Children Born Small for Gestational Age: Differential Diagnosis, Molecular Genetic Evaluation, and Implications

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ABSTRACT Children born small for gestational age (SGA), defined as a birth weight and/or length below −2 SD score (SDS), comprise a heterogeneous group. The causes of SGA are multifactorial and include maternal lifestyle and obstetric factors, placental dysfunction, and numerous fetal (epi)genetic abnormalities. Short-term consequences of SGA include increased risks of hypothermia, polycythemia, and hypoglycemia. Although most SGA infants show catch-up growth by 2 years of age, ~10% remain short. Short children born SGA are amenable to GH treatment, which increases their adult height by on average 1.25 SD. Add-on treatment with a gonadotropin-releasing hormone agonist may be considered in early pubertal children with an expected adult height below −2.5 SDS. A small birth size increases the risk of later neurodevelopmental problems and cardiometabolic diseases. GH treatment does not pose an additional risk. ***(Endocrine Reviews 39: 851 – 894, 2018)***

It has been recognized for many decades that low birth weight poses a risk factor for stillbirth and infant death (1). The World Health Organization defines low birth weight as a weight <2500 g. This definition includes preterm infants who generally have an appropriate size for their gestational age as well as infants born at term with a small birth size. Small for gestational age (SGA) is the term used to describe infants with a birth weight and/or length below the normal range for gestational age.

In neonatology SGA is usually defined as a birth weight below the 10th percentile for gestational age. A panel of pediatric endocrinologists agreed in 2001 to define SGA as a birth weight and/or length of at least 2 SDs below the mean for gestational age, based on data derived from an appropriate reference population (2). The choice of definition was found to have a considerable impact on the risk of a host of outcomes (3); for example, the relative risk of neonatal death for infants with a birth weight below the 3rd percentile was much higher than for those having a birth weight below the 10th percentile (6.28 vs 3.51, respectively) (4).

The terms *intrauterine growth restriction* (IUGR) and *SGA*, although often used as synonyms, are not interchangeable. SGA infants have not necessarily experienced IUGR and, conversely, infants with documented IUGR are not inevitably born SGA. Unlike SGA, IUGR always refers to a pathological process that results in decelerating fetal growth velocity. Serial ultrasound assessment (of fetal anthropometric traits, umbilical cord flow, and amniotic fluid) is necessary to confirm IUGR (5). Recently, consensus was reached about the definition of "growth restriction in the newborn" (6).

Among the causes of SGA are maternal health and obstetric factors, placental insufficiency, and fetal (epi) genetic factors. Numerous genetic causes of SGA have been identified during the past decades and, owing to advances in genetics, the list with involved genes continues to expand. Smaller birth size poses a risk factor for cardiovascular disease, hypertension, and type 2 diabetes mellitus (DM) (7–9). Many of these risks may be amplified by rapid postnatal weight gain (10, 11).

Although most SGA infants show catch-up growth by the age of 2 years, ~10% do not (12, 13). Children born SGA who remain short may be amenable to GH treatment. The children who participated in the initial GH studies have now reached adult height, so that currently there are robust data on the long-term efficacy and safety of GH for short children born SGA (14–16).

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ESSENTIAL POINTS

- SGA can be the result of maternal lifestyle and obstetric factors, placenta dysfunction, and fetal genetic factors
- Current genetic strategies will lead to an increase in the numbers of children born SGA with a molecular diagnosis, which may guide GH treatment in the individual patient in terms of response prediction and contraindications
- GH treatment increases adult height by ~1.25 SD and normalizes body composition
- A small birth size increases the risk of later noncommunicable conditions such as neurodevelopmental problems and cardiometabolic diseases, and GH treatment does not pose an additional risk
- After discontinuation of GH treatment, fat percentage increases and lean body mass decreases, for which prolonged surveillance may be indicated, particularly in those at risk for cardiometabolic diseases

This review presents our current understanding of SGA, including its causes and consequences, the mechanisms linking small birth size to future health, and the effects of GH treatment.

Physiology of Intrauterine Growth

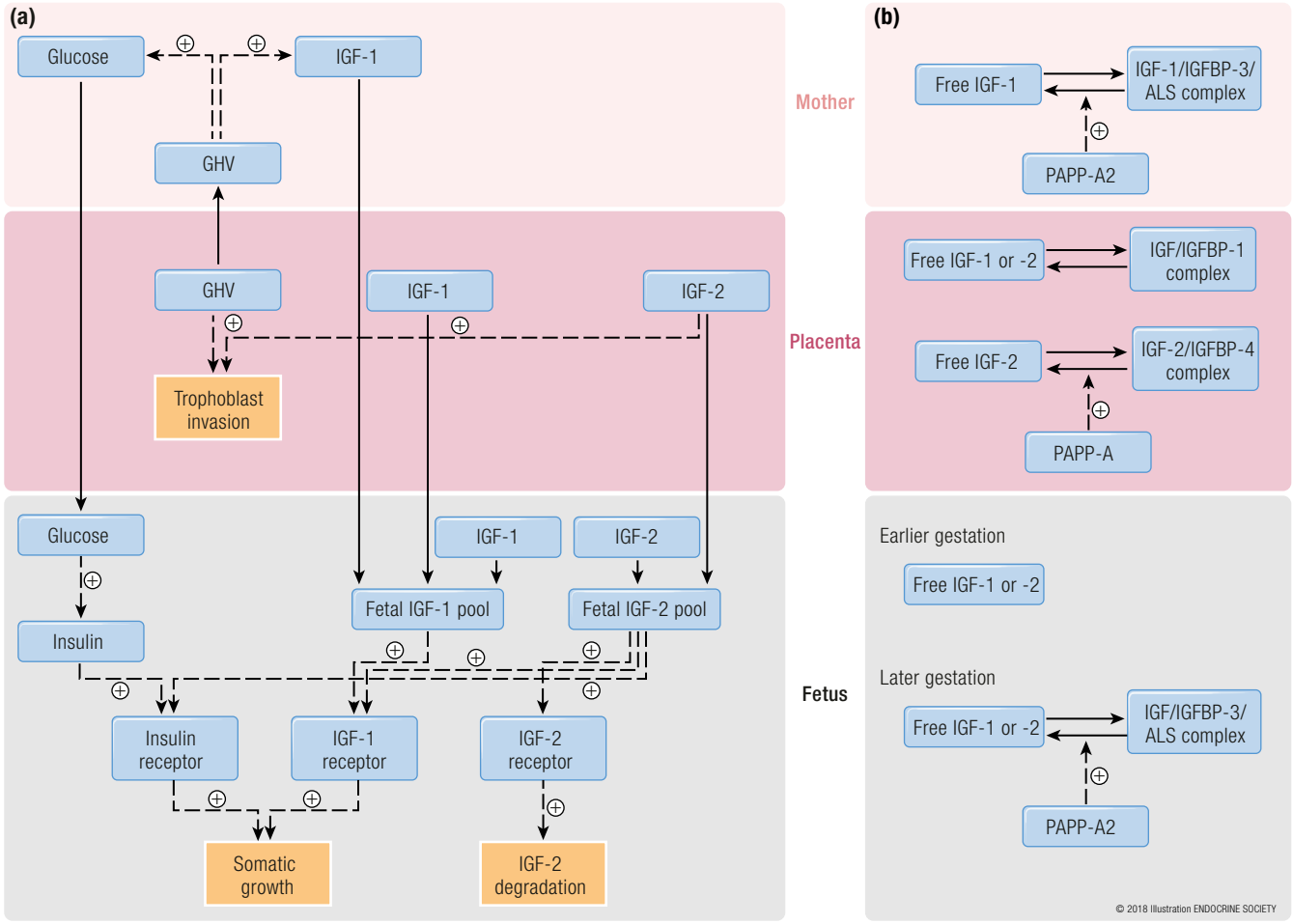
Fetal growth is regulated by a complex interplay of maternal, placental, and fetal factors (Fig. 1) [for graphical representations of postnatal growth regulation, see (17) and (18)]. One of the key regulators of fetal growth is insulin, acting mainly in the third trimester when fetal weight velocity peaks. A striking example of the growth-promoting actions of fetal insulin is the macrosomia commonly observed in infants born to mothers with pre-existent or gestational diabetes. Fetuses of diabetic mothers gain excess weight as a result of insulin hypersecretion in response to sensing of maternal hyperglycemia rather than of increased nutrient transfer across the placenta *per se*. Even in normal pregnancies, the maternal glucose concentration in the third trimester correlated positively with the infant's birth weight (19, 20). Growth-restricted fetuses had lower insulin levels both before and after a glucose load (of 0.75 g/kg of estimated fetal weight) in the umbilical vein, as compared with their non–growth-restricted counterparts (21). The importance of insulin signaling in fetal growth is also illustrated by the severe SGA in Donohue syndrome [Mendelian Inheritance in Man (MIM) 246200], caused by a mutation in the insulin receptor gene (*INSR*).

At midgestation, a GH variant (GHV) secreted by the placenta appears in the maternal circulation. GHV, encoded by *GH2* on chromosome 17q23.3, is expressed in the syncytiotrophoblast and the extravillous cytotrophoblast layers of the placenta (22). Although GHV levels were found to increase in the maternal circulation up to term, pituitary-derived GH progressively fell to undetectable levels (23). GHV may promote fetal growth by increasing the availability of maternal IGF-1 (24, 25), and by stimulating trophoblast invasion (26), in addition to stimulation of gluconeogenesis, lipolysis, and anabolism in maternal tissues. The expression of GHV in placentas from pregnancies complicated by IUGR was decreased, along with decreases in the expression of IGF-1 and IGF binding protein (IGFBP)-1 (27).

In the mouse there is overwhelming evidence demonstrating that IGF-1 and IGF-2, as well as their binding proteins and receptors, are key regulators of fetal growth (28). Also in humans these proteins are ubiquitously expressed starting from early embryonic development. The main site of fetal IGF production is the liver. IGFs circulate as a ternary complex with IGFBP-3 or IGFBP-5 and an acid-labile subunit (ALS). IGFBPs and ALS protect IGFs against early elimination from the circulation (29). Before the third trimester neither ternary complex formation (between IGF-1, IGFBP-3, and ALS) nor ALS is detectable in the fetal circulation (30). IGF-1 and IGF-2 are also expressed by the placenta, with a higher abundance of IGF-2 mRNA than IGF-1 mRNA at all gestational ages (31). In addition to directly impacting fetal growth, IGF-2 is probably involved in processes such as cytotrophoblast proliferation and/or differentiation and trophoblast invasion (31). IGF-2 was found to also interact with IGFBP-1 synthesized by the maternal decidual cells, thereby influencing the bioavailability of both IGFs (31, 32). CpG methylation of the P2 promoter of the IGF1 gene appears to contribute to the interindividual variation of fetal growth by regulating *IGF1* expression in fetal tissues (33).

The gene encoding IGF-2 (*IGF2*) located on chromosome 11p15 is an imprinted gene, expressed only from the paternal allele, whereas the adjacent H19 gene is only expressed from the maternally inherited chromosome. *H19* encodes a long noncoding RNA and contains a differentially methylated region that is also an imprinting control region (ICR). Methylation of the ICR, as is the case on the paternal chromosome, prevents *H19* gene expression, which allows gene enhancers becoming available to act upstream on the *IGF2* promoter, leading to *IGF2* expression. The ICR on the maternal chromosome is unmethylated, resulting in *H19* expression and inhibition of *IGF2* expression.

Figure 1. Regulation of fetal growth. (a) GHV expressed from the syncytiotrophoblast stimulates trophoblast invasion. It is also released into the maternal circulation. By stimulation of lipolysis and gluconeogenesis, GHV increases the maternal glucose level, which passes through the placenta. Fetal insulin secretion increases in response to sensing of maternal glucose. GHV also stimulates the synthesis of maternal IGF-1, which is able to cross the placental barrier. The placenta produces both IGF-1 and IGF-2, which are secreted in the fetal circulation. IGF-1 binds primarily to the IGF1R. The growth-promoting actions of IGF-2 are mediated through interactions with IGF-1 and insulin receptors. IGF-2 binding to the IGF2R targets IGF-2 for degradation. IGF-2 can also promote fetal growth indirectly by stimulating trophoblast invasion. (b) Maternal IGF-1 circulates as a ternary complex with IGFBP-3 and ALS, preventing IGF-1 from early elimination from the circulation. PAPP-A2 releases IGF-1 from the ternary complex. The placenta harbors multiple IGFBPs, influencing the bioavailability of IGFs in the fetus. IGFBP-1 binds to both IGFs, whereas IGFBP-4 binds solely to IGF-2. PAPP-A mediates the release of IGF-2 from IGFBP-4. During early embryonic development, the fetus harbors no ternary complexes, in contrast to later in gestation. [© 2018 Illustration ENDOCRINE SOCIETY].



Whereas IGF-1 binds primarily to the IGF-1 receptor (IGF1R), the growth-promoting actions of IGF-2 are mediated through interactions with IGF-1 and insulin receptors. IGF-2 has a higher affinity for the IGF1R than for the insulin receptor. IGF-2 binding to the IGF2R targets IGF-2 for degradation. IGF-2 has an essential role in the proper timing of chondrocyte maturation and perichondrial cell differentiation, as well as in the regulation of glucose metabolism in chondrocytes (34).

IGFBP-4 and its protease [pregnancy-associated plasma protein-A (PAPP-A)] are expressed in extravillous trophoblast and decidual cells (31, 35). IGFBP-4 has a high affinity for IGF-2 and, therefore, IGFBP-4 proteolysis (by PAPP-A) is required for the delivery of IGF-2 to the fetus (36, 37). PAPP-A2 is a metalloproteinase that plays a role in the proteolytic cleavage of IGFBP-3 and IGFBP-5, resulting in increased IGF-1 bioavailability (38). Homozygous *PAPPA2* mutations cause prenatal and postnatal growth failure (39).

The regulation of the maternal hypothalamic–pituitary–adrenal axis changes dramatically during pregnancy mainly due to the third trimester increase in placental CRH. Placental CRH stimulates the release of ACTH from the pituitary, and this, in turn, stimulates the adrenal cortex to produce cortisol. In contrast to the inhibitory effect of glucocorticoids on the secretion of CRH by the hypothalamus, glucocorticoids stimulated the expression of the CRH gene

in cultures of human placenta (40). Owing to this physiological feed-forward response, maternal cortisol increases steeply in the last part of gestation (41). The placental barrier enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2, by catalyzing the conversion of cortisol to inert cortisone, acts as a gatekeeper that protects the fetus against exposure to excess maternal cortisol. The expression of 11β-HSD type 2 was decreased in the placentas of pregnancies complicated by IUGR or preeclampsia (42, 43). This was accompanied by a higher ratio of cortisol to cortisone in cord blood (42).

Intrauterine Growth Charts

Intrauterine growth charts can be based on (population-based or customized) neonatal anthropometric or fetal sonographic measurements. More than 50 years ago, Lubchenco *et al.* (44) presented the first neonatal anthropometric chart, based on a population living at an altitude of 1600 m. Subsequent charts were constructed from populations living at an altitude closer to sea level. Neonatal anthropometric charts tend to underestimate the degree of IUGR with increasing immaturity (45).

Some have suggested that intrauterine growth charts need to take into account physiological factors known to affect fetal growth, to allow for a better discrimination between growth-restricted infants and constitutionally small infants. Whereas population-based charts only account for gestational age and sex, customized growth charts additionally account for maternal height and weight, parity, and ethnicity. However, in a Bayesian meta-analysis of data from >1 million mother/infant pairs, both customized and population-based charts were able to predict adverse neonatal outcomes (46). Similar conclusions were drawn by a recent population-based linkage study of nearly 1 million mother/infant pairs, demonstrating that partial customization (for maternal height and parity) did not improve prediction performance (47). There are still insufficient data of good quality to support the routine use of customized growth charts for the postnatal diagnosis and management of SGA infants (48).

Fetal growth charts are based on ultrasound measurements of anthropometric traits, such as crown–heel length, biparietal diameter, abdominal circumference, and femur length during pregnancy. Currently, there is controversy as to whether one global fetal growth curve could be applied to all pregnancies (49–51). The INTERGROWTH-21st study found only small differences (between sexes and populations) in fetal growth rate among 4321 healthy women with uncomplicated pregnancies from middle- and higher-income neighborhoods in eight different countries (49). For simplicity, the data were pooled to produce a universal fetal growth chart. In contrast, a World Health Organization project group found larger differences in estimated fetal weight between populations and sexes, with boys having an estimated fetal weight at birth 3.5% to 4.5% higher than that of girls (50). Worldwide, the proportion of SGA births is highest in South Asia (52) and, in European countries, the birth weights of babies of South Asian origin are lower than of those of babies from other ethnic backgrounds (53).

