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GH-IGF-IGFBP Axis and Metabolic Profile in Short Children Born Small for Gestational Age

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1. Introduction

Small for gestational age (SGA) is defined as a birth weight and/or birth length below -2 standard deviation scores (SDS), adjusted for gestational age (Clayton et al., 2007). To determine whether a child is born SGA, accurate knowledge of gestational age, accurate measurements of weight and length at birth, and an appropriate reference population to calculate the standard deviation scores are required. The child can be further subclassified as SGA for weight, SGA for height or SGA for height and weight.

SGA only refers to size at birth and does not take fetal growth into account. The term intrauterine growth retardation (IUGR) is used when the fetus suffers from reduced fetal growth, based on at least 2 subsequent ultrasound measurements. A child born SGA has not necessarily suffered from IUGR, whereas a child with IUGR late in gestation can have a normal size at birth. These different fetal growth patterns are shown in Figure 1.

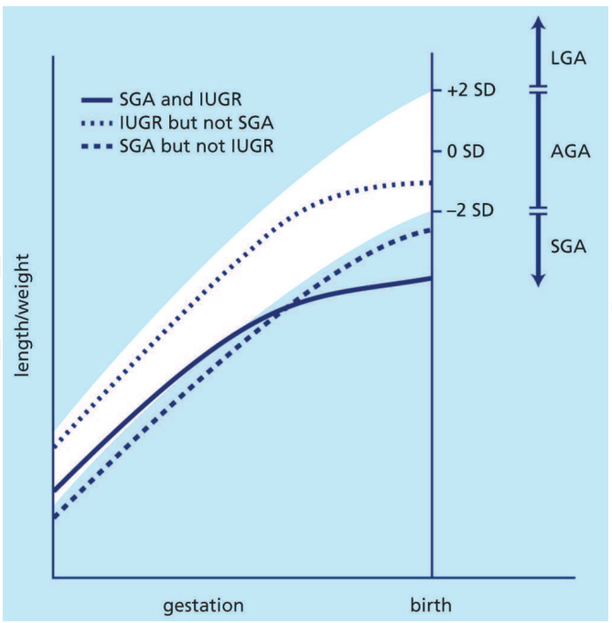

Fig. 1. Fetal growth chart demonstrating various growth curves in SGA and IUGR newborns. LGA=large for gestational age, AGA=appropriate for gestational age, SGA=small for gestational age, IUGR=intrauterine growth retardation.

1.1 Prevalence and etiology of SGA

By definition, 2.3% of all live-born neonates are born SGA when SGA is defined as a birth weight and/or length below -2 SDS. Intrauterine growth retardation might be caused by numerous fetal, maternal, placental and environmental factors which are outlined in Table 1. The cause of IUGR remains, however, unidentified in 40% of the children.

Fetal factors	
Multiple births	
Congenital malformations	
Chromosomal anomalies	Turner syndrome Down syndrome
Inborn errors of metabolism	
Intrauterine infections	Toxoplasmosis, Other infections, Rubella, Cytomegalovirus, Herpes simplex (TORCH)
Maternal factors	
Medical conditions	Pre-eclampsia Acute or chronic hypertension Severe chronic disease Severe chronic infections Systemic lupus erythematosus Antiphospholipid syndrome Anemia Malignancy Abnormalities of the uterus
Social conditions	Malnutrition Low prepregnancy body mass index Low maternal weight gain Delivery at age < 16 or > 35 years Low socioeconomic status Drug use (smoking, alcohol, illicit drugs)
Placental factors	
Reduced blood flow Reduced area for exchange of oxygen and nutrients	Infarcts Hematomas Partial abruption
Environmental factors	
Toxic substances High altitude	

Table 1. Factors associated with intrauterine growth retardation. Adapted from Bryan and Hindmarsh (Bryan & Hindmarsh, 2006).

2. GH-IGF-IGFBP axis

Fetal and postnatal growth and development are regulated by metabolic and endocrine processes, which are influenced by genetic and environmental factors. The Growth Hormone – Insulin-like Growth Factor – Insulin-like Growth Factor Binding Protein (GH-IGF-IGFBP) axis plays a major role in this system (Figure 2).

Growth hormone is secreted by the pituitary gland under the control of the hypothalamic hormones growth hormone releasing hormone (GHRH), somatostatin and ghrelin. The major effects of growth hormone on growth are mediated via Insulin-like Growth Factor I (IGF-I) expression. The physiological actions of growth hormone involve longitudinal bone growth and bone remodeling, skeletal muscle growth and immunomodulation (Holt, 2002).

The IGF-family consists of insulin, IGF-I and IGF-II. The metabolic actions of insulin are mediated through binding to the insulin receptor. The growth-promoting effects of IGF-I and IGF-II are primarily mediated through binding to the IGF-I receptor. Interactions between IGFs and the insulin receptor exist, because of strong homology between IGFs and insulin, and between the insulin receptor and IGF-I receptor (Steele-Perkins et al., 1988). Between 0.4% and 2% of IGF-I circulates as free or very easily dissociable IGF-I, the main biological active fraction. The physiological actions of IGFs involve growth, development and function of the central nervous system, skeletal muscle and reproductive organs.

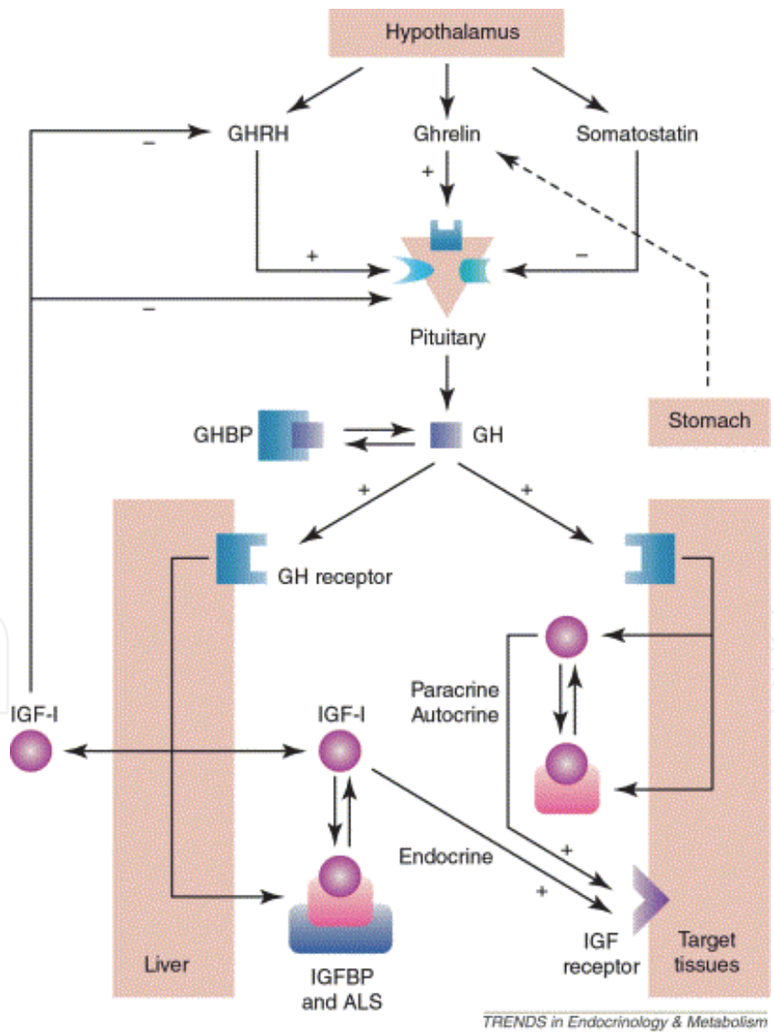

Fig. 2. Physiology of the GH-IGF-IGFPB axis (Holt, 2002).

