and Veening *et al.* (201), mentioned earlier, illustrate this link in children and young adults born SGA. In a study of 8-yr-old Indian children, insulin resistance, lipid concentrations, and blood pressure were inversely correlated with birth weight and positively correlated with current ponderal index, such that the highest values for each of these parameters were seen in children with birth weights in the lowest tertile and current ponderal index in the highest tertile (225).

4. Data from the Haguenau cohort. Insulin resistance in adulthood was not affected by birth weight within the range of 1130–3080 g or gestational age within the range of 32–42 wk (203). Conversely, ponderal index was inversely correlated with parameters of insulin resistance. In this cohort, mean adult height SDS was 0.75 ± 1.43 higher, compared with birth length ($P < 0.0001$); however, 10% of individuals exhibited short stature in adulthood (height SDS < -2). Although catch-up in height was not associated with insulin resistance or other components of the metabolic syndrome, catch-up in BMI was significantly associated with a rise in fasting serum insulin concentrations and other indicators of insulin resistance. As anticipated, catch-up in BMI was inversely proportional to BMI at birth; however, those individuals who experienced greater catch-up were not obese as young adults (Fig. 9).

It is well established that catch-up growth affects both weight and height. It appears to be an adaptive response, which aims to promote individuals born thin or small at birth to their full genetic height or weight potential. In other con-

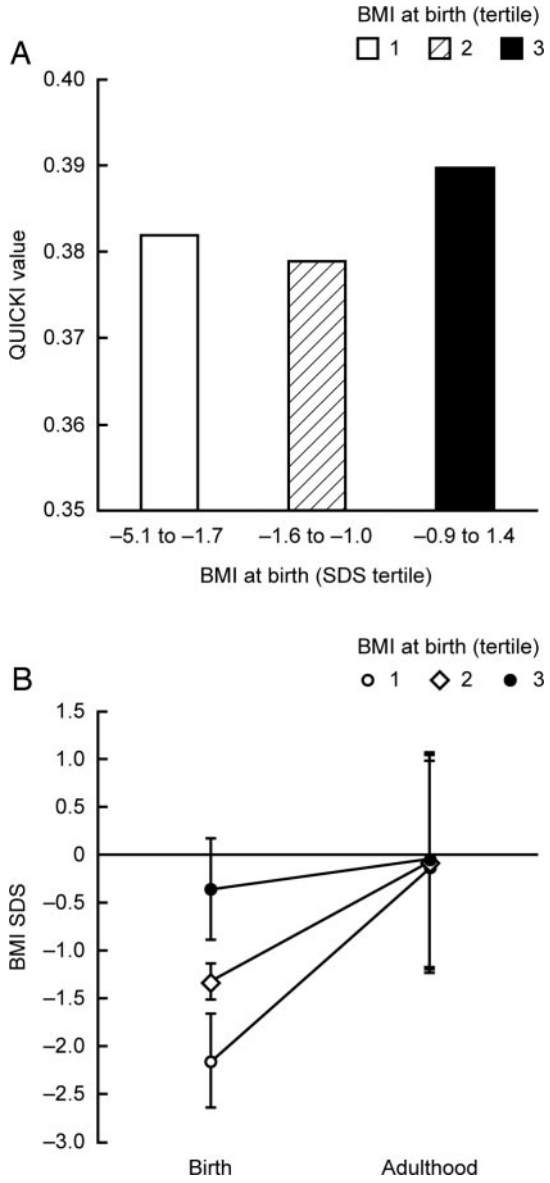

FIG. 9. Catch-up in adiposity and insulin resistance in individuals born SGA in the Haugenau cohort (n = 734). A, Effect of BMI at birth on the QUICKI measured in adulthood. BMI at birth is expressed as SDS tertiles according to gender and gestational age. B, Catch up in BMI according to BMI at birth in individuals born SGA. Individuals were divided into SDS tertiles of BMI at birth according to gender and gestational age. Adult BMI was expressed in SDS according to gender. [Reproduced with permission from Lévy-Marchal and Czernichow (204).]

ditions where rapid or dramatic wasting is a feature, however, it has been shown that catch-up growth promotes excessive fat deposition during nutritional rehabilitation, which may in itself favor selective insulin resistance (226). It has been proposed that insulin resistance associated with fetal growth restriction results from the remodeling of body composition and from the impaired development of adipose tissue, independently of obesity (Fig. 10) (204).

5. The specific role of fat accumulation in insulin resistance. The work of Colle *et al.* (227) first established that glucose-stimulated plasma insulin concentrations in infants and children born SGA were higher during catch-up growth. This and other studies (18, 228) emphasize that insulin resistance is an early manifestation of the mechanisms by which catch-up growth may predispose to other diseases in later life. Dulloo *et al.* (229) have provided good evidence that the insulin resistance seen in catch-up growth is intricately related to the fact that, during catch-up growth, fat mass is accumulated much faster than muscle mass, a phenomenon that has frequently been demonstrated in children and adults recovering from wasting diseases and protein-energy malnutrition (Table 3). This diversity in body composition, which is also associated with disturbed glucose metabolism, has been shown to endure into adulthood, as demonstrated by the work of Eriksson *et al.* (224) cited above. In addition, studies from Denmark reveal that healthy young men who were born SGA have somewhat less lean tissue mass, more total body fat, and distinctly more abdominal fat than age-matched and BMI-matched controls (230). The same group also reported that glucose uptake and expression of proteins involved in insulin and glucose metabolism were reduced in these individuals (231, 232).

So, do the processes that regulate fat storage during fat accumulation in catch-up growth induce a state of insulin resistance? Certainly, as indicated in Table 3, an increased ratio of fat mass to lean mass has been reported in adults recuperating from weight loss due to a wide range of conditions, including cancer, starvation, and AIDS (229). Hence, the disproportionate catch-up in fat mass compared with lean mass is not exclusive to individuals born SGA. Interestingly, accumulation of fat in individuals experiencing catch-up or recovery growth is not simply a result of overeating or exceeding the daily energy requirements. Fat accumulation continues during catch-up or recovery growth, despite consumption of a balanced diet low in fat and independently of the individual's energy requirements (229). This would suggest that deposition of fat during catch-up or recovery growth is a fundamental physiological process that may be designed to promote efficient utilization of cellular energy. It has been proposed that this manner of fat deposition may be a result of suppressed thermogenesis, an energy-conserving mechanism that occurred in the preceding period of nutritional deficit (229). There seems to be an autoregulatory negative feedback mechanism in place between thermogenesis and depletion of fat stores during periods of weight loss and weight recovery. This mechanism has been called "adipose-specific control of thermogenesis" (233), and it would appear to have a slow time-constant due to the fact that it responds only to signals arising from the state of depletion or repletion of fat stores. In other words, there is a self-regulating feedback system in place, such that depletion of fat stores signals theromogenesis to be suppressed and fat accumulation to be accelerated.

