

Catch-up growth in early treated patients with growth hormone deficiency

B Boersma, B Rikken, J M Wit, and the Dutch Growth Hormone Working Group*

Abstract

Catch-up growth of 26 children with growth hormone deficiency during four years of growth hormone treatment, which was started young (<3 years), was compared with that of 16 children with coeliac disease on a gluten free diet. In children with growth hormone deficiency mean (SD) height SD score increased from -4.3 (1.8) to -1.9 (1.4) and in patients with coeliac disease from -1.8 (0.9) to -0.1 (0.8). Height SD score after four years correlated positively with injection frequency and height SD score at start of treatment in children with growth hormone deficiency. All patients with coeliac disease reached a height above -2 SD scores after four years, while the height of 26% of children with growth hormone deficiency on daily injections and of 86% of children on 2 or 4 injections/week was still below -2 SD scores. In patients with growth hormone deficiency on daily injections with an initial height SD score between -2 and -4 catch-up was similar to that of patients with coeliac disease with a comparable initial height deficit. Growth hormone deficient children with an initial height SD score <-4 did not reach full catch-up growth within four years. In conclusion, catch-up growth in early treated children with growth hormone deficiency over four years is adequate provided that daily injections are given and the initial height SD score is not less than -4.

(Arch Dis Child 1995; 72: 427-431)

Keywords: growth hormone deficiency, coeliac disease, catch-up growth.

outcome. The first one is that the therapeutic regimen has not been optimal. Whereas it is nowadays generally believed that daily growth hormone injections are more effective than 2 or 4 injections/week,¹¹ the optimal substitution dosage is still unknown, which is illustrated by the wide range of the dosages applied in various countries.¹² The second explanation is that treatment on average has been started too late. A long period of untreated growth hormone deficiency might either directly affect the growth plate or leave insufficient time to catch up before the onset of puberty. In fact, a large international survey showed that the median chronological age at start for 4462 children with idiopathic growth hormone deficiency was 10.0 years (10th centile=4.2, 90th centile 14.4).¹²

The third explanation is that growth hormone deficiency causes permanent damage to one or more levels of the growth regulatory axis in the intrauterine period and shortly after birth. If this last explanation is true, even early initiation of treatment could not overcome the resulting growth retardation.¹³ We tested this hypothesis by studying the growth pattern of children with growth hormone deficiency who started growth hormone treatment before the age of 3 years, either with daily injections or 2 or 4 times/week.

In order to assess the adequacy of catch-up growth in growth hormone deficiency, it was compared with the growth response in coeliac disease. In children with coeliac disease the cause of the growth retardation is eliminated at the moment that a gluten free diet is started, in general before the age of 3 years, and catch-up growth is usually complete after 2-3 years.¹⁴⁻¹⁷

Patients and methods

Patients with growth hormone deficiency were selected from the files of the Dutch national registry on growth hormone treatment, which contains growth data of nearly all growth hormone treated children in the Netherlands. Inclusion criteria were: peak serum growth hormone concentrations of less than 10 µg/l (20 mU/l) during at least two standard provocation tests, start of growth hormone treatment before the age of 3.0 years, and completion of four years of growth hormone treatment. Patients with isolated growth hormone deficiency as well as patients with growth hormone deficiency in combination with other pituitary deficiencies were included, whereas patients with intracerebral tumours were excluded. Twenty six growth hormone deficient children (16 boys and 10 girls) fulfilled the inclusion

University Hospital
Leiden, The
Netherlands,
Department of
Paediatrics
B Boersma
J M Wit

University Hospital
Leiden, Bureau of the
Dutch Growth
Foundation
B Rikken

Correspondence to:
B Boersma, Department of
Paediatrics, University
Hospital Leiden, Building 1,
Room J6-S, PO Box 9600,
2300 RC Leiden, The
Netherlands.

Accepted 5 December 1994

*Participating investigators:
M Jansen, Wilhelmina
Children's Hospital, Utrecht;
S M P F de Muinck Keizer-
Schrama, Sophia Children's
Hospital, Rotterdam; W
Oostdijk, University Hospital
Leiden; B J Otten, St
Radboud Hospital,
Nijmegen; T Vulmsma,
Academic Medical Center,
Amsterdam.