Six IGF binding proteins (IGFBPs) form complexes with IGF-I and IGF-II, ensuring that more than 95% of IGF-I is bound. The majority of IGF-I and IGF-II (75%) is bound in a ternary complex with IGFBP-3 and an acid-labile subunit (ALS). IGFBP-3 is mainly produced in the liver. The concentration of IGFBP-3 in serum exceeds that of other IGFBPs and the affinity of IGFBP-3 for IGFs is higher than those of most other IGFBPs, reflecting its most important function as a carrier protein for IGFs. *In vitro* and *in vivo* studies have demonstrated that IGFBP-3 has IGF-mediated as well as IGF-independent effects on growth promotion and inhibition (Collet-Solberg & Cohen, 2000; Conover et al., 1996).

2.1 Genes involved in the GH-IGF-IGFBP axis

2.1.1 Growth hormone and growth hormone receptor gene

Common polymorphisms have small effects on a phenotype, but can provide important contributions to understanding complex diseases. Single nucleotide polymorphisms in the growth hormone gene have been associated with variability in normal adult height (Esteban et al., 2007). A common polymorphism in the growth hormone receptor gene (growth hormone receptor d3 polymorphism) was associated with size at birth and response to growth hormone treatment in some cohorts, although these findings were not reproduced by others (Carrascosa et al., 2006; de Graaff et al., 2008; Tauber et al., 2007).

Laron syndrome is caused by inactivating mutations affecting the expression or function of the growth hormone receptor. Clinical characteristics include severe postnatal growth failure, facial dysmorphism, truncal obesity, delayed puberty, hypoglycemia, elevated growth hormone levels, low IGF-I levels, absent/low or dysfunctional growth hormone binding protein (GHBP) and resistance to growth hormone (Laron et al., 1966).

2.1.2 IGF and IGF receptor genes

Animal knockout studies have demonstrated that IGF-I, IGF-II and their receptors are important regulators of fetoplacental growth. IGF-I gene knockout mice are 40% smaller than their littermates, without an alteration in placental size, whereas IGF-II gene knockout mice are also 40% smaller and have reduced placental growth. IGF-I gene receptor knockout mice are the most severely growth retarded (45% of normal birth weight) because of the loss of both IGF-I and IGF-II action (Baker et al., 1993). Liver IGF-I deficient mice, a mouse model where the IGF-I gene is specifically knocked out in the liver, have a normal birth weight and postnatal growth despite reduced circulating IGF-I and IGFBP3 levels. These data show that, at least in mice, liver-derived IGF-I is not essential for postnatal growth and development (Yakar et al., 1999).

Case reports in humans with defects in the IGF-I gene or IGF-I receptor gene demonstrated variable pre- and postnatal growth retardation as well as mental retardation in some cases (de Lacerda et al., 1999; Ester et al., 2009a; Veenma et al., 2010, Walenkamp et al., 2005).

Twin studies have shown that 40-65% of interindividual variability in IGF-I, IGF-II and IGFBP-3 levels is genetically determined (Harrela et al., 1996). Single nucleotide polymorphisms in the IGF-I gene are correlated with IGF-I levels, head circumference in short SGA children, birth weight and increased risk of type 2 diabetes and ischemic heart disease, although not all studies found similar associations (Ester et al., 2009b; Frayling et al., 2002; Johnston et al., 2003; Vaessen et al., 2001).

2.1.3 IGFBP genes

Knockout studies of genes encoding for IGFBPs or the acid-labile subunit demonstrated little effect on fetal growth. Knockout of the ALS gene resulted in a 60% reduction in IGF-I and IGFBP-3 levels, without an effect on fetal growth, only minor effects on postnatal growth and no effects on glucose metabolism, questioning the role of circulating IGF-I levels versus local autocrine-paracrine production of IGF-I (Ueki et al., 2000). Polymorphic variation in the IGFBP-3 gene promoter region is associated with IGFBP-3 levels, spontaneous growth and response to growth hormone treatment in short children born SGA (van der Kaay et al., 2009a).

3. The GH-IGF-IGFBP axis in fetal and postnatal growth

3.1 Fetal growth

Infants with congenital absence of the pituitary often have birth weights and birth lengths below the mean, although within the normal range, demonstrating that pituitary growth hormone has limited impact on late third trimester growth (Gluckman et al., 1992).

Fetal growth is determined by adequate delivery of oxygen and nutrients, in particular glucose, amino acids and lactate or ketone bodies across the placenta. Insulin, IGF-I and IGF-II and their receptors are the most important regulators of fetoplacental growth. IGF-II is the main growth factor in early embryonic growth, whereas IGF-I is more important during later stages of gestation. IGF-I and IGF-II levels are significantly influenced by the availability of adequate glucose levels. Glucose increases IGF-I levels through an increase in insulin secretion. In fetuses with intrauterine growth retardation, IGF-I levels are decreased during the second half of gestation. Cord blood IGF-I levels are significantly lower in infants born small for gestational age, compared to infants born appropriate for gestational age (Giudice et al., 1995; Gluckman et al., 1987).

All 6 IGFBPs have been found in fetal plasma and tissues. IGFBP-1 is the major IGF binding protein found in amniotic fluid. It binds IGF in fetal plasma, increases 20-fold from week 9 to week 12 and is the most important regulator of IGF-I bioavailability during pregnancy (Murphy et al., 2006). IGFBP-1 production is suppressed by insulin. IGFBP-1 levels are increased in infants born SGA, possibly reflecting the low insulin levels found in fetuses with intrauterine growth retardation (Holt, 2002). IGFBP-3 levels are significantly lower in infants born small for gestational age, compared to those born appropriate for gestational age (Giudice et al., 1995).

3.2 Postnatal growth

Growth hormone receptor expression is gradually upregulated after birth. Around 6 months of life, growth becomes dependent on pulsatile growth hormone secretion and growth hormone induced IGF-I and IGFBP-3 production. Serum IGF-I and IGFBP-3 levels are influenced by various factors such as sex steroids, nutritional status and liver function.

Catch-up growth is defined as a growth velocity greater than the median for chronological age and gender and is associated with a rise in IGF-I and IGFBP-3 levels (Cance-Rouzaud et al., 1998). In infants born SGA, catch-up growth occurs during the first 6 months of life in more than 80% of children. Prematurely born infants may take longer to catch-up (Hokken-Koelega et al., 1995). Catch-up growth is completed by the age of 2 years in most children born SGA (Figure 3).