During nutritional insufficiency, skeletal muscle is an important site of energy conservation. The adipose-specific control of thermogenesis may function as a feedback loop between adipose tissue triglyceride stores and skeletal muscle metabolism. Because skeletal muscle is also the major site of insulin-mediated glucose disposal, a fall in the metabolic rate of skeletal muscle would precipitate a concomitant drop in glucose utilization, resulting in hyperinsulinemia. Furthermore, the unutilized glucose would be available for *de novo* lipogenesis and storage in adipose tissue, thereby increasing fat mass. Suppression of thermogenesis in skeletal muscle, therefore, is important for energy conservation and glucose recruitment for synthesis of fat during catch-up or recovery growth. Returning to the question of whether the processes that regulate storage of fat during its accumulation in catch-up growth induce a state of insulin resistance, a new theory is emerging. Suppression of thermogenesis in skeletal muscle during recovery growth redirects glucose toward

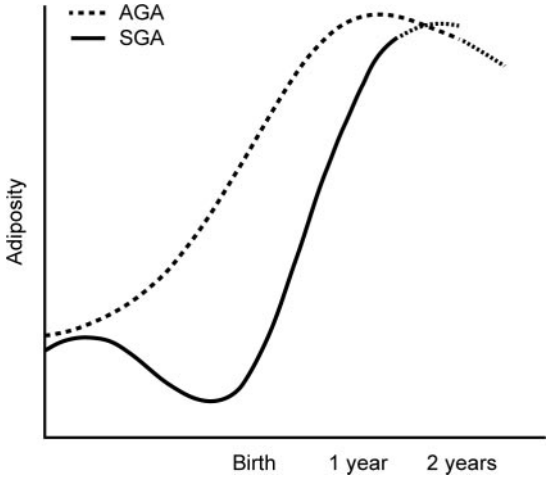

FIG. 10. Representation of the growth curves of adiposity in individuals born SGA at risk of insulin resistance, from midgestation to 2 yr of age, and in individuals born AGA over the same time period. [Reproduced with permission from Lévy-Marchal and Czernichow (204).]

TABLE 3. Selection of studies reporting a disproportionately faster rate of recovery of adipose tissue compared with lean tissue during weight gain

Population showing adipose catch-up during weight gain or catch-up growth	Ref.
Infants and children recovering from protein-energy malnutrition	397–399
Adults after substantial weight loss due to protein-energy malnutrition	400
Anorexics regaining weight	401, 402
Men after experimental starvation	403
Emaciated children recovering from tuberculosis	404
Concentration camp prisoners	405
Men and women after 2 yr of limited nutrition	406
Cancer patients	407
Intensive-care patients with septicemia	408
Patients with AIDS receiving parenteral nutrition	409

Adapted from Dulloo (226).

rapid reestablishment of adequate fat stores. This effectively constitutes a thrifty phenotype, bringing with it a tendency toward hyperinsulinemia and insulin resistance, thereby predisposing individuals experiencing catch-up growth to other metabolic conditions, such as abdominal obesity, type 2 diabetes, and cardiovascular disease (226).

The postnatal acquisition of fat is of great importance in the development of insulin resistance and therefore has a significant impact on the management of infant nutrition. The neonatologist must balance the positive effect of nutrition on the brain and neural development against rapid fat deposition and the attendant future risk of insulin resistance. Interestingly, the colostrum content of early breast milk may also limit inappropriate gains in fat deposits (234).

Two systematic reviews have examined the evidence that nutrition in early infancy affects long-term risks of developing obesity and that breastfeeding in infancy may have a protective effect in this regard (235, 236). Neither review specifically addressed individuals born SGA; however, in view of their findings, calorie-dense formula feeding in infants born SGA may not be appropriate.

Several mechanisms have been proposed to explain the effect of breast-feeding on later obesity risk. Breast-fed infants have lower calorie and protein intakes and show different patterns of insulin response to feeding. In addition, breast milk contains a number of substances that could affect body composition and obesity risk, such as long-chain polyunsaturated fatty acids. These substances are absent from traditional infant milk formulas. Consistent with this hypothesis, preterm infants fed formula containing docosahexanoic and arachidonic acid were recently shown to have a greater lean mass and lower fat mass than controls at 1 yr of age (237).

Breast-feeding is associated with a slower rate of weight gain in infancy (238), which could affect later body composition. Although these data cannot prove a causal link, they do suggest that growth in early life and, hence, early nutrition have an effect on long-term body composition. Long-term exclusive breast-feeding (24 wk or more) may prevent some of the intellectual impairment seen in SGA.

It has been demonstrated that birth weight is weakly associated with later BMI, whereas rapid weight gain in infancy is associated with an increased incidence of obesity in later life (239–241). In view of this evidence, existing feeding practices for infants born SGA may require revision.

X. Reversibility of Metabolic Programming

Vickers *et al.* (242) recently showed that neonatal administration of leptin to rats that were undernourished *in utero* reverses the metabolic phenotype of insulin resistance and obesity that would otherwise develop in these animals when fed a high-fat diet. It is possible that maternal undernutrition results in hypoleptinemia during a critical period of development and that this reduction in leptin initiates the programming cascade. In the rat, there appears to be an early postnatal window to reverse developmental programming. Although the precise mechanism for this reversal is currently unclear, the study demonstrates that early intervention can reset the programming that was initiated *in utero*. It has also been shown that leptin-deficient animals have reduced neural projections from the arcuate nucleus to a number of other hypothalamic nuclei involved in energy homeostasis. These projections can be normalized by exogenous leptin treatment, but only if administered during the neonatal period (243, 244). It has been suggested that leptin overrides the undernutrition signals received by the developing fetus by mimicking a well-nourished state (8). On the other hand, it is possible that leptin affects hypothalamic maturation or pancreatic development.