The interpretation of fetal growth is strongly dependent on the accuracy of gestational age determination. The most accurate method for the determination of gestational age is ultrasound assessment obtained in early pregnancy (54), which has therefore become an essential part at the first consultation to an obstetric caregiver, at least in industrialized countries. Failure to adequately determine gestational age could lead to flaws in the interpretation of fetal growth.

Maternal Medical and Social Conditions Associated With SGA

SGA births cluster in families, because the risk of SGA was increased for women who previously gave birth to an SGA infant as well as for men and women who were born SGA themselves (55–58). These observations argue for a role for genetic and/or shared environmental factors in the etiology of SGA. Determinants of fetal growth all relate to conditions or circumstances affecting the delivery of nutrients and oxygen to the maternal–fetal interface, as well as intrauterine space, in addition to fetal genetic factors. Table 1 summarizes the various geographic, environmental, maternal, paternal, placental, and fetal factors that are associated with birth size.

Maternal age, parity, and obstetric history

During the first pregnancy the fetus experiences more resistance to distend the mother's uterus and abdominal wall than in later pregnancies. Consequently, the first-born infant is on average 282 g smaller than subsequent siblings (59). As compared with 18- to 35-year-old women who were parity 1 or 2, nulliparous women <18 years of age had the highest odds of SGA offspring: 1.80 vs 1.51 for nulliparous women aged 18 to 35 years (60). The risk of SGA was also increased with short (<18 months) or long (>60 months) intervals between births, and after previous stillbirth, preterm birth, or SGA birth (61, 62). The greater risk of SGA associated with use of assisted reproductive technologies could not fully be explained by twin pregnancies (63, 64).

Maternal ethnicity, education, and income inequality

Globally, there are only minor differences in birth weight between populations from different ethnic

Table 1. Geographic, Maternal, Paternal, Placental, and Fetal Conditions Associated With Offspring Birth Size

Group	Factor	Direction of Association
Environmental factors	Altitude	−
	Pollution	−
Maternal factors	Birth weight	+
	Parity	+
	Age	+
	Short or long intervals between births	−
	Previous stillbirth, preterm birth, or SGA birth	−
	Assisted reproductive technologies	−
	South Asian ancestry	−
	Socioeconomic status	+
	Maternal education	+
	Income inequality	−
	Smoking	−
	Drugs such as cannabis and cocaine	−
	Alcohol	−
	Height	+
	Weight and BMI prior to pregnancy	+
	Weight loss between pregnancies	−
	Gestational weight gain	+
	Twin pregnancy	−
	Infections and parasite infestations (Table 2)	−
	Anemia	−
	Antiphospholipid syndrome	−
	Carriage of prothrombotic gene variants	−
	Inflammatory bowel disease	−
	Celiac disease	−
	Epilepsy	−
	Depression or intimate partner violence	−
Paternal factors	Being born SGA	−
	Height	+
Placental factors	Preeclampsia	−
	Other placental abnormalities	−
Fetal factors	Multiple genetic syndromes (Tables 4–7)	−/+

backgrounds, with few exceptions. Women of South Asian ancestry, living in their home country or elsewhere, give birth to babies with lower birth weight (52, 53). The ethnic difference in low-birth-weight rate in the United States can probably be attributed to differences in socioeconomic status (65). Lower maternal education was linked to an appreciable risk of preterm and SGA births across 12 European countries. The

excess risk of SGA birth in absolute terms (Slope Index of Inequality) associated with low maternal education was 3.64 for all cohorts combined (66). Higher levels of income inequality were associated with greater numbers of low-birth-weight infants (67).

Maternal lifestyle factors

Maternal smoking has been recognized for more than half a century as one of the largest preventable risk factors for IUGR (68, 69). Exposure to cigarette smoke has been postulated to affect fetal growth by complex interactions with the maternal immune system, hormones, and metabolism (70), possibly via differential methylation of multiple genomic loci (71). Despite a downward trend in the proportion of mothers who smoke during pregnancy, ~10% continue to do so (72, 73).

Fetuses of mothers who smoked during pregnancy exhibited reductions in fetal anthropometric parameters such as head size and femur length after the first trimester (74). Active maternal smoking was associated with a twofold increased risk of low birth weight (75). The risk of poor scholastic achievement among children born SGA to mothers who smoked was 29.4%, which was higher than in any other strata of maternal smoking and fetal growth (76). Passive smoking and smokeless tobacco use were associated with small reductions in birth weight (77–79).

Pregnant women undergoing a smoking cessation intervention were 2.47-fold less likely to smoke at the end of gestation (80). The odds ratio for the effect of smoking cessation interventions on low birth weight was 0.65 (95% CI, 0.42 to 0.88) (80). Apparently, smoking cessation early in pregnancy is more effective than in the third trimester for the prevention of IUGR (74, 81).

Use of cannabis, cocaine, or alcohol during pregnancy also increased the odds of SGA offspring (82–84). These relationships may be either causal or confounded by concurrent smoking or poor maternal health status. Similarly, higher maternal caffeine intake during pregnancy was associated with an increased risk of delivering low-birth-weight infants (85, 86).

Maternal body mass index and gestational weight gain

Maternal underweight [*i.e.*, a body mass index (BMI) <18.5 kg/m^2] prior to pregnancy was associated with a 1.81-fold increased odds of SGA (87). Conversely, maternal overweight and obesity were found to decrease the odds of SGA, most likely due to increased glucose transport across the placenta (87). In a study on weight changes across three consecutive parities in 5079 women (88), the risk of SGA at the second and third pregnancy was increased by ~100% in mothers experiencing significant weight loss (*i.e.*, ~9 kg) between pregnancies, even after correction for the initial BMI.

Gestational weight gain seems to be equally important for the risk of SGA (89). Gestational weight gain below the Institute of Medicine recommendation (of 11.5 to 16 kg for women with a normal prepregnancy BMI) was associated with a 1.53-fold increased risk of SGA (90). Mothers who gained less weight than expected in the second and third trimesters, but not the first trimester, more often gave birth to SGA offspring (91).

The risk of SGA was increased in women with hyperemesis gravidarum, probably through lower gestational weight gain (92). Infants of mothers with anorexia nervosa were on average 190 g lighter at birth (93), and appropriate weight gain could partially compensate for the increased risk caused by a low prepregnancy BMI (93).

Parental height

Maternal and paternal height together accounted for 3% to 12% of the variation in birth weight within each study (94). A systematic review showed that infants born to shorter fathers were on average 125 to 150 g lighter than the offspring of taller fathers (95). Maternal height was found to have a greater impact on birth weight (94), most likely due to the contributions of environmental factors such as intrauterine space and maternal physiology in addition to genetic factors. In a meta-analysis the odds of SGA (defined as a birth weight $<$3rd percentile) was 1.36 for mothers with a height of 150 to 155 cm, increasing to 2.11 for mothers of <145 cm (96). Maternal height showed a weak positive correlation with crown–rump length in the first trimester but stronger positive correlations with most fetal anthropometric parameters in the second and third trimester, in addition to birth size (97).

Twin pregnancies

The intrauterine growth of twins is similar to that of singletons up until the 30th week of gestation, especially in dichorionic twins (98). From 33 weeks of gestation twins exhibited a progressive decline in abdominal circumference, whereas head circumference and femur length remained unaffected, as compared with singletons (99).

Fifteen to 25% of twin pairs have a birth weight discordance of $\geq$20% (100–103). Birth weight discordance was more frequent with assisted reproduction, preterm delivery, premature rupture of membranes, and pregnancy-induced hypertension (100, 102). Among twin pairs discordant for birth weight, IUGR of at least one fetus was more common compared with pairs of similar birth weight (69% vs 20%, respectively) (103).

Maternal diseases and stress

Infections

Several infectious diseases in pregnant women have been associated with delivery of low-birth-weight babies, including viral infections (cytomegaly,

rubella, HIV, Zika virus, influenza A), parasite infestations (toxoplasmosis, malaria), and peridontitis (Table 2) (104–108). HIV or Zika virus infections may disturb fetal growth through placental inflammation (107, 109). The brain damage caused by congenital Zika virus infection may be attributed to placental dysfunction occurring in early gestation, with subsequent elevation of proinflammatory proteins and/or disruption of placental genes associated with microcephaly (110).

Multiple mechanisms have been implicated to play a role in the birth-weight reduction associated with malaria, including maternal anemia and placental inflammation, with subsequent alterations in placental growth and angiogenic factors (111–114). Placental involvement is presumed to play a role only in infections with *Plasmodium falciparum*, which, unlike *Plasmodium vivax*, cytoadheres to the placenta (115). Among pregnant women in sub-Saharan Africa intermittent preventive therapy with three or more doses of sulfadoxine/pyrimethamine was associated with a 56-g higher birth weight than the standard two-dose regimens, probably due to a lower risk of moderate to severe maternal anemia at the end of gestation (113), although these findings may not be applicable to areas with a high degree of drug resistance (116).

Hematological diseases

In low- and middle-income countries, >40% of women experience anemia during pregnancy (117), which is associated with increased risks of low birth weight, preterm birth, perinatal mortality, and neonatal morbidity (117). Moderate to severe maternal anemia—that is, a hemoglobin level <9 g/dL—was associated with a 1.53 increased odds of SGA offspring (118).

Antiphospholipid syndrome is characterized by thrombotic events and/or obstetric morbidities in patients persistently positive for antiphospholipid antibodies. Recurrent pregnancy loss is one of the key obstetric features of antiphospholipid syndrome, in addition to increased risks of complications associated with ischemic placental insufficiency, such as stillbirth, intrauterine death, preeclampsia, preterm birth, and IUGR (119). Carriage of prothrombotic gene variants, such as factor V Leiden and methylenetetrahydrofolate reductase C677T, may also increase the risk of SGA (120, 121).

Other somatic diseases

Maternal inflammatory bowel disease was found to increase the odds of SGA offspring, probably through a combination of placental inflammation and suboptimal nutritional status (122). Maternal celiac disease, both treated and untreated, was associated with increased risks of IUGR (OR 2.48) and SGA (OR 4.52) (123), and this may be particularly evident for undiagnosed celiac disease (124). Maternal epilepsy was also associated with a higher likelihood of SGA (OR 1.28), irrespective of antiepileptic drugs (125).

Psychosocial stress and depression

Infants exposed antenatally to untreated maternal depression, antidepressants, or intimate partner violence were more often born preterm or with low birth weight (126–128). Symptoms of anxiety and/or depression were associated with reduced fetal head

Table 2. Infectious and Parasitic Causes of SGA

Agent	Signs and Symptoms	
	Mother	Infant
Influenza A virus	Fever, upper airway tract infection, headache, muscle pain	Asymptomatic
HIV	• Early stage (within 2-4 wk after HIV infection): flu-like symptoms, lymphadenopathy, mouth ulcers	Asymptomatic, stunting, developmental delay, full-blown AIDS
	• Clinical latency stage: no or mild atypical symptoms	
	• AIDS: progressive weight loss, opportunistic infections, Kaposi sarcoma	
Zika virus	Flu-like symptoms, rash	Microcephaly, subcortical calcifications, chorioretinitis
Plasmodium sp.	High (cyclical) fever, chills, profuse sweating, anemia, headache, nausea, vomiting, (bloody) diarrhea, muscle pain, convulsions	Fever, anemia, jaundice, hepatosplenomegaly, irritability
Cytomegalovirus	Asymptomatic or mononucleosis-like symptoms	Microcephaly, periventricular calcifications, chorioretinitis, hearing loss, petecchiae, hepatosplenomegaly, pneumonitis
Rubella virus	Flu-like symptoms, lymphadenopathy, maculopapular rash	Microcephaly, meningoencephalitis, cataracts, retinopathy, hearing loss, hepatosplenomegaly
Toxoplasma gondii	Asymptomatic, mild mononucleosis-like symptoms, lymphadenopathy	Microcephaly, periventricular calcifications, hydrocephalus, chorioretinitis, hepatosplenomegaly, pneumonitis, myocarditis

growth, but their impact on other fetal growth parameters was less clear (129). Maternal psychosocial stress had negligible effects on fetal growth (130).

Environmental conditions

In several populations associations between altitude and infant birth weight were demonstrated. The reduction in birth weight was estimated at 50 to 150 g for every 1000 m of elevation in altitude (131–133), with considerable variation between populations. Tibetans are more resilient to the effects of high altitude than any other population (134). Adaptive mechanisms that could protect against severe IUGR all relate to the delivery of oxygen to the fetoplacental unit (134).

Pollution is a global problem that has also been associated with adverse birth outcomes, including SGA, along with specific health risks. Among pollutants that have been linked to decreased fetal growth are ambient air pollutants such as sulfur dioxide, fine particulate matter (*i.e.*, a heterogeneous mixture of substances that sometimes includes accumulated heavy metals and toxic organic pollutants such as polycyclic aromatic hydrocarbons), and solid fuels (including biomass and coal) (135–139), and concurrent prenatal exposures are additively associated with lower fetal growth (140). Exposure to environmental noise or electromagnetic fields may also increase the odds of SGA (141, 142).

Abnormalities of the Placenta

Pathogenesis

Placental insufficiency is the failure of the placenta to deliver an adequate supply of nutrients and oxygen to the fetus, resulting in IUGR. Conditions that interfere with placental vascular development, such as preeclampsia, account for most cases of placental insufficiency, although placental abnormalities such as circumvallate placenta and placenta accreta (which occur in ~1% of pregnancies) are also associated with IUGR (143, 144). Preeclampsia affects 3% to 5% of pregnancies (145).

During early pregnancy, the extravillous cytotrophoblast invades the spiral arteries, transforming them into large vessels of low resistance. In preeclampsia only the superficial endometrial parts of the spiral arteries are invaded. Owing to the lack of distal dilation, the villous tree is easily damaged by the higher speed at which the maternal blood enters the intervillous space. Moreover, the spiral arteries retain their capacity to vasoconstrict, leading to ischemia/reperfusion damage. It is of no surprise that these processes could impact fetal growth, either directly, by impeding the delivery of nutrients and oxygen to the fetus, or indirectly, through interactions with local growth factors, hormones, and cytokines (Table 3) (27, 146–184). In the pathophysiology of preeclampsia, hypermethylation of IGF-1 promotor mediated by DNA methyltransferase 1 may also play a role (185), as well as increased IGFBP-1 phosphorylation in decidualized stromal mesenchymal cells (186). Free radicals and inflammatory proteins released by hypoxia and ischemia/reperfusion enter the maternal circulation, eventually leading to life-threatening eclampsia with organ dysfunction, cerebral edema, and seizures. Mothers with preeclampsia may be at risk for cardiovascular diseases and the metabolic syndrome later in life (145).

Table 3. Alterations in the Expression Patterns in Placentas of Pregnancies Complicated by SGA, IUGR, or Preeclampsia

Mechanism	Involved Factors	References
Placental growth and/or angiogenic factors	WNT2, PlGF, VEGF, VEGF receptor 1 (Flt-1), EGF, PDGF, VCAM-1, matrix metalloproteinases, decorin, endoglin, syncytin, angiogenin, glycodelin A, proteins encoded by placental homeobox genes (HLX, ESX1L, DLX3, DLX4, NKX3.1, TGIF-1), PPARs, RXRα	(146–158)
Nutrient transporters	SNAT2, GLUT3, glycolytic enzyme-related genes (lactate dehydrogenase C, dihydrolipoamide S-acetyltransferase, 6 phosphofructo-2-kinase/fructose-2,6-biphosphatase 2, oxoglutarate dehydrogenase, phosphorylase), receptor for advanced glycation end products, glutamate dehydrogenase, lactate transport, lipoprotein lipase, low-density lipoprotein transport, transferrin transport	(159–166)
Hormonal systems	GH-V, IGFs, H19/IGF-2 ICR methylation status, CDKN1C, PLAGL1, leptin, leptin receptor, insulin, insulin receptor, GRB10, 11β-HSD type 2	(27, 148, 167–174)
Cytokines	IL-1α, Il-1β, IL-4, IL-6, IL-8, IL-10, IL-12, TNFα, IFN-γ, TGF-β, galectins (including placental protein 13), macrophage counts	(175–178)
Apoptosis genes	Bcl-2, caspase3	(179, 180)
Senescence	Telomere length, telomerase	(181)
Miscellaneous	Confined placental mozaicism, microRNAs, mitochondrial DNA	(182–184)

Abbreviation: IFN, interferon.

Diagnosis

Preeclampsia is defined as hypertension occurring after 20 weeks of gestation, combined with (1) proteinuria (>300 mg/d), and/or (2) other maternal organ dysfunction, and/or (3) evidence of placental insufficiency (145, 187). Risk factors for preeclampsia include older age, obesity, hypertension, and previous or familial preeclampsia. In women at risk for preeclampsia, early initiation (*i.e.*, <16 weeks of gestation) of acetylsalicylic acid treatment may be beneficial (188, 189).