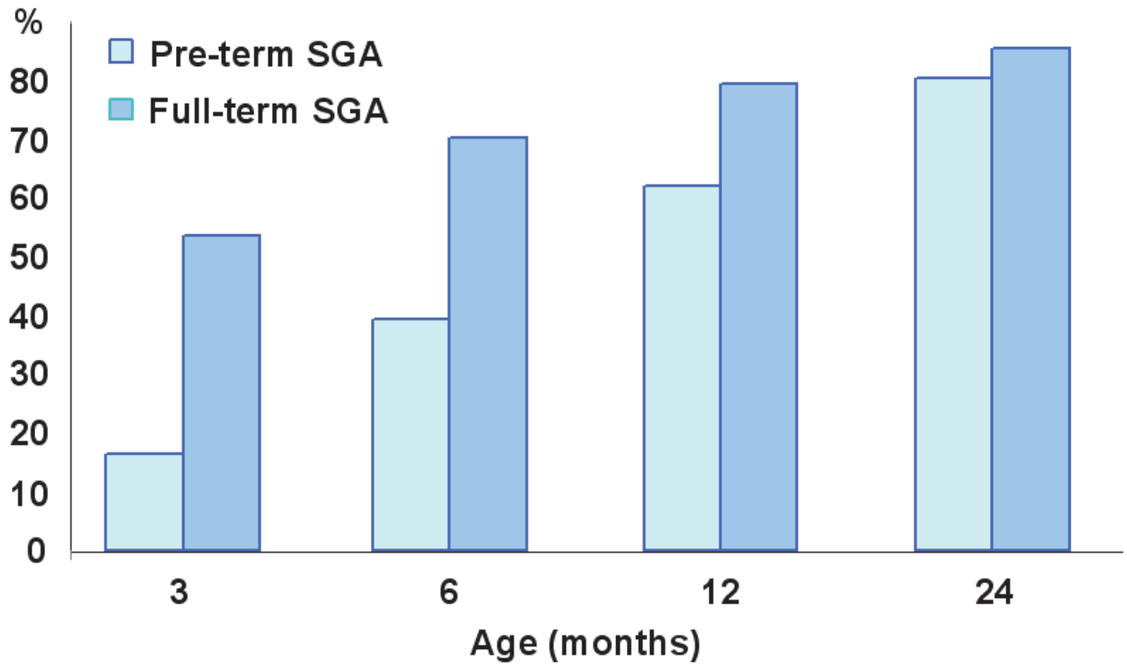

Fig. 3. Percentage of pre-term and full-term SGA infants with postnatal catch-up growth (Hokken-Koelega et al., 1995).

It is recommended that a child born SGA has measurements of height, weight, and head circumference every 3 months for the first year of life and every 6 months thereafter. Children without significant catch-up growth in the first 6 months of life and those who remain short by 2 years of age may have other conditions that are associated with short stature. These children require referral to a pediatrician because such conditions need to be identified and managed (Clayton et al., 2007).

Although catch-up growth occurs in most children born SGA, around 10% of infants remain short throughout childhood and adulthood (Leger et al., 1997). Alterations in the GH-IGF-IGFBP axis might underlie this failure in catch-up growth in short SGA children. Subnormal to low growth hormone levels during overnight growth hormone profiles have been found in prepubertal short SGA children in some cohorts, although others found normal growth hormone levels (Boguszewski et al., 1995; de Waal et al., 1994; Volkl et al., 2004). The wide variability in – and overlap between – growth hormone secretion in SGA cohorts and control populations are consistent phenomena. Within the heterogeneous SGA population, this probably reflects a continuum in growth hormone secretion, ranging from partial growth hormone deficiency to normal growth hormone secretion.

IGF-I and IGFBP-3 levels are significantly lower in short prepubertal and pubertal children, and young adults who were born SGA, compared to their age-matched peers with normal stature (de Waal et al., 1994; Carel et al., 2003; Verkauskiene et al., 2005).

4. Short children born small for gestational age

4.1 Metabolic status of short children born SGA

Body composition is greatly influenced by gender and height. It is important to adjust for these variables when comparing body composition in short SGA children and controls.

Prepubertal short SGA children have a significantly decreased fat mass. Lean body mass is comparable to controls in young prepubertal short SGA children. During a 3-year follow-up, however, it tended to decrease over time resulting in significantly lower levels in older prepubertal short SGA children compared to controls (Willemsen et al., 2007).
Epidemiological studies have demonstrated that development of type 2 diabetes mellitus and associated disorders such as hypertension, dyslipidemia and cardiovascular disease in adults is associated with low birth weight (Barker, 2004; Barker et al., 2005). Reduced insulin sensitivity plays a central role in the pathogenesis of these disorders. Short children born SGA are more insulin resistant, compared to controls born appropriate for gestational age. The disposition index – reflecting the capability of beta cells to compensate for the reduction in insulin sensitivity by increasing their insulin secretion – was comparable between short SGA subjects and controls (Leunissen et al., 2008). Young adults born SGA have a higher incidence of metabolic risk factors than those born appropriate for gestational age (2.3% versus 0.4%). More recent data indicate that insulin resistance and metabolic risk factors are mainly related to the accumulation of fat mass during early childhood. Rapid weight gain during the first 3 months of life results in a higher percentage of body fat, more central adiposity, reduced insulin sensitivity, lower high-density lipoprotein cholesterol levels and higher triglyceride levels in early adulthood (Arends et al., 2005; Jaquet et al., 2005; Leunissen et al., 2009). High blood pressure in childhood has been associated with an increased risk of developing hypertension in adulthood (Bao et al., 1995; Primatesta et al., 2005).

4.2 Intellectual consequences and health-related quality of life of short children born SGA

In large observational studies, cognitive impairment is independently associated with low birth weight, short birth length, and small head circumference. SGA children have poorer school performance and have more emotional, conduct, and attention deficit hyperactivity disorders, although the differences are mostly subtle (de Bie et al., 2010; van Pareren et al., 2004).
Adults who were born SGA show no difference in frequency of employment, marital status, or satisfaction with life. However, lower academic achievement and professional attainment with lower income have been found (Strauss, 2010).
Short children have reported to experience juvenilization and more teasing. Reports on health-related quality of life, the subjective perception of health, have been inconclusive (Sandberg & Colsman, 2005). More recently, a large British population study found that adult short stature may be associated with a reduction in health-related quality of life on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) (Christensen et al., 2007).

5. Growth hormone treatment in prepubertal short children born SGA

5.1 Effects on linear growth

Growth hormone treatment in short children born SGA has been explored for over 40 years. Several studies have demonstrated that growth hormone treatment effectively induces catch-up growth in prepubertal short SGA children (Dahlgren & Wikland, 2005; de Zegher et al., 2006; Sas et al., 1999). Adult height data from a Dutch multicenter study demonstrated that 85% of children reached a height above -2 SDS and 98% reached a height within the target height range (Van Pareren et al., 2003) (Figure 4).