Relative undernutrition in early life in preterm infants has been shown to be associated with diminished insulin resistance in adolescence (234). The authors of this study investigated the relationship between relative undernutrition in infancy and the fasting concentrations of 32–33 split proinsulin at 13–16 yr of age. High levels of fasting 32–33 split proinsulin, which is a natural precursor of insulin, may indicate insulin resistance (245) as a result of programming in early life (188). Hales *et al.* (188) showed that individuals fed ordinary formula or breast milk in infancy had lower fasting 32–33 split proinsulin levels in adolescence than did individuals fed in infancy with nutrient-enriched formula. Fasting 32–33 split proinsulin concentrations were associated with weight gain in the first 2 wk of life, independently of gestational age, birth weight, and other confounding factors. These findings support the theory that accelerated weight gain in early life programs insulin resistance and implies that this programming can be reversed or prevented by dietary modulation at a critical stage of postnatal development. In other words, the effect of intrauterine growth on later fasting 32–33 split proinsulin concentration (and by inference, insulin resistance) can be displaced by rapid postnatal weight gain, suggesting that the fetal origins hypothesis proposed by Barker *et al.* (246) may be a postnatal event.

XI. Other Potential Sequelae

A. Premature adrenarche and puberty

A number of animal models of SGA have shown a delayed onset of puberty in both sexes (247–249); however, data in humans are scarce. One group has shown early onset of puberty in girls born SGA (250–252). Other studies have shown that the ages at pubertal onset and at menarche are advanced by about 5–10 months (253–255). In a Swedish cohort of children born SGA, there was a tendency to start puberty early, especially if catch-up growth had not occurred in early childhood (256). Several other groups, however, have not been able to show earlier puberty or menarche in either naive or GH-treated children born SGA (190, 257–259).

The sequence and tempo of puberty appear to be normal, although Hernandez *et al.* (260) recently reported that baseline estradiol levels were slightly higher at the beginning of puberty in girls born SGA than in AGA controls of the same age. A Dutch longitudinal study of children born SGA showed no difference for girls in the timing of pubertal onset or in the tempo of pubertal progression, including menarche (261). This was also the case in children born SGA who had been treated with GH. The onset of puberty was slightly

delayed in boys, but the tempo was unaltered. Although there are currently few data in males born SGA, early puberty is seen in some children with pronounced weight gain in prepuberty; however, the effect of weight on initiation of puberty is well known.

Francois and de Zegher (262) made the early observation that dehydroepiandrosterone sulfate levels were higher in prepubertal children born SGA. This led to extensive studies by these and other authors who documented premature or exaggerated adrenarche in many children with a history of SGA (262–264). A Dutch study, however, showed no relationship between birth size and levels of dehydroepiandrosterone sulfate, and no increased incidence of premature adrenarche was observed (265–267).

B. Reproductive function

Not only is hyperandrogenism a feature of individuals born SGA (250, 268), but such individuals also exhibit abnormalities of ovarian function, such as polycystic ovarian syndrome (PCOS) (269). Furthermore, reduced fetal growth has been associated with unexplained male subfertility (270), and Cicognani *et al.* (271) found gonadal dysfunction, such as reduced testicular size and decreased testosterone levels, in postpubertal teenage boys born SGA.

Adolescent girls born SGA were found to have a reduced ovulation rate, which was responsive to insulin-sensitizing treatment with metformin (185). The metformin-induced increase in ovulation rate in the cohort of Ibáñez *et al.* (272) was accompanied by a reduction in excess abdominal fat, a gain in lean body mass, a decrease in fasting insulin and serum androgen concentrations, and an improved lipid profile. More recently, Ibáñez and colleagues (273) have also provided evidence that these girls have low-grade inflammation, as judged by a high ratio of neutrophils to lymphocytes, by low adiponectin levels, and by high circulating levels of C-reactive protein, IL-6, and TNF-α. It has been shown that metformin is capable of delaying menarche and prolonging the growth period in girls born SGA, who often do not meet their target height (274) because of subnormal growth during prepuberty. These data support the concept that insulin is a major codeterminant of the pubertal tempo and pubertal height gain in girls. It should be noted that these girls did not have type 2 diabetes mellitus, they were not obese, and they were not at high risk of adult short stature to begin with. Treatment with metformin in this constellation must be considered experimental and awaits confirmation by other groups.

The surge in serum FSH, LH, inhibin B, and sex steroids during the first months of infancy and the persistence of high levels of FSH until early childhood in girls may be important for later optimal gonadal function (275, 276). The rise in FSH levels is greater during infancy in both boys and girls born SGA, whereas inhibin B levels are similar to those in infants born AGA (277). When studied in young adulthood, females who were born SGA also had FSH hypersecretion and evidence of reduced growth of the uterus and ovaries as assessed by ultrasound examination (278). Ovulation rates were reduced in adolescent girls born SGA when determined in the short term using serial blood spot progesterone measurements (185). Although anovulatory cycles can be a normal feature during the initial years postmenarche, insulin sensitization with metformin induced ovulatory cycles in a significant proportion of nonobese SGA adolescent females (272). Hyperinsulinemic insulin resistance with hyperandrogenemia and an adipose body composition is a setting for the subsequent development of a PCOS-like state in adolescence (279). Although fetal growth restraint is not mentioned as a dominant etiological factor in current reviews of established PCOS in adult women (280, 281), there is evidence that the use of insulin-sensitizing agents in girls born SGA, administered soon after menarche, prevents the onset of a PCOS-like state associated with hyperinsulinemia (282).

There is less direct evidence for an association with gonadal dysfunction in adolescent males born SGA. One study of 24 postpubertal boys born SGA reported a reduced testicular volume, decreased serum inhibin B and testosterone concentrations, and increased LH but normal FSH values (271). Studies of spermatogenesis in adult males related to their birth weights provide little evidence of an adverse effect of low birth weight. A small reduction in birth weight associated with an abnormal sperm count in unexplained infertility was not replicated in results analyzed from another similar population (270, 283). The postulate that fetal growth restraint may impede development of the pool of Sertoli cells was not borne out by a Danish study on male fecundity (284). Contrary to expectations, males with birth weights within the normal range had a tendency to abnormal spermatogenesis in this study. Maternal smoking, which clearly can reduce birth weight, has a significant impact in reducing sperm counts subsequently in male offspring, an effect that is dose dependent (285, 286).

