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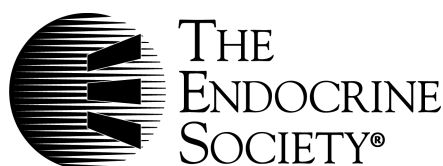
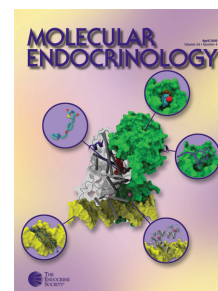
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Management of the Child Born Small for Gestational Age through to Adulthood: A Consensus Statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society

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CONSENSUS STATEMENT: Management of the Child Born Small for Gestational Age through to Adulthood: A Consensus Statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society

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Objective: Low birth weight remains a major cause of morbidity and mortality in early infancy and childhood. It is associated with an increased risk of health problems later in life, particularly coronary heart disease and stroke. A meeting was convened to identify the key health issues facing a child born small for gestational age (SGA) and to propose management strategies.

Participants: There were 42 participants chosen for their expertise in obstetrics, peri- and neonatal medicine, pediatrics, pediatric and adult endocrinology, epidemiology, and pharmacology.

Evidence: Written materials were exchanged, reviewed, revised, and then made available to all. This formed the basis for discussions at the meeting. Where published data were not available or adequate, discussion was based on expert clinical opinions.

Consensus Process: Each set of questions was considered by all and then discussed in plenary sessions with consensus and unresolved issues identified. The consensus statement was prepared in plenary

sessions and then edited by the group chairs and shared with all participants.

Conclusions: The diagnosis of SGA should be based on accurate anthropometry at birth including weight, length, and head circumference. We recommend early surveillance in a growth clinic for those without catch-up. Early neurodevelopment evaluation and interventions are warranted in at-risk children. Endocrine and metabolic disturbances in the SGA child are recognized but infrequent. For the 10% who lack catch-up, GH treatment can increase linear growth. Early intervention with GH for those with severe growth retardation (height SD score, < -2.5 ; age, 2–4 yr) should be considered at a dose of 35–70 $\mu\text{g/kg}\cdot\text{d}$. Long-term surveillance of treated patients is essential. The associations at a population level between low birth weight, including SGA, and coronary heart disease and stroke in later life are recognized, but there is inadequate evidence to recommend routine health surveillance of all adults born SGA outside of normal clinical practice. (*J Clin Endocrinol Metab* 92: 804–810, 2007)

LOW BIRTH WEIGHT remains a major cause of morbidity and mortality in early infancy and childhood throughout the world (1). In addition, being born small has been associated with increased mortality from a wide range of disorders, in particular coronary heart disease (CHD) and stroke (2). For children born small for gestational age (SGA), it is important to integrate such data into their health-care management. Therefore, a meeting was convened in Manchester, United Kingdom, in February 2006, with representation from pediatric endocrine societies and the Growth Hormone Research Society, to examine current data relevant to the early, mid-, and long-term outcome of children born SGA. This statement presents a summary of key

health issues and proposed management of these children while recognizing topics that require further investigation.

Definition

The definition of SGA is not straightforward. It requires the following: 1) accurate knowledge of gestational age (ideally based on first trimester ultrasound exam), 2) accurate measurements at birth of weight, length, and head circumference, and 3) a cutoff against reference data from a relevant population. This cutoff has been variably set at the 10th centile, 3rd centile, or at less than -2 SD from the mean (~ 2 nd centile) (3). We recommend that SGA should be defined as a weight and/or length less than -2 SD because this will identify the majority of those in whom ongoing growth assessment is required.

Babies can then be subclassified into SGA for weight, SGA for length, or SGA for both weight and length (3). Additionally, those SGA babies who have small head circumference should be recognized. This subclassification may help in understanding the mechanisms and implications of being born SGA.

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Abbreviations: AGA, Appropriate for gestational age; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; HPA, hypothalamic-pituitary-adrenal; IUGR, intrauterine growth retardation; SDS, SD score; SGA, small for gestational age.

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With knowledge of intrauterine growth performance, it is possible to identify intrauterine growth retardation (IUGR; slow fetal growth based on two ultrasound measurements), which may result in a SGA baby. IUGR babies irrespective of birth size may require ongoing surveillance.

Definition of SGA does not take into account background growth-modifying factors such as maternal size, ethnicity, and parity. These modifying factors can be used in statistical computations to generate a corrected birth weight, which increases the chance of correctly identifying a baby with abnormal fetal growth (4). Application of this method to those with modest growth restriction (birth size between the 3rd and 10th percentiles) may allow identification of pathological growth within this group. Infants identified in this way have a higher risk of perinatal morbidity than those identified by an anthropometric definition. The concept of a customized individual growth assessment has merit in the perinatal period but as yet has an unproven role in identification of those at risk of long-term morbidity.