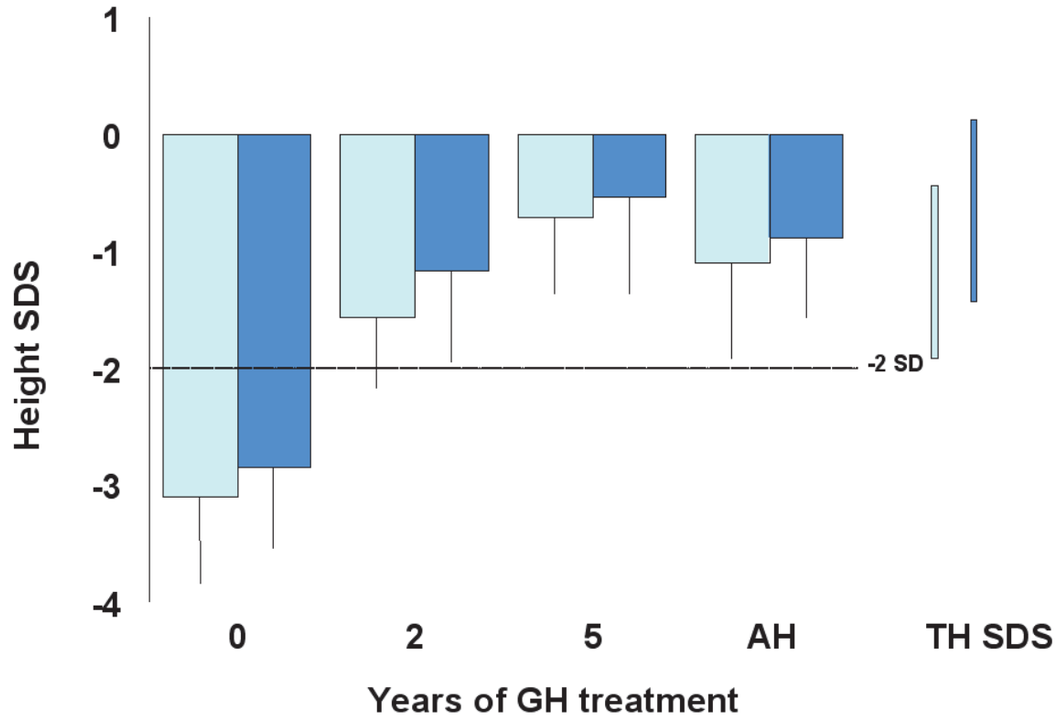

Fig. 4. Height SDS (± SD) during growth hormone treatment and at adult height (AH), in relation to target height (TH) SDS. Light blue boxes: 1 mg GH/m²/day, dark blue boxes: 2 mg GH/m²/day (Van Pareren et al., 2003).

This has led to the official registration of GH treatment for short children born SGA by the US Food and Drug Administration (FDA) in 2001 and by the European Agency for the Evaluation of Medicinal Products (EMEA) in 2003 (Table 2).
Discrepancies, for example in height at start of treatment and dose, between the 2 approved indications are recognized (Chernausek, 2005). A dose-dependent effect on growth is found during the first 4-5 years of growth hormone treatment, although growth hormone dose is less important for long-term growth (de Zegher & Hokken-Koelega, 2005; Van Pareren et al., 2003). Furthermore, there is no evidence for excluding children from growth hormone treatment when the distance to target height is less than 1 SDS (Lem et al., 2010).
There is considerable variation in the growth response to growth hormone treatment. This variation remains after adjustment for factors such as age, target height and duration of treatment. Short children born SGA form a heterogeneous group of patients and genetic variability in growth-related genes probably accounts for part of the variation in growth response.
A positive response to GH treatment could arbitrarily be defined as a height velocity SDS of more than 0.5 in the first year of treatment. In case of an inadequate response, reevaluation is necessary, including consideration of compliance, GH dose, diagnosis, and the decision to discontinue treatment. Discontinuation of GH treatment in adolescence is recommended when the growth rate is less than 2 cm/yr (Clayton et al., 2007).

5.2 Effects on the GH-IGF-IGFBP axis

Serum growth hormone, IGF-I and IGFBP-3 levels significantly increase in a dose-dependent manner during growth hormone treatment (Boguszewski et al., 1996; Sas et al., 1999; Van Dijk

et al., 2006). During 1 year of treatment, IGF-I and IGFBP3 levels had increased to respectively +1.2 SDS and +0.2 SDS in children treated with 1 mg GH/m²/day and to respectively +1.9 SDS and +0.5 SDS in children treated with 2 mg GH/m²/day (Sas et al., 1999).

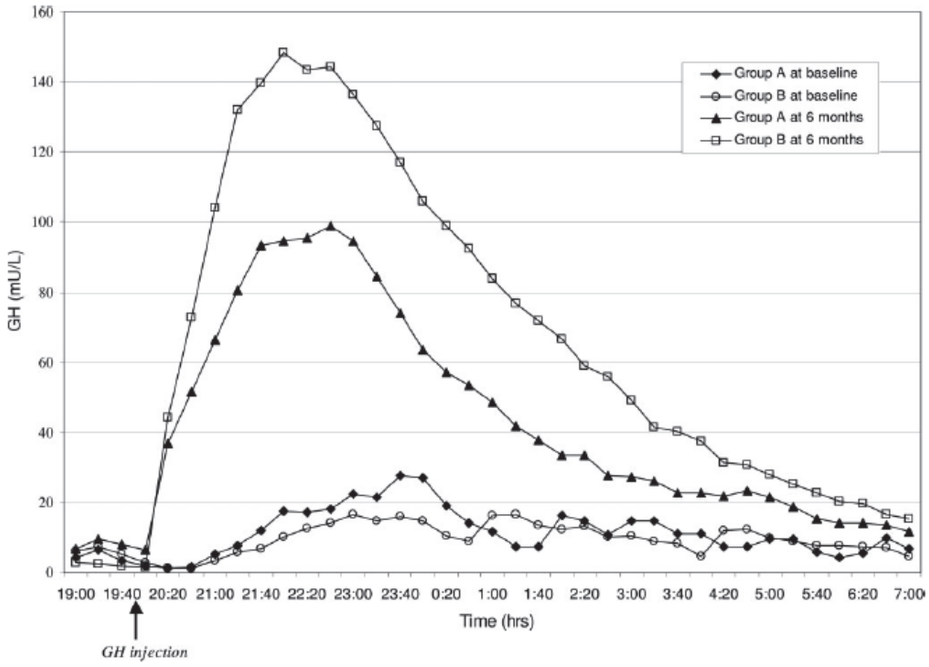

Fig. 5. Mean GH levels for each time point during an overnight GH profile before and after 6 months of growth hormone treatment. Closed figures: 1 mg GH/m²/day, open figures: 2 mg GH/m²/day (Van Dijk et al., 2006).

At 6.5 years after discontinuation of growth hormone treatment, IGF-I and IGFBP-3 levels had returned to levels comparable with those found in untreated short subjects born SGA and thus significantly lower than levels found in controls (Van Dijk et al., 2007).

5.3 Effects on insulin sensitivity, lipid profile and body composition

Large surveillance databases have demonstrated that growth hormone treatment is well-tolerated and adverse events are not more common in short SGA children than in other conditions that require growth hormone treatment (Cutfield et al., 2006).

Monitoring of glucose and insulin levels during growth hormone treatment is necessary, because growth hormone has insulin-antagonistic effects. Prepubertal short SGA children develop a relative insulin resistance during growth hormone treatment, which is largely reversible when treatment is terminated. Six years after discontinuation, insulin sensitivity in short SGA children who were treated with growth hormone was similar compared to untreated short individuals born SGA (de Zegher et al., 2002; van Dijk et al., 2007). Growth hormone treatment has positive effects on lipid metabolism and blood pressure in prepubertal short SGA children and these effects persisted after discontinuation (Sas et al., 2000; van Dijk et al., 2007). Growth hormone has well-documented anabolic effects on muscle mass and lipolytic effects on adipose tissue (Mukherjee et al., 2004). During treatment in prepubertal short SGA children, the increase in lean mass SDS adjusted for

gender and height reflected the normal increase as a result of the increase in height, without an additional anabolic effect. Fat mass SDS adjusted for gender and height declined in prepubertal SGA children, especially during the first treatment year (Willemsen et al., 2007).

5.4 Effects on intellectual outcome and health-related quality of life

During 9 yr of GH treatment, IQ and psychosocial functioning had improved from scores significantly below average to scores comparable to Dutch peers (Figure 6) (van Pareren et al., 2004).