C. Reproductive tract abnormalities

There is a quartet of reproductive tract abnormalities affecting males that has now assumed a syndromic designation, the testis dysgenesis syndrome (TDS) (287). This comprises abnormal spermatogenesis, testicular cancer, cryptorchidism, and hypospadias. It has been proposed that TDS has a fetal origin (288). Germ cell tumors, such as seminomas, account for most tumors of the testis. They arise from a common precursor known variously as carcinoma-*in-situ* cells or intratubular germ cell neoplasia (289). These cells are believed to originate from primordial germ cells or fetal gonocytes that have failed to differentiate and mature into spermatogonia. Low birth weight is a common risk factor for testicular cancer, hypospadias, and cryptorchidism (290). In turn, each component of the TDS shares risk factors linked to each other, including poor semen quality and testicular cancer.

There are several other independent factors that influence the risk of developing testicular cancer. These include maternal age and weight, parity, ethnicity, family history, twinning and whether men had been breast-fed (291–296). The association with birth weight appears to be U-shaped, and adult height is also positively associated with testicular cancer, a link that is independent of perinatal factors (297, 298). These observations imply a possible nutritional link with the risk of testicular cancer, the incidence of which has been

rising in concert with secular trends in growth (299, 300). Consumption of milk, dairy products, and animal fats has been found to be positively and strongly linked to the incidence of testicular cancer in numerous countries (301). Their content is high in sex hormones (302).

Hypospadias is a common congenital malformation that is readily recognized at birth. Epidemiological studies conducted worldwide report a prevalence rate within the range of 0.4–0.8 per 1000 births (303–306). Denmark has a particularly high birth prevalence of 10 per 1000 births, which increased later to a level of 46 per 1000 births when additional mild cases were found after the foreskin could be retracted (307). In most cases of isolated hypospadias, the cause is unknown, despite extensive hormonal and genetic investigations (308, 309). However, a consistent finding is an association with low birth weight, which also pertains to monozygotic twins discordant for hypospadias (310–312). There is a clear difference in birth weights and birth lengths in normal males and females (311). This difference has been attributed to androgen effects based on birth weights in male infants thought to have genital anomalies due to abnormalities in androgen action (313). However, a recent analysis of birth weight corrected for gestational age in a large group of male infants with hypospadias from the Cambridge Disorder of Sex Development Database shows a normal birth weight in infants with a documented deleterious mutation in the androgen receptor; in contrast, the birth weight was reduced in hypospadic infants in whom the androgen receptor was normal. Formation of the penile urethra from fusion of the endodermal urethral folds and dorsal growth of the urethral plate is complete by the beginning of the second trimester (309). Early fetal growth restraint, which generally results in symmetric SGA, may also underlie the strong association between idiopathic, isolated hypospadias and low birth weight.

Cryptorchidism is a common congenital anomaly in males, but prevalence figures are inconsistent due to the imprecision of examination techniques and definition of the ascending testis (314). Low birth weight for gestational age is a recognized association (315). Prospective cohort studies using standardized examination techniques have reported prevalence rates in Denmark and Finland of 9.0 and 2.4%, respectively (316). The pronounced difference between the two Nordic countries is unexplained, other than to invoke adverse effects from environmental factors, especially because the prevalence of cryptorchidism in Denmark has quadrupled in 40 yr. In both Nordic populations there was an increasing prevalence of cryptorchidism with decreasing birth weight, particularly associated with being SGA. A contemporary ongoing prospective longitudinal Cambridge Birth Cohort Study shows a prevalence of 4.5% for cryptorchidism at birth and confirms the significant association with low birth weight for gestational age (C. L. Acerini and I. Hughes, personal observations).

Descent of the testis is a two-stage process. An initial transabdominal phase involves anchoring the testis close to the inguinal region through enlargement of the distal ligamentous gubernaculum while the abdominal cavity grows (317, 318). This is under the control of insulin-like hormone 3 produced by the Leydig cells. The second stage occurs between 25 and 35 wk gestation and is the inguinoscrotal phase, which is predominantly androgen dependent. The reproductive consequences associated with SGA therefore depend on the timing of fetal growth restraint (Fig. 11). The definition of SGA is seldom sufficiently refined in practice to delineate the nature of intrauterine growth restraint that results in a low birth weight infant. However, there is indirect evidence from studying the spectrum of reproductive abnormalities associated with SGA that causative mechanisms can be invoked based on whether the fetal developmental phases affected are differentiative or maturational in nature.

D. Effects on other organ systems

Besides cardiovascular disease, glucose intolerance, and disorders of puberty, low birth weight has been implicated in multiple unrelated conditions, including coronary heart disease (319), stroke (320), liver cirrhosis (321), respiratory infection and obstructive airway disease (187), and renal disease (322). All may have the commonality of development occurring in a nutritionally deficient environment.

Renal disease is increased in individuals born with a low birth weight (322, 323), perhaps due to a reduction in nephron number, with compensatory glomerular hypertrophy (324). Even young adults born SGA with grossly normal renal function are found to have microalbuminuria and reduced glomerular filtration rates (325). Children born SGA with minimal-change nephritic syndrome are at greater risk of a complicated and progressive course of renal disease (326, 327).

Being born SGA may be associated with impaired pulmonary development, with a greater risk of bronchopulmonary dysplasia and chronic lung disease in the newborn (328). Harding *et al.* (329) found that prenatal development of the brainstem or chemoreceptors may be affected by fetal hypoxia or hypoglycemia in infants born SGA. They found that the air-blood barrier in the lungs was thicker and that, consequently, the diffusion capacity for carbon monoxide in the lungs was lower in children born SGA. Furthermore, impaired fetal growth and adult fatness were reported to be risk factors for adult asthma (330). Another study found that maternal smoking in pregnancy increases the risk of asthma during the first 7 yr of life, with only a small fraction of the effect apparently mediated through impaired fetal growth (331).