In 1958 growth hormone was introduced for the treatment of growth hormone deficiency.¹ Since then many investigators have studied the efficacy of growth hormone treatment in growth hormone deficient patients.²⁻⁷ These studies have demonstrated that, although growth hormone treatment of children with growth hormone deficiency induces a significant increase of height velocity during the first years of treatment, the average height after several years of treatment, as well as final height has remained approximately 2 SD below the population's mean. Early diagnosis and treatment of growth hormone deficiency gives a greater improvement in gained height.^{4-6 8-10}

Theoretically, there are at least three possible explanations for this disappointing

criteria. Seven (27%) patients had an isolated growth hormone deficiency and in the other 19 patients it was accompanied by a thyroid stimulating hormone deficiency, 16 (64%) of whom also had a deficiency of adrenocorticotrophic hormone. In five cases (19%) one of the parents was also growth hormone deficient.

The standard regimen of growth hormone treatment in the Netherlands has changed over the years. From 1970 to 1986 a fixed dose of 8 IU/week was given, initially administered in 2 intramuscular, and from 1983 in 4 subcutaneous, injections/week. From 1987 the substitution regimen was individually adjusted to body surface and the frequency of injections was increased to 6 or 7 times/week. The current standard treatment is 12–14 IU/m²/week divided into 6 or 7 subcutaneous injections.

The growth hormone deficient patients were subdivided in three subgroups according to the frequency of growth hormone administration. Subgroup 1 contained the patients who in the first four years received a weekly dosage of 8 IU divided into 2 or 4 injections/week (n=7), subgroup 2 was formed by the patients who started on 8 IU in 4 injections/week but were transferred to 6 or 7 injections/week within this period (n=7), and subgroup 3 contained the patients who always received 6 or 7 injections/week (n=12).

The growth data of the patients with coeliac disease were obtained from an earlier study.¹⁴ Inclusion into the coeliac disease group was restricted to patients diagnosed before 3 years of age by at least two small bowel biopsies and a positive gluten challenge. Data of 16 coeliac disease patients (seven boys and nine girls) were suitable for this analysis.

Supine length (in infants and children less than 2–3) or height (in older children) was measured with standard equipment and expressed as SD score for chronological age calculated by [patient's height–mean height]/SD, in which the appropriate mean height and SD for age and sex were taken from the 1980 nationwide Dutch references.¹⁸ If parental heights were available and neither parent was growth hormone deficient, height SD score was corrected for target height by subtracting the mean parental SD score from the child's SD score. The mean parental height SD score was computed as the average of the height SD scores for both parents, using the

references for adult height from the 1965 Dutch nationwide survey.¹⁹ Height SD score was corrected for parental height in 13 (81%) patients with coeliac disease and in 20 (77%) growth hormone deficient patients.

In order to enable a comparison between the patients with growth hormone deficiency, for whom height measurements generally had been performed at three monthly intervals, and the patients with coeliac disease for whom growth data were often available at less regular intervals, we have modelled the SD score curves of the patients with coeliac disease. Each individual curve was fitted to a growth function as previously described.²⁰

Unless otherwise specified, results are expressed as mean (SD). Paired *t* tests and repeated measures analysis of variance or in case of non-normality, Wilcoxon signed rank or Friedman statistic tests, were performed to assess differences within the groups. To test differences between the groups unpaired *t* tests or analysis of variance and in case of non-normality Wilcoxon signed rank or Kruskal-Wallis tests were used. A comparison of nominal variables among the groups was made using a χ^2 analysis. The correlations between various parameters were calculated by univariate linear regression analysis and expressed by the Pearson's correlation coefficient.

Results

Clinical data at onset of treatment of the patients with growth hormone deficiency and coeliac disease are presented in the table. No significant differences between the subgroups of growth hormone deficient patients were found with respect to the maximum serum growth hormone peak and the total weekly growth hormone dose. Whereas midparental height SD score and age at onset of treatment were similar in all growth hormone deficient subgroups and the coeliac disease group, birth length and height SD score at start of treatment was significantly lower in patients with growth hormone deficiency than in coeliac disease patients ($p < 0.001$). The birth length of patients with isolated growth hormone deficiency was 46.1 (5.8) cm (n=7), similar to that of patients with multiple pituitary deficiencies (45.7 (3.7) cm, n=14; not significant).