Health-related quality of life improves in growth hormone treated adolescents born SGA, according to the disorder-specific questionnaire which is designed to assess the impact of short stature on quality of life for children aged 5-15 years (The TNO AZL Children's Quality of Life-short stature (TACQOL-S)). This improvement continued until adult height. Health-related quality of life was not different between individuals treated with 1 or 2 mg GH/m²/day (Bannink et al., 2010). Other studies did not find a significant improvement (Stephen et al., 2011).

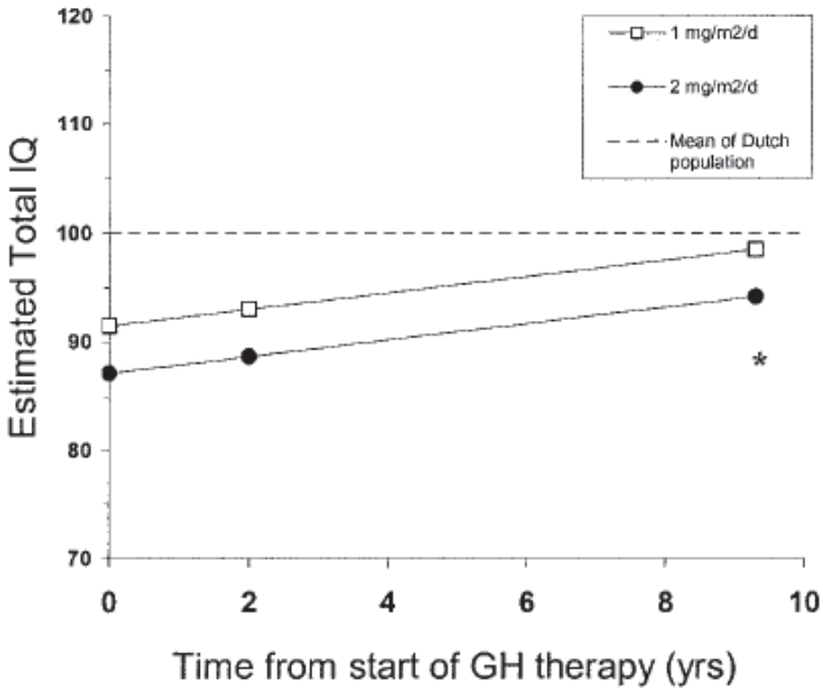

Fig. 6. Estimated total IQ score for both GH groups during growth hormone treatment, corrected for gender and age at start. Significant increase from start: *, $P < 0.001$ (van Pareren et al., 2004).

6. Puberty in short children born small for gestational age

Controversies exist about the relationship between being born SGA and reproductive function. In men born SGA, lower testosterone levels and smaller testicular size have been described (Cicognani et al., 2002). In women born SGA, smaller ovaries and uterus and lower anti-Mullerian hormone levels – a marker of follicle pool size – have been described

(Ibanez et al., 2003). These findings could not be replicated by others (Hernandez et al., 2006; Jensen et al., 2007). In a large cohort, it was recently shown that being born SGA does not have a negative effect on gonadal function in adult men. Factors that affect gonadal function are socio-economic status, fat mass, and maternal smoking during gestation, although all values of gonadal parameters remained within the normal range (Kerkhof et al., 2009). In women, being born SGA does not result in lower anti-Mullerian hormone levels. Catch-up growth after being born SGA might, however, be associated with increased anti-Mullerian hormone levels. Testosterone and androstenedione levels were comparable to levels in a control population. Other factors associated with serum anti-Mullerian hormone levels are oral contraceptive use, age at menarche, maternal smoking during gestation and socio-economic status (Kerkhof et al., 2010).
Growth hormone treatment has no detrimental effect on gonadal function in prepubertal short children born SGA (Boonstra et al., 2008; Lem et al., 2011).

7. Postponement of puberty in pubertal short children born small for gestational age

It has been indicated that a better growth response and greater adult height is achieved when children start growth hormone treatment at an early age (Carel et al., 2003). Although the age of onset and progression of puberty in short SGA children is comparable to healthy peers, some of these children only come under medical attention at onset of puberty.
Postponement of puberty with gonadotropin releasing hormone analogue (GnRH analogue) is the treatment of choice in children with central precocious puberty or early puberty. Most of these children reach an adult height within their target height range (Mul et al., 2002; Palmert et al., 1999; Pasquino et al., 2008). It is yet unknown whether the same applies to short children bon SGA who come under medical attention at onset of puberty.

7.1 Effects of GnRH analogue treatment on growth and the GH-IGF-IGFBP axis

During GnRH analogue treatment, a decline in growth velocity – even to levels below the age-appropriate normal range in some patients – is a well-known phenomenon (Carel et al., 1996; Saggese et al., 1993). Some studies in children with central precocious puberty found lower stimulated and spontaneous growth hormone levels during GnRH analogue treatment, others could not replicate these findings (DiMartino-Nardi et al., 1991; Sklar et al., 1991; Stanhope et al., 1988). Poor growth might also be directly related to reduced sex steroid levels or growth plate senescence by prior estrogen exposure (Savendahl, 2005; Weise et al., 2004).
In girls with normal stature, growth hormone secretion increases during puberty with the highest levels found at Tanner stage 3 and stage 4 (Rose et al., 1991). In contrast, pubertal short SGA girls have similar growth hormone levels compared to prepubertal short SGA girls (van der Kaay et al., 2009b). The lack of a rise in growth hormone levels during puberty in short SGA girls might play a role in the less intense pubertal growth spurt found in short SGA children who do not receive growth hormone treatment (Luo et al., 2003).
Treatment with subcutaneous leuprorelide acetate depots of 3.75mg every 4 weeks results in adequate pubertal suppression in pubertal short SGA children (van der Kaay et al., 2009c; van der Kaay et al., 2009d).
GnRH analogue treatment in pubertal short SGA girls results in a reduction of serum growth hormone levels, to levels lower than those found in prepubertal short SGA girls. The

interindividual variability in growth hormone secretion in response to a GnRH analogue is significant (Figure 7). One third of short SGA girls had a reduction in growth hormone levels of more than 40%. These girls also demonstrated a greater decrease in IGF-I and IGFBP-3 levels, compared to girls who showed a reduction in growth hormone levels between 0 and 40%. There is no association between growth hormone levels and estrogen levels, or between growth hormone levels and luteinizing hormone levels. This implies that girls with the same degree of pubertal suppression have different growth hormone responses during GnRH analogue treatment (van der Kaay et al., 2009b).

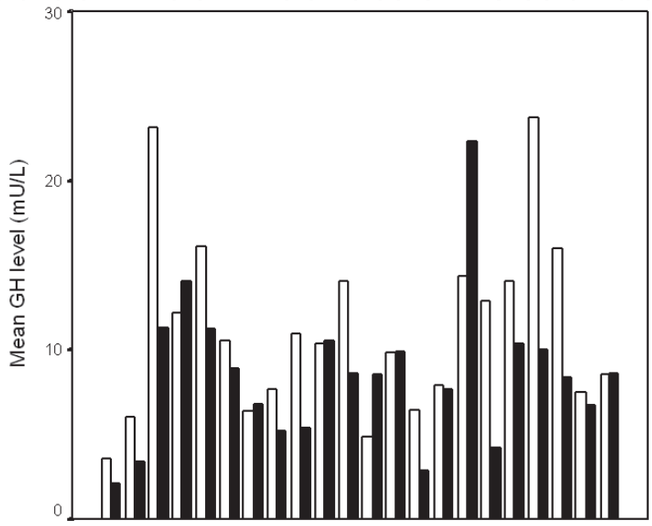

Fig. 7. Mean growth hormone levels for each individual girl during an overnight growth hormone profile before (white bars) and after 3 months of GnRHa treatment (black bars) (van der Kaay et al., 2009b).