Identification of the SGA and/or IUGR baby is important because these infants are at an increased risk for perinatal morbidity, associated health problems (such as neurodevelopmental disorders), persistent short stature, and metabolic alterations in later life.

Early Growth and Development

Growth

Children born SGA are shorter during childhood and as adults, reaching adult heights that on average are approximately 1 SD lower than the mean (5, 6). The typical infant born SGA experiences a period of accelerated linear growth during the first 12 months of life that results in a stature above -2 SD in up to 90%. Most of the catch-up growth occurs during the first year and is near completion by 2 yr of age (5, 7). Those born very prematurely and with more severe degrees of growth retardation, especially reduced birth length, are less likely to reach a stature within the normal range, whereas those with taller parents are more likely to reach a normal adult height (8). Catch-up growth may be incomplete in recognized syndromes, such as Silver Russell or 3M. Neither circulating concentrations of GH, IGF-I, IGF-binding protein-3 nor ponderal index are predictive of subsequent growth (9). The relationship between etiology of fetal growth retardation and postnatal growth pattern is not extensively delineated.

We recommend that a child born SGA should have measurements of length, weight, and head circumference every 3 months for the first year of life and every 6 months thereafter. Those individuals who do not manifest significant catch-up growth in the first 6 months of life or those who remain short by 2 yr of age may have other conditions that limit growth. These should be identified and managed.

The preterm infant is a special case. The preterm SGA infant can take four or more years to achieve a height in the normal range (10). The preterm infant born appropriate for gestational age (AGA) often grows slowly in the first weeks, and the risk of this is increased with increasing prematurity (11). These infants are small at expected date of delivery.

Body composition

Individuals born SGA have low lean mass and may have increased central adiposity. Dual-energy x-ray absorptiometry is the definitive investigation to assess body composition and is used for research purposes. Body mass index (BMI) is used for clinical purposes but is of limited value in defining body composition in SGA children because of its poor prediction of lean tissue and fat compartments.

Birth weight is weakly positively associated with later BMI (12), whereas rapid weight gain in infancy is associated with increased incidence of obesity in later life (13, 14). Two systematic reviews have shown that breast feeding in infancy may protect against the long-term risk of developing obesity (15, 16). However, neither specifically addressed SGA infants. Nevertheless, in view of these data, calorie-dense feeding for SGA infants may not be appropriate.

Neurological and intellectual consequences

In large observational studies, cognitive impairment is independently associated with low birth weight, short birth length, and small head circumference for gestational age. The effect is moderate but significant. Those without catch-up in height and/or head circumference have the worst outcome (17, 18). Being born SGA is associated in particular with lower cognitive ability in mathematics and reading comprehension and with more emotional, conduct, and attention deficit hyperactivity disorders. In view of these data, early neurodevelopment evaluation and interventions are warranted in at-risk children.

Long-term exclusive breastfeeding (24 wk or more) may prevent some of the intellectual impairment (19). GH treatment induces catch-up growth in head circumference particularly in those with small head circumference at birth. There is some evidence that GH also improves IQ in short SGA children, but additional data are required (20). Long-term outcome data for children born SGA show no difference in frequency of employment, marital status, or satisfaction with life. However, these individuals hold fewer professional or managerial jobs and have significantly lower income than individuals of normal size at birth (21).

Endocrine Consequences

Intrauterine endocrine programming

There is experimental evidence in animal models for the presence of intrauterine programming of growth, weight gain, puberty, and metabolic and endocrine function (22). However, in humans, the evidence for programming is limited (23).

GH-IGF axis

The GH-IGF axis has been extensively studied in SGA children. Classic GHD is rare in this population. However, alterations in diurnal GH secretion patterns have been observed but are of limited diagnostic and prognostic utility (24, 25). Mean IGF-I and IGF-binding protein-3 levels are reduced in SGA children by approximately 1 SD, but the range of levels is wide, indicating possible heterogeneity in the mechanisms of growth failure from insufficient IGF-I

generation to IGF-I insensitivity (26–28). The status of the GH-IGF axis at birth or in early postnatal life is not predictive of later growth, and therefore hormone measurements in the SGA infant or child are not indicated in routine care (9).

However, in the short SGA child, assessment of the GH-IGF-I axis may be required if growth velocity is persistently reduced and signs of GH deficiency or hypopituitarism are present. Genetic abnormalities and polymorphisms in the GH-IGF axis have been associated with small size at birth and reduced postnatal growth. These include IGF-I and IGF-I receptor gene deletions, point mutations, and polymorphisms (29–32). However, current diagnostic utility of genetic analysis is limited. Additional research is needed to identify other candidate genes such as insulin and IGF-II.

Hypothalamic-pituitary-adrenal (HPA) axis

In animal models of prenatal stress, maternal malnutrition and maternal corticosteroid therapy have produced low-birth-weight offspring with basal and stimulated HPA hyperactivity and life-long hypertension and glucose intolerance (33, 34). Studies in humans to date suggest that there is no lasting effect of prenatal glucocorticoids on function of the postnatal HPA axis. Therefore, assessment of the HPA axis in the SGA child is not recommended.