Preeclampsia may be predicted from first-trimester Doppler ultrasonography (190). Maternal biomarkers such as PAPP-A, placental protein 13, βHCG, placental growth factor, pentraxin, soluble endoglin, inhibin A, and sFlt-1 could aid in the early detection of placental insufficiency, although their predictive accuracy is limited (191–193). Prediction performance might be improved by the use of algorithms that combine maternal biomarker data with findings from Doppler ultrasonography and the background risk (as assessed from data such as maternal ethnicity, BMI, and personal or family history of preeclampsia) (194).

Genetic Disorders of the Fetus

The rapidly expanding use of next-generation sequencing, particularly whole-exome sequencing but also chromosomal microarrays, RNA sequencing, and methylation arrays, has led to the identification of many novel genetic causes of short stature, and birth weight and length can either be low ("SGA") or normal [apparent "idiopathic short stature" (ISS)]. In some syndromes, SGA is present in nearly 100% of cases, whereas in others it is unusual. In this review, we discuss a selection of genetic causes of conditions in which SGA is one of the documented clinical features. After a discussion of imprinting disorders and methylation disturbances (Table 4) (195–205), we follow a diagnostic classification based on the regulation of the epiphyseal growth plate (17, 206-208), with examples of disorders of the GH–IGF axis (Table 5) (39, 209–231), paracrine factors, cartilage extracellular matrix and intracellular pathways (Table 6) (232–244), and fundamental cellular processes (Table 7) (245–256). Other examples can be found in previous reviews (206–208). We foresee that in the coming decades, the advancement and increasing use of genetic diagnostic techniques will further expand the knowledge about the genetic origin of prenatal and postnatal growth.

Imprinting disorders and methylation disturbances

Imprinting disorders are a group of congenital diseases characterized by overlapping clinical features regarding growth, development and metabolism, and common molecular disturbances affecting genomically imprinted chromosomal regions and genes. The term genomic imprinting describes the expression of specific genes in a parent-of-origin specific manner—that is, they are expressed only from the maternal or from the paternal gene copy but not biparentally (257). Imprinted genes in the placenta have been shown to be important for the control of fetal growth (258). One of the best-known and most well-studied examples is Silver–Russell syndrome (SRS), but there are several other disorders associated with SGA (Table 4). Additionally, methylation disturbances can occur in nonimprinted genes (259).

SRS

Children with SRS (MIM 180860) are almost universally (>90%) born SGA, remain short, and show various dysmorphic features, such as relative macrocephaly, a triangular-shaped head with frontal bossing, clinodactyly, and asymmetry of face and/or body (195). Severe feeding difficulties can be present, especially during infancy and early childhood, as well as other gastrointestinal manifestations (196). Untreated, the mean adult height is around −4 SDS (195, 260). SRS is primarily a clinical diagnosis, which can be established by using the Netchine–Harbison clinical scoring system (204).

In ~60% of patients clinically diagnosed with SRS, an underlying molecular cause can be identified (195). Approximately 50% of cases are caused by a loss of methylation (LOM) of the telomeric domain in the 11p15.5 region (261–263), resulting in downregulation of paternal *IGF2* expression, in line with studies on the role of IGF2 in fetal humans and mice (263, 264). The 11p15.5 region contains two ICRs, both of which control imprinted genes that are important for the regulation of prenatal and postnatal growth. Besides the relatively frequent epigenetic causes, two rare genetic causes have been discovered in the same 11p15 region. First, increased expression of *CDKN1C* (by a gain-of-function mutation or maternal duplication) can cause SRS (224, 265), but this is also associated with the Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital anomalies (IMAGe) syndrome (MIM 614732), characterized by IUGR, metaphyseal dysplasia, congenital adrenal hypoplasia, and genital anomalies (198), as well as a syndrome of prenatal and postnatal growth failure with early-onset DM (266, 267). Second, a paternally transmitted SRS can be due to an *IGF2* loss-of-function mutation (MIM 616489) (224, 225) (Table 5). Also, disruptions in the HMGA2–PLAG1–IGF2 pathway can cause an SRS phenotype (268), as well as copy number variants (CNVs) involving the 11p15.5 region, with the specific SRS phenotype depending on CNV size, location, and parental origin (195, 224, 269, 270).

An additional 5% to 10% of SRS cases are caused by a maternal uniparental disomy (UPD) of chromosome 7

Table 4. Examples of Imprinting Disorders and Methylation Disturbances Associated With SGA

Syndrome (MIM)	Genetic or Epigenetic Defect	Incidence	Mean BW SDS	Mean BL SDS	Clinical Features Besides SGA	Treatment	Reference
SRS (180860)	11p15 LOM (30%–60%), upd(7)mat (5%–10%), *CDKN1C* (act), *IGF2* (pat), *HMAG2*, *PLAG1*, CNVs, 14q32 abnormalities, upd (20)mat, upd(16)mat	1/30,000–100,000	−3.2[a] −2.3[a] −2.7[a]	−4.5[a] −2.5[a] −1.8[a]	Postnatal growth failure, relative macrocephaly at birth (difference with length SDS of 3.9, 2.1, and 1.7 SDS, respectively[a]), protruding forehead, body asymmetry, feeding problems, and/or low BMI	GH effective	(195, 196)
Temple syndrome (616222)	14q32 abnormalities: upd(14)mat, paternal microdeletions, hypomethylation of DLK1/GTL2 intergenic differentially methylated region (IG-DMR)	>50 cases	−1.9	−1.6	Postnatal growth failure, hypotonia, delayed development of motor skills, feeding problems in infancy, early puberty, broad forehead, short nose with wide nasal tip, small hands and feet	Insufficient data	(197)
IMAGe syndrome (614732)	Maternally inherited activating mutations in *CDKN1C*	>15 cases	−2.0 to −4.0	—	Relative macrocephaly at birth, normal or mild intellectual disability, frontal bossing, low-set ears, flat nasal bridge, short nose, congenital adrenal hypoplasia, metaphyseal and/or epiphyseal dysplasia, male genital anomalies, early-onset type 1 DM	Insufficient data	(198, 199)
PWS (176270)	Paternal 15q11.2q13 deletion (65%–75%), upd(15)mat (20%–30%), or imprinting center mutation (1%–3%). Loss of *SNRPN* and *NDN* expression	1/16,000–27,000	−1.2	−1.1	Diminished fetal activity, obesity, muscular hypotonia, intellectual disability, short stature, hypogonadotropic hypogonadism, small hands and feet	GH effective	(200, 201)
Pseudohypoparathyroidism type 1a/c (103580)[b]	Heterozygous *GNAS1* mutation inherited from the mother	1/150,000 for all types together	−0.6	−1.1	Resistance to PTH and other hormones (TSH, LH, FSH, and GHRH), Albright hereditary osteodystrophy (short stature, obesity, round face, subcutaneous ossifications, brachydactyly, intellectual disability). 37% SGA	Insufficient data	(202)
Pseudopseudohypoparathyroidism (612463)[b]	Heterozygous *GNAS1* mutation inherited from the father	See above	−2.7	−3.0	Albright hereditary osteodystrophy without multiple hormone resistance. 95% SGA	Insufficient data	(202)

(*Continued*)

Table 4. *Continued*

Syndrome (MIM)	Genetic or Epigenetic Defect	Incidence	Mean BW SDS	Mean BL SDS	Clinical Features Besides SGA	Treatment	Reference
Maternal UPD of chromosome 20	Upd(20)mat	12 cases	−2.4[c]	−1.6[c]	Short stature, prominent feeding difficulties, failure to thrive, fifth finger clinodactyly	GH effective in 4 cases	(203)

Abbreviations: act, activating; BL, birth length; BW, birth weight.
[a]Data are presented for three subgroups: (1) 11p15 ICR1 hypomethylation; (2) mUPD(7)mat; and (3) clinical SRS (204).
[b]The third type of pseudohypoparathyroidism (type 1b, 603233) is associated with normal or increased BW and overgrowth in childhood (205). Genetic causes include paternal-specific imprinting pattern on both alleles, a maternally derived 3-kb microdeletion involving *STX16* or upd(20)pat. Characteristics are resistance to PTH without signs of Albright hereditary osteodystrophy.
[c]Calculated from eight patients with isolated upd(20)mat.

[upd(7)mat]. The primary candidate genes associated with SRS are *GRB10* (7p12.1) and *MEST* (7q32) (195). In ~40%, the genetic cause remains unknown, which is referred to as *clinical* SRS. Patients with 11p15 LOM have a more classic SRS phenotype than do those with upd(7)mat, but patients with upd(7)mat carry a higher risk of behavioral problems (271). More widespread use of methylation studies will probably uncover many more epigenetic disorders associated with short stature, as illustrated by a study in patients with suspected SRS or unexplained short stature/IUGR, in whom 37% showed a methylation abnormality in 11 imprinted loci (272).

There is little information regarding the natural history of SRS (195). In a study of 29 young adults with SRS, including 14 patients with 11p15 LOM and nine patients with no identified molecular anomaly, the metabolic health profile was similar to that of non-SRS subjects born SGA (273). In contrast, three reports suggest that patients may be at risk for later metabolic disorders. Patients with an 11p15 anomaly (two having received GH treatment for several years during childhood) developed obesity, hypertension, and type 2 DM in their early 20s (274), a young adult with 11p15 LOM suffered from severe obesity, type 2 DM, and microalbuminuria, leading to the indication of bariatric surgery (275), and the oldest patient with SRS known so far had type 2 DM, osteopenia, and hypercholesterolemia at the age of 69 years (276). Long-term follow-up studies on large cohorts of molecularly confirmed adult patients will be necessary to chart the long-term natural history of SRS and identify an adequate adult follow-up.

According to limited published information, early bone-age delay is followed by rapid advancement, typically at ~8 to 9 years of age, whereas the onset of puberty is usually at the younger end of the normal spectrum. Adrenarche can be early and aggressive (195). Males with SRS have an increased risk of genital abnormalities such as cryptorchidism and hypospadias (271, 277, 278), which could be associated with reproductive problems later in life. In females, Mayer–Rokitansky–Küster–Hauser syndrome, characterized by hypoplasia or aplasia of the uterus and upper part of the vagina, has been reported (279, 280).

Long-term GH treatment has proven to be safe and effective in improving adult height in SRS (281–283), to a similar degree as nonsyndromic children born SGA (282). However, the rapid bone maturation observed during adrenarche and/or puberty can compromise the long-term efficacy of GH treatment. A 2-year course of GnRH agonist (GnRHa) treatment is recommended for patients with SRS with a poor adult height prognosis at the onset of puberty (195, 282).

Other imprinting disorders

Besides upd(7)mat (associated with SRS), there are several other UPD syndromes associated with short stature and various additional clinical features. Maternal upd(14)mat, as well as paternal deletions, distal 14q duplications, and LOM at the intergenic differentially methylated region cause the Temple syndrome (MIM 616222) (197, 284, 285), characterized by SGA, hypotonia, early puberty, and markedly short adult stature. There is clinical overlap with Prader–Willi syndrome (PWS) and SRS (195, 197, 286, 287). Also, upd(16)mat has been associated with SGA (195).

Most children with PWS (MIM 176270) carry a paternal chromosome 15q11q13 deletion or a maternal UPD of chromosome 15 (20% to 30% of cases), but in 1% to 3% there is an imprinting center mutation. The lack of expression of the paternal copies of the imprinted genes *SNRPN*, *NDN*, and possibly others may be responsible for the phenotype (200). Approximately 50% of children with PWS have a birth weight below the 10th percentile (288).

Loss-of-function mutations of *GNAS*, encoding the α-subunit of the Gs protein, are associated with a spectrum of growth disorders dependent of the parental origin of the mutation (202, 289). Genetic and epigenetic defects at the *GNAS* locus on chromosome 20q.13.3 lead to distinct patterns of skeletal growth but similar early-onset obesity. Whereas heterozygous *GNAS* mutations on either parental allele are associated with IUGR, IUGR is considerably more pronounced when these mutations are located on the paternal *GNAS* allele (pseudopseudohypoparathyroidism) than with mutations on the maternal allele

Table 5. Disorders of the GH–IGF Axis Associated With SGA

Syndrome (MIM)	Genetic Defect (Inheritance)	Incidence	Mean BW SDS	Mean BL SDS	Clinical Features	Biochemical Profile	Treatment	References
GH deficiency	Multiple genes	1/5000	−0.9	−0.6	Variable height deficit	↓GH peak during GH stimulation test, ↓IGF-1, ↓IGFBP-3, ↓ALS	GH effective	(209)
Laron syndrome (262500)	*GHR* (AR, rarely AD)	>300 cases	−0.6	−1.6	Variable height deficit, midfacial hypoplasia	↑GH, ↓IGF-1, ↓IGFBP-3, ↓ALS, variable GHBP	rhIGF-I treatment moderately effective	(210)
GH insensitivity with immunodeficiency (245590)	*STAT5B* (AR, AD)	10 cases	−0.4	+0.5	Midfacial hypoplasia, immunodeficiency	↑GH, ↑prolactin, ↓IGF-1, ↓IGFBP-3, ↓ALS	Insufficient data	(211)
Multisystem infantile-onset autoimmune disease (615952)	*STAT3* (act) (AD)	19 cases	−1.7	−1.8	Early-onset multiorgan autoimmune disease	↓IGF-1, ↑TSH, abnormal immunoglobulins	Insufficient data	(212–214)
Immunodeficiency 15 (615592)	*IKBKB* (AD)	2 cases	−0.7	−0.7	Ectodermal dysplasia, immunodeficiency, growth retardation	↑GH, ↓IGF-1, ↓IGFBP-3	Insufficient data	(215)
X-linked severe combined immunodeficiency (300400)	*IL2RG* (XLR)	1 case	−1.7	−1.5	Immunodeficiency	Normal GH, ↓IGF-1 nonresponding to GH injections	Insufficient data	(216)
SHORT syndrome (269880)	*PIK3R1* (AD)	32 cases	−3.3 (22/26 SGA)	—	Short stature, hyperextensibility of joints, inguinal hernia, ocular depression, Rieger abnormality, teething delay, lipoatrophy, insulin resistance	↓IGF-1 nonresponding to GH injections	Insufficient data	(217, 218)
IGF-1 deficiency (608747)	*IGF1* (AR, AD)	4 homozygotes and 7 heterozygotes	Hom −3.7; het −1.9	Hom −4.5; het −1.8	Microcephaly, deafness	↑GH, variable IGF-1, ↑IGFBP-3,	Insufficient data	(219–223)
Severe growth restriction with distinctive facies (616489)	*IGF2* (AD, paternal)	8 cases	−3.9	−4.6	Variant of SRS	↓/↑/normal GH, normal IGF-1, ↓/↑/normal IGFBP-3	GH treatment probably as effective as in other genetic variants of SRS	(224, 225)
ALS deficiency (615961)	*IGFALS* (AR)	>65 cases	−2.2 (1.1)		Mild height deficit	Unknown GH, ↓IGF-I, ↓IGFBP-3, ↓ALS	Probably no benefit of GH or rhIGF-1 treatment	(226–229)
PAPP-A2 deficiency	*PAPPA2* (AR)	5 cases	−1.6	−1.3	Microcephaly, skeletal abnormalities	↑GH, ↑IGF-I,1, ↑IGFBP-3, ↑IGFBP-5, ↑ALS	rhIGF-1 possibly effective	(39)
Resistance to IGF-1 (1270450)	*IGF1R* (AD)	1%–2% of SGA	−2.5	−2.4	Microcephaly	↑/normal GH, ↑/normal IGF-1, ↑/normal IGFBP-3	GH treatment moderately effective	(230, 231)

Abbreviations: act, activating; AD, autosomal dominant; AR, autosomal recessive; BL, birth length; BW, birth weight; het, heterozygous; hom, homozygous; rh, recombinant human; XLR, X-linked recessive.

(pseudohypoparathyroidism type 1A) (202). Patients with pseudohypoparathyroidism type 1A with mutations involving exon 1 had a slightly lower birth weight than did patients with mutations in exons 2 to 13, in contrast to patients with pseudopseudohypoparathyroidism with mutations in exon 1 who were less severely affected than those with a mutation in exons 2 to 13 (202).

Maternal UPD of chromosome 20, upd(20)mat, causes a syndrome characterized by SGA, short stature, and prominent feeding difficulties with failure to thrive. These patients differ from SRS because there is no asymmetry, prominence of the forehead, and relative macrocephaly (203). With the expanding use of single nucleotide polymorphism (SNP) array technology, it is likely that the phenotypic and epigenetic definitions of imprinting disorders will further broaden in the coming years (286).