The growth response to four years of treatment in growth hormone deficiency,

Clinical data at onset of treatment in patients with growth hormone deficiency and coeliac disease; values are mean (SD) except for serum growth hormone peak, which is median (range)

	Growth hormone deficiency			Coeliac disease (n=16)
	2 or 4 injections/week (n=7)	Transfer group* (n=7)	6 or 7 injections/week (n=12)	
Birth length (cm)	45.6 (1.8)	46.4 (3.0) [n=5]	45.7 (6.4) [n=9]	51.2 (2.0) [n=13]
Birth length SD score†	-1.6 (0.4) [n=5]	-2.3 (1.7) [n=5]	-2.0 (3.0) [n=9]	NA§
Age of start of treatment (years)	1.6 (0.7)	1.4 (0.7)	1.4 (0.8)	1.5 (0.6)
Serum growth hormone peak ($\mu\text{g/l}$)‡	1.5 (0.3–4.5)	1.0 (0.5–6.0)	3.9 (0.3–9.0)	NA
Growth hormone substitution dose (IU/m ² /week)	15.4 (1.6)	15.6 (3.1)	15.8 (2.4)	–
Midparental height SD score	-0.3 (1.0) [n=5]	-0.2 (0.8) [n=5]	0.1 (0.7)	0.0 (0.6) [n=13]
Height at start of treatment (cm)	68.4 (8.0)	67.0 (10.3)	67.1 (7.4)	75.7 (5.5)
Height SD score at start of treatment	-4.5 (1.6)	-4.4 (1.8)	-4.1 (2.1)	-1.8 (0.9)

*Transfer from 2 or 4 to 6 or 7 injections/week within four years. †SD score corrected for gestational age.²⁵

‡To convert from $\mu\text{g/l}$ to mU/l multiply by 2. §Not available (NA) as gestational age was unknown.