Puberty and adrenarche

Most children born SGA have pubertal timing within normal limits (35). However, some studies in boys and girls born SGA indicate that pubertal growth is modestly decreased, whereas in girls, menarche occurs 5–10 months earlier than normal. These aberrations may result in a reduced adult stature (36, 37). In those who do have early puberty, there is typically a rapid progression through puberty leading to loss of adult height (38, 39). The variations in pubertal timing and progression recognized in the SGA child are likely to be related to many factors, including ethnicity, background population trends, nutrition, and other unknown influences.

SGA girls who display rapid weight gain during early childhood are more likely to have premature adrenarche (40–43). Puberty and menarche in SGA girls with premature adrenarche can be earlier than in AGA girls with premature adrenarche (44). Adrenarche onset is not different from the general population in children born SGA who do not catch up in height and weight.

Bone age is a poor predictor of pubertal timing and of adult height in SGA children (45). Its assessment is not recommended during routine follow-up.

In boys born SGA, hypospadias and cryptorchidism are more common (46).

Ovarian function

There are no substantial data to support ovarian dysfunction, reduced fertility, or early menopause in those born SGA (47, 48). However, some adolescents who were born SGA may have reduced ovulation rates, increased secretion of adrenal and ovarian androgens, excess abdominal fat (even in the absence of obesity), and hyperinsulinemia (47, 49). In these young women with evidence of clinical androgen ex-

cess, investigation in a standard manner is recommended. This variation in the frequency of polycystic ovary syndrome in women born SGA may be due to ethnic and geographic background and variation in the definition of the syndrome.

Thyroid and bone metabolism

There is currently no evidence for major alteration of the thyroid axis (27). In relation to bone health, being born SGA has been associated with reduced bone mineral content and bone mineral density, but the association is greatly reduced once adjusted for adult height (50). Low birth weight is not a significant predictor of fractures in adults (51).

Metabolic Consequences

Definition and assessment

Metabolic syndrome or the insulin resistance syndrome is a cluster of metabolic abnormalities characterized by insulin resistance/hyperinsulinemia, abnormalities in glucose metabolism, dyslipidemia, hypertension, and obesity (52). As in adulthood, there is no consensus regarding the definition of the metabolic syndrome in childhood.

Although the ideal means of evaluating insulin resistance is the hyperinsulinemic-euglycemic clamp, practical means of monitoring metabolic risk factors include measurement of blood pressure (BP), BMI, fasting glucose, and lipids. The measurement of fasting insulin is not recommended for clinical care because of the absence of accepted criteria to differentiate normality from abnormality. There are no established definitions in childhood for normal body composition, but BMI is the best clinical surrogate. Reference data are available from the International Obesity Task Force, the Centers for Disease Control, and other regional data.

Metabolic status in childhood, adolescence, and young adulthood in those born SGA

In children born SGA, insulin resistance may be present as early as 1 yr (53), and in prepubertal children, this is more evident in those with rapid weight gain and a BMI of at least 17 kg/m² (54, 55). Limited studies in SGA adolescents and young adults have shown that insulin-mediated glucose uptake is lower than in individuals with normal birth weight (6, 56), whereas those born SGA who develop high BMI in childhood are at increased risk of developing abnormal glucose metabolism in adulthood (57). Young adults born SGA have a higher incidence of metabolic risk factors (2.3%) than those born AGA (0.4%) (58). Nevertheless, the overall prevalence of risk factors is very low.

There is, however, no evidence that type 2 diabetes mellitus, impaired glucose tolerance, or dyslipidemia occurs more commonly among children born SGA than in the normal childhood population (59). There is a small effect of SGA on BP, primarily systolic, but no increased risk of childhood or adolescent hypertension (59, 60).

Although in well-established cohorts (61–63), there is evidence of tracking of metabolic risk factors from childhood to adulthood, there are no such data specifically for SGA children. As in the general childhood population, obesity and accelerated weight gain are likely to be major risk factors.

Neither the prevalence of SGA in childhood obesity nor the prevalence of obesity in SGA is known.

It is recognized that any risk for metabolic disorders associated with SGA can be amplified by the presence of other risk factors, such as weight gain, ethnicity, and family history. Nevertheless, routine evaluation of metabolic parameters is not justified in all children born SGA. Management of obese SGA children should occur in line with general pediatric practice, including lifestyle interventions.

Endocrine Management: Growth and Puberty

Early evaluation of short children born SGA is recommended, and those under 2 yr of age with a current length below -2.5 sd should be referred for evaluation. Short children born SGA form a heterogeneous group with various etiologies, and treatment should be preceded by an effort to identify the diagnosis.

The use of GH in short children born SGA has been explored for nearly 40 yr (64–66). This has led to official indications by the Food and Drug Administration in 2001 and by the European Agency for the Evaluation of Medicinal Products in 2003 (Table 1).