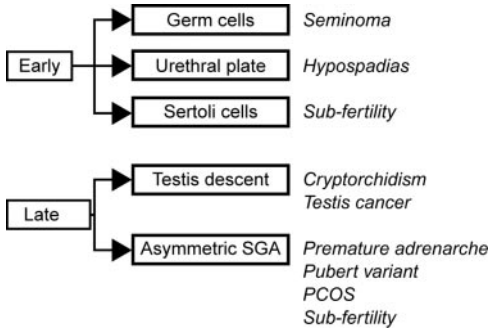

FIG. 11. Target effects of early *vs.* late fetal growth restraint and association with reproduction-related abnormalities.

SGA has also been associated with an increased risk of mortality from cirrhosis of the liver (321).

Visual function may be impaired subsequent to abnormal intrauterine development in individuals born SGA (332). Retinal damage, often found only with highly sophisticated assessments (332–334), is the most common abnormality, although the persistence of the dysfunction varies. The occurrence of sensorineural hearing loss is increased in young adults born SGA, but the increased risk appears to be independent of the childhood growth pattern or the presence of obesity (335). The size of the chochlea and auditory neurons, the innervation of the auditory sensory cells, along with postnatal development of auditory ganglion cells, appears to be impaired in these patients. Brainstem auditory-evoked potential studies also show abnormalities (336).

There is increasing evidence that nutritional deficit *in utero* can lead to abnormal bone development and predispose to osteoporosis in later life (337). Indeed, the bone mineral density adjusted for bone size of children born SGA has been shown to be significantly less than that of normal children (338), and children in the lowest quartile for height gain are almost twice as likely to incur a hip fracture in later life than are children in the highest quartile (339). In addition, bone maturation may show idiosyncratic variations in untreated children born SGA, particularly between 6 and 9 yr of age. This leads to difficulties in bone age interpretation, and large inter- and intraindividual observer variation (340).

E. Neurodevelopmental, psychosocial, and behavioral outcomes

Reduced oxygen or nutrient delivery to the fetus may have adverse effects on brain development and differentiation. This can lead to impaired learning and cognition (340).

In a comparison of the psychomotor development of healthy infants born SGA with those of infants born AGA, at 13–14 months of age, infants born SGA scored lower than those born AGA on mental scales, but equally well on scales of motor function (341). McCarton *et al.* (342) found that premature children born SGA had significantly lower cognitive scores at 1, 2, 3, and 6 yr of age than premature children born AGA. They concluded that premature infants born SGA are at greater risk of developmental impairment than equally premature infants born AGA (342).

In another study, Larroque *et al.* (192) found that late entry into secondary school was more common in children born SGA than in those born AGA, even after correcting for socioeconomic status, maternal age and educational level, family size, and gender. In addition, more SGA than AGA adolescents failed to pass the baccalaureate examination at the end of secondary school (192).

A large United Kingdom study of 1,064 individuals born SGA out of a cohort of 14,189 infants born in the United Kingdom during 1 wk in 1970 showed that those born SGA have increased academic difficulties that continue into adolescence and also experience deficits in professional achievement. However, those born SGA were no more likely to have emotional or social difficulties than those born AGA (343).

In a study of 254,426 Swedish males aged 18 yr, short birth length, small head circumference at birth, and preterm birth were all found to increase the risk of subnormal performance on standard psychological and intelligence tests. The most important predictor of subnormal performance among individuals born SGA in this study was the absence of catch-up growth (344).

Several studies have found an association between small stature and psychosocial disadvantages (345–348). Shorter individuals are perceived as less competent than taller individuals, both during childhood and as adults. They are seen less positively by their peers and perceive themselves less favorably. They are also more likely to be in lower positions within a given profession. Finally, a low birth weight has been linked to an increased risk of schizophrenia (349).

XII. GH Treatment in Short Children Born SGA

A. Natural history of growth after an SGA birth

Persistent short stature is one of the most frequent complications after being born SGA. Approximately 10% of children born SGA will remain less than −2 SD for height throughout childhood and adolescence and into adulthood. Among children who are born SGA and do not achieve catch-up growth by 2 yr of age, the relative risk of short stature at 18 yr of age is 5.2 for those born light and 7.1 for those born short (177). Importantly, in a long-term study of 213 individuals born SGA compared with 272 born AGA, 13.6% of those born SGA had a final height at 20–21 yr of age of more than 2 SD below the mean, compared with only 1.8% of those born AGA (350).

B. Indications for treatment

A short child who was born SGA and has not caught-up (*i.e.* > 2 SD below the mean) by 2–3 yr of age and who is growing at an average or subnormal rate for age could become a candidate for GH therapy (190, 351). In addition to the above criteria, treatment with GH is indicated only when other causes of short stature, such as growth-inhibiting medication, chronic disease, endocrine disorders such as hypothyroidism, emotional deprivation, or syndromes associated with poor growth have been ruled out (15). One exception to this is Silver-Russell syndrome, where GH therapy has been shown to ameliorate short stature (352) and produces a similar growth response to that seen in children born SGA. A recent study of the effect of more than 7 yr of GH treatment in patients with Silver-Russell syndrome showed that height was improved from -2.86 ± 1.15 at the start of therapy to -1.8 ± 1.25 at final height ($n = 19$), with a better response in the younger patients. GH therapy may also have a beneficial effect on BMI and the lipid profile in patients with Silver-Russell syndrome. As yet, there are no auxological data for children with this syndrome who have the 11p15 mutation on chromosome 7 (353)

Whether measures of GH secretion provide clinically useful information for the routine treatment of short children who were born SGA is controversial. Arguments that favor evaluation for GH deficiency stem from data suggesting that many short patients who were born SGA have diminished

GH output, as evidenced by low levels of spontaneous GH secretion and depressed circulating levels of markers of GH secretion, such as IGF-I (152–154, 340, 354–356). The present recommendation is that tests of adequate GH release should be performed when GH deficiency is suspected on clinical or biochemical grounds. Accordingly, the measurement of circulating concentrations of IGF-I and IGFBP-3 before the start of GH therapy not only provides a baseline against which to assess the biochemical response to GH therapy, but also serves as a useful screen for possible GH deficiency in this population.

As would be expected, GH therapy in short children born SGA provokes a dose-dependent rise in the serum concentrations of both IGF-I and IGFBP-3 from low normal and normal baseline levels. On a molar basis, the increase in IGF-I exceeds that of IGFBP-3 and, consequently, the molar IGF-I/IGFBP-3 ratio is significantly increased (340, 357).

