

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

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*Written on behalf of The European Society of Paediatric Endocrinology, The Growth Hormone Research Society, The Lawson Wilkins Pediatric Endocrine Society, Sociedad Latino-Americana de Endocrinologia Pediatrica, The Asia Pacific Paediatric Endocrine Society, The Australasian Paediatric Endocrine Group, and The Japanese Society for Pediatric Endocrinology

Disclosure Statement: PeCI has consulting arrangements with Tercica and receives lecture fees from Pfizer, Serono and Novo Nordisk; SC has nothing to declare; PaCz has consulting arrangements with Pfizer, Novo Nordisk, and Ipsen and receives lecture fees from Pfizer, Novo Nordisk, Ipsen, and Ferring; GJ has consulting arrangements with Pfizer, Novo Nordisk and receives lecture fees from Pfizer, Lilly and Novo Nordisk; RR has consulting arrangements with Serono, Pfizer and Lilly and receives lecture fees from Lilly and Pfizer; AR has consulting arrangements with Genentech, Pfizer, Novo Nordisk, Insmad and Tercica and receives lecture fees from Novo Nordisk, Genentech and Pfizer; he has equity ownership in Insmad, Inc.

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Abbreviated title - SGA: Management through to adulthood

Structured Abstract

Objective: Low birth weight (LBW) 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, in particular 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, paediatrics, paediatric and adult endocrinology, epidemiology and pharma.

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 with consensus and unresolved issues identified. The consensus statement was prepared in plenary session 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 recognised, 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 SDS <-2.5, age 2-4 y) should be considered at a dose of 35-70µg/kg/day. Long-term surveillance of those treated is essential. The associations at a population level between LBW, including SGA, and coronary heart disease and stroke in later life are recognised, but there is inadequate evidence to recommend routine health surveillance of all adults born SGA, outside of normal clinical practice.

The Management of the Small for Gestational Age (SGA) Child

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 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, UK in February 2006, with representation from paediatric 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 recognising topics that require further investigation.

1. Definition

The definition of SGA is not straightforward. It requires:

1. Accurate knowledge of gestational age (ideally based on first trimester ultrasound exam).
2. Accurate measurements at birth of weight, length and head circumference.
3. A cut-off against reference data from a relevant population.

This cut-off has been variably set at the 10th centile, 3rd centile or at < -2 standard deviations (SD) from the mean (~ 2 nd centile) (3). We recommend that SGA should be defined as a weight and/or length < -2 SD cut-off as this will identify the majority of those in whom ongoing growth assessment is required.

Babies can then be sub-classified into SGA for weight (SGA_w), SGA for length (SGA_L), or SGA for both weight and length (SGA_{wL}) (3). Additionally those SGA babies who have small head circumference should be recognised. This sub-classification may help in understanding the mechanisms and implications of being born SGA.

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 to 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 as 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.

2. Early Growth and Development

2.1 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 years 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, while those with taller parents are more likely to reach a normal adult height (8). Catch-up growth may be incomplete in recognised syndromes, such as Silver Russell or 3M. Neither circulating concentrations of GH, IGF-I, IGFBP-3 nor ponderal index are predictive of subsequent growth (9). The relationship between aetiology 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 years 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 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.

2.2 Body Composition

Individuals born SGA have low lean mass and may have increased central adiposity. Dual energy x-ray absorptiometry (DXA) 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), while 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.

2.3 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 weeks or more) may prevent some of the intellectual impairment (19). Growth hormone (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 further 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).

3. Endocrine consequences

3.1 Intrauterine endocrine “programming”

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

3.2 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 IGFBP-3 levels are reduced in SGA children by ~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 post-natal growth. These include IGF-I and IGF-IR gene deletions, point mutations and polymorphisms (29-32). However current diagnostic utility of genetic analysis is limited. Further research is needed to identify other candidate genes such as insulin and IGF-II.

3.3 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.

3.4 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, while 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 recognised 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).

3.5 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 excess 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.

3.6 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).

4. Metabolic consequences

4.1 Definition and Assessment

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

While the ideal means of evaluating insulin resistance is the hyperinsulinaemic-euglycaemic clamp, practical means of monitoring metabolic risk factors include measurement of blood pressure, 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 (IOTF), the Centre for Disease Control (CDC) and other regional data.

4.2 Metabolic status in Childhood, Adolescence and Young Adulthood in those born SGA

In children born SGA, insulin resistance may be present as early as one year (53) and in prepubertal children this is more evident in those with rapid weight gain and a BMI ≥ 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), while 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 DM, impaired glucose tolerance (IGT) or dyslipidaemia occurs more commonly among *children* born SGA than in the normal childhood population (59). There is a small effect of SGA on blood pressure, 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 recognised 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 paediatric practice including life-style interventions.