Genes reported to be aberrantly methylated in SGA or known to be involved in the regulation of DNA methylation

Aberrant methylation associated with SGA and SRS has been reported for a large number of genes, and, in turn, DNA methylation is regulated by many genes (259, 290). One could therefore hypothesize that a targeted search for aberrant methylation would be a rational diagnostic approach in short children born SGA. In fact, quantitative DNA methylation analysis at differentially methylated regions of 10 imprinted loci uncovered several DNA methylation changes at single loci (291) and even more in a recent study (259).

Table 6. Examples of Disorders Affecting Paracrine Factors, Cartilage Extracellular Matrix, or Intracellular Pathways Associated With SGA

Syndrome (MIM)	Genetic Defect (Inheritance)	Incidence	Mean BW SDS	Mean BL SDS	Clinical Features	Treatment	References
Achondroplasia (100800)	*FGFR3* (act) (AD)	1/15,000-40,000	−0.7	−1.0	Rhizomelic limb shortening, frontal bossing, midface hypoplasia, exaggerated lumbar lordosis, limitation of elbow extension, genu varum, trident hand	Effect of GH treatment generally considered insufficient	(232)
Hypochondroplasia (146000)	*FGFR3* (act) (AD)	1/15,000-40,000	—	—	Rhizomelic limb shortening, limitation of elbow extension, brachydactyly, relative macrocephaly, generalized laxity, specific radiologic features	Effect of GH treatment generally considered insufficient	(233)
Short stature with nonspecific skeletal abnormalities (616255)	*NPR2* (AD)	1%–2% of short stature	−0.8	−2.3	Disproportionate short stature, phenotypic or radiographic indicators of *SHOX* haploinsufficiency (except for Madelung deformity)	Insufficient data	(234–236)
Brachydactyly type A (1112500)	*IHH* (AD)	17 cases (1.6% of short stature)	—	−1.4	Increased sitting height/height ratio (+2.4 SDS), shortening of the middle phalanx of the second and fifth fingers with cone-shaped epiphyses	Positive preliminary data on GH treatment	(237)
Short stature with or without advanced bone age, early-onset osteoarthritis, or osteochondritis dissecans (165800)	*ACAN* (AD)	1%–2% of short stature	−0.7	−1.5	Proportionate or disproportionate short stature, brachydactyly, early-onset osteoarthritis, and degenerative disc disease	Insufficient data	(238, 239)
SHOX-associated short stature (300582)	*SHOX* (AD)	2%–17% of short stature	−0.4	−1.1	Short forearm and lower leg, bowing of forearm and tibia, dislocation of ulna at elbow, Madelung deformity, muscular hypertrophy, radiologic signs at wrist and forearm	Registered for GH treatment	(240–242)
Noonan syndrome (163950)	*PTPN11* (AD)	1/1000–2500	—	−1.0	Short stature, facial dysmorphism, wide spectrum of congenital heart defects, coagulation defect	Only registered for GH in United States, uncertain effect on adult height	(243)
Neurofibromatosis type I (162200)	*NF1* (AD)	1/3000	−1.1	−0.8	≥2 out of the following: (1) ≥6 café au lait spots (>0.5 cm before puberty, >1.5 cm after puberty); (2) ≥2 (sub)cutaneous neurofibromas or ≥1 plexiform neurofibromas; (3) melanotic freckling in axillae or groins; (4) optic pathway glioma; (5) ≥2 Lisch nodules (iris hamartomas); (6) specific bone lesions; (7) first-degree relative with NF1 Precocious puberty, GH deficiency, osteoporosis	No consensus on treatment	(244)

Abbreviations: act, activating; AD, autosomal dominant.

Table 7. Examples of Genetic Defects in Fundamental Cellular Processes Associated With SGA

Syndrome (MIM)	Genetic Defect (Inheritance)	Incidence	Mean BW SDS	Mean BL SDS	Clinical Features[a]	References
Associated with relative normocephaly or macrocephaly						
Floating-Harbor syndrome (136140)	*SCRAP* (AD)	>52 cases	−2.5	—	Proportionate short stature, delayed bone age and speech, triangular face, deep-set eyes, long eyelashes, bulbous nose, wide columella, short philtrum, thin lips	(245)
Mulibrey nanism (253250)	*TRIM37* (AR)	>110 cases	−2.8	—	Progressive cardiomyopathy, characteristic facial features, hypogonadotropic or hypergonadotropic hypogonadism, type 2 DM, predisposition to Wilms tumor	(246)
3-M syndrome (273750, 612921, 614205)	*CUL7*, *OBSL1*, *CCDC8* (AR)	≈200 cases	−3.1	—	Facial features, normal mental development, long, slender tubular bones, reduced anteroposterior diameter of vertebral bodies, delayed bone age	(247)
Microcephalic primordial dwarfism						
Cornelia de Lange syndrome 1–5	*NIPBL*, *SMC1A*, *SMC3*, *RAD21*, *HDAC8* (AD)	1/40,000	−3.4	—	Low anterior hairline, arched eyebrows, synophrys, anteverted nares, maxillary prognathism, long philtrum, thin lips, "carp" mouth, upper limb anomalies	(248)
Meier-Gorlin syndrome 1–5	*ORC1*, *ORC4*, *ORC6*, *CDT1*, *CDC6* (AR)	>67 cases	−3.8	—	Bilateral microtia, aplasia or hypoplasia of the patellae, normal intelligence	(249)
MOPD I (210710)	*RNU4ATAC* (AR)	<1/1,000,000	Extremely low	—	Neurologic abnormalities, including intellectual disability, brain malformations, ocular or auditory sensory deficits	(250)
MOPD II (210720)	*PCNT* (AR)	?	−3.9	—	Radiologic abnormalities, absent or mild mental impairment in comparison with Seckel syndrome, truncal obesity, DM, moyamoya disease, small loose teeth	(251)
Seckel syndrome 1–8	*ATR*, *RBBP8*, *CENPJ*, *CEP152*, *CEP63*, *NIN*, *DNA2*, *ATRIP* (AR)	<1/1,000,000	−6	—	Intellectual disability, characteristic "bird-headed" facial appearance	(251)
DNA repair defects						
Bloom syndrome (210900)	*RECQL3* (AR)	1/48,000 (Ashkenazi Jews)	−4.7	—	Sun-sensitive, telangiectatic, hypopigmented and hyperpigmented skin lesions, predisposition to cancer, maturity-onset DM	(252)
Fanconi anemia (multiple types)	*FANCA* and multiple genes	1/160,000	−1.8	—	Heterogeneous disorder causing genomic instability, abnormalities in major organ systems, bone marrow failure, predisposition to cancer	(253)
Nijmegen breakage syndrome (251260)	*NBN* (AR)	1/100,000	−1.8	—	Microcephaly, immunodeficiency, predisposition to cancer	(254)
LIG 4 syndrome[b]	*LIG4* (AR)	Rare	−3.0	−3.8	Radiosensitive, severe combined immunodeficiency, microcephaly	(255)
XRCC4 syndrome[b]	*XRCC4* (AR)	Rare	−1.6	−2.5	Microcephaly, progressive postnatal growth failure, hypergonadotropic hypogonadism, multinodular goiter, DM	(256)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; LIG, ligase; MOPD, microcephalic osteodysplastic primordial dwarfism.
[a]Scarce information on treatment. GH and recombinant human IGF-I treatment are strictly contraindicated in DNA repair defects.
[b]Other genes involved in nonhomologous end-joining (NHEJ) DNA damage repair include *NHEJ1*, *ARTEMIS*, *DNA-PKCs*, and *PRKDC*.

Disorders associated with decreased signaling of IGFs

GH signaling

In humans, the role of GH in prenatal growth is considerably less than that of IGF-1 but is not negligible (Table 5). In individuals with GH deficiency, mean birth weight and length are decreased (209) and the same applies to various forms of GH insensitivity, caused by inactivating defects of *GHR*, *STAT5B*, *IKBKB*, *IL2RG*, and *PIK3R1* as well as activating *STAT3* mutations.

IGFs

The important role of IGF-1 for human intrauterine growth and development has been shown by four individuals (in three unrelated families) carrying pathogenic *IGF1* mutations (MIM 608747) (219, 220, 223). All patients had an extremely low birth weight, length, and head circumference, and carriers of complete loss-of-function mutations also had sensorineural deafness. Two families with heterozygous *IGF1* defects presented a milder phenotype (221, 222). For a description of the characteristics of *IGF2* mutations (causing SRS), see the "SRS" section above.

IGF1R

The IGF1R has a similar structure as the insulin receptor (292). Clinical characteristics of terminal 15q deletions (resulting in allelic loss of *IGF1R*) include prenatal and postnatal growth retardation (293) and various other clinical manifestations, for example, cardiac symptoms (294), intellectual disability (230), diaphragmatic hernia (295), hearing problems (230), aortic root dilatation, neonatal lymphedema, and aplasia cutis (296).

Since the initial report on two patients (one heterozygous and another compound heterozygous for *IGF1R* mutations) (MIM 270450) (297), >25 pathogenic mutations have been reported. Birth weights vary from −3.5 to −1.5 SDS, birth lengths from −5.0 to 0.3 SDS, and height at presentation from −5.0 SDS to −2.1 (231, 298), and two patients with homozygous mutations had an even more severe phenotype (299, 300). In 18 additional patients carrying pathogenic mutations and seven patients with deletions detected in our laboratory, birth weight ranged from −3.7 to −0.4 SDS and birth length from −5.0 to −1.0 SDS, and 65% complied with the definition of SGA. Mean head circumference at birth was −1.6 (range, −3.0 to 0) SDS. Other phenotypic features described in these patients include feeding problems (301), delay in motor and mental development (297), impaired glucose tolerance (302), and mild dysmorphic features, such as clinodactyly, pectus excavatum, triangular face, brachycephaly, mild hypotelorism, and prominent ears. GH treatment leads to a moderate growth response but less pronounced compared with short children born SGA without *IGF1R* defects (231). The prevalence of *IGF1R* mutations or deletions was estimated at 1% to 2% of short children born SGA (230, 303).

ALS

In the absence of ALS due to homozygous *IGFALS* mutations (MIM 615961), serum IGF-1 SDS is low and IGFBP-3 SDS is even lower (226). In three reports on a total of 12 patients, birth weight ranged from −3.0 to −0.1 SDS (226–228) and, in 24 subjects from five families, birth weight varied from −3.7 to −2.0 SDS (229). GH treatment is thought to be ineffective (226). Heterozygosity for an *IGFALS* defect leads to a height SDS decrease of ~1.5 SD compared with noncarriers, and preliminary data suggest that GH treatment may increase growth (304).

PAPP-A2

Recently, homozygous *PAPPA2* mutations were described in a total of five children in two families. They presented with progressive growth failure, moderate microcephaly, thin long bones, mildly decreased bone density, and elevated levels of serum IGF-1, IGFBP-3, IGFBP-5, ALS, and IGF-2 (39). The authors hypothesized that, due to the absence of a normal PAPP-A2 protein, IGF-1 and IGF-2 cannot be liberated from the ternary complex, resulting in decreased IGF bioavailability. Birth weight varied from −2.2 to −1.3 and birth length from −2.8 to −0.1. Two out of five affected children were born SGA (39). Two years of treatment with biosynthetic IGF-1 led to a 0.4 to 1.0 SDS gain in height and tended to improve bone mass and microstructure (305).

Disorders affecting paracrine factors or cartilage extracellular matrix in the growth plate

Most of the genetic defects of paracrine pathways and matrix formation result in some form of skeletal dysplasia (206, 306). Because most genes associated with short stature in childhood are already expressed *in utero*, birth length SDS can be low, usually lower than birth-weight SDS. Many skeletal dysplasias can be diagnosed soon after birth by an experienced pediatrician or clinical geneticist based on the clinical presentation and specific anthropometric measurements, but clinical features can be so mild in infancy that many of these babies are initially just labeled SGA or ISS. In each SGA newborn with a low birth length, the clinician should carefully assess body proportions (most forms of skeletal dysplasia show short-limb dwarfism) (Table 6). If in doubt, a series of skeletal radiographs can be made (307), although in many skeletal dysplasias body disproportion and skeletal abnormalities develop with time. A customized gene panel now appears the most efficient diagnostic approach.

A description of the very large number of skeletal dysplasias is far beyond the scope of this review, and

the interested reader is referred to the recent nosology (306). For illustrative purposes, we summarize the clinical features of genetic defects in three of the various paracrine pathways in the growth plate and one example of a disorder of matrix formation. More examples (*e.g.*, BMPs, WNT, and PTHrP/IHH) were recently reviewed (206–208).

Several fibroblast growth factors (FGFs) and their receptors play an important role in growth plate regulation. Heterozygous activating mutations in *FGFR3* impair bone elongation and lead to a spectrum of disorders, ranging from the nonviable thanatophoric dysplasia (MIM 187600, 187601) to achondroplasia (MIM 100800), hypochondroplasia (MIM 146000) and even proportionate short stature (308). Birth length SDS distribution of babies with achondroplasia is shifted to the left by ~1 SD, birth-weight SDS by 0.7 SD (Table 6) (232). Thus, SGA is uncommon in achondroplasia, whereas the clinical picture tends to be quite specific and easily recognizable. The effect of GH treatment (only registered for this indication in Japan) on adult height is 0.5 SDS (~3 cm) (309).

The clinical presentation of hypochondroplasia (MIM 146000) includes rhizomelic limb shortening, limitation of elbow extension, brachydactyly, relative macrocephaly, generalized laxity, and specific radiologic features (233). Mean birth size of children may be decreased, based on the high frequency of dyschondrosteosis and hypochondroplasia in patients with ISS and SGA (310). GH treatment leads to increased height SDS in the first years, but no data are available on its effect on adult height (311).

Another important paracrine factor is CNP (encoded by *NPPC*), which signals predominantly via its receptor encoded by *NPR2*. Homozygous inactivating mutations of *NPR2* cause severe acromesomelic dysplasia, Maroteaux type (MIM 602875) (312). Heterozygous carriers of *NPR2* mutations (MIM 616255) show a similar phenotype as short stature homeobox (*SHOX*) haploinsufficiency (Leri–Weill syndrome, MIM 127300), with short forearms and short lower legs (mesomelia), but without Madelung deformity (234). Heterozygous *NPR2* mutations may explain up to 2% of cases with assumed ISS or SGA (235, 313). No data on GH treatment are available. Recently, two children with heterozygous *NPPC* mutations with short stature and small hands were reported (314).

Heterozygous mutations of *IHH* are known to be associated with brachydactyly type A1 (MIM 1112500) (315), but recently these were also demonstrated in mildly disproportional short children with nonspecific skeletal abnormalities. Most cases were born SGA for length, and 50% of cases presented abnormal hand radiographs, including shortening of the middle phalanx of the second and fifth fingers with cone-shaped epiphyses (Table 6) (237).

An example of a genetic defect leading to an aberration of cartilage matrix formation is a syndrome caused by a heterozygous mutation of *ACAN* (encoding aggrecan). Cases present with a mild skeletal dysplasia, spondyloepiphyseal dysplasia type Kimberley (MIM 608361), or as short stature without evident radiographic skeletal dysplasia (MIM 165800) (238). It was originally thought that heterozygous *ACAN* mutations would invariably lead to advanced bone age and early cessation of growth. In fact, Sanger sequencing for *ACAN* in short children born SGA with documented bone age advancement (>0.5 years) (n = 29 out of a total cohort of 290) led to the detection of four cases with pathogenic *ACAN* mutations. In all these cases birth length SDS was lower than birth-weight SDS (316). However, bone age can also be normal or slightly delayed (239, 317). A prevalence of 1.4% was found in children referred for short stature (239). Mean birth weight and length is in the lower half of the normal range (238), and ~30% to 40% of cases are SGA at birth. Patients with this condition can suffer from early-onset osteoarthritis and/or osteochondritis dissecans. At present, data are still insufficient to assess the effects of GH treatment, either alone or combined with a GnRHa and/or an aromatase inhibitor (238).

Disorders affecting intracellular pathways

A relatively frequent genetic defect in short children is an aberration of the gene encoding *SHOX*, located at the tip of the X and Y chromosome, and transmitted in a pseudoautosomal fashion (240). SHOX acts as a transcriptional activator and a gene-dose effect is apparent: biallelic inactivating *SHOX* mutations cause the severe Langer mesomelic dysplasia (MIM 249700), whereas heterozygous mutations or deletions of *SHOX* or its enhancers [or even duplications (318)] cause a milder skeletal dysplasia, Leri–Weill dyschondrosteosis (MIM 127300) (with the classic Madelung deformity of the wrist) or present as ISS or SGA with minor or no dysmorphic features or body disproportion (MIM 300582) (Table 6). Body proportions are usually mildly affected (mesomelia), but they may also be normal, particularly in children with *SHOX* enhancer deletions (241). *SHOX* mutations account for 2% to 15% of individuals presenting with ISS (240). GH treatment results in a similar short-term growth response and adult height gain as observed in Turner syndrome (319), and preliminary data suggest that addition of a GnRHa may increase the GH effect (320).