Factors associated with the response to GH over the first 2–3 yr include age and height sd score (SDS) at start of treatment, midparental height, and dose. Average height gains after 3 yr of GH treatment range from 1.2–2.0 sd for doses of 35–70 $\mu\text{g}/\text{kg}\cdot\text{d}$. After the initial catch-up, most of this height gain is maintained up to adult height. The maintenance phase of GH treatment seems to be less dose dependent (66). Children with a recognized syndrome respond less well to GH than those with nonsyndromic SGA (66).

The discrepancies between the two approved indications are recognized (67). It is proposed that SGA children aged between 2–4 yr who show no evidence of catch-up with a height less than -2.5 sd should be eligible for GH treatment. In addition, for those SGA children over 4 yr old who are showing no evidence of catch-up, there was discussion about whether the cutoff for GH treatment should be at a height SDS of less than -2 or less than -2.5 . No consensus was obtained, although a majority was in favor of initiating treatment at a height SDS of less than -2 . With regard to GH dose, it is proposed that the starting dose should cover the range 35–70 $\mu\text{g}/\text{kg}\cdot\text{d}$, with the higher doses used in those with the most marked growth retardation.

In the majority of short SGA children treated with GH during childhood, pubertal development begins on time and progresses normally (68). At present, there is no convincing evidence that the addition of GnRH analog treatment to inhibit pubertal progression is associated with additional height gain.

There should be a positive response to GH treatment (height velocity SDS more than $+0.5$ in the first year of treatment). If there is an inadequate response, reevaluation is indicated, including consideration of compliance, GH dose, diagnosis, and the decision to discontinue treatment. In those with a positive response to GH, withdrawal of GH therapy after 2–3 yr leads to catch-down growth and is not recommended (66). Discontinuation of GH treatment in adolescence is recommended when the growth rate falls to less than 2 cm/yr.

Pretreatment IGF-I levels may have a role in predicting responsiveness to GH (69), whereas in those children receiving GH, IGF-I monitoring as a tool for dose optimization may be useful. In all other respects, standard monitoring of GH therapy should be applied (70). Some syndromes (*e.g.* Bloom and Fanconi) may carry a specific risk, which may contraindicate GH treatment.

Treatment-emergent adverse events are not more common in this population than in other conditions treated with GH, nor have additional safety concerns arisen (71). It is currently unknown whether GH therapy for the SGA subject through childhood and adolescence is associated with benefits or amplification of risks (such as metabolic consequences) in adult life.

Consequences in Adulthood

There is a large body of evidence that suggests that low birth weight is associated with a wide range of metabolic and physiological disorders in later life (2). However, systematic reviews have suggested that the associations are small and that the possible impact on public health is uncertain (15, 72). The following discussion refers to risks in populations as opposed to individual risk. Most of the data are derived from cohorts not specifically restricted to SGA individuals.

Cardiovascular and metabolic consequences

Most of the evidence for the associations between birth weight and subsequent outcomes is derived from observational studies, so that there is potential for confounding. For example, poor socioeconomic position is associated with both lower birth weight and increased levels of cardiovascular risk factors in later life (*e.g.* obesity, BP, and smoking) (73, 74).

A modest positive association between birth weight and subsequent BMI and waist circumference has been reported (75). The typical effect size ranges from 0.6–0.7 kg/m^2 for each 1-kg increment in birth weight (75). In a systematic review, obesity risk has been reported to be related to rapid weight gain in infancy (12).

TABLE 1. GH use in short SGA children

	FDA-approved indication (2001)	EMA-approved indication (2003)
Age at start (yr)	2	4
Height SDS at start	Not stated	-2.5 sd
Growth velocity before treatment	No catch-up	<0 sd for age
Reference to midparental height	Not stated	Height SDS > 1 sd below midparental height SDS
Dose ($\mu\text{g}/\text{kg}\cdot\text{d}$)	70	35

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

An inverse association was also reported in many studies between birth weight and both BP and hypertension, but the overall effect size was 0.5 mm Hg lower systolic BP per 1-kg higher birth weight (72). There is little evidence that variation in preterm nutrition is associated with raised BP in later life (76).

For CHD, a 1-kg higher birth weight is associated with 10–20% lower incidence of CHD (Huxley, R., personal communication). However, potential residual confounders include maternal smoking and parental hypertension. A recent systematic review of cardiovascular disease has indicated that a 1-kg higher birth weight is associated with a 20% lower risk of CHD and stroke (77).

Both small and large size at birth has been reported to be associated with increased risk of type 2 diabetes and glucose intolerance (78).

Cancer

Low birth weight has not been shown to be associated with increased risk of cancer in general with the possible exceptions of testicular and to a lesser extent renal cancer (79, 80). By contrast, there is good evidence that high birth weight is associated with an increased risk of cancer, best documented for breast cancer (81, 82).