7.2 Effects of GnRH analogue treatment on the metabolic profile

Most of the studies performed in children with central precocious puberty have focused on adult height, bone mineral density and restoration of the reproductive system after long-term treatment with GnRH analogues. Much less attention has been paid to changes in body composition. Some studies report an increase in fat mass or BMI during GnRH analogue treatment, with a return to values comparable to those at baseline after discontinuation (Pasquino et al., 2008; van der Sluis et al., 2002), whereas others report no changes (Palmert et al., 1999) or even a decreased BMI during GnRH analogue treatment (Arrigo et al., 2004). Lean body mass SDS decreases during GnRH analogue treatment (van der Sluis et al., 2002).

There is a physiological decrease in insulin sensitivity with pubertal progression (Hannon et al., 2006). Since both growth hormone and IGF-I levels significantly increase during puberty, the higher GH levels during puberty are thought to contribute to the pubertal insulin resistance (Moran et al., 2002). A brief period of GnRH analogue treatment in young, healthy women did not result in changes in insulin secretion (Toth et al., 2008). The effect of GnRH analogue treatment on insulin sensitivity in children with central precocious puberty is, however, unknown.

8. Combined treatment with a GnRH analogue and growth hormone in pubertal short children born small for gestational age

Studies in patients with idiopathic growth hormone deficiency demonstrated a beneficial effect on adult height in favor of combined treatment with a GnRH analogue and growth hormone, compared to growth hormone treatment alone (Mericq et al., 2000; Saggese et al., 2001). In children with idiopathic short stature contradictory results have been found (Lanes et al., 1998; Pasquino et al., 2000).

8.1 Effects on the GH-IGF-IGFBP axis

Similar to prepubertal short SGA children treated with either 1 or 2 mg GH/m²/day, pubertal short SGA children treated with a GnRH analogue and either 1 or 2 mg GH/m²/day show a dose-dependent increase in growth hormone levels (Figure 8). Growth hormone levels in pubertal short SGA children were, however, lower than levels in prepubertal short SGA children treated with a similar dose of growth hormone. Moreover, growth hormone levels in pubertal short SGA children treated with a GnRH analogue and 2 mg GH/m²/day were similar to growth hormone levels in prepubertal short SGA children treated with 1 mg GH/m²/day. Since growth hormone levels decrease during GnRH analogue treatment, these lower growth hormone levels might be the result of simultaneous treatment with a GnRH analogue, next to growth hormone (van der Kaay et al., 2010). Nevertheless, growth hormone levels in pubertal short SGA children treated with a GnRH analogue and 2 mg GH/m²/day remain elevated for a great part of the day. Similar to prepubertal short SGA children, there is a wide interindividual variation in growth hormone levels in response to either 1 or 2 mg

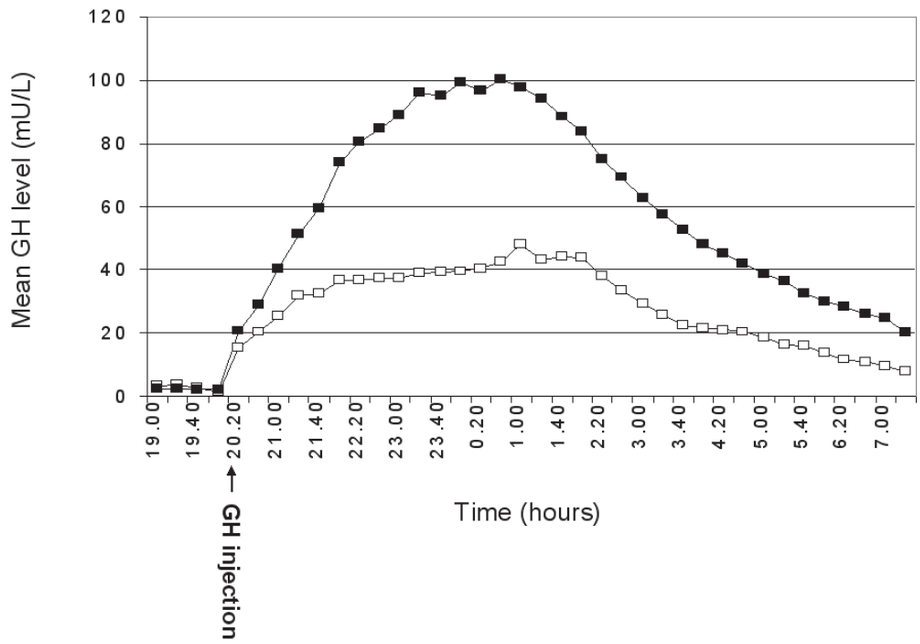

Fig. 8. Mean growth hormone levels for each time point during an overnight growth hormone profile after 1 year of combined treatment with a GnRH analogue and growth hormone. Open squares: 1 mg GH/m²/day, solid squares: 2 mg GH/m²/day (van der Kaay et al., 2010).

GH/m²/day. Genetic variability in growth-related genes probably accounts for part of this variation, next to variations in physiological mechanisms involved in degradation of growth hormone at the site of injection and in the systemic circulation.

Pubertal short SGA children treated with a GnRH analogue and either 1 or 2 mg GH/m²/day show a dose-dependent increase in IGF-I levels. Compared to the population mean, IGF-I levels are significantly lower at start of growth hormone treatment and significantly higher after 1 year of combined treatment. IGFBP-3 levels increase as well, but to a lesser extent than IGF-I levels. This results in an increase in levels of free, biologically active IGF-I which stimulates growth. Similar to prepubertal short SGA children treated with 2 mg GH/m²/day, a greater percentage of pubertal short SGA children treated with a GnRH analogue and 2 mg GH/m²/day have IGF-I SD scores in the highest quintile (> 0.84 SDS), compared to children treated with a GnRH analogue and 1 mg GH/m²/day. Reassuringly, the percentage of children with IGF-I SD scores above +2 SDS was not different between both growth hormone dosage groups (van der Kaay et al., 2010). Concern has been expressed about the association between high IGF-I levels during several years and long-term cancer risk (Renehan et al., 2004). Although pubertal short SGA children will be treated with growth hormone for a relatively short period of time, it is important to monitor IGF-I levels during growth hormone treatment in order to titrate the growth hormone dose to IGF-I levels within the age-appropriate normal range.

8.2 Effects on insulin sensitivity

In pubertal short SGA children, insulin sensitivity (Si) – measured by frequently sampled intravenous glucose tolerance tests – is lower and insulin secretion (acute insulin response (AIR)) is higher, compared to prepubertal short SGA children. This was expected since pubertal children have a physiological decrease in insulin sensitivity.

During combined treatment with a GnRH analogue and either 1 or 2 mg GH/m²/day, insulin sensitivity decreases and insulin secretion increases. The disposition index remained comparable to baseline, reflecting that β-cells are able to compensate for the reduction in insulin sensitivity by increasing their insulin secretion. Insulin sensitivity and secretion was comparable between children treated with either 1 or 2 mg GH/m²/day (Table 3) (van der Kaay et al., 2010).