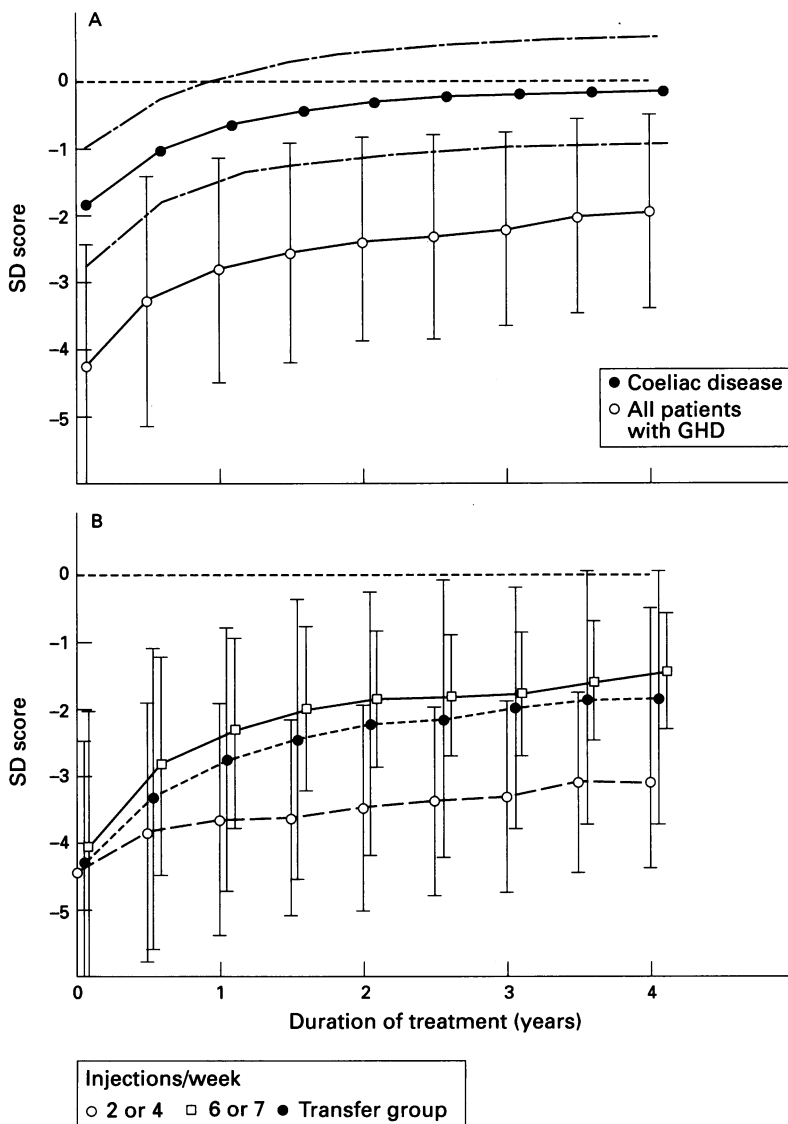


Figure 1 Mean (SD) height SD score against duration of treatment. (A): Coeliac disease and all patients with growth hormone deficiency (GHD). (B): GHD, divided into subgroups according to injection frequency.

irrespective of initial height SD score and therapeutic regimen, and in coeliac disease is shown in fig 1(A). Both groups showed significant catch-up growth (Δ SD score 2.4 (1.6), $p < 0.05$ and 1.7 (0.7), $p < 0.001$ respectively), but height remained below -2 SD in 11 children with growth hormone deficiency in contrast to none of the coeliac disease patients. In the growth hormone deficient group height SD score after four years of treatment correlated significantly with height SD score at the start of treatment ($r = 0.74$, $p < 0.01$), but not with birth length ($r = 0.21$; not significant). Height SD score increment over four years showed an inverse relationship with height SD score at the start ($r = -0.63$, $p < 0.001$).

When the growth hormone deficient patients were subdivided according to injection frequency (fig 1(B)), catch-up growth on the regimen of daily injections, either during the full four years or started later in that period, was superior ($p < 0.05$) to the regimen of 2 or 4 injections/week, while the dosages were similar. The increment of height SD score over four years of treatment was 1.4 (1.1), 2.6 (1.9),

and 2.7 (1.6) in subgroups 1, 2, and 3 respectively. While 14 of the 19 patients (74%) from subgroups 2 and 3 had a height above -2 SD score after four years of treatment, this was reached by only one of the seven patients (14%) on 2 or 4 injections ($p < 0.05$). When growth hormone deficient patients receiving daily injections were subdivided in those with isolated growth hormone deficiency ($n = 4$) and multiple pituitary deficiencies ($n = 8$), no significant difference was found with respect to their growth response (height SD score increased from -4.3 (0.9) to -1.3 (0.8) and from -4.0 (2.5) to -1.4 (1.0), respectively).

Because of the differences between the patients with growth hormone deficiency and coeliac disease with regard to initial height SD score, and the importance of the latter for the success of catch-up growth, we grouped all patients according to initial height SD score (fig 2). The number of growth hormone deficient patients with an initial height SD score below -2 (fig 2(B), (C)) allowed for a further subdivision according to injection frequency. There were no coeliac disease patients with an initial height SD score < -3 . Patients with growth hormone deficiency with an initial height SD score between -2 and -4 and treated with 6 or 7 injections/week (age at start 1.3 (1.1) years) showed similar catch-up as coeliac disease patients. In growth hormone deficient patients with a severe initial growth retardation (< -4 SD score, age at start 1.6 (0.6) years) the present therapeutic regimen was more efficacious than the previous regimens but did not lead to full catch-up within four years, although the increment of height SD score did not reach a plateau.

Discussion

The hypothesis that congenital growth hormone deficiency would lead to a permanent impairment of growth potential can be rejected at least for the children with an initial height SD score between -2 and -4 , as on the present growth hormone therapeutic regimen they showed similar catch-up growth as observed in coeliac disease. In children with an initial height SD score < -4 , the hypothesis can neither be rejected nor proved, as catch-up was not complete after four years, while no comparison with coeliac disease was possible. In this subgroup with severe initial growth retardation the incomplete catch-up may be caused by permanent impairment of growth potential, a suboptimal growth hormone regimen, insufficient time for reaching full catch-up, or a combination of these factors. The observation that catch-up did not reach a plateau after four years would suggest that the last factor is at least responsible for part of the effect. We found no evidence that the degree of intrauterine growth retardation affects the completeness of catch-up growth, as birth length was not correlated with height SD score after four years of treatment.