Intergenerational effects

Women (and possibly men) who were themselves SGA are reported to be at increased risk of having a SGA infant (83). Women born SGA are also at increased risk of preeclampsia and gestational diabetes (83).

Summary

Based on these population data, there is insufficient evidence to justify specific surveillance of adults born SGA. Screening procedures for cardiovascular risk factors, cancer, and osteoporosis should be in accordance with current clinical practice. Lifestyle interventions seem equally appropriate for this group as in the general population.

There are no long-term surveillance data on adults who have been treated with GH for short stature due to SGA. It is therefore prudent to follow up this group systematically.

Conclusions

The diagnosis of SGA should be based on accurate anthropometry at birth including weight, length, and head circumference. We recommend early surveillance in a growth clinic for those with lack of catch-up. Early intervention with GH for those with severe growth retardation should be considered. Long-term surveillance of all those who receive GH is essential. In view of the cognitive impairment reported in some children born SGA, early neurodevelopment evaluation and interventions are warranted in at-risk children.

Endocrine and metabolic disturbances in the SGA child are recognized, but there is no evidence to recommend routine investigation of all SGA children. We recognize significant gaps in knowledge with regard to the genesis of metabolic profile and outcome in SGA children. Research studies using

genomic, proteomic, and/or metabolomic approaches are likely to identify risk factors related to fetal and postnatal growth that generate insulin resistance and associated complications.

The associations at a population level between low birth weight, including those born SGA, and CHD and stroke in later life are recognized, but there is inadequate evidence to recommend routine health surveillance of all adults born SGA outside of normal clinical practice.