C. Clinical experience with GH in children born SGA

The initial objective of GH therapy is to accelerate linear growth in early childhood as much as possible to achieve rapid catch-up growth and to maintain normal growth later in childhood. The ultimate objective is to normalize adult height. Clinical trials have shown that the growth response to GH therapy is better when children begin therapy in early childhood and that age at the initiation of therapy is a major determinant of the growth response (340, 354, 358). Parental height and birth length are the only variables that seem to be predictive of adult height in untreated children born SGA (350). In GH-treated short children who were born SGA and followed to adult height, GH therapy effectively increased adult height above the predicted height, with patients achieving their target heights (359).

In a subsequent study, Ranke *et al.* (360) analyzed data from 613 children who were born SGA and enrolled in the Kabi International Growth Study (KIGS), the Pfizer International Growth Database. They developed a robust clinical prediction model that allows GH therapy to be individualized in children born SGA who fail to show spontaneous catch-up growth. In their model, 52% of the variability of the growth response in the first year of GH therapy could be readily explained. The GH dose was the most important predictor, accounting for 35% of the variability in response. Other predictors during the first year were, in order of importance, age at the start of therapy, weight SDS at the start of therapy, and midparental height SDS (Table 4). A model for the second-year response showed that height velocity during the first year of GH therapy was the most important predictor of subsequent growth. These data suggest that final height outcome may be determined by the initial response to GH therapy, which is dose dependent.

In a study of children who were at a mean age of 4.5 yr and had severe short stature (that is, more than 3 SD below the mean for chronological age and gender) and had been born SGA (birth weight below the 10th percentile), GH therapy induced sustained catch-up growth (361). All children received GH at a dose of 0.48 mg/kg·wk for 3 yr, although one of the two treatment groups initially underwent a 1-yr observation period, which confirmed that no clinically significant spontaneous acceleration of height velocity occurred. After 3 yr of treatment, mean height SDS for chronological age had increased by 2.0 ± 0.7 in the two groups, and no clinically adverse events were noted.

TABLE 4. Variables for the regression equation predicting first-year growth response to GH therapy in children born SGA (n = 613)

	Parameter estimate	Rank	Partial R^2
GH dose (mg/kg·d)	56.51	1	0.35
Age at start (yr)	−0.31	2	0.11
Weight SDS at start	0.30	3	0.05
MPH score SDS	0.11	4	0.01
Intercept (constant)	9.40		
R^2	0.52		
Error SD	1.30		

Adapted from Ranke *et al.* (360). MPH, Midparental height.

The results of three short-term French studies showed that growth rate accelerated markedly, nearly doubling after 1 yr of treatment, with GH doses up to 0.48 mg/kg·wk (362). This dose is up to two times greater than the standard replacement doses used to treat children with GH deficiency. Mean height increased by nearly 2.0 SD over the 3-yr treatment period, although, as in all GH studies, a progressive decrease in the effect on growth rate occurred over time. This treatment was well-tolerated without significant adverse effects.

Studies of long-term treatment with GH, starting from around 8 yr of age and continuing for 7–8 yr, using doses of 33 or 67 μg/kg·d (0.22 or 0.48 mg/kg·wk) suggest that GH is effective at increasing adult height by 1 or more SDS (19, 352, 363–365). A recent analysis of adult height data from published clinical trials suggests that in children born SGA in whom GH therapy is initiated at a mean age of 5 yr, a dose of 0.48 mg/kg·wk for 10 yr elicits gains in adult height SDS that are about 0.4 greater than those achieved with a lower dose of 0.22 mg/kg·wk (363).

Early catch-up growth may therefore require a higher dose of GH. The time to achieve an increase in height SDS of 2 was approximately 2.5 yr with a GH dose of 0.067 mg/kg·d and approximately 5.5 yr with a dose of 0.033 mg/kg·d (Fig. 12) (366). This provides evidence for a dose-dependent effect at least in the first 4–5 yr of GH therapy. One study carried out to final height, however, suggested that there was no dose effect, although this would need to be confirmed in further trials (365)

There is considerable variation in the growth response to GH therapy in children born SGA, even after adjusting for differences in parental height, age at start of treatment, and duration of treatment (367). As in all indications for GH therapy, children born SGA with the greatest parental-height-adjusted height deficit respond most to GH therapy (19, 368, 369). Studies also suggest that the younger the child at the start of GH therapy, the quicker the initial GH response (368–370). In a study of GH treatment in Swedish children born SGA, those who started GH therapy at least 2 yr before the onset of puberty gained a mean adult height SDS of 1.7, which corresponded to a 12-cm increase in adult height, compared with pretreatment predictions (364). In contrast, children who started GH therapy at a later age gained a mean adult height SDS of +0.9, corresponding to a 6-cm increase in adult height. Similarly, studies in which children started

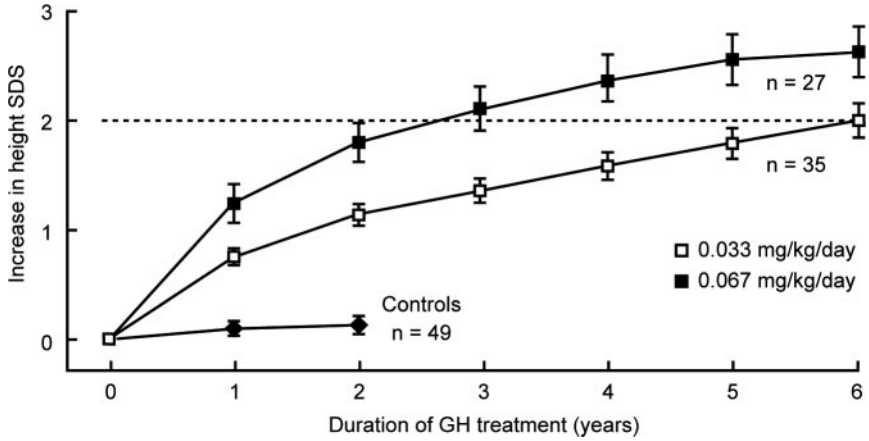

FIG. 12. Time to achieve an increase in height SDS of 2 was approximately 2.5 yr with a GH dose of 0.067 mg/kg·d and approximately 5.5 yr with a dose of 0.033 mg/kg·d in short children born SGA. [Adapted with permission from de Zegher *et al.* (366).]

treatment at a mean age of 7.8 yr estimated that the gains in adult height SDS were about +2 (352), whereas such estimates were only +0.6 in studies where GH therapy was started at 10–12 yr of age (365, 371).