8.3 Effect on lipid profile and blood pressure

In pubertal short SGA children, mean total cholesterol (TC), low density lipoprotein-cholesterol (LDL-c), high density lipoprotein-cholesterol (HDL-c), triglycerides (TG), non-esterified fatty acids (FFAs), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo B) and lipoprotein (a) (lp(a)) are within the normal range. Lipoprotein (a) levels are, however, above the normal range in 27% of pubertal short SGA children. High lipoprotein (a) levels have been associated with an increased risk of developing cardiovascular disease (Danesh et al., 2000).

During combined treatment with a GnRH analogue and either 1 or 2 mg GH/m²/day, very small increases and/or decreases of lipid levels are found. The clinical significance of these small changes is considered negligible. Lipid levels are comparable between children treated with either 1 or 2 mg GH/m²/day (Table 3) (van der Kaay et al., 2010).

Systolic blood pressure (BP) is higher in pubertal short SGA children than in controls and 27% of pubertal short SGA children have a systolic blood pressure above + 2 SDS adjusted for gender and height. Higher blood pressure in childhood has been associated with an

increased risk of developing hypertension in adulthood. Systolic blood pressure does not change during 2 years of combined treatment with a GnRH analogue and either 1 or 2 mg GH/m²/day (Table 3). This is in line with previous findings, where a decrease in blood pressure was found only after 3 years of growth hormone treatment (Willemsen et al., 2008).

	Start of GnRHa treatment (n=41)	One year of combined treatment (n=41)	Three months after the stop of GnRHa treatment (n=41)
Systolic BP SDS	1.59 (1.24–1.94)*	1.26 (0.87–1.65)*	1.39 (1.04–1.74)*
Diastolic BP SDS	0.22 (0.00–0.45)	0.52 (0.27–0.78)†	0.57 (0.36–0.79)‡
Si×10^{-4}/min (μU/ml)	7.38 (6.00–8.76)	4.61 (3.71–5.50)†	ND
Sg×10^{-2}/min	3.47 (2.98–3.96)	3.42 (2.94–3.89)	ND
AIR (mU/l)	421 (326–543)	790 (643–971)†	ND
DI (AIR×Si)	2569 (2012–3279)	3105 (2514–3838)	ND
Insulin (pmol/l)	48.1 (41.7–55.5)	75.0 (63.8–88.1)†	79.2 (66.7–94.0)‡
HOMA-IR	0.91 (0.79–1.06)	1.39 (1.19–1.63)†	1.43 (1.20–1.70)‡
TC (mmol/l) (3.0–5.5)	4.16 (3.99–4.33)	4.20 (4.00–4.40)	4.33 (4.13–4.53)‡
LDL-c (mmol/l) (1.3–3.4)	2.28 (2.11–2.46)	2.44 (2.25–2.64)†	2.36 (2.19–2.52)
HDL-c (mmol/l) (0.9–1.9)	1.41 (1.31–1.52)	1.63 (1.51–1.76)†	1.55 (1.44–1.66)‡,§
TG (mmol/l) (0.4–1.6)	0.76 (0.66–0.86)	0.79 (0.67–0.94)	0.92 (0.75–1.13)‡
FFA (mmol/l) (0.2–1.0)	0.52 (0.45–0.59)	0.69 (0.59–0.79)†	0.51 (0.42–0.60)§
Apo-A1 (g/l) (0.9–1.6)	1.39 (1.32–1.46)	1.56 (1.47–1.65)†	1.45 (1.38–1.53)§
Apo-B (g/l) (0.5–1.3)	0.71 (0.66–0.75)	0.73 (0.68–0.77)	0.72 (0.67–0.77)
Lp(a) (g/l) (≤0.3)	0.09 (0.06–0.13)	0.14 (0.09–0.21)†	0.14 (0.09–0.22)‡

ND = not determined; *P<0.0001 compared with the population mean (0 SDS); †P<0.03: 1 year of combined treatment, compared with the start of GnRH analogue treatment; ‡P<0.03: 3 months after the stop of GnRH analogue treatment, compared with the start of GnRH analogue treatment; §P<0.02: 3 months after the stop of GnRH analogue treatment, compared with 1 year of combined treatment (van der Kaay et al., 2010).

Table 3. Blood pressure, insulin sensitivity, and lipids at the start of GnRH analogue treatment, after 1 year of combined treatment and 3 months after the stop of GnRH analogue treatment in short SGA children with continuation of growth hormone treatment. Data are expressed as model estimate (95% CI), after adjustment for gender and Tanner stage at baseline. The values between brackets represent reference ranges for healthy children.

8.4 Effects on body composition

Fat mass adjusted for height and gender (SDS_{height}) in pubertal short SGA children is significantly lower than the population mean, consistent with findings in prepubertal short SGA children (Willemsen et al., 2007). During treatment with a GnRH analogue and 1 mg GH/m²/day, fat mass SDS_{height} significantly increases to values comparable to the population mean. In contrast, during 1 year of treatment with a GnRH analogue and 2 mg GH/m²/day, fat mass SDS_{height} decreases. During 2 years of combined treatment, fat mass SDS_{height} values return to those comparable before start of treatment – remaining significantly lower than the population mean in children treated with a GnRH analogue and 2 mg GH/m²/day (Figure 9). Although the percentage of trunk fat increases in pubertal short SGA children treated with GnRHa and either 1 or 2 mg GH/m²/day, values are lower in children treated with GnRHa and 2 mg GH/m²/day (Figure 9). This indicates that pubertal short SGA children develop relatively more fat mass around the waist, but that the increase is less when GnRH analogue treatment is combined with 2 mg GH/m²/day. In prepubertal short SGA children treated with 2 mg GH/m²/day, percentage trunk fat remains comparable to untreated children. Thus, the increase in percentage trunk fat in pubertal short SGA children is most likely due to treatment with a GnRH analogue, next to growth hormone (van der Kaay et al., 2010).

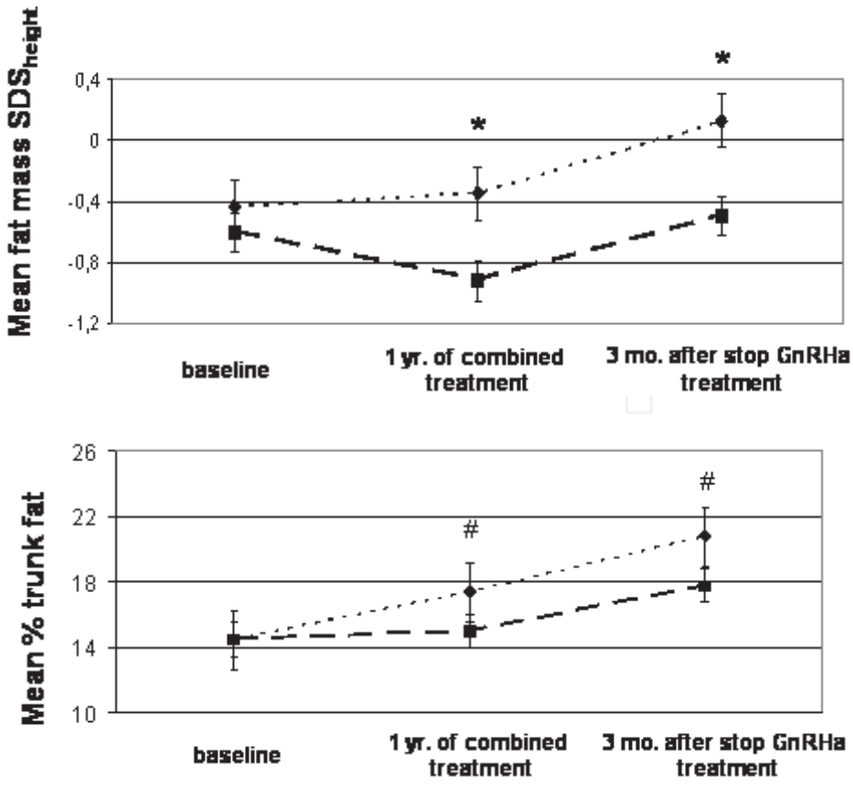

Fig. 9. Changes in fat mass SDS_{height} and percentage trunk fat during 27 months of GnRH analogue and growth hormone treatment. Data are expressed as mean (± standard error of the mean (SEM)). Diamonds represent values during treatment with a GnRH analogue and 1 mg GH/m²/day. Squares represent values during treatment with a GnRH analogue and 2 mg GH/m²/day. Mean percentage trunk fat=(trunk fat/total trunk mass)x100. * P<0.01, # P<0.05 (van der Kaay et al., 2010).