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References

1. **World Health Organization** 2002 WHO report: reducing risks, promoting healthy life. Geneva: World Health Organization
2. **Barker DJ** 1998 Mothers, babies, and disease in later life. London: British Medical Journal Publishing Group
3. **Lee PA, Chernauek SD, Hokken-Koelega AC, Czernichow P** 2001 International Small for Gestational Age Advisory Board consensus development conference statement: management of the short child born small for gestational age. *Pediatrics* 111:1253–1261
4. **Gardosi J** 2005 Fetal growth: towards an international standard. *Ultrasound Obstet Gynecol* 26:112–114
5. **Karlberg J, Albertsson-Wikland K** 1995 Growth in full term small-for-gestational-age infants: from birth to final height. *Pediatr Res* 38:733–739
6. **Léger J, Levy-Marchal C, Bloch J, Pinet A, Chevenne D, Porquet D, Collin D, Czernichow P** 1997 Reduced final height and indications for early development of insulin resistance in a 20 year old population born small for gestational age: regional cohort study. *BMJ* 315:341–347
7. **Hokken-Koelega AC, De Ridder MA, Lemmen RJ, Den Hartog H, De Muinck Keizer-Schrama SM, Drop SL** 1995 Children born small for gestational age: do they catch up? *Pediatr Res* 38:267–271
8. **Luo ZC, Albertsson-Wikland K, Karlberg J** 1998 Length and body mass index at birth and target height influences on patterns of postnatal growth in children born small for gestational age. *Pediatrics* 102:E72
9. **Leger J, Noel M, Limal JM, Czernichow P** 1996 Growth factors and intrauterine growth retardation. II. Serum growth hormone, insulin-like growth factor (IGF) I, and IGF-binding protein 3 levels in children with intrauterine growth retardation compared with normal control subjects: prospective study from birth to two years of age. *Study Group of IUGR. Pediatr Res* 40:101–107
10. **Gibson AT, Carney S, Cavazzoni E, Wales JK** 2000 Neonatal and postnatal growth. *Horm Res* 53(Suppl 1):42–49
11. **Wit JM, Finken MJ, Rijken M, de Zegher F** 2006 Preterm growth restraint: a paradigm that unifies intrauterine growth retardation and preterm extrauterine growth retardation and has implications for the small-for-gestational-age indication in growth hormone therapy. *Pediatrics* 117:e793–e795
12. **Rogers I, EURO-BLCS Study Group** 2003 The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life. *Int J Obes Relat Metab Disord* 27:755–777
13. **Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C** 2005 Being big or growing fast: systematic review of size and growth in infancy and later obesity. *BMJ* 331:929
14. **Monteiro PO, Victora CG** 2005 Rapid growth in infancy and childhood and obesity in later life: a systematic review. *Obes Rev* 6:143–154
15. **Arenz S, Ruckerl R, Koletzko B, Von Kries R** 2004 Breast-feeding and childhood obesity. *Int J Obes* 28:1247–1256
16. **Owen CG, Martin RM, Whincup PH, Davey Smith G, Cook DG** 2005 Effect of infant feeding on the risk of obesity across the life course. *Pediatrics* 115:1367–1377
17. **Sommerfelt K, Markestad T, Ellertsen B** 1998 Neuropsychological performance in low birth weight preschoolers: a population-based, controlled study. *Eur J Pediatr* 157:53–58
18. **Lundgren EM, Cnattingius S, Jonsson B, Tuvemo T** 2001 Intellectual and psychological performance in males born small for gestational age with and without catch-up growth. *Pediatr Res* 50:91–96
19. **Rao M, Hediger ML, Levine RJ, Naficy AB, Vik T** 2002 Effect of breastfeeding on cognitive development of infants born small for gestational age. *Acta Paediatr* 91:267–274
20. **van Pareren YK, Duivenvoorden HJ, Slijper FS, Koot HM, Hokken-Koelega AC** 2004 Intelligence and psychosocial functioning during long-term growth hormone therapy in children born small for gestational age. *J Clin Endocrinol Metab* 89:5295–5302
21. **Strauss RS** 2000 Adult functional outcome of those born small for gestational age: twenty-six-year follow-up of the 1970 British Birth Cohort. *JAMA* 283:625–632
22. **Fowden AL, Forhead AJ** 2004 Endocrine mechanisms of intrauterine programming. *Reproduction* 127:515–526
23. **Geremia C, Cianfarani S** 2006 Laboratory test and measurements in children born small for gestational age (SGA). *Clin Chim Acta* 364:113–123
24. **de Waal WJ, Hokken-Koelega AC, Stijnen T, de Muinck Keizer-Schrama SM, Drop SL** 1994 Endogenous and stimulated GH secretion, urinary GH excretion, and plasma IGF-I and IGF-II levels in prepubertal children with short stature after intrauterine growth retardation. The Dutch Working Group on Growth Hormone. *Clin Endocrinol (Oxf)* 41:621–630
25. **Boguszewski M, Rosberg S, Albertsson-Wikland K** 1995 Spontaneous 24-hour growth hormone profiles in prepubertal small for gestational age children. *J Clin Endocrinol Metab* 80:2599–2606
26. **Albertsson-Wikland K, Boguszewski M, Karlberg J** 1998 Children born small for gestational age: postnatal growth and hormonal status. *Horm Res* 49(Suppl 2):7–13
27. **Cianfarani S, Maiorana A, Geremia C, Scire G, Spadoni GL, Germani D** 2003 Blood glucose concentrations are reduced in children born small for gestational age (SGA), and thyroid-stimulating hormone levels are increased in SGA with blunted postnatal catch-up growth. *J Clin Endocrinol Metab* 88:2699–2705
