The Royal Society of Medicine

Current Medical Literature

Volume 18 | Number 1 | 2003

GH and Growth Factors

International Literature Review Service

PHARMACIA

ADVISORY BOARD
- MA PREECE
- E VICENS-CALVET
- O WESTPHAL

CLINICAL EDITORS
- C BUCHANAN
- P HINDMARSH
- R ROSS

ISSN 1460-8480

Comment

Treatment Strategies to Normalize Growth, Weight and Body Composition in Prader-Willi Syndrome

URS EIHOLZER

Foundation Growth Puberty Adolescence, Zurich, Switzerland

Prader-Willi syndrome (PWS) remains a complex disorder in many respects, despite major advances in recent research. Patients with PWS usually have many medical problems. The main symptoms and signs include neonatal and infantile hypotonia, neonatal severe feeding problems and failure to thrive, facial dysmorphisms, hypogonadism, short stature, mental retardation and behavioural disturbances, as well as sleep disorders. After infancy, these patients are affected by uncontrollable hyperphagia and consequent obesity. The pathogenesis of the disturbed energy regulation with hyperphagia and hypoactivity and the abnormal body composition are still largely unknown. For decades, most physicians and researchers, as well as the authors of many publications, have focused primarily on hyperphagia and the increased fat mass.

LIMITATION OF NUTRITIONAL INPUT

Limitation of nutritional input was the first and remains the most important type of intervention in limiting weight gain and body disturbance. Obesity is the main cause of morbidity and mortality in PWS [1,2]. The huge fat accumulation in PWS is caused by an imbalance between energy intake and energy expenditure, which results in an increase in energy storage. Between 1 and 4 years of age, the feeding difficulties are generally replaced by the PWS-specific insatiable hunger drive, which develops insidiously and causes life-threatening obesity [3,4].

For a long time, treatment was limited to non-specific measures, mainly to the reduction of energy intake and fat content, for example, to less than 8–11 kcal/cm length, and about 25% fat [5]. This was only possible by means of strict supervision and permanent locking-up of food. Yet, even close supervision of nutrient intake only contributed to limit obesity, and was not sufficient to avoid it.

GROWTH HORMONE TREATMENT

The first papers demonstrating that lean body mass (LBM) is reduced in PWS [6–9] shed new light on the etiology of obesity in this syndrome. Short stature and increased fat mass in the presence of decreased muscle mass are typical symptoms of GH deficiency. Subsequently, it was thought that body composition in PWS, being abnormal as a consequence of GH deficiency, could be normalized by substitution of human GH.

Several studies on GH treatment in PWS children were initiated (reviewed in [10]). In general the observed changes of growth document