Children in whom growth hormone deficiency is diagnosed at a young age can usually

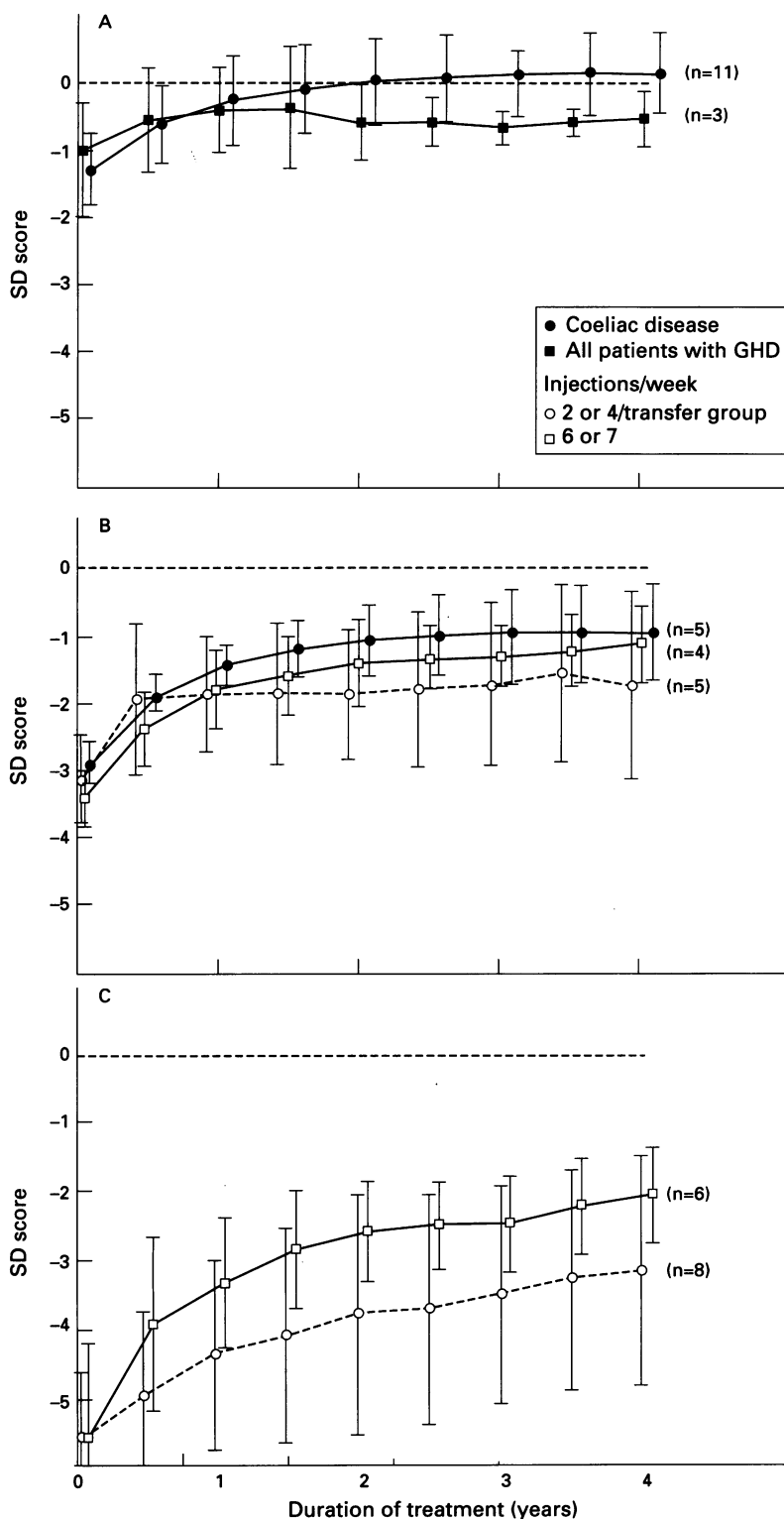


Figure 2 Mean (SD) height SD score against duration of treatment according to height SD score at start of treatment: (A) > -2 , (B) between -2 and -4 , and (C) < -4 ; GHD = growth hormone deficiency.