28. **Tenhola S, Halonen P, Jaaskelainen J, Voutilainen R** 2005 Serum markers of GH and insulin action in 12-year-old children born small for gestational age. *Eur J Endocrinol* 152:335–340
29. **Woods KA, Camacho-Hubner C, Savage MO, Clark AJ** 1996 Intrauterine growth retardation and postnatal growth failure associated with deletion of the insulin-like growth factor I gene. *N Engl J Med* 335:1363–1367
30. **Abuzzahab MJ, Schneider A, Goddard A, Grigorescu F, Lautier C, Keller E, Kiess W, Klammt J, Kratzsch J, Osgood D, Pfaffle R, Raile K, Seidel B, Smith RJ, Chernauek SD** 2003 Intrauterine Growth Retardation (IUGR) Study Group: IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. *N Engl J Med* 349:2211–2222
31. **Vaessen N, Janssen JA, Heutink P, Hofman A, Lamberts SW, Oostra BA, Pols HA, van Duijn CM** 2002 Association between genetic variation in the gene for insulin-like growth factor-I and low birthweight. *Lancet* 359:1036–1037
32. **Arens N, Johnston L, Hokken-Koelega A** 2002 Polymorphism in the IGF-I gene: clinical relevance for short children born small for gestational age (SGA). *J Clin Endocrinol Metab* 87:2720
33. **Langley-Evans SC, Gardner DS, Jackson AA** 1996 Maternal protein restriction influences the programming of the rat hypothalamic-pituitary-adrenal axis. *J Nutr* 126:1578–1585
34. **Nyirenda MJ, Lindsay RS, Kenyon CJ, Burchell A, Seckl JR** 1998 Glucocorticoid exposure in late gestation permanently programs rat hepatic phosphoenolpyruvate carboxykinase and glucocorticoid receptor expression and causes glucose intolerance in adult offspring. *J Clin Invest* 101:2174–2181
35. **Preece MA** Puberty in children with intrauterine growth retardation. *Horm Res* 48(Suppl 1):30–32
36. **Bhargava SK, Ramji S, Srivastava U, Sachdev HP, Kapani V, Datta V, Satyanarayana L** 1995 Growth and sexual maturation of low birthweight children: a 14 year follow-up. *Indian Pediatr* 32:963–970
37. **Persson I, Ahlsson F, Ewald U, Tuvemo T, Qingyuan M, von Rosen D, Proos L** 1999 Influence of perinatal factors on the onset of puberty in boys and girls: implications for interpretation of link with risk of long term diseases. *Am J Epidemiol* 150:747–755
38. **Albertsson-Wikland K, Boguszewski M, Karlberg J** 1998 Children born small-for-gestational-age: postnatal growth and hormonal status. *Horm Res* 49(Suppl 2):10–13
39. **Vicens-Calvet E, Espadero RM, Carrascosa A, Spanish SGA Collaborative Group, Small for Gestational Age** 2002 Longitudinal study of the pubertal growth spurt in children born small for gestational age without postnatal catch-up growth. *J Pediatr Endocrinol Metab* 15:381–388
40. **Ibáñez L, Potau N, Francois I, de Zegher F** 1998 Precocious pubarche, hyperinsulinism and ovarian hyperandrogenism in girls: relation to reduced fetal growth. *J Clin Endocrinol Metab* 83:3558–3562
41. **Ibáñez L, Potau N, Marcos MV, de Zegher F** 1999 Exaggerated adrenarche and hyperinsulinism in adolescent girls born small for gestational age. *J Clin Endocrinol Metab* 84:4739–4741
42. **Ong K, Potau N, Petry CJ, Ness AR, Jones R, the ALSPAC Study Team, Honour JW, de Zegher F, Ibáñez L, Dunger DB** 2004 Adrenarche is paradoxically modulated by prenatal and postnatal weight gain. *J Clin Endocrinol Metab* 89:2647–2651
43. **Neville KA, Walker JL** 2005 Precocious pubarche is associated with SGA, prematurity, weight gain and obesity. *Arch Dis Child* 90:258–261
44. **Ibáñez L, Jiménez R, de Zegher F** 2006 Early puberty-menarche after precocious pubarche: relation to prenatal growth. *Pediatrics* 117:117–121
45. **Job JC, Rolland A** 1986 Histoire naturelle des retards de croissance à début intra-utérin. Croissance pubertaire et taille adulte. *Arch Fr Pediatr* 43:301–306
46. **Hughes IA, Northstone K, Golding J, and the ALSPAC Study Team** 2002 Reduced birth weight in boys with hypospadias: an index of androgen dysfunction? *Arch Dis Child Fetal Neonatal* Ed 87:F150–F151
47. **Ibáñez L, Potau N, Ferrer A, Rodriguez-Hierro F, Marcos MV, de Zegher F** 2002 Reduced ovulation rate in adolescent girls born small for gestational age. *J Clin Endocrinol Metab* 87:3391–3393
48. **Ibáñez L, Potau N, Enríquez G, Marcos MV, de Zegher F** 2003 Hypergonadotropinemia with reduced uterine and ovarian size in women born small-for-gestational-age. *Hum Reprod* 18:1565–1569
49. **Ibáñez L, Potau N, Ferrer A, Rodriguez-Hierro F, Marcos MV, de Zegher F** 2002 Anovulation in eumenorrheic, nonobese adolescent girls born small for gestational age: insulin sensitization induces ovulation, increases lean body mass, and reduces abdominal fat excess, dyslipidemia and subclinical hyperandrogenism. *J Clin Endocrinol Metab* 87:5702–5705
50. **Antoniades L, MacGregor AJ, Andrew T, Spector TD** 2003 Association of birth weight with osteoporosis and osteoarthritis in adult twins. *Rheumatology* 42:791–796
51. **Cooper C, Eriksson JG, Forsen T, Osmond C, Tuomilehto J, Barker DJ** 2001 Maternal height, childhood growth and risk of hip fracture in later life: a longitudinal study. *Osteoporos Int* 12:623–629
52. **American Heart Association; National Heart, Lung, and Blood Institute; Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA,**