Several studies reported an increase in fat mass or BMI during GnRH analogue treatment in children with central precocious puberty. This might be explained by the lower growth hormone levels found during GnRH analogue treatment, as reported in children with growth hormone deficiency (Boot et al., 1997). Growth hormone has well-documented lipolytic effects and growth hormone treatment in prepubertal short SGA children results in a significant decrease in fat mass SDS_{height}, especially in the first treatment year. In pubertal short SGA children, treatment with 2 mg GH/m²/day counteracts the fat-accumulating effect of simultaneous treatment with a GnRH analogue, whereas treatment with 1 mg GH/m²/day is insufficient to prevent children from gaining fat mass during GnRH analogue treatment.
Epidemiological studies have shown that low birth weight followed by catch-up in fat mass during childhood and adolescence is associated with a higher risk of developing type 2 diabetes and cardiovascular disease, even when fat mass remains within the normal range. Follow-up until adult height is required to investigate the long-term effects of changes in body composition and metabolic profile in short SGA children treated with a combination of GnRH analogue and growth hormone.
Lean body mass SDS_{height} in pubertal short SGA children is significantly lower than the population mean. It was previously shown that older prepubertal short SGA children have a

lower lean body mass SDS_{height} compared with younger prepubertal short children born SGA (Willemsen et al., 2007).
During combined treatment with a GnRH analogue and either 1 or 2 mg GH/m²/day, lean body mass SDS_{height} increases only in pubertal short SGA children treated with a GnRH analogue and 2 mg GH/m²/day, although values remain significantly lower than the population mean. It is known that in children with central precocious puberty, lean body mass decreases during GnRH analogue treatment. Only combining 2 mg GH/m²/day with a GnRH analogue results in an increase in lean body mass SDS_{height} in older short SGA children (Figure 10) (van der Kaay et al., 2010).

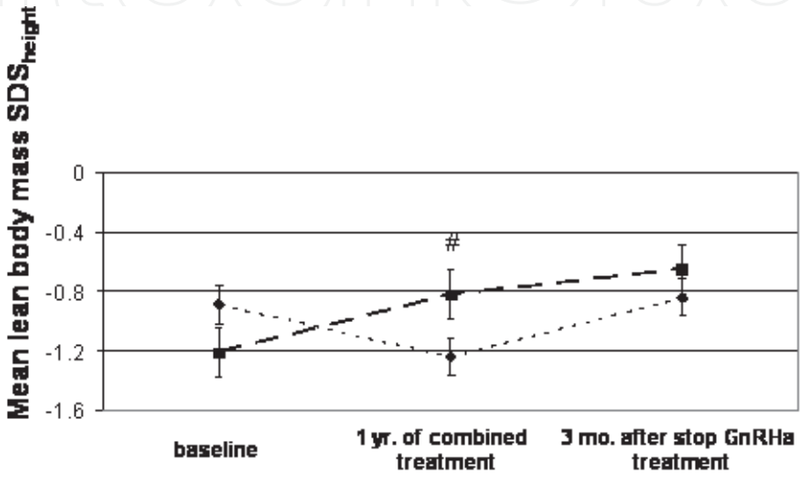

Fig. 10. Changes in lean body mass SDS_{height} during 27 months of GnRH analogue and growth hormone treatment. Data are expressed as mean (± standard error of the mean (SEM)). Diamonds represent values during treatment with a GnRH analogue and 1 mg GH/m²/day. Squares represent values during treatment with a GnRH analogue and 2 mg GH/m²/day. # $P<0.05$ (van der Kaay et al., 2010).

9. General conclusions and practical implications

Since growth hormone treatment was approved by the US Food and Drug Administration (FDA) in 2001 and by the European Agency for Evaluation of Medicinal Products (EMEA) in 2003, short children born small for gestational age comprise a large group of growth hormone treated children.
Various studies demonstrated that growth hormone treatment in prepubertal short SGA children effectively and safely induces catch-up growth. Better growth responses and greater adult height are achieved when children start growth hormone treatment at an early age. Some short SGA children, however, come under medical attention at onset of puberty.
Pubertal short SGA girls lack the usual increase in growth hormone levels that accompanies the pubertal growth spurt, as found in pubertal girls with normal stature. Furthermore, GnRH analogue treatment results in a decrease in growth hormone levels to levels lower than those found in prepubertal short SGA girls. The lack of a rise in growth hormone levels during puberty in short SGA girls might play a role in the less intense pubertal growth spurt found in short SGA children who do not receive growth hormone treatment.

During combined treatment with a GnRH analogue and either 1 or 2 mg GH/m²/day, growth hormone and IGF-I levels show a dose-dependent increase, although growth hormone levels are lower compared to levels in prepubertal short SGA children treated with the same GH dose. Moreover, growth hormone levels in pubertal short SGA children treated with a GnRH analogue and 2 mg GH/m²/day are similar to growth hormone levels in prepubertal short SGA children treated with 1 mg GH/m²/day. During 2 years of combined treatment, the higher dose of 2 mg GH/m²/day has a favorable effect on fat mass SDS, percentage trunk fat and lean body mass SDS. Blood pressure, insulin sensitivity and lipid profile are similar between children treated with a GnRH analogue and 1 or 2 mg GH/m²/day. Combined treatment has no adverse effect on these metabolic parameters.
Thus, combined treatment with a GnRH analogue and either 1 or 2 mg GH/m²/day – possibly in favor of treatment with a GnRH analogue and 2 mg GH/m²/day – can be considered as a safe treatment strategy in the short run for short children born small for gestational age who come under medical attention at onset of puberty. Adult height data need to be awaited before definitive conclusions can be drawn concerning the long-term efficacy and safety of this combined treatment.

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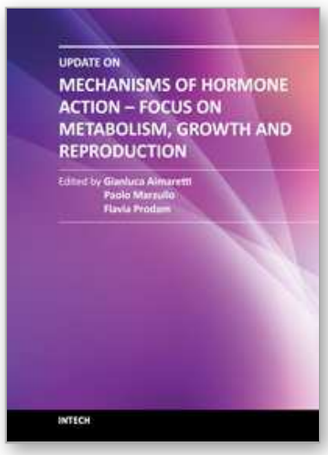

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The purpose of the present volume is to focus on more recent aspects of the complex regulation of hormonal action, in particular in 3 different hot fields: metabolism, growth and reproduction. Modern approaches to the physiology and pathology of endocrine glands are based on cellular and molecular investigation of genes, peptide, hormones, protein cascade at different levels. In all of the chapters in the book all, or at least some, of these aspects are described in order to increase the endocrine knowledge.

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