Combination treatment with GH and a GnRH agonist has been attempted in short pubertal children born SGA. Such combination treatment currently, however, has to be considered experimental because no good final height data are available (372). This approach may also be associated with short-term negative effects on psychosocial functioning (373).

1. Effect of discontinuation of therapy. To maximize the therapeutic response, treatment with GH should be continuous rather than intermittent (361, 374). There is definite catch-down growth after discontinuation of GH therapy (Fig. 13) (366).

2. Intelligence, psychosocial function, and metabolic effects of GH therapy. Intelligence and psychosocial functioning have been shown to be enhanced during GH treatment (375), and the association of intelligence quotient and IGF-I levels (376) suggests important neurodevelopment processes yet to be studied in the SGA population. In addition, Huisman *et al.* (348) concluded that there is a positive short-term effect of GH therapy on psychosocial functioning.

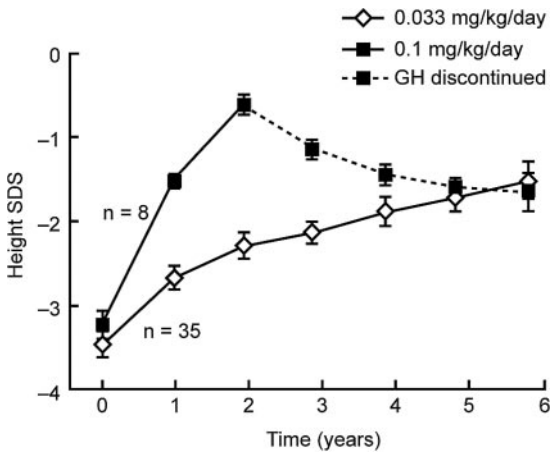

FIG. 13. Discontinuation of GH treatment, 0.1 mg/kg·d, after 2 yr leads to a reduction in height velocity and a subsequent decrease in height SDS compared with the sustained improvement in height SDS achieved with a continuous dose of 0.033 mg/kg·d. [Reproduced with permission from de Zegher *et al.* (366).]

GH therapy in short children born SGA has been shown to improve body composition, blood pressure, and lipid metabolism. In a 6-yr study of 79 patients, BMI SDS was significantly lower than zero before treatment ($P < 0.001$) but increased during therapy ($P < 0.001$) to values that were not significantly different from zero (377). This normalization of BMI was not accompanied by overall changes in percentage body fat, but was accompanied instead by an increase in muscle mass. Children born SGA but not receiving GH therapy served as controls in this study.

Similarly, Leger *et al.* (378) studied the effects of 3 yr of GH therapy in 14 short children born SGA. By the end of the third year, muscle tissue mass was significantly greater in the SGA group than in the control group, whereas adipose tissue mass was similar in the two groups (378).

Short prepubertal children born SGA have lower caloric, fat, and carbohydrate intake compared with the recommended daily intake for age-matched controls. During GH therapy, food intake increases significantly in association with a decrease in leptin levels, indicating that this feedback loop is intact in children born SGA (379).

3. Pharmacogenomic findings in GH-treated children born SGA. Recently, a common genetic variant in the GH receptor that is associated with variation in the GH response in children born SGA and those with idiopathic short stature has been described (380). Children carrying an exon 3 deletion of the GH receptor gene demonstrated 1.7–2 times more growth acceleration induced by GH than children with the full-length variant. This finding was confirmed by another group of investigators in GH-deficient children both in their initial growth response and in their adult height (381). It has recently been shown, however, that the d3-GH receptor polymorphism did not influence the effects of GH treatment in 68 prepubertal short children born SGA (382). Such studies may lead to genetic tests that could contribute to individualized and more effective GH therapy. Increased responsiveness to high-dose GH may be associated with the d3-GH receptor phenotype. The magnitude of this effect may, however, depend on the primary origin of the short stature (383).

4. Treatment differences in the United States and Europe. The use of GH was approved by the U.S. Food and Drug Adminis-

tration (FDA) in 2001 at a dose of 0.48 mg/kg·wk for children born SGA. The prescribing information in the United States says that GH is indicated for the long-term treatment of growth failure in children born SGA who fail to manifest catch-up by the age of 2 yr. In contrast, the European Agency for the Evaluation of Medicinal Products (EMEA) approved GH in 2003 for the treatment of children born SGA after the age of 4 yr at a dose of 0.22 mg/kg·wk. This is because there may still be a small possibility of spontaneous catch-up growth between 2 and 4 yr of age, especially in infants who are born prematurely. These divergent regulatory approvals (Table 5) will hamper efficacy comparisons in future studies.

D. Safety of GH therapy

GH therapy has been shown to have a good safety profile and to be highly effective at promoting growth in those infants (approximately 10%) born SGA who do not show early signs of spontaneous catch-up growth (384, 385).

Bone age has been shown to be normal or delayed in individuals born SGA. Hokken-Koelega and colleagues showed that GH treatment is associated with an acceleration of bone maturation regardless of the GH dose given (338, 340). Even in untreated infants born SGA, bone age occasionally advances by more than 1 yr in a single calendar year. Furthermore, bone age is a poor predictor of pubertal timing and adult height in children born SGA (386). Its assessment is not recommended during routine follow-up (387). The change in bone age/chrononological age was positively correlated to the observed catch-up growth in height (A. Hokken-Koelega, personal communication). This phenomenon has also been seen in many other GH treatment studies (388).