A second intracellular pathway that plays a role in cellular proliferation and differentiation of growth plate chondrocytes is the Ras/MAPK signaling pathway. Activation of this pathway results in a number of overlapping syndromes, called "rasopathies," including Noonan (MIM 163950), LEOPARD (MIM 151100), Costello (MIM 218040), cardiofaciocutaneous (MIM 115150), and neurofibromatosis-Noonan syndromes (MIM 601321), all characterized by postnatal growth failure of varying degree and sometimes without

obvious clinical features (321). Birth length was significantly below the population's mean (−1.0 ± 1.4 SDS) and 24% complied with the definition of SGA (243). GH treatment of Noonan syndrome leads to a taller height SDS in childhood and possibly also adult height (322). GH is registered for Noonan syndrome in the United States, but not in Europe and Japan.

Children with neurofibromatosis type 1, caused by a heterozygous mutation in *NF1*, also tend to be short in addition to the other classical clinical features, and their birth weight and length are shifted to the left by ~1 SD (244).

Genetic defects in fundamental cellular processes

Mutations in genes encoding proteins involved in fundamental cellular processes can produce severe global growth deficiencies, termed primordial dwarfism, which affect not just the growth plate but multiple other tissues throughout the body and typically impair both prenatal and postnatal growth (Table 7). These conditions can be associated with a normal or low head circumference, and with or without DNA repair defects (206). Most are characterized by specific clinical features, which usually would lead to targeted genetic testing, but in some the phenotype can be close to normal except SGA.

From the various primordial dwarfism syndromes associated with a normal head circumference, the Floating-Harbor syndrome (MIM 136140, caused by heterozygous mutations in *SRCAP*) can have a mild phenotype (323). Thirteen out of 49 individuals had a birth weight below −2 SDS (245). Insufficient data are available to evaluate the effect of GH treatment (324). Mulibrey nanism (MIM 253250, caused by biallelic *TRIM37* mutations) presents with a similarly low birth size. 3-M syndrome is caused by defects in *CUL7* (MIM 273750), *OBSL1* (MIM 610991), or *CCDC8* (MIM614205) and is characterized by prenatal and postnatal growth failure (325). This syndrome is associated with a gene expression profile of reduced *IGF2* expression and increased *H19* expression similar to that found in SRS (326). There are insufficient data on the effect of GH treatment.

The forms of primordial dwarfism with distinct microcephaly can usually be easily recognized clinically [*e.g.*, Cornelia de Lange syndrome (MIM 122470), Meier–Gorlin syndrome (MIM 224690), microcephalic osteodysplastic primordial dwarfism (MOPD) types I (MIM 210710) and II (MIM 210720), and Seckel syndrome (MIM 210600)] [reviewed in (327) and (328)]. Also, mutations in aminoacyl-tRNA synthetases are characterized by SGA (329).

Of the DNA repair defects, the best-known example is Bloom syndrome (MIM 210900), caused by a mutation in the gene encoding DNA helicase RecQ protein-like-3 (*RECQL3*). Fanconi anemia (MIM 227650) is a clinically and genetically heterogeneous disorder that causes genomic instability. Characteristic clinical features include developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer (206). Other syndromes in this category include Cockayne syndrome (MIM 216400), Rothmund–Thomson syndrome (MIM 268400), and *LIG4* (MIM 606593) (255) and *XRCC4* mutations (MIM 616541) (256). For these types of disorders, GH treatment is contraindicated, given the uncertain long-term side effects on cell division and possible oncogenesis.

Chromosomal abnormalities and CNVs

Turner syndrome can be diagnosed prenatally or early postnatally based on the classical clinical features (*e.g.*, lymphedema of hands and feet, or webbed neck) but in many cases the diagnosis is made at a much later stage, particularly in girls carrying X-chromosome abnormalities other than the classical 45,X karyotype—for example, mosaicisms. Full-term babies with Turner syndrome are on average 3 cm shorter and 500 g lighter than normal female newborns, and approximately one-third are born SGA (330). The disturbed prenatal and postnatal growth is probably mainly caused by *SHOX* haploinsufficiency, but there is only partial overlap between the clinical features of Turner syndrome (331) and *SHOX* haploinsufficiency (242).

There are several other chromosomal abnormalities and CNVs associated with prenatal and postnatal short stature, but these are usually detected based on their phenotype (206, 332). However, CNVs can also be found in nonsyndromic SGA and ISS (333), as shown in a combined analysis of five cohorts. Out of 671 patients with short stature of unknown cause evaluated by chromosomal microarray (probably) pathogenic CNVs were identified in 87 patients (13%) (332). Seven recurrent CNVs, that is, 22q11.21, 15q26, 1p36.33, Xp22.33, 17p13.3, 1q21.1, and 2q24.2, were responsible for ~40% of all pathogenic/probably pathogenic genomic imbalances found in short stature of unknown cause (332).

"One of the likely causes for the lack of catch-up growth is a genetic abnormality associate with prenatal and postnatal growth failure."

Diagnostic approach

Figure 2 shows a flowchart of the evaluation of the SGA newborn. The clinician searches for diagnostic clues through the medical history (including maternal health, teratogens, pregnancy, placental pathology) and physical examination, including weight, length and head circumference SDS (symmetric vs asymmetric), ophthalmologic evaluation, and hearing screen. Traditionally, babies have been evaluated for several congenital infections, but it has been suggested to limit this to urinary cytomegalovirus testing (334).

In Fig. 3, a flowchart is shown of our diagnostic approach of the short child born SGA. First, the clinician will try to detect diagnostic clues from the medical history, physical examination, growth pattern, an X-ray of the left hand and wrist, and a screening laboratory panel. The X-ray should not only be used to assess skeletal age, but also to check for anatomic

abnormalities associated with genetic disorders (*e.g.*, *SHOX*, *NPR2*, *ACAN*, *IHH*). Genetic testing for Turner syndrome should be performed in girls when height SDS is >1.6 SD lower than target height SDS, for which we favor an array analysis (SNP array or comparative genomic hybridization array) above a karyotype. The diagnostic power to detect Turner syndrome is similar (335), but with an array also CNVs and (with a SNP array) uniparental isodisomy can be detected. If Turner syndrome and pathogenic CNVs or UPDs are excluded in girls, the clinician can consider performing further genetic testing using a specific exome-based gene panel targeted on growth-related genes (206, 251, 336). Similarly, boys can be tested with array analysis, and if there is sufficient suspicion of a primary growth disorder, with a growth-specific gene panel. If there are strong indications for a specific genetic syndrome (*e.g.*, Madelung deformity, which is pathognomonic for *SHOX* haploinsufficiency), Sanger sequencing combined with a multiplex ligation-dependent probe amplification test of the pertinent gene can be performed ("candidate gene approach"), but the wide phenotypic range of most genetic syndromes (17) implies that there is a risk that a number of sequential genes will have to be tested before the genetic etiology is found (206, 251). Potential third and fourth steps include RNA sequencing and a methylation array (259). In special cases, for example, if a novel monogenic disorder is suspected, whole-exome sequencing in a "trio" (patient and both parents, or including siblings) can be performed. We expect that with future genetic techniques the total diagnostic yield will further increase. However, this will probably also show that in many cases SGA is caused by a combination of multiple (epi)genetic variants (259).

The prior probability of a secondary growth disorder in short children born SGA is low. However, if there are

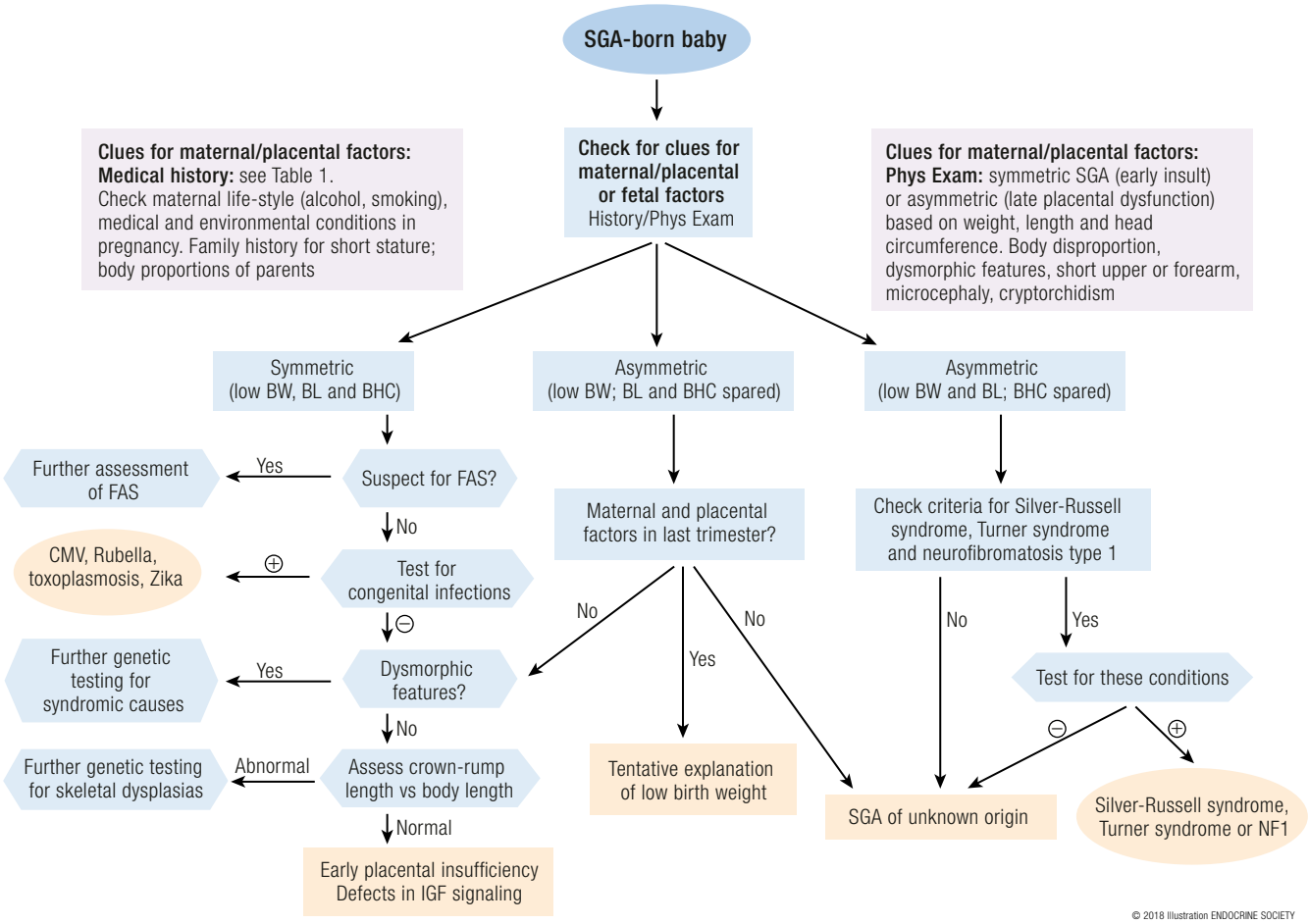
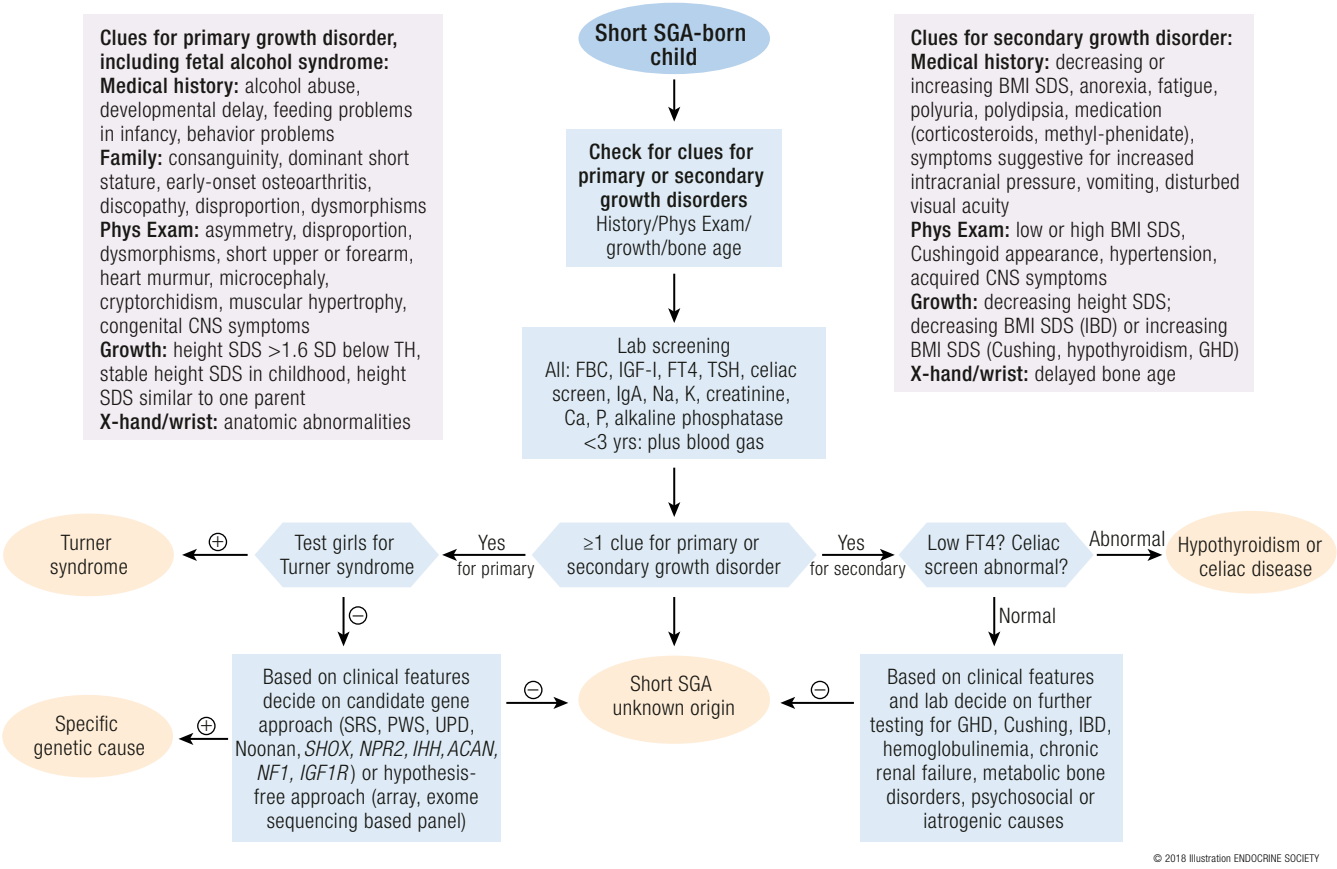


Figure 2. Clinical assessment of the SGA newborn. The medical history and the balance between birth weight (BW), birth length (BL), and birth head circumference (BHC) determine the likelihood of maternal or placental causes vs fetal causes. Symmetric SGA (with similar reductions in BW, BL, and BHC) may be associated with fetal alcohol syndrome, congenital infections, dysmorphic syndromes, early placental insufficiency, or defects in IGF signaling. The most frequent type of asymmetric SGA (with a low BW in comparison with BL and BHC) may be caused by placental insufficiency at later gestation but also by some dysmorphic syndromes and skeletal dysplasias. The other type of asymmetric SGA (with a low BW and BL relative to BHC) may point toward SRS, Turner syndrome, or neurofibromatosis type 1. CMV, cytomegalovirus; FAS, fetal alcohol syndrome; IGF, insulin-like growth factor; NF1, neurofibromatosis 1; Phys, physical; SRS, Silver-Russell syndrome. [© 2018 Illustration ENDOCRINE SOCIETY].

Figure 3. Clinical assessment of the child born SGA with persistent short stature. With a thorough medical history, physical examination, growth analysis, and an X-ray of the left hand and wrist, the clinician searches for clues for primary or secondary growth disorders. Although the prior probability of secondary growth disorders is lower than that of primary growth disorders in short children born SGA, we advise laboratory screening for the detection of anemia, GH deficiency (GHD), hypothyroidism, chronic renal failure, celiac disease and disturbances in electrolytes, and bone metabolism, in infants and toddlers also tests for renal tubular acidosis. Based on relevant clinical features, further investigations should be performed for other secondary disorders, such as inflammatory bowel disease (IBD) or Cushing disease. The hand/wrist radiograph should not only be assessed for skeletal age but also for anatomic abnormalities associated with primary growth disorders such as defects of *SHOX, NPR2, IHH,* and *ACAN*. Girls who are >1.6 SD shorter than their target height SDS should be tested for Turner syndrome, either with array analysis or metaphase cytogenetics. If that test is negative, further genetic studies should be considered, such as Sanger sequencing for a candidate gene, array analysis, or an exome sequencing-based gene panel. FBC, full blood count; Phys, physical; X-hand/wrist, hand/wrist radiograph. [© 2018 Illustration ENDOCRINE SOCIETY].



diagnostic clues for such disorders from clinical, laboratory, and radiologic assessment, further testing is obviously indicated, including GH stimulation tests if serum IGF-1 is low or in the lower half of the reference range for age and sex. A relatively high serum IGF-1 in a short child born SGA should lead to genetic testing of *IGF1R*. In case of a positive Netchine–Harbison score (195), genetic testing for SRS is indicated.