- Gordon DJ, Krauss RM, Savage PJ, Smith Jr SC, Spertus JA, Costa F 2005 Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 112:2735–2752
53. Soto N, Bazaes RA, Pena V, Salazar T, Avila A, Iniguez G, Ong KK, Dunger DB, Mericq MV 2003 Insulin sensitivity and secretion are related to catch-up growth in small-for-gestational-age infants at age 1 year: results from a prospective cohort. *J Clin Endocrinol Metab* 88:3645–3650
 54. Veening MA, Van Weissenbruch MM, Delemarre-Van De Waal HA 2002 Glucose tolerance, insulin sensitivity, and insulin secretion in children born small for gestational age. *J Clin Endocrinol Metab* 87:4657–4661
 55. Crowther NJ, Cameron N, Trusler J, Gray IP 1998 Association between poor glucose tolerance and rapid post natal weight gain in seven-year old children. *Diabetologia* 41:1163–1167
 56. Jaquet D, Gaboriau A, Czernichow P, Levy-Marchal C 2000 Insulin resistance early in adulthood in subjects born with intrauterine growth retardation. *J Clin Endocrinol Metab* 85:1401–1406
 57. Murtaugh MA, Jacobs Jr DR, Moran A, Steinberger J, Sinaiko AR 2003 Relation of birth weight to fasting insulin, insulin resistance, and body size in adolescence. *Diabetes Care* 26:187–192
 58. Jaquet D, Deghmoun S, Chevenne D, Collin D, Czernichow P, Levy-Marchal C 2005 Dynamic change in adiposity from fetal to postnatal life is involved in the metabolic syndrome associated with reduced fetal growth. *Diabetologia* 48:849–855
 59. Veening MA, Van Weissenbruch MM, Delemarre-Van De Waal HA 2004 Sequelae of syndrome X in children born small for gestational age. *Horm Res* 61:103–107
 60. Primatesta P, Falaschetti E, Poulter NR 2005 Birth weight and blood pressure in childhood: results from the Health Survey for England. *Hypertension* 45:75–79
 61. Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall C, Osmond C, Winter PD 1991 Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 303:1019–1022
 62. Phillips DI, Barker DJ, Hales CN, Osmond C 1994 Thinness at birth and insulin resistance in adult life. *Diabetologia* 37:150–154
 63. Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell UB, Leon DA 1996 Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. *BMJ* 312:406–410
 64. Tanner JM, Ham TJ 1969 Low birthweight dwarfism with asymmetry (Silver's syndrome): treatment with human growth hormone. *Arch Dis Child* 44:231–243
 65. Lee PA, Blizzard RM, Cheek DB, Holt AB 1974 Growth and body composition in intrauterine growth retardation (IUGR) before and during human growth hormone administration. *Metabolism* 23:913–919
 66. de Zegher F, Hokken-Koelega A 2005 Growth hormone therapy for children born small for gestational age: height gain is less dose dependent over the long term than over the short term. *Pediatrics* 115:e458–e462
 67. Chernauek SD 2005 Treatment of short children born small for gestational age: US perspective 2005. *Horm Res* 64(Suppl 2):63–66
 68. Boonstra V, van Pieren Y, Mulder P, Hokken-Koelega A 2003 Puberty in growth hormone-treated children born small for gestational age (SGA). *J Clin Endocrinol Metab* 88:5753–5758
 69. de Zegher F, Du Caju MV, Heinrichs C, Maes M, De Schepper J, Craen M, Vanweser K, Malvaux P, Rosenfeld RG 1999 Early, discontinuous, high dose growth hormone treatment to normalize height and weight of short children born small for gestational age: results over 6 years. *J Clin Endocrinol Metab* 84:1558–1561
 70. Wilson TA, Rose SR, Cohen P, Rogol AD, Backeljauw P, Brown R, Hardin DS, Kemp SF, Lawson M, Radovick S, Rosenthal SM, Silverman L, Speiser P 2003 Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. *J Pediatr* 143:415–421
 71. Cutfield WS, Lindberg A, Rapaport R, Wajnrajch MP, Saenger P 2006 Safety of growth hormone treatment in children born small for gestational age: the US trial and KIGS analysis. *Horm Res* 65(Suppl 3):153–159
 72. Huxley R, Neil A, Collins R 2002 Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? *Lancet* 360:659–665
 73. Elford J, Whincup P, Shaper AG 1991 Early life experience and adult cardiovascular disease: longitudinal and case-control studies. *Int J Epidemiol* 20:833–844
 74. Ben-Shlomo Y, Davey-Smith G 1991 Deprivation in infancy or in adult life: which is more important for mortality risk? *Lancet* 337:530–534
 75. Sorensen HT, Sabroe S, Rothman KJ, Gillman MW, Fischer P, Sorensen TIA 1997 Relation between weight and length at birth and body mass index in young adulthood: cohort study. *BMJ* 315:1137
 76. Lucas A, Fewtrell MS, Cole TJ 1999 Fetal origins of adult disease: the hypothesis revisited. *BMJ* 319:245–249
 77. Rich-Edwards J 2004 Epidemiology of the fetal origins of an adult disease: cohort studies of birth weight and cardiovascular disease. In: Langley-Evans SC, ed. *Frontiers in nutritional sciences: fetal nutrition and adult disease*. Cambridge, MA: CAB International Press; 87–104
 78. Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM 2003 Is birth weight related to later glucose and insulin metabolism? A systematic review. *Diabet Med* 20:339–348
 79. Brown LM, Pottern LM, Hoover RN 1986 Prenatal and perinatal risk factors for testicular cancer. *Cancer Res* 46:4812–4816
 80. English PB, Goldberg DE, Wolff C, Smith D 2003 Parental and birth characteristics in relation to testicular cancer risk among males born between 1960 and 1995 in California (United States). *Cancer Causes Control* 14:815–825
 81. Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JM 2001 Height, leg length, and cancer risk: a systematic review. *Epidemiol Rev* 23:313–342
 82. Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI 2004 Growth patterns and the risk of breast cancer in women. *N Engl J Med* 351:1619–1626
 83. Drake AJ, Walker BR 2004 The intergenerational effects of fetal programming: non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk. *J Endocrinol* 180:1–16