5. Endocrine Management: Growth and Puberty

Early evaluation of short children born SGA is recommended, and those under 2 years 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 aetiologies and treatment should be preceded by an effort to identify the diagnosis.

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

Factors associated with the response to GH over the first 2 to 3 years include age and height SDS at start of treatment, mid-parental height and dose. Average height gains after 3 years of GH treatment range from 1.2 to 2.0 SD for doses of 35 to 70 μ g/kg/day. 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 recognised syndrome respond less well to GH than those with non-syndromic SGA (66).

The discrepancies between the two approved indications are recognised (67). It is proposed that SGA children aged between 2-4 years who show no evidence of catch-up with a height <-2.5 SD should be eligible for GH treatment. In addition for those SGA children >4 years old who are showing no evidence of catch-up, there was discussion about whether the cut-off for GH treatment should be at a height SDS <-2 or <-2.5 . No consensus was obtained although a majority was in favour of initiating treatment at a height SDS <-2 . With regard to GH dose, it is proposed that the starting dose should cover the range 35 to 70 μ g/kg/day 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 gonadotrophin releasing hormone (GnRH) analogue treatment to inhibit pubertal progression is associated with further height gain.

There should be a positive response to GH treatment (height velocity SD score $>+0.5$ in the first year of treatment). If there is an inadequate response, re-evaluation 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 to 3 years leads to catch-down growth and is not recommended (66). Discontinuation of GH treatment in

adolescence is recommended when the growth rate falls below 2 cm/year.

Pre-treatment IGF-I levels may have a role in predicting responsiveness to GH (69) while in those children receiving GH, IGF-I monitoring as a tool for dose optimization may be useful. In all other respects, standard monitoring of growth hormone therapy should be applied (70). Some syndromes (eg Bloom, 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.

6. 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.

6.1 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 both associated with lower birth weight and increased levels of cardiovascular risk factors in later life (e.g. obesity, blood pressure 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/m² for each 1kg increment in birth weight (75). In a systematic review, obesity risk has been reported to be related to rapid weight gain in infancy (12).

An inverse association was also reported in many studies between birth weight and both blood pressure (BP) and 'hypertension', but the overall effect size was a 0.5mmHg lower systolic BP per 1kg higher birth weight (72). There is little evidence that variation in preterm nutrition is

associated with raised BP in later life (76).

For coronary heart disease (CHD), a 1kg higher birth weight is associated with between 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 1kg 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).

6.2 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).

6.3 Intergenerational effects

Women (and possibly men) who were themselves small for gestational age (SGA) are reported to be at increased risk of having a SGA infant (83). Women born SGA are also at increased risk of pre-eclampsia and gestational diabetes (83).

6.4 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. Life style 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 growth hormone for short-stature due to SGA. It is therefore prudent to follow-up this group systematically.

7 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 recognised, but there is no evidence to recommend routine investigation of all SGA children. We recognise significant gaps in knowledge with regard to the genesis of metabolic profile and outcome in SGA children. Research studies utilising 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 coronary heart disease and stroke in later life are recognised, but there is inadequate evidence to recommend routine health surveillance of all adults born SGA outside of normal clinical practice.

References

1. WHO Report 2002, Reducing risks, promoting healthy life.
2. Barker DJP. Mothers, babies, and disease in later life. London: BMJ.
3. Lee PA, Chernausk SD, Hokken-Koelega AC, Czernichow P. International Small for gestational age Advisory Board consensus development conference statement: Management of the short child born small for gestational age. *Pediatrics* 2001; 111: 1253-1261.
4. Gardosi J. Fetal growth: towards an international standard. *Ultrasound Obstet Gynecol* 2005; 26:112-4.
5. Karlberg J, Albertsson-Wikland K. Growth in full term small-for-gestational-age infants: from birth to final height. *Pediatr Res* 1995; 38: 733-739.
6. Léger J, Levy-Marchal C, Bloch J, Pinet A, Chevenne D, Porquet D, Collin D, Czernichow P. 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* 1997; 315: 341-47.
7. Hokken-Koelega AC, De Ridder MA, Lemmen RJ, Den Hartog H, De Muinck Keizer-Schrama SM, Drop SL. Children born small for gestational age: do they catch up? *Pediatr Res* 1995; 38: 267-271.
8. Luo ZC, Albertsson-Wikland K, Karlberg J. Length and body mass index at birth and target height influences on patterns of postnatal growth in children born small for gestational age. *Pediatrics* 1998; 102: E72
9. Leger J, Noel M, Limal JM, Czernichow P. 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* 1996; 40: 101-107.
10. Gibson AT, Carney S, Cavazzoni E, Wales JK. Neonatal and postnatal growth. *Horm Res* 2000; 53 suppl 1: 42-49.
11. Wit JM, Finken MJ, Rijken M, de Zegher F. 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* 2006; 117(4): e793-5.
12. Rogers I; EURO-BLCS study group. The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life. *Int J Obes Relat Metab Disord* 2003; 27(7): 755-77.
13. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. *BMJ* 2005 22; 331: 929.
14. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life -- a systematic review. *Obes Rev* 2005; 6: 143-54.
15. Arenz S, Ruckerl R, Koletzko B, Von Kries R. Breast-feeding and childhood obesity. *Int J Obes* 2004; 28: 1247-1256.
16. Owen CG, Martin RM, Whincup PH, Davey Smith G, Cook DG. Effect of infant feeding on the risk of obesity across the life course. *Pediatrics* 2005; 115: 1367-1377.