Short-Term Consequences of SGA

Mortality

Being born SGA is associated with increased mortality. Pooled risk ratios for babies who were SGA (*i.e.*, with a birth weight in the lowest 10th percentile of the reference population) were 1.83 for neonatal mortality and 1.90 for postneonatal mortality (337), and in a secondary analysis of nine studies the likelihood of neonatal mortality among SGA infants (<10th percentile) was threefold higher compared with their appropriate-for-gestational-age (AGA) counterparts (338). The neonatal mortality risk of babies who were both preterm and SGA was higher than that of babies with either characteristic alone (337).

Hypoglycemia

Approximately one-third of SGA infants become hypoglycemic after birth (338), for which various causes are known. First, glycogen depletion is an important factor in neonatal hypoglycemia (340). Second, SGA infants have lower levels of free fatty acids and ketone bodies, even at low glucose concentrations, suggestive of reduced fat stores or an

inability to mobilize fuels, for example, by a lower capacity to secrete counterregulatory hormones such as cortisol (341). Third, ~20% of SGA infants have inappropriately raised insulin levels at the time of hypoglycemia, indicative of hypoglycemic hyperinsulinism (339). Although this is usually transient, some SGA infants exhibit prolonged hypoglycemic hyperinsulinism, requiring treatment with diazoxide (342). This condition was reported to resolve within 3 to 9 months (342). Unrecognized, it may put infants at risk for brain damage due to the lack of alternative substrates such as ketone bodies. There is some evidence suggesting that SGA infants with hypoglycemic hyperinsulinism have an increased risk of ketotic hypoglycemia in childhood (343). Fourth, contributing factors to the development of hypoglycemia in SGA infants are asphyxia, hypothermia, and polycythemia.

Thermoregulation

SGA infants have an inferior thermoregulatory response compared with their appropriate-sized counterparts, which predisposes them to hypothermia. Although brown adipose tissue stores for heat production are usually not depleted, excessive heat loss occurs through an increase in body surface area due to a relatively large head size as well as increased transdermal insensible losses. Lower subcutaneous and body fat stores provide less thermogenesis and lower levels of insulation, both of which contribute to hypothermia. Additionally, hypoxia and hypoglycemia can negatively affect the thermoregulatory response (344).

Hematologic sequelae

Chronic intrauterine hypoxia induces erythropoietin production, resulting in excessive red cell production and impairment of thrombopoiesis. Polycythemia with hyperviscosity increases the risk of necrotizing enterocolitis and thrombosis. Placental-to-fetal transfusion during labor can further contribute to the development of polycythemia (344–346). Chronic fetal hypoxia with hepatic underperfusion may lead to disordered coagulation (345).

Thrombocytopenia is a frequent finding (>50%) in SGA infants, 2.7-fold more often than in infants born AGA (347). Impaired thrombopoiesis, placental vascular pathology, fetal consumptive coagulopathy, platelet destruction, local imbalance of thromboxane A2 causing placental vasoconstriction, and platelet aggregation are all suggested mechanisms. Most cases of neonatal thrombocytopenia are mild to moderate and do not need intervention (346).

Long-Term Consequences of SGA

Longitudinal growth and the GH–IGF-1 axis

Most children born SGA show spontaneous catch-up growth to a normal height (*i.e.*, above −2 SDS). Catch-up growth is usually completed within the first 2 years of life but is most pronounced during the first 6 months. However, catch-up growth may take longer in those children born prematurely, up to the age of 4 years (12). By the age of 8 years, 91% of children born SGA had attained a normal height (348).

The 10% of children born SGA remaining short (12, 13, 348) will reach an adult height well below the normal range and/or target height range. If no catch-up has been attained before the age of 3 years, there is a sevenfold increased risk of persistent short stature in those born with a birth length below −2 SDS, and a fivefold increased risk in those born with a birth weight below −2 SDS (349). Therefore, a child with a height below −2 SDS at the age of 3 years should be referred to a pediatrician with expertise in endocrinology (2, 350). Persistent short stature of children born SGA is indeed commonly encountered in children presenting to endocrine clinics with short stature, accounting for ~20% of all cases (351, 352).

The reasons for insufficient catch-up growth in children born SGA are poorly understood. Growth retardation confined to the last trimester (leading to asymmetric SGA) appears to have a relatively good prognosis for catch-up growth (353), but, in contrast, other studies indicated that short children with a birth weight and length below −2.0 SDS have a better postnatal growth than do those with only a birth length or birth weight below −2.0 SDS (354, 355). One of the likely causes for the lack of catch-up growth is a genetic abnormality associated with prenatal and postnatal growth failure, but disturbances in the GH–IGF-1 axis may also play a role (356, 357). Approximately 60% of short children born SGA showed reduced spontaneous GH secretion during a 24-hour sampling period and/or a low GH peak during GH provocation tests (358–360), and serum levels of IGF-1 and IGFBP-3 were lower in short children born SGA than in healthy controls (361–363). However, IGFBP-3 proteolytic activity was increased in short children born SGA, suggesting that the bioavailability of IGF-1 is relatively high in spite of a low concentration (364). In contrast, some short children born SGA had normal or high serum IGF-1 levels, suggestive of IGF-1 resistance. ALS levels were decreased by 0.5 SDS in short children born SGA compared with healthy controls, and less reduced than the IGF-1 and IGFBP-3 levels (365). In prepubertal children born SGA with a normal height, ghrelin and IGF-1 concentrations were higher than in short children born SGA, or in children born AGA with a short or normal stature (366), suggestive for a possible role of ghrelin in catch-up growth. At the age of 12 years, the (BMI-, sex-, and puberty-adjusted) serum IGF-1 concentration was higher and the leptin concentration was lower in SGA than in children born AGA, whereas no differences were found in the indices of insulin action or sensitivity between the SGA and AGA groups (367).

Owing to a complicated neonatal course, preterm infants often tend to exhibit early postnatal growth failure, labeled as extrauterine growth restriction (EUGR). The risk of EUGR was found to increase with lower gestational age and birth weight, acute illnesses, bronchopulmonary dysplasia, postnatal corticosteroid treatment, and feeding problems (368–370). Very preterm infants with EUGR grew similarly during childhood as those born SGA (370). Preterm infants with a length or weight below −2 SDS at the corrected age of 3 months who failed to catch up subsequently had a similar risk of a short adult stature as SGA infants (370).

Pubertal development

In children born SGA, puberty starts slightly earlier than average but still within the normal range (371, 372), and adrenarche is probably age appropriate (373). The progression of puberty is normal, although age at menarche is slightly younger (374).

Body composition

Weight gain during infancy and early childhood is a more important determinant of body composition in young adulthood than birth size (375). In children born SGA total and abdominal fat mass at 4 years of age was closely related to the rate of weight gain in the first 2 years of life (10, 376). By the age of 4 years, children born SGA had a normal amount of visceral fat in the abdominal region but their subcutaneous fat was strikingly reduced, resulting in an elevated ratio of visceral over subcutaneous fat (377). One of the putative mechanisms involved in catch-up growth in weight after SGA could be an increased insulin sensitivity as part of various adaptation phenomena to ensure weight recovery (378, 379).

The difference in body composition observed during childhood persists into early adulthood (Table 8) (380–384). Compared with adults born AGA, the percentage of fat mass was similar in short adults born SGA but higher in adults born SGA who had experienced spontaneous catch-up growth to a normal height and weight. Compared with adults born AGA, the percentage of lean body mass was lower in adults born SGA, regardless of previous catch-up growth or GH treatment (375, 380, 383). These observations suggest that, in subjects born SGA, lean body mass is reprogrammed during fetal and early life, with long-lasting effects on body composition.

Blood pressure

In short children born SGA, an increased prevalence of cardiovascular risk factors has been described (385, 386). Blood pressure was increased in children born SGA, especially in those born prematurely (386–389). Several studies have shown inverse associations between birth weight and risk factors for hypertension and cardiovascular disease in adults (390–392). Short adults born SGA had a higher systolic and diastolic blood pressure compared with adults born AGA (382, 393), irrespective of whether they had remained short or had caught up (382, 393) (Table 8).

Dyslipidemia and other cardiovascular risks

In subjects born SGA, accumulation of fat mass during childhood significantly determined serum lipid levels, whereas birth size had no significant contribution (394). At the age of 1 year, short children born SGA had a serum triglyceride level above the upper limit for age, as compared with children born AGA of normal stature (395). Metabolic and transcriptomic profiles in children born SGA aged 4 to 9 years displayed changes associated with increased cardiometabolic risk (396). A lower serum adiponectin level in short prepubertal children born SGA compared with short controls was associated with an unfavorable lipid profile (397). However, another study indicated that lipid levels were within the normal range in prepubertal short children born SGA (386). Reassuringly, lipid levels were similar in short adults born SGA and in adults born AGA (398, 399).

Table 8. Metabolic and Cardiovascular Consequences in Early Adulthood of Being Born SGA in Comparison With AGA-Born Subjects

	SGA With Persistent Short Stature	SGA With Catch-up Growth	References
Fat mass[a]	Similar	Higher ($P < 0.001$)	(380)
Lean body mass[a]	Lower ($P < 0.05$)	Lower ($P < 0.05$)	(380)
Systolic blood pressure,[b] mm Hg	Similar	Similar	(381)
Diastolic blood pressure,[b] mm Hg	Similar	Similar	(381)
Cholesterol concentration[c]	Similar	Similar	(381)
Carotid intima-media thickness[d]	Similar	Higher ($P = 0.025$)	(382)
Insulin sensitivity[c]	Similar	Lower ($P = 0.006$)	(383, 384)
β-Cell function[c]	Similar	Similar	(383, 384)

[a]Adjusted for age, sex, gestational age, and height SDS.
[b]Adjusted for sex and height.
[c]Adjusted for sex.
[d]Adjusted for age, sex, and arterial diameter.

In the Hagenau cohort (France), a twofold increased risk of the metabolic syndrome was found among young adults born SGA during 8 years of follow-up, and, at the age of 22 the prevalence of the metabolic syndrome was 2.4% compared with 0.4% in young adults born AGA (400). In contrast, a recent study showed that the incidence of the metabolic syndrome at age 21 years was similar in short adults born SGA, adults born SGA of normal height, and adults born AGA (383).

Carotid intima media thickness (cIMT), a valid marker for generalized atherosclerosis (401), at the ages of 3 and 6 years was higher in children born SGA with spontaneous catch-up growth than in children born AGA with a similar height, weight, and BMI (402). Similarly, cIMT was higher in SGA-born adults with spontaneous catch-up growth compared with short adults born either SGA or AGA (382, 403). Furthermore, short adults born SGA had a similar cIMT as did adults born AGA of normal height (Table 8) (382).

Insulin resistance and type 2 DM

Adults born with a low birth weight often have metabolic perturbations, such as insulin resistance, glucose intolerance, and type 2 DM (390–392, 399). In the Japanese Nurses' Health Study, birth weight and its percentile for gestational age were inversely associated with adult-onset DM, and among women with a BMI in the lower half of the normal range (18.5 to 20.9 kg/m^2) the odds ratio for DM in the <2500-g birth-weight group reached 4.75 (95% CI, 1.22 to 18.44), as compared with the reference group with birth weights between 3000 and 3499 g (404).

In short children born SGA, insulin sensitivity adjusted for BMI was reduced by 38% compared with short children born AGA, whereas the acute insulin response was higher (386, 405). At the age of 4 years, children born SGA with spontaneous catch-up growth were more insulin-resistant than were children born AGA (376, 406). The rapid fat accumulation in the first months of life was associated with a lower insulin sensitivity in early adulthood (10). Insulin sensitivity, as assessed by a frequently sampled intravenous glucose tolerance test, was similar in short adults born SGA and in AGA-born adults, whereas it was lower in adults born SGA with spontaneous catch-up growth to a normal height (Table 8) (384).

In conclusion, metabolic alterations in adults born SGA are particularly evident in those who experienced early spontaneous catch-up growth to a normal height and weight, as opposed to those who remained short (394, 407–409).

Neurodevelopment

A study using the Swedish Birth Register, including the data of >200,000 SGA-born males, showed that small birth size and preterm birth increased the risk of subnormal intellectual and psychological performance at the age 18 to 25 years. Among SGA-born males, the most important predictor of poorer intellectual outcome was the absence of sufficient catch-up growth (410). Long-term neurodevelopmental sequelae included a lower IQ score, school failure, and more problem behavior (attention deficit and social behavior), particularly in children with persistent short stature (411–415).

There are only few studies on brain architecture in children born SGA (416–418), showing decreases in brain weight, total brain volume, brain cell number, and the total amount and concentration of myelin lipids compared with those born AGA, particularly in children who had experienced placenta insufficiency in fetal life (417). However, these studies had small sample sizes and the analyses were not adjusted for the smaller head circumference of the short children born SGA.

In most studies, the IQ of children born SGA was within the normal range but on average lower than that of children born AGA. In none of the studies did this difference exceed 1 SD (15 IQ points) (419–421). Among children born SGA those born smallest (420) or those who had experienced fetal growth restriction (421) had the lowest IQ. This is in line with findings from the Copenhagen Perinatal Cohort, showing positive associations between birth weight and IQ scores at the ages of 19, 28, and 50 years (422).

A population-based register study in Sweden described school performance of 1,088,980 children born at term between 1973 and 1988. At the ages of 5, 10, and 16 years, those born SGA demonstrated small but significant deficits in academic achievement compared with those born AGA (423). Additionally, teachers were more likely to recommend special education in them (424, 425). Furthermore, the risk of poor school performance was no longer increased when adequate catch-up growth was achieved. At the age of 26 years, SGA-born subjects were not different from those born AGA in years of education, employment, hours of work per week, marital status, or satisfaction with life, but they reported lower weekly income (424).

Fetal thyroid function may partly explain the link between IUGR and future neurodevelopmental problems. Growth-restricted fetuses had lower levels of circulating free T4 (426), which is the substrate for cerebral T3, in spite of an increased expression of thyroid receptor isoforms in the placenta. There is also evidence linking IUGR to reduced thyroid hormone transport within the brain, as the expression of MCT8 was reduced in the cortices of growth-restricted fetuses (427). Moreover, IUGR was accompanied by reductions in the expression patterns of thyroid receptor isoforms in the fetal cerebral cortex and cerebellum (428). At age 11.3 years, thyroid function of short children born SGA was not different from the reference population (429).

Bone mineral density

In short children born SGA, bone mineral density (BMD) was decreased (430–432). After correction for age, sex, adult height and weight, and lean body mass, BMD was similar in adults born SGA with or without sufficient catch-up growth (433).

Gonadal function

In SGA-born males, increased serum FSH levels in infancy, decreased testosterone levels in late puberty, and a smaller testicular size in adulthood have been found (434, 435). However, these studies did not exclude males with SRS, who often have genital abnormalities known to influence reproductive function in later life, such as cryptorchidism and hypospadia (271, 277, 278). Among prepubertal boys without cryptorchidism, serum inhibin B and anti-Müllerian hormone (AMH) levels were not different between those born SGA or AGA (436). Furthermore, in adulthood, no differences in serum levels of inhibin B, AMH, testosterone, sex hormone–binding globulin, non–sex hormone–binding globulin-bound testosterone, LH, and FSH were found between men born SGA or AGA (436–438). Young SGA-born women had normal serum AMH levels, indicating that they do not have a smaller follicle pool size than do AGA-born women (439). More long-term follow-up studies on gonadal function are needed before definite conclusions can be drawn.

Kidney function

Several studies, both in humans and animals, have shown that IUGR leads to smaller kidneys with lower nephron numbers and more apoptotic cells (440, 441). According to the hyperfiltration hypothesis, this may result in glomerular hyperfiltration and, consequently, albuminuria with progressive loss of kidney function (442). Indeed, in a meta-analysis low birth weight was associated with the future development of albuminuria (OR 1.81), low estimated glomerular filtration rate (OR 1.79), and end-stage renal disease (OR 1.58) (443). SGA was associated with decreased creatinine clearance in a dose-dependent fashion at age 20 to 30 years (444).