be classified retrospectively as having congenital growth hormone deficiency and their degree of growth hormone deficiency is generally more severe than that of children diagnosed later. In this study we have confirmed our earlier data¹³ showing that congenital growth hormone deficiency, even in the isolated form, affects intrauterine growth, as birth length was 5 cm less than that of infants with coeliac disease. This is in concordance with the

recent observation that growth hormone has a definite role in prenatal human growth regulation.²¹

There was no effect of the presence of additional pituitary deficiencies, indicating that substitution treatment with thyroid hormone and cortisol was adequate, in line with the clinical impression. However, there was a strong effect of growth hormone injection frequency which appears more manifest in these infants and young children than in older children.^{11 22 23} This may be due to the tendency to hypoglycaemia in infants and toddlers on a schedule of 2 or 4 injections/week.²⁴

As an indicator for the pattern of catch-up growth that could be expected on adequate treatment, we chose the model of coeliac disease. This disease has a causal and fully efficacious treatment, which usually leads to complete catch-up growth within 2–3 years.^{14–17} While suitable as a model for catch-up growth, there are some relevant differences with congenital growth hormone deficiency. The growth retardation in coeliac disease starts after the introduction of gluten at approximately 6 months of age, while growth of approximately 50% of the infants with congenital growth hormone deficiency start deviating in utero. This is one of the reasons why the growth deficit at diagnosis is less pronounced in coeliac disease than in growth hormone deficiency. Another reason for the less extreme growth deficit at diagnosis is that coeliac disease is usually associated with more severe clinical symptoms and therefore often diagnosed before an extreme growth retardation has occurred. On the basis of these differences, it would have been no surprise if catch-up growth would have been less successful in growth hormone deficiency than in coeliac disease. In contrast, we found that catch-up was similar when only growth hormone deficient children with comparable initial height SD scores and daily growth hormone injections were included.

In conclusion, early treatment of growth hormone deficient children with daily injections leads to similar catch-up growth as observed in coeliac disease with a similar initial height SD score, indicating that congenital growth hormone deficiency does not result in a permanent impairment of growth potential. If the initial height deficit is more extreme, full catch-up growth is not reached within four years. This emphasises the importance of early diagnosis and treatment. Daily injections are much more effective than 2 or 4 injections/week.

- 1 Raben MS. Treatment of a pituitary dwarf with human growth hormone. *J Clin Endocrinol Metab* 1958; 18: 901–3.
- 2 Hibi I, Tanaka T, Yano H, et al. An attempt to assess the replacement dose of human growth hormone in the treatment of growth hormone deficient children. *Acta Paediatr Scand Suppl* 1987; 337: 87–92.
- 3 Joss E, Zuppinger K, Schwarz HP, Roten H. Final height of patients with pituitary growth failure and changes in growth variables after long term hormonal therapy. *Pediatr Res* 1983; 17: 676–9.
- 4 Bundak R, Hindmarsh PC, Smith PJ, Brook CGD. Long-term auxologic effects of human growth hormone. *J Pediatr* 1988; 112: 875–9.
- 5 Burns EC, Tanner JM, Precece MA, Cameron N. Final height and pubertal development in 55 children with idiopathic growth hormone deficiency, treated for between