The effect of GH on glucose metabolism in children born SGA is of potential concern. Carbohydrate metabolism should therefore continue to be reassessed during GH therapy, with fasting serum glucose and insulin levels measured annually. No adverse effects on serum glucose levels and glycosylated hemoglobin were found in 70 prepubertal children who were treated with GH continuously at a dose of 0.24 or 0.48 mg/kg·wk for 6 yr (384). In a U.S. trial, although insulin and glycosylated hemoglobin concentrations and insulin sensitivity scores, as measured by the homeostasis model assessment (HOMA) and QUICKI, rose slightly in children born SGA receiving GH therapy, these changes were not clinically significant (385). Although children born SGA tend to develop higher fasting insulin levels and relative insulin resistance during GH treatment (224, 340, 389), reassuringly these changes appear to be largely reversible when treatment is terminated (357, 365, 384) (Fig. 14). In a recent study of 37 young adults born SGA and treated with GH during childhood for a mean period of 7.3 yr, there was no increased risk of the metabolic syndrome or type 2 diabetes mellitus after a mean period of discontinuation of GH of 6.5 yr, when compared with individuals born SGA who had not received GH treatment (390).

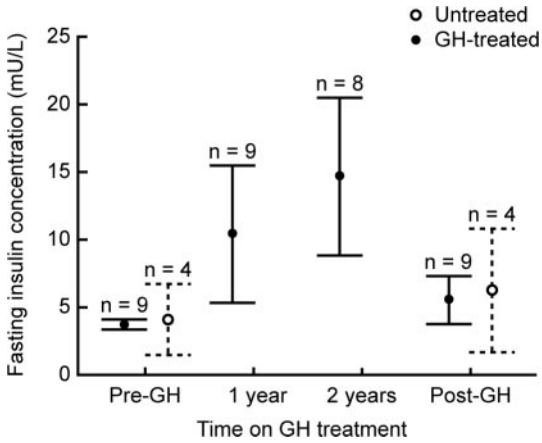

FIG. 14. Fasting insulin concentrations (mean and 95% confidence intervals) in untreated short children born SGA and in those receiving GH therapy at a dose of 100 μg/kg·d for up to 2 yr. [Adapted with permission from de Zegher *et al.* (357).]

The International SGA Advisory Board provides useful guidance regarding glucose tolerance in the treatment of children born SGA, stating "the majority of prepubertal children who are SGA are not at risk of glucose intolerance. Because insulin resistance may increase during GH therapy, parents should be asked whether there is a family history of type 2 diabetes mellitus, although any potential long-term risk as a consequence of elevated insulin levels is unknown. In lean children without a family history of diabetes, screening of the carbohydrate status (*e.g.*, fasting, postprandial glucose and insulin levels) is suitable. More stringent measures are recommended for those who are at puberty, are obese, or have other increased risks" (15). These include acanthosis nigricans, belonging to an ethnic group at risk, and having a family history of type 2 diabetes mellitus (15)

Children born SGA may also have an inherent risk of cardiovascular disease and dyslipidemia in later life (53, 391). Reassuringly, a 4-yr study of children born SGA treated with GH showed that those who had elevated systolic blood pressure before treatment had a reduction in blood pressure over time (377). Furthermore, total cholesterol and low-density lipoprotein cholesterol levels fell during the first year of treatment and remained stable thereafter (377, 392). Similar reductions in blood pressure and serum cholesterol were also observed in the long-term study of van Dijk *et al.* (390).

TABLE 5. Use of GH therapy in short children born SGA in the United States and Europe

	FDA approved indication in 2001	EMEA approved indication in 2003
Age at start of treatment (yr)	2	4
Height SDS at start	Not stated	−2.5 SD
Growth velocity before treatment	No catch-up growth	Less than 0 SD for age
Reference to midparental height	Not stated	Height SDS > 1 SD below midparental height SDS
Dose (μg/kg·d)	70	35

FDA, U.S. Food and Drug Administration; EMEA, European Agency for the Evaluation of Medicinal Products.

Large postmarketing surveillance databases have also shown that GH therapy is well tolerated. Importantly, there is no evidence that the risk of malignancy is increased (385). As in other children treated with GH, benign intracranial hypertension is a rare complication of children born SGA, occurring in approximately one in 1000 individuals. Finally, there is convincing epidemiological evidence that children born SGA, even those not treated with GH, may be at an increased risk of insulin resistance and type 2 diabetes mellitus in later life (190, 202). These inherent risks of obesity and later insulin resistance appear to be greatest among those children born SGA who show spontaneous catch-up growth, rather than among the population of short children born SGA who would qualify for GH therapy (176, 393–395).

XIII. Conclusion

The incidence of SGA births is relatively frequent at 2.3–10% of all live births. It is now well established that several childhood and adult diseases are related to size at birth and are particularly influenced by early postnatal growth. The developing fetus prepares itself for postnatal life by responding to endocrine and metabolic signals in its uterine environment. It appears to adapt to prolonged oxygen deficit or malnutrition by developing resistance to GH, insulin, and IGF-I, thereby slowing its rate of growth and minimizing its need for nutrients *in utero* and *ex utero*. Although this is an essential adaptation when undernourishment persists through gestational and postnatal life, the permanent changes it brings about are detrimental in an environment of nutritional abundance and predisposes the individual to an array of diseases in later life. There is evidence to suggest that some of the metabolic consequences of this fetal reprogramming can be mitigated by ensuring early appropriate catch-up growth, while avoiding excessive weight gain.

Although there is strong evidence for a panoply of endocrine and metabolic disturbances in children and adults born SGA, there is currently no robust evidence to recommend routine endocrine investigation in all children born SGA. Further studies are likely to identify factors related to fetal and postnatal growth that may be responsible for generating insulin resistance and related complications (387).

The prevention of SGA births is a formidable public health issue, and no ready answers are at hand. In stark contrast to the findings of Barker *et al.* (11), recent observational studies would suggest that accelerated weight gain during infancy, even during the first weeks of life, can result in overweight, insulin resistance, high leptin and cholesterol levels, and elevated blood pressure one or two decades later. As M. W. Gillman states in a recent editorial (396), getting the right answers is more than a mere academic issue. If rapid weight gain in infancy is indeed resulting in adult disease, then physicians are faced with many challenges in overcoming deep-seated cultural stereotypes: that "a big baby is a healthy baby." We have to consider whether our growth charts are appropriate, and we have to question the widespread use of energy-enriched formula for SGA infants to "fatten them up" quickly. Most of all, we have to devise effective strategies for ensuring an adequate duration and exclusivity of breastfeeding (396). The well-being of newborn children can have substantial health-promoting effects in the next generation.

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