Psychosocial consequences

It is assumed that short children can suffer from physical, social, and psychological problems (445), although research has provided little support (446). Theoretically, this could be caused by short stature *per se* or might be associated with the underlying condition. The physical limitations of short stature and the younger appearance may result in being treated differently by peers and, sometimes, in being bullied (447). Short children born SGA had lower scores on tests of social functioning and health-related quality of life compared with reference populations (448, 449). Adult short stature is often perceived to be a disadvantage, and it can cause difficulties in getting the preferred job or career and lead to reduced health-related quality of life (450).

Mechanisms of Fetal Programming

Fetal programming refers to the concept that insults acting during a critical window early in life could exert effects on the body's structure and function that may persist for life. During embryonic development, the organism adapts itself to the environment. Developmental plasticity is the ability to develop in various ways, depending on the particular environment. The match-mismatch paradigm describes that if the prenatal and postnatal environments do match, the settings of systems will leave the organism well prepared for the postnatal environment, whereas a mismatch between the prenatal and postnatal environment may render the organism more susceptible to later cardiometabolic diseases (451).

Thrifty phenotype hypothesis

The thrifty phenotype hypothesis, proposed by Hales and Barker, states that fetal undernutrition leads to reduced numbers of pancreatic β-cells, allowing diversion of nutrients to the developing brain at the expense of somatic growth (452). Whether and when type 2 DM becomes manifest is dependent on the rate of β-cell senescence and the development of insulin resistance, mostly by obesity. A variant of the thrifty phenotype hypothesis is the fetal salvage model, which proposes that fetal undernutrition programs peripheral insulin resistance rather than reduced β-cell mass (385).

There are several animal models of fetal undernutrition, including unilateral uterine artery ligation, and maternal dietary restriction of proteins or calories by ~50% (453). In these models, birth weight was reduced by ~10% to 20% (in unilateral uterine artery ligation and calorie restriction models) to 40% (in the protein restriction model). These experiments showed that the undernourished offspring exhibited permanent reductions in the secretion and action of insulin. These alterations were accompanied by morphological changes as well as functional impairments of β-cells and insulin-sensitive tissues such as skeletal muscle, adipose tissue, and liver (453, 454). The molecular mechanisms behind these alterations are thought to involve processes such as epigenetic modifications, oxidative stress, and mitochondrial dysfunction (454).

The Dutch Hunger Winter of 1944 to 1945, although a historical disaster, provided a unique opportunity to study the long-term effects of severe fetal undernutrition in humans. Owing to the sudden cessation by the German occupier of food transports from the rural east to the urban west, food stocks

"Prenatal exposure to famine was associated with less DNA methylation of the imprinted IGF_2 gene."

shrank rapidly in big cities such as Amsterdam starting in November 1944. Consequently, adults were only granted 400 to 1000 kcal of food per day. The food shortages were nullified after the liberation in early May 1945. Dutch investigators traced subjects born at the Wilhelmina Gasthuis Amsterdam in the period between 1 November 1943 and 28 February 1947 for participation in a survey at middle age. In summary, the Dutch famine studies showed that undernutrition in early gestation was associated with cardiovascular disease propensity (455, 456). Undernutrition in late gestation was associated with an increased risk of developing type 2 DM (457). Later studies, in a composite sample from Amsterdam, Rotterdam, and Leiden (458), showed that prenatal exposure to famine was associated with less DNA methylation of the imprinted *IGF2* gene (459) as well as alterations in the degree of methylation of other genes involved in developmental pathways (460). Remarkably, the birth weights of subjects who were exposed to famine in the third trimester, when fetal weight velocity peaks, were only reduced by 200 to 300 g (455).

Fetal insulin hypothesis

According to the fetal insulin hypothesis, associations between IUGR and type 2 DM could be explained by polygenic variation associated with insulin secretion or action (461). This hypothesis was fueled by observations in mother/infant pairs discordant for mutations in the glucokinase gene (462). Glucokinase acts as the pancreatic glucose sensor, and inactivating mutations in the glucokinase gene cause maturity-onset diabetes of the young type 2. Babies born to mothers carrying a mutation in the glucokinase gene were on average 601 g heavier at birth, attributable to increased fetal insulin secretion in response to maternal hyperglycemia (462). Conversely, babies carrying such a mutation were 533 g lighter at birth due to decreased insulin secretion (462). When mothers and their babies carried the same mutation, the two opposing effects cancelled out and birth weight was normal (462).

Type 2 DM susceptibility genes could either reduce or improve fetal growth, dependent on the parent of origin. Maternal and paternal genes may influence birth weight directly, by being inherited by the fetus. Maternal genes may influence birth weight also indirectly, through alterations in the supply of nutrients to the fetus. In the data from the UK Biobank (n = 236,030), associations between parental DM, birth weight, and participants' type 2 DM were demonstrated (463). Paternal DM was associated with a 45 g lower birth weight, and maternal diabetes with a 59 g higher birth weight. Birth weight was found to be a mediator of the association between parental diabetes and type 2 DM. The authors concluded that findings with paternal diabetes are consistent with a role for the same genetic factors influencing fetal growth and type 2 DM (463).

A recent genome-wide association study meta-analysis of birth weight, encompassing the data of 153,781 subjects, identified 60 loci where fetal genotype was associated with birth weight, nine of which had also been associated with type 2 DM (464). Fetal genetic variation could explain ~15% of the variance in birth weight. Subsequent analyses revealed that genetic factors contributed substantially to the inverse association between birth weight and cardiometabolic risk.

Fetal cortisol hypothesis

The fetal cortisol hypothesis postulates that a lower activity of the placental barrier enzyme 11β-HSD type 2 allows for a larger proportion of maternal cortisol to reach the fetus, leading to IUGR, permanent alterations in hypothalamic–pituitary–adrenal axis settings, and, hence, predisposition to cardiometabolic and neuropsychiatric diseases. Offspring of rats treated during pregnancy with dexamethasone, which bypasses placental 11β-HSD type 2 activity, had lower birth weights as well as persistent increases in blood pressure and glucose level (465, 466). Studies with the 11β-HSD type 2 inhibitor carbenoxolone, by increasing the supply of maternal corticosterone—the principal glucocorticoid in rodents—to the fetus, yielded similar results (467, 468). Glycyrrhizin in licorice is known to inhibit 11β-HSD type 2 activity, and children born to mothers who consumed at least 500 mg of licorice per week during their pregnancies had lower scores on several tests of cognitive function and more externalizing behavior (469). However, heavy licorice consumption, although being associated with gestational duration, was unrelated to birth weight (470).

Growth acceleration or fat accumulation hypothesis

The growth acceleration or fat accumulation hypothesis aims to offer an explanation for the association between restricted fetal growth, early postnatal catch-up growth, and later cardiometabolic disease (471, 472). It was postulated that the growth-restricted newborn becomes insulin-resistant after birth, when abundant food intake leads to markedly elevated concentrations of insulin and IGF-1 (471). In animal models overfeeding in the early postnatal period permanently increased obesity risk, insulin resistance, and cholesterol levels (472). In humans rapid gain in weight relative to length during the first 3 months of life was associated with reduced insulin sensitivity, increased abdominal fat, and a less favorable lipid profile at young adult age (10).

Stem cell hypothesis

The stem cell hypothesis proposes that intrauterine malnutrition reduces the number of stem cells in

tissues, leading to an earlier exhaustion of organs (473). This hypothesis implies that efforts should be aimed at inducing proliferation, differentiation, and survival of stem cells, or reversing the differentiation state of more mature cells. Some studies have demonstrated positive associations between size at birth and leukocyte telomere length (LTL) (474, 475), which is considered an index for biological aging. LTL is influenced by oxidative and replicative stress, and shorter LTL is associated with cardiovascular disease predisposition (476, 477).

Growth Hormone Treatment of Children Born SGA

Recombinant human GH has been used since 1986 and has replaced GH extracted from human cadaveric pituitaries for the treatment of children with GH deficiency. The indications for GH treatment have gradually extended from replacement therapy in children with GH deficiency to enhancing growth in an increasing number of conditions in which short stature is not due to GH deficiency, such as persistent short stature in children born SGA.

The formal indications for GH treatment of short children born SGA are slightly different between the United States (Food and Drug Administration) and Europe (European Medicines Agency), but in essence they are based on the same principles: documented small birth weight and/or length, short stature, an age range at which (further) catch-up growth is unlikely (and young enough to expect substantial adult height gain), and absence of actual catch-up growth. However, the age at which treatment can be initiated is 2 years in the United States and 4 years in Europe, and a cut-off for height SDS at start of treatment according to European Medicines Agency (−2.5 SDS) is missing in the Food and Drug Administration indication. An important additional issue is less objective, namely the absence of clinical features suggestive of a dysmorphic syndrome (with the exception of SRS, which has been accepted under the SGA indication from the beginning). Obviously, this criterion depends on the clinical skills of the physician but also on which physical signs are considered abnormal and, in particular, which additional (genetic) testing is performed.

In most countries, a fixed GH dose per kilogram body weight or per square meter body surface area is used, with a recommended dose of 0.033 mg/kg/d (~1 mg/m^2/d) in Europe and Japan (350). In the United States, the recommended dose ranges from 0.033 to 0.067 mg/kg/d (~1 to 2 mg/m^2/d). A more personalized approach has also been advocated, based either on clinical predictors of the growth response or titration of serum IGF-1 concentrations (478).

In all clinical trials involving short children born SGA, the growth response to GH has been quite variable, and it is likely that at least part of this variability is associated with multiple gene variants (479). We believe that in SGA cohorts treated with GH, particularly those who have reached adult height, it is important that studies be carried out to identify the specific genetic cause, so that at least retrospectively the effect of certain genetic diagnoses on the growth response to GH will be known. Such valuable data could ultimately lead to improved GH response prediction in short children born SGA.

Effect on longitudinal growth

The assumption underlying GH treatment in short children born SGA is that faster growth and a taller adult height (possibly reaching the normal range for the population and/or target height) is of benefit to the short child. We agree with Allen (480) and Sandberg and Gardner (446) that there is quite some uncertainty about the validity of this assumption, but a discussion on the various arguments on the value of GH treatment in non–growth hormone deficiency conditions is beyond the scope of this review.

Several studies have shown that GH treatment effectively induces catch-up growth and improves adult height in most short children born SGA (14–16, 481–483). A systematic review published in 2009 identified four high-quality trials with adult height outcome in short children born SGA treated with GH and concluded that among the 391 children participating in these studies the mean height gain was on average 1.25 SDS (484). The GH-induced catch-up growth is accompanied by normal body proportions and proportional head growth (354, 485).

"Apart from the positive effects on linear growth, GH has well-documented lipolytic, anabolic, and insulin antagonistic effects."

As mentioned above, the GH-induced growth response in short children born SGA is highly variable (15), which led to studies aimed at identifying clinical predictors. In the first year of GH treatment, the growth response correlated positively with GH dose, weight at start of GH treatment, and midparental height SDS, and negatively with age at start of treatment (486). When these predictors were put in a model, 52% of the variability of the growth response in the first year of treatment was explained, with GH dose being the most important predictor (35% of variance), followed by age at start of treatment.

In the second year of GH treatment, height velocity during the first year of GH treatment, age at start of treatment, and GH dose explained 34% of the variance in growth response. The first-year response to GH treatment was the most important predictor of the second-year response, accounting for 29% of the variance (486). Height velocity in the second year of GH treatment, chronological age, weight SDS, midparental height SDS, and GH dose explained 33% of the variance in growth response during the third prepubertal year of GH treatment (487). Adult height SDS was explained by height (SDS) at GH start (+), height gain (ΔSDS) during the first year on GH (+),

years on GH (+), maternal height SDS (+), length (SDS) at birth (+), and the diagnosis of SRS (−) (explained variability 70%; error 0.6 SD). Adult height gain SDS was explained by height gain (ΔSDS) during the first year on GH (+), years on GH (+), and height – midparental height (SDS) at GH start (−) (explained variability 60%; error 0.7 SD) (488).

In another prediction model, patient characteristics found to be related to adult height SDS were height SDS at start of GH treatment, target height SDS, GH dose, bone age delay at start, and baseline IGFBP-3 SDS, explaining ~40% of the variance in adult height SDS (489). Determination of serum ALS levels before start of GH treatment modestly improved the long-term prediction of height SDS with 5% (365).

Prematurity increases the risk of insufficient postnatal catch-up growth (490). However, among short children born SGA, the growth response to GH treatment did not differ between those born preterm or at term (491). Pretreatment adiposity predicted a greater height gain and IGF-1 response during the first year of GH treatment, providing support for a causal role of insulin resistance in linking reduced body fat to GH insensitivity (492). Equivocal data have been reported on the possible predictive effect of the exon 3–deleted *GHR* polymorphism on the growth response to GH (493–496).

Few studies have analyzed the effects of a higher GH dose, for example, 0.067 mg/kg/d instead of 0.033 mg/kg/d. No difference in adult height SDS was found between these two GH dose regimens when children started GH treatment during prepuberty (15, 362, 393). Because the average serum IGF-1 is around +2 SDS when children are treated with a GH dose of 0.067 mg/kg/d, whereas their adult height is not different from that of children treated with a dose of 0.033 mg/kg/d (15, 362, 497), we recommend to treat short children born SGA with a GH dose of 0.033 mg/kg/d, and to only increase the GH dose when the growth response is unsatisfactory and other causes of a poor growth response are ruled out. GH dosing based on IGF-1 titration resulted in a poorer growth response than a treatment strategy based on a fixed GH dose, and it is therefore not recommended (498).

When considering the start of GH treatment, adult height is significantly greater (by 0.4 SDS) when treatment was started >2 years before the onset of puberty (16). Adult height of short early pubertal children born SGA with a predicted adult height below −2.5 SDS at the start of GH treatment may be improved by the addition of a GnRHa. From the onset of puberty boys treated with combined GH/GnRHa grew on average 34.5 cm and girls 24.2 cm, which exceeds the average total pubertal growth of the reference population (499). Children born SGA who are treated with combined GH/GnRHa treatment had a shorter pubertal duration after discontinuation of GnRHa than did those treated with GH only (500). However, their total height gain was greater (500). As a result, adolescents who started combined GH/GnRHa treatment in early puberty at a significantly shorter height than those treated with GH only reached a similar adult height as those treated with GH only (500).

Effect on pubertal development

On average, GH-treated children born SGA start puberty at a similar age as the normal population, although some start relatively early (372, 501–504). GH treatment had no influence on the onset and progression of puberty compared with AGA controls, regardless of GH dose (0.033 vs 0.067 mg/kg/d) (372, 505). Additionally, pubertal duration and pubertal height gain were not significantly different between the GH-dosage groups (372, 482, 502).

Effect on metabolic and cardiovascular health

Apart from the positive effects on linear growth, GH has well-documented lipolytic, anabolic, and insulin-antagonistic effects (506). Long-term GH treatment resulted in increased lean body mass due to its anabolic effects on muscle mass, and decreased fat mass due to its lipolytic effects (380, 431, 507–510). Short children born SGA had reduced insulin sensitivity before the start of GH treatment (386), and GH resulted in a further reduction in insulin sensitivity with a compensatory increase in insulin secretion (510–515). However, long-term GH treatment in large study groups showed that HbA1c levels remained within the normal range, and that none of the GH-treated SGA-born subjects developed type 2 DM (383, 393, 513).

During long-term GH treatment, blood pressure SDS and cholesterol levels decreased in GH-treated children, and became significantly lower than in untreated children (393, 507, 510, 516, 517). The decrease in blood pressure might be explained by decreased matrix metalloproteinases, which are thought to play a role in the development of atherosclerosis (518). The few studies reporting on cIMT in GH-treated children born SGA showed no effect of GH treatment (403, 519), whereas prepubertal and pubertal children born SGA with spontaneous catch-up growth had a higher cIMT than did GH-treated children born SGA (403).

As both GH and GnRHa treatment may have negative effects on body composition, insulin sensitivity, and blood pressure, combining these treatments has raised concerns about the possible long-term effects on metabolic and cardiovascular health. However, children treated with combined GH/GnRHa for 2 years had similar body composition, insulin sensitivity, β-cell function, blood pressure, and lipid levels at adult height as did those treated with GH only (520, 521).