17. Sommerfelt K, Markestad T, Ellertsen B. Neuropsychological performance in low birth weight preschoolers: a population-based, controlled study. *Eur J Pediatr*. 1998; 157: 53-8.
18. Lundgren EM, Cnattingius S, Jonsson B, Tuvemo T. Intellectual and psychological performance in males born small for gestational age with and without catch-up growth. *Pediatr Res*. 2001; 50: 91-6.
19. Rao M, Hediger ML, Levine RJ, Naficy AB, Vik T. Effect of breastfeeding on cognitive development of infants born small for gestational age. *Acta Paediatr* 2002; 91: 267-74.
20. van Pareren YK, DuivenvoordenHJ, Slijper FS, Koot HM, Hokken-Koelega AC. Intelligence and psychosocial functioning during long-term growth hormone therapy in children born small for gestational age. *J Clin Endocrinol Metab* 2004; 89: 5295-302.
21. Strauss RS. Adult functional outcome of those born small for gestational age: twenty-six-year follow-up of the 1970 British Birth Cohort. *JAMA* 2000; 283:625-32.
22. Fowden AL, Forhead AJ. Endocrine mechanisms of intrauterine programming. *Reproduction* 2004; 127: 515– 26.
23. Geremia C, Cianfarani S. Laboratory test and measurements in children born small for gestational age (SGA). *Clin Chim Acta* 2006; 364:113-123.
24. de Waal WJ, Hokken-Koelega AC, Stijnen T, de Muinck Keizer-Schrama SM, Drop SL. 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)*. 1994; 41: 621-30.
25. Boguszewski M, Rosberg S, Albertsson-Wikland K. Spontaneous 24-hour growth hormone profiles in prepubertal small for gestational age children. *J Clin Endocrinol Metab* 1995; 80: 2599-606.
26. Albertsson-Wikland K, Boguszewski M, Karlberg J Children born small for gestational age: postnatal growth and hormonal status. *Horm Res* 1998; 49 Suppl 2: 7-13.
27. Cianfarani S, Maiorana A, Geremia C, Scire` G, Spadoni GL, Germani D. 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* 2003; 88: 2699–2705.
28. Tenhola S, Halonen P, Jaaskelainen J, Voutilainen R. Serum markers of GH and insulin action in 12-year-old children born small for gestational age. *Eur J Endocrinol* 2005; 152: 335-340.
29. Woods KA, Camacho-Hubner C, Savage MO, Clark AJ. Intrauterine growth retardation and postnatal growth failure associated with deletion of the insulin-like growth factor I gene. *N Engl J Med* 1996; 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, Chernausek SD; Intrauterine Growth Retardation (IUGR) Study Group. IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. *N Engl J Med* 2003; 349: 2211-2222.
31. Vaessen N, Janssen JA, Heutink P, Hofman A, Lamberts SW, Oostra BA, Pols HA, van Duijn CM. Association between genetic variation in the gene for insulin-like growth factor-I and low

birthweight. *Lancet* 2002; 359: 1036-7.

32. Arens N, Johnston L, Hokken-Kolega A: Polymorphism in the IGF-I gene: clinical relevance for short children born small for gestational age (SGA). *J Clin Endocrinol Metab* 2002; 87: 2720.

33. Langley-Evans SC, Gardner DS, Jackson AA. Maternal protein restriction influences the programming of the rat hypothalamic-pituitary-adrenal axis. *J Nutr* 1996; 126: 1578–1585.