- 2 and 15 years with human growth hormone. *Eur J Pediatr* 1981; **137**: 155-64.
- 6 Josefsberg Z, Bauman B, Pertzalan A, Laron Z. Greater efficiency of human growth hormone therapy in children below five years of age with growth hormone deficiency. A 5-year follow-up study. *Horm Res* 1987; **27**: 126-33.
 - 7 Dean HJ, Friesen HG. Long-term growth of children with growth hormone deficiency and hypoglycemia. *J Pediatr* 1989; **115**: 598-600.
 - 8 Mugnier E, Ployard F, Roy MP, Fermanian J, Rappaport R. Resultats du traitement par l'hormone de croissance humaine chez les enfants insuffisants hypophysaires ages de moins de 7 ans. *Arch Fr Pediatr* 1985; **42**: 671-6.
 - 9 Zadik Z, Chalew S, Zung A, et al. Effect of long-term growth hormone therapy on bone age and pubertal maturation in boys with and without classical growth hormone deficiency. *J Pediatr* 1994; **125**: 189-95.
 - 10 Vanderschueren-Lodeweyckx M, Van den Broeck J, Wolter R, Malvaux P. Early initiation of growth hormone treatment: influence on final height. *Acta Paediatr Scand Suppl* 1987; **337**: 4-11.
 - 11 Kastrop DW, Christiansen JS, Anderson JK, Orskov H. Increased growth rate following transfer to daily sc administration from three weekly im injection of hGH in growth hormone deficient children. *Acta Endocrinol (Copenh)* 1983; **104**: 148-52.
 - 12 Maes M, Isaksson AC. Demographic information. *Kabi international growth study. Biannual report 1993 No 10*. Stockholm: Kabi, 1993:7-17.
 - 13 Wit JM, Van Unen H. Growth of infants with neonatal growth hormone deficiency. *Arch Dis Child* 1992; **67**: 920-4.
 - 14 Damen GM, Boersma B, Wit JM, Heymans HSA. Catch-up growth in 60 prepubertal children with celiac disease. *J Pediatr Gastroenterol Nutr* 1994; **19**: 394-400.
 - 15 Barr D, Shmerling D, Prader A. Catch-up growth in malnutrition studied in celiac disease after institution of gluten-free diet. *Pediatr Res* 1972; **6**: 521-7.
 - 16 Cacciari E, Salardi S. Growth in coeliac disease. In: Hernandez M, Argente J, eds. *Human growth: basic and clinical aspects*. Amsterdam: Elsevier, 1992: 103-6.
 - 17 Cacciari E, Corazza GR, Salardi S, et al. What will be the adult height of coeliac patients? *Eur J Pediatr* 1991; **150**: 407-9.
 - 18 Roede MJ, Van Wieringen JC. Growth diagrams 1980. Netherlands third nationwide survey. *Tijdschrift voor Sociale Gezondheidszorg* 1985; **63** (suppl): 1-34.
 - 19 Wieringen JC, Wafelbakker F, Verbrugge HP, de Haas JH. *Growth diagrams 1965 Netherlands*. Nederlands Instituut Praeventieve Geneeskunde — Toegepast Natuurwetenschappelijk Onderzoek, Groningen: Leiden/Wolters-Noordhoff, 1971.
 - 20 Boersma B, Wijnne HJ, Wit JM. A mathematical model describing catch-up growth in celiac disease. *Acta Paediatr* 1994; **83**: 1097-9.
 - 21 Gluckman PD. Growth hormone deficiency diagnosed and treated in the first 2 years of life: evidence of the role of growth hormone in human perinatal growth. In: Ranke MB, Gunnarsson R, eds. *Progress in growth hormone therapy - 5 years of KIGS*. Mannheim: J and J Verlag, 1994: 88-96.
 - 22 Albertsson-Wikland K, Westphal O, Westgren U. Daily subcutaneous administration of human growth hormone in growth hormone deficient children. *Acta Paediatr Scand* 1986; **75**: 89-97.
 - 23 Hermanussen M, Geiger-Benoit K, Sippell WG. Catch-up growth following transfer from three times weekly into daily sc administration of hGH in GH deficient patients, monitored by knemometry. *Acta Endocrinol (Copenh)* 1985; **109**: 163-8.
 - 24 Press M, Notarfrancesco A, Genel M. Risk of hypoglycaemia with alternate-day growth hormone injections. *Lancet* 1987; **i**: 1002-4.
 - 25 Usher R, McLean F. Intrauterine growth of live-born caucasian infants at sea level: standards obtained from measurements in seven dimensions of infants born between 25 and 44 weeks of gestation. *J Pediatr* 1969; **74**: 901-10.