Effect on neurodevelopment and quality of life

As mentioned above, lower cognitive functioning has been described in short children born SGA (410). The

presence of GH receptors in the brain implies that the brain is a target for GH, and thus that GH treatment could affect brain function. This was supported by observations showing that GH treatment improved cognitive functioning and mood in GH-deficient adults (522). However, the sparse data on the cognitive effects of GH treatment in children born SGA (523–525) have yielded equivocal results. In a Dutch study, GH treatment was found to improve total and performance IQ as well as attention (524): after 8 years of treatment, the average estimated total IQ scores of children born SGA had significantly increased by five to ten points and were in the same range as the normal population. In contrast, in a cohort of children born SGA from Belgium, no beneficial effect of 2 years of GH treatment on IQ score was found (525). Several methodological issues may explain this discrepancy, such as small sample sizes and the duration of GH treatment (which was considerably shorter in the study from Belgium). Another explanation may lie in the observation that GH treatment was found to result in a gradual improvement in cognitive functioning that only becomes apparent after >2 years of treatment, as was demonstrated in GH-treated children with PWS (526). Larger and better controlled follow-up studies in GH-treated children born SGA are required to resolve this issue.

Long-term GH treatment has been reported to improve health-related quality of life (HRQoL) in short children born SGA (448, 449, 527, 528). Short adolescents born SGA treated with GH had higher scores on "physical abilities" and "contact with adults" at age 16 years than did untreated short adolescents born SGA (448). There was also a tendency for them to score higher on "body image," but this difference was not statistically significant (448). Another study showed that HRQoL improved in prepubertal and pubertal short children born SGA during GH treatment. Additional GnRHa treatment had no adverse effect on HRQoL (449).

Effect on bone mineral density

The GH–IGF-1 axis also plays a role in the accrual of bone mass (529, 530). Before the start of GH treatment, short children born SGA had a decreased total-body and lumbar-spine BMD, even after adjustment for their shorter stature (430–433, 531). During ~10 years of GH treatment, total-body BMD improved from −1.00 SDS to −0.44 SDS, and lumbar-spine BMD improved from −0.48 SDS to −0.14 SDS (531). Adding GnRHa to GH treatment of 2 years had no adverse effect on BMD (432).

Safety issues

Since the early 1990s, multiple large cohort studies in short children born SGA have been conducted, showing that GH treatment is well tolerated and that serious adverse effects are uncommon (350, 513, 516, 517, 532). Before GH treatment is initiated in a short SGA-born child, it is recommended to perform a thorough diagnostic workup (350), which may include an evaluation by a clinical geneticist. For example, children with a heterozygous *IGF1R* defect may need a higher GH dosage to obtain an acceptable growth response, and an elevated serum IGF-1 on treatment may be accepted due to the partial IGF-1 insensitivity. The detection of a mild form of skeletal dysplasia (*e.g.*, *SHOX* haploinsufficiency, hypochondroplasia, heterozygous *ACAN* defects) will also influence the decision whether to start GH treatment, or the dosage regimen. GH treatment is contraindicated in several disorders, such as chromosomal breakage syndromes and DNA repair disorders. Diagnosing these syndromes can be challenging, but identifying the genetic etiology is important for health prognosis, genetic counseling, and treatment options (252, 316).

Monitoring during growth hormone treatment

Table 9 shows the current standard of care for the monitoring of short children born SGA during GH treatment. During GH treatment, it is essential that height, weight, and Tanner pubertal stage are monitored regularly. It is recommended to determine the IGF-1 level 3 to 6 months after the start of treatment to evaluate whether the GH dose requires adjustment. Thereafter, it is advised to determine the serum IGF-1 level annually. When IGF-1 levels remain high even with a relatively low GH dose, one should consider to perform *IGF1R* mutational analysis and to examine the presence of a possible underlying dysmorphic syndrome such as Bloom syndrome (252). Serum free T4 levels decreased to levels just below the norm in 14% of GH-treated SGA children but TSH levels remained normal (429), so it seems reasonable to annually perform thyroid function tests.

As bone maturation in short children born SGA is highly variable and unreliable for growth prediction, radiological investigations are not very informative in the prepubertal age range (362). Because GH has limited effects on cardiometabolic parameters during treatment and no long-term adverse effects beyond the treatment period, it is debatable whether metabolic and cardiovascular parameters should be monitored on a regular basis during GH treatment. Because SGA-born subjects are at risk for the metabolic syndrome (533–535), one could argue to follow metabolic syndrome parameters on an annual base. In practice, monitoring of metabolic changes includes the assessment of BMI, abdominal waist circumference, fasting glucose and lipid levels, and blood pressure. Periodical measurement of fasting insulin is not recommended for clinical care because of the absence of criteria to differentiate normal from abnormal. Obviously, additional monitoring and testing should be performed when indicated, for example, in case of a positive family history for DM or cardiometabolic diseases.

"GH treatment is well tolerated and serious adverse effects are uncommon."

Table 9. Standard of Care for the Monitoring During GH Treatment of Children Born SGA Who Are Short

	At Start of GH Treatment	Every 3 to 4 Months During GH Treatment	Yearly During GH Treatment	At Cessation of GH Treatment
Physical examination				
Height	X	X	X	X
Weight	X	X	X	X
Blood pressure	X	—	X	X
Tanner stage	X	X	X	—
Laboratory investigations				
IGF-1, IGFBP-3	X	—	X	X
Thyroid function tests: TSH, free T4	X	—	X	X
Lipid levels: cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides	X	—	—	X
Glucose metabolism: fasting glucose and insulin, HbA1c	X	—	—	X
Imaging				
X-ray hand/wrist	X	—	X[a]	X

The contents of this table are based on Clayton *et al.* (350) and our own clinical experience.
[a]In prepuberty twice yearly.

Summary

GH treatment in short children born SGA increases longitudinal growth and adult height, and it has positive effects on cardiometabolic health and possibly cognitive functioning (Fig. 4). The addition of GnRHa for 2 years in early pubertal children with a low predicted adult height appears to improve adult height gain. The safety profile of GH treatment alone or combined with GnRHa is good.

Epidemiological and Longitudinal Observations in Growth Hormone–Treated Adults Born SGA

Because lower birth weight is associated with cardiovascular and metabolic diseases in later adulthood (536, 537), and because GH treatment reduces insulin sensitivity and has stimulating effects on tumor cell proliferation (538), concerns were raised about the long-term side effects of GH treatment.

In an attempt to evaluate long-term mortality in patients treated with GH during childhood, the Safety and Appropriateness of Growth Hormone Treatments in Europe project was launched in eight European Union countries (539). Preliminary French data suggested that GH treatment during childhood might increase the risk of cardiovascular mortality in SGA-born subjects (540). However, these findings could not be replicated by the preliminary data from three other countries (Belgium, Netherlands, and Sweden) participating in the same project (541). The data from these countries showed that there were no deaths due to any form of cardiovascular disease or cancer (542). One of the main limitations of the Safety and Appropriateness of Growth Hormone Treatments in Europe project, however, is that data of participants were compared with national reference data and not with an appropriate control group of untreated short subjects born SGA.

Recently, a large cohort of GH-treated young adults born SGA was investigated during 5 years after discontinuation of GH treatment of cardiometabolic risks (381, 383, 531). It included previously GH-treated adults born SGA (n = 88) who were compared with untreated controls (n = 285), consisting of 51 untreated adults born SGA with short stature (below −2 SDS), 92 adults born SGA who experienced spontaneous catch-up growth to a normal stature (above −1 SDS), and 142 adults born AGA with a normal stature (above −1 SDS) (381, 383). Discontinuation of GH treatment was associated with a significant increase in percentage body fat and fat mass SDS, whereas lean body mass SDS decreased (542). The gradual increase in fat mass percentage persisted until at least 5 years after discontinuation of GH treatment, and could not be explained by aging or by lower serum IGF-1 level, indicating that the changes reflected the loss of GH-mediated lipolysis (383). A persistent increase in fat mass over time could have detrimental effects on metabolic and cardiovascular health, and longer term follow-up is therefore necessary. Lean body mass

decreased during the first 6 months after GH cessation but stabilized thereafter. At 5 years after discontinuation of GH treatment, lean body mass was similar compared with levels at discontinuation of treatment (383).

Besides the longitudinal changes during 5 years after discontinuation of GH treatment, body composition of previously GH-treated SGA subjects was comparable to untreated subjects. GH-treated adults born SGA had a similar fat mass at 5 years after discontinuation of GH treatment as untreated short adults born SGA, adults born SGA with spontaneous catch-up growth, and adults born AGA (380, 383). However, lean body mass was lower in all categories of SGA-born subjects compared with AGA subjects, suggesting programming of lean body mass by (factors associated with) SGA rather than by postnatal growth or GH treatment.

Studies on insulin sensitivity in the first year after discontinuation of GH treatment reported variable results, with some studies describing an increase in insulin sensitivity to age-matched controls (15, 514) and another study reporting no change in insulin sensitivity after discontinuation of treatment (511). Studies on insulin sensitivity based on the frequently sampled intravenous glucose tolerance test showed that the GH-induced lower insulin sensitivity increased during 6 months after discontinuation of GH treatment and remained stable thereafter until at least 5 years after discontinuation of treatment (383, 542). At 5 years after discontinuation of GH treatment, insulin sensitivity and β-cell function were similar in previously GH-treated SGA adults and untreated adults. Adults born SGA with spontaneous catch-up growth to a normal height and weight had the lowest insulin sensitivity at 21 years of age, which is consistent with previous findings showing that accelerated catch-up in weight relative to length in early life was associated with a less favorable cardiometabolic health profile in adulthood (10, 376, 384).

After discontinuation of GH treatment, systolic and diastolic blood pressure initially increased, followed by a decrease, resulting in a similar blood pressure at 5 years after discontinuation of treatment compared with levels at discontinuation of treatment (381, 393). There is only one study reporting on cIMT after discontinuation of GH treatment in adults born SGA, showing that cIMT did not change after discontinuation of GH treatment (381). The beneficial effect of GH treatment on serum lipid levels was sustained during 5 years after discontinuation of treatment (381). Besides insulin sensitivity and β-cell function, also lipid levels and BMD were similar between GH-treated adults born SGA and untreated short adults born SGA (382, 393, 531). Serum lipid levels were significantly lower in GH-treated subjects compared with untreated short adults born SGA (381). The prevalence of metabolic syndrome was similar in GH-treated SGA adults and untreated short adults born SGA (383).

In contrast, the beneficial effect of GH treatment on BMD during treatment was followed by a trend toward a gradual deterioration after GH discontinuation (531). At discontinuation of GH treatment, total-body BMD was −0.4 SDS in males and −0.5 SDS in females. During 5 years after discontinuation of GH treatment total-body BMD decreased in males to −0.6 SDS whereas it remained similar in females. The mean BMD of the lower spine decreased in both males and females after discontinuation of GH treatment, but remained above −1 SDS (531).

In conclusion, at age 21 years metabolic and cardiovascular health in previously GH-treated adults born SGA was similar to that of untreated short adults born SGA or AGA, indicating that long-term GH treatment during childhood has no unfavorable effects in young adulthood (381, 383). Longer follow-up is required to investigate whether differences in cardiometabolic health emerge with age.

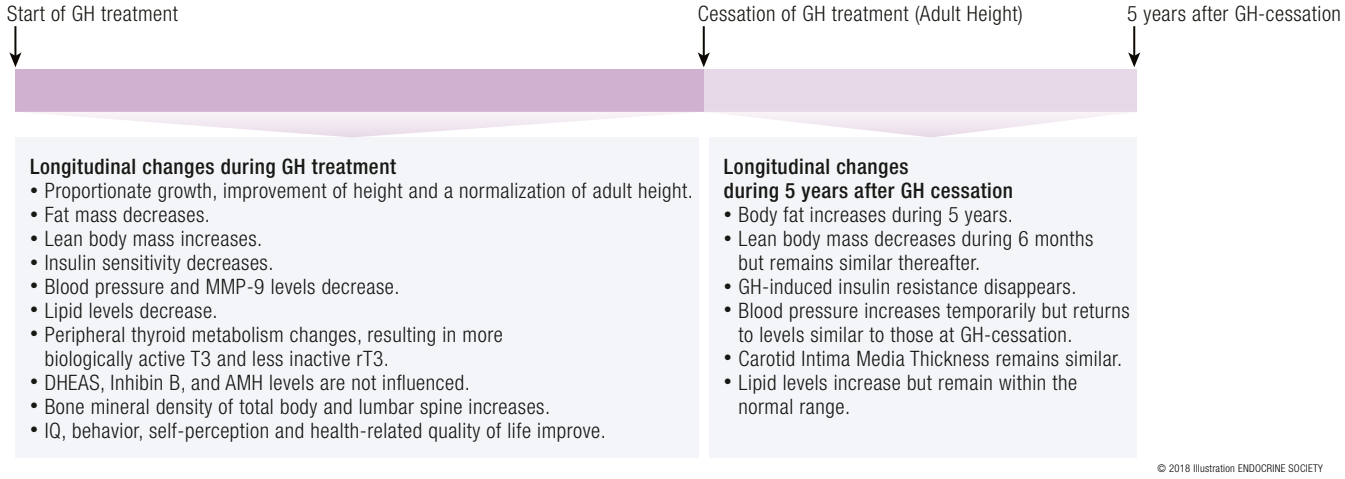


Figure 4. Effects of GH treatment during and after cessation of treatment in SGA-born subjects. DHEAS, dehydroepiandrosterone sulfate; MMP-9, matrix metallopeptidase 9. [© 2018 Illustration ENDOCRINE SOCIETY].

Suggestions for Follow-Up of Previously GH-Treated Adults Born SGA

At present, there is limited knowledge as to how often previously GH-treated adults born SGA should be monitored. Based on the gradual increase in fat mass after discontinuation of GH treatment, previously GH-treated adults born SGA may be advised to adopt a healthy life style, and not to become overweight. The frequency and intensity of cardiovascular and metabolic disease monitoring will vary depending on factors such as the presence of overweight and a family history of DM and/or cardiometabolic diseases. When none of these risk factors is present, no regular follow-up may be required (2). However, we would advise previously GH-treated adults born SGA to seek medical consultation in case of chronic fatigue, considerable weight gain, and hypertension, particularly in case of a family history of DM, cardiovascular disease, or hypertension (532). Besides, based on the available data it seems important to also inform SGA-born subjects with spontaneous catch-up growth to a normal stature that they might have a higher risk of metabolic and cardiovascular diseases in later life, because metabolic alterations are particularly evident in these SGA-born subjects. As subjects with SRS have medical problems beyond short stature and the long-term health profile of older subjects with SRS is not yet known, we recommend transition of previously GH-treated subjects with SRS from the pediatric endocrine to an adult endocrine care setting.

Conclusions

The causes of SGA are multifactorial. Clinicians should attempt to establish the causes leading to SGA, particularly if GH treatment is considered for persistent short stature, because in some syndromes GH treatment is contraindicated or adaptation of the GH dose is needed.

Clinicians should use appropriate charts for the assessment of fetal growth. If available, a growth chart from the background population should be used. It is currently unclear whether customization for factors known to influence fetal growth adds value. For the assessment of postnatal growth representative charts should be used to allow appropriate monitoring of postnatal (catch-up) growth.

SGA poses a risk factor for several infant and adult conditions. It is, therefore, paramount to reduce the number of SGA births. Possible strategies to do this include smoking cessation intervention programs, prevention of maternal underweight, and early identification (and prompt treatment) of pregnancies at risk for preeclampsia. After birth, rapid weight gain should be avoided, given the evidence suggesting that the metabolic consequences of being born SGA can be mitigated by ensuring appropriate catch-up growth while avoiding excessive weight gain.

Nonsyndromic short children born SGA as well as children with SRS are amenable to GH treatment. A set of recent data has shown that the average gain in adult height is 1.25 SDS, with considerable variation in the response to treatment. Add-on treatment with a GnRHa may result in an even greater height gain, and may thus be considered in children with a predicted adult height below −2.5 SDS at early puberty. Longer-term follow-up data have shown that no unfavorable effects are to be expected at young adult age. However, it remains to be explored whether side effects emerge with age.

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Abbreviations

11β-HSD, 11β-hydroxysteroid dehydrogenase; AGA, appropriate for gestational age; ALS, acid-labile subunit; AMH, anti-Müllerian hormone; BMD, bone mineral density; BMI, body mass index; cIMT, carotid intima media thickness; CNV, copy number variant; DM, diabetes mellitus; EUGR, extrauterine growth restriction; FGF, fibroblast growth factor; GHV, GH variant; GnRHa, GnRH agonist; HRQoL, health-related quality of life; ICR, imprinting control region; IGFBP, IGF binding protein; IGF1R, IGF-1 receptor; ISS, idiopathic short stature; IUGR, intrauterine growth restriction; LOM, loss of methylation; LTL, leukocyte telomere length; MIM, Mendelian Inheritance in Man; PAPP-A, pregnancy-associated plasma protein-A; PWS, Prader–Willi syndrome; SDS, SD score; SGA, small for gestational age; SHOX, short stature homeobox; SNP, single nucleotide polymorphism; SRS, Silver–Russell syndrome; UPD, uniparental disomy; upd(7)mat, maternal uniparental disomy of chromosome 7.