34. Nyirenda MJ, Lindsay RS, Kenyon CJ, Burchell A, Seckl JR. 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* 1998; 101: 2174–2181.

35. Preece MA. Puberty in children with intrauterine growth retardation. *Horm Res* 1997; 48 Suppl.1: 30-32.

36. Bhargava SK, Ramji S, Srivastava U, Sachdev HP, Kapani V, Datta V, Satyanarayana L. Growth and sexual maturation of low birthweight children: a 14 year follow-up. *Indian Pediatr* 1995; 32: 963-970.

37. Persson I, Ahlsson F, Ewald U, Tuvemo T, Qingyuan M, von Rosen D, Proos L. 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* 1999; 150: 747-755.

38. Albertsson-Wikland K, Boguzewski M, Karlberg J. Children born small-for-gestational-age: postnatal growth and hormonal status. *Horm Res* 1998; 49 suppl 2:10-13.

39. Vicens-Calvet E, Espadero RM, Carrascosa A; Spanish SGA Collaborative Group. Small for Gestational Age. Longitudinal study of the pubertal growth spurt in children born small for gestational age without postnatal catch-up growth. *J Pediatr Endocrinol Metab* 2002; 15:381-388.

40. Ibáñez L, Potau N, Francois I, de Zegher F. Precocious pubarche, hyperinsulinism and ovarian hyperandrogenism in girls: relation to reduced fetal growth. *J Clin Endocrinol Metab* 1998; 83: 3558-3662.

41. Ibáñez L, Potau N, Marcos MV, de Zegher F. Exaggerated adrenarche and hyperinsulinism in adolescent girls born small for gestational age. *J Clin Endocrinol Metab* 1999; 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. Adrenarche is paradoxically modulated by prenatal and postnatal weight gain. *J Clin Endocrinol Metab* 2004; 89: 2647-2651.

43. Neville KA, Walker JL. Precocious pubarche is associated with SGA, prematurity, weight gain and obesity. *Arch Dis Child* 2005; 90: 258-261.

44. Ibáñez L, Jiménez R, de Zegher F. Early puberty-menarche after precocious pubarche: relation to prenatal growth. *Pediatrics* 2006; 117: 117-121.

45. Job JC, Rolland A. Histoire naturelle des retards de croissance à début intra-utérin. Croissance pubertaire et taille adulte. *Arch Fr Pediatr* 1986 ; 43 :301-306.

46. Hughes IA, Northstone K, Golding J, and the ALSPAC Study Team. Reduced birth weight in boys with hypospadias: an index of androgen dysfunction? *Arch Dis Child Fetal and Neonatal Ed.* 2002; 87: F150-F151.

47. Ibáñez L, Potau N, Ferrer A, Rodriguez-Hierro F, Marcos MV, de Zegher F. Reduced

ovulation rate in adolescent girls born small for gestational age. *J Clin Endocrinol Metab* 2002; 87: 3391-3393.

48. Ibáñez L, Potau N, Enríquez G, Marcos MV, de Zegher F. Hypergonadotropinemia with reduced uterine and ovarian size in women born small-for-gestational-age. *Hum Reprod* 2003; 18: 1565-1569.

49. Ibáñez L, Potau N, Ferrer A, Rodriguez-Hierro F, Marcos MV, de Zegher F. Anovulation in eumenorheic, non-obese 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* 2002; 87: 5702-5705.

50. Antoniadou L, MacGregor AJ, Andrew T, T. D. Spector TD. Association of birth weight with osteoporosis and osteoarthritis in adult twins. *Rheumatology* 2003; 42: 791-796.

51. Cooper C, Eriksson JG, Forsen T, Osmond C, Tuomilehto J, Barker DJ. Maternal height, childhood growth and risk of hip fracture in later life: a longitudinal study. *Osteoporosis Int* 2001; 12(8): 623-9.

52. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and Management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 2005; 112: 2735-52.

53. Soto N, Bazaes RA, Pena V, Salazar T, Avila A, Iniguez G Ong KK, Dunger DB, Mericq MV. 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* 2003; 88: 3645-3650.

54. Veening, MA, Van Weissenbruch, MM, Delemarre-Van De Waal HA. Glucose tolerance, insulin sensitivity, and insulin secretion in children born small for gestational age. *J Clin Endocrinol Metab* 2002; 87: 4657-61.

55. Crowther NJ, Cameron N, Trusler J, Gray IP. Association between poor glucose tolerance and rapid post natal weight gain in seven-year old children. *Diabetologia* 1998; 41: 1163-1167.

56. Jaquet D, Gaboriau A, Czernichow P, Levy-Marchal C. Insulin resistance early in adulthood in subjects born with intrauterine growth retardation. *J Clin Endocrinol Metab* 2000; 85: 1401-6.

57. Murtaugh MA, Jacobs DR JR, Moran A, Steinberger J, Sinaiko AR. Relation of birth weight to fasting insulin, insulin resistance, and body size in adolescence. *Diabetes Care* 2003; 26: 187-92.

58. Jaquet D, Deghmoun S, Chevenne D, Collin D, Czernichow P, Levy-Marchal C. Dynamic change in adiposity from fetal to postnatal life is involved in the metabolic syndrome associated with reduced fetal growth. *Diabetologia* 2005; 48: 849-55.

59. Veening, M. A., Van Weissenbruch, M. M. & Delemarre-Van De Waal, H. A. Sequelae of Syndrome X in children born small for gestational age. *Horm Res* 2004; 61: 103-107.

60. Primatesta P, Falaschetti E, Poulter NR. Birth weight and blood pressure in childhood: results from the Health Survey for England. *Hypertension* 2005; 45: 75-9.

61. Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall C, Osmond C, Winter PD. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991; 303: 1019-1022.

62. Phillips DIW, Barker DJP, Hales CN, Osmond C. Thinness at birth and insulin resistance in adult life. *Diabetologia* 1994; 37: 150-154.

63. Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell U-B, Leon DA. Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50-60 years. *BMJ* 1996; 312: 406-410.
64. Tanner JM, Ham TJ. Low birthweight dwarfism with asymmetry (Silver's syndrome): treatment with human growth hormone. *Arch Dis Child* 1969; 44:231-243.
65. Lee PA, Blizzard RM, Cheek DB, Holt AB. Growth and body composition in intrauterine growth retardation (IUGR) before and during human growth hormone administration. *Metabolism* 1974; 23: 913-919.
66. de Zegher F, Hokken-Koelega A. 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* 2005; 115: e458-462.
67. Chernausek SD. Treatment of short children born small for gestational age: US perspective 2005. *Horm Res* 2005; 64 Suppl 2: 63-6.
68. Boonstra V, van Pareren Y, Mulder P, Hokken-Koelega A. Puberty in growth hormone-treated children born small for gestational age (SGA). *J Clin Endocrinol Metab* 2003; 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. 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* 1999; 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. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. *J Pediatr* 2003; 143:415-421.
71. Cutfield WS, Lindberg A, Rapaport R, Wajnrajch MP, Saenger P. Safety of growth hormone treatment in children born small for gestational age: the US trial and KIGS analysis. *Horm Res* 2006; 65 Suppl 3: 153-9.
72. Huxley R, Neil A, Collins R. Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? *Lancet*. 2002; 360: 659-65.
73. Elford J, Whincup P, Shaper AG. Early life experience and adult cardiovascular disease: Longitudinal and case-control studies. *Int J Epidemiol* 1991; 20:833-844.
74. Ben-Shlomo Y, Davey-Smith G. Deprivation in infancy or in adult life: which is more important for mortality risk? *Lancet* 1991; 337:530-534.
75. Sorensen HT, Sabroe S, Rothman KJ, Gillman MW, Fischer P, Sorensen TIA. Relation between weight and length at birth and body mass index in young adulthood: cohort study. *BMJ* 1997; 315:1137.
76. Lucas A, Fewtrell MS, Cole TJ. Fetal origins of adult disease - the hypothesis revisited. *BMJ* 1999; 319: 245-9.
77. Rich-Edwards J. In: *Fetal Nutrition and Adult Disease*. Editor Langley-Evans SC. CAB International, 2004, Cambridge, MA.
78. Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM. Is birth weight related to later

glucose and insulin metabolism?--A systematic review. *Diabet Med* 2003; 20: 339-48.

79. Brown LM, Pottern LM, Hoover RN. Prenatal and perinatal risk factors for testicular cancer. *Cancer Res* 1986; 46(9): 4812-6.

80. English PB, Goldberg DE, Wolff C, Smith D. Parental and birth characteristics in relation to testicular cancer risk among males born between 1960 and 1995 in California (United States). *Cancer Causes Control* 2003;14(9): 815-25.

81. Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JM. Height, leg length, and cancer risk: a systematic review. *Epidemiol Rev* 2001; 23(2): 313-42.

82. Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI. Growth patterns and the risk of breast cancer in women. *N Engl J Med* 2004 14; 351(16):1619-26.

83. Drake AJ, Walker BR. The intergenerational effects of fetal programming: non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk. *J Endocrinol* 2004; 180(1):1-16.

Table 1: GH use in short SGA children

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