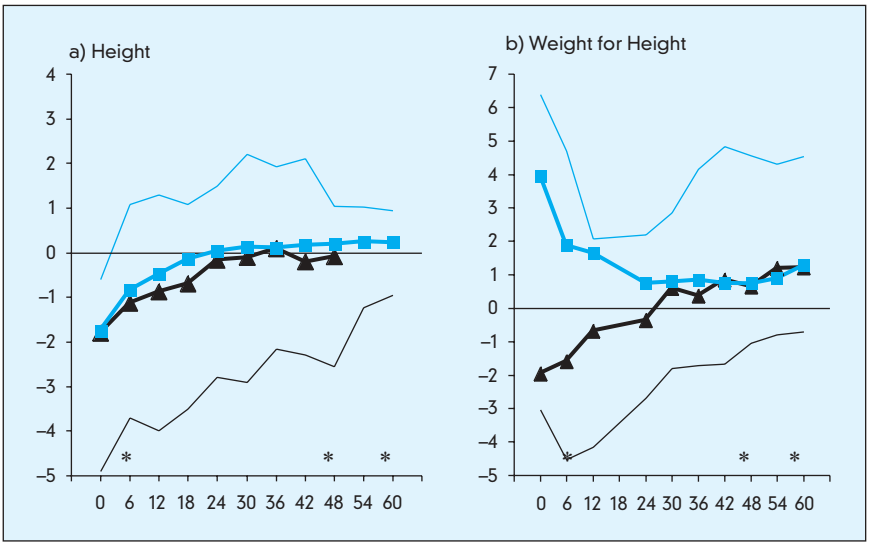

FIGURE 1 Height SDs (a) and weight-for-height SDs (b) of children with PWS, referring to normative data of the Zurich Longitudinal Study [13], before and during <5.5 years of GH therapy. Values are shown for young, initially underweight children (▲, *n*=10) and overweight prepubertal children (■, *n*=8). Medians are shown as thick lines; minimum and maximum values of the combined group are shown as thin lines. Significant differences, tested at 6, 48 and 60 months by the Wilcoxon test in each group versus the value before therapy, are indicated as **p*<0.05 (reproduced from Eiholzer et al, Horm Res 2000; 53[Suppl 3]: 44-53, with permission).

the efficacy of GH treatment in PWS. In our study, mean growth velocity in the first year increased in the prepubertal obese children from –1.4 to 8.5 standard deviations (SDs) and remained above 2 SD throughout 3 years of therapy [11]. After 4 years of human GH treatment, height gain reached 1.8 SD, yielding an average height of 0 SD and a normalization of hand and, less markedly, foot length. Furthermore, prediction of final height markedly improved in the prepubertal children and reached the range of their parental target height, despite the average adult height of untreated PWS reported as being reduced to –2.5 SD of reference values [12]. The results on growth of all other studies are similar.

Body weight, too, became normal (Figure 1). In the prepubertal obese children, weight for height (WfH) dropped during the first 2 years of GH therapy, the decrease in WfH being greatest during the first 6 months of therapy; after 2 years WfH-SDS stabilized at +0.8 SD. In contrast, WfH in the very young children was reduced before therapy and continuously increased up to 0.4 SD at 36 months of treatment.

Unlike other studies, we adjusted lean body mass not only for age and sex, but also for height, in order to correct for a growth-related increase. In this way we could show that the initial deficit in LBM (–3.0 SD in overweight children) is counteracted by GH only during the first year of therapy (increase to –1.79 SD) [14], and that no significant additional gain of muscle mass beyond the first year was achieved by GH therapy (–1.33 SD at 42 months). In contrast to what could be concluded from basal studies [7] or 1- and 2-year GH treatment [9,15–17], GH therapy could not, even in the long term, compensate for the initial deficit of lean mass [14]. This finding was corroborated by another study on resting energy expenditure – it was found that resting energy expenditure, which is dependent on muscle mass, only increased to a minor extent during GH therapy [18].

GH therapy has greatly changed the phenotype of children with PWS. Height and weight are nearly normalized in prepubertal children. Thanks to this new treatment option a large number of children with PWS no longer become

grossly obese – provided the restriction of calorie intake is maintained.

Experience, however, has shown that hyperphagia persists during therapy with exogenous GH. For this reason, and because weight and body fat will decrease only if energy input is not increased during GH therapy [14,19], energy input has to be continuously monitored. We evaluated nutrition protocols 3 years after institution of GH treatment, during a phase of stable weight. The energy intake in children with PWS was significantly reduced by about 25% compared with healthy control children. From these results, it is concluded that, even during GH treatment, children with PWS can keep their weight stable only if they reduce their energy intake to about 75% of what is recommended for healthy children.

Although LBM is improved, it still remains far from being normalized by GH treatment. Normalizing, or at least improving, body composition, however, continues to be the main objective of treatment of children with PWS.

Possible adverse effects of growth hormone treatment

Cardiovascular risk factors

Several cardiovascular risk factors are already present in prepubertal children with PWS, most importantly, the percentage of body fat is increased in all children [8,16,17,20–23], and waist-to-hip ratio in one-third of the children older than 4 years [20]. In roughly 25% of the children with PWS, elevated levels of LDL-cholesterol and apolipoprotein B or decreased levels of HDL-cholesterol were found [24]. In the context of an increased prevalence of abnormalities in lipid profiles, there was concern that GH treatment, in addition, raises the concentration of atherogenic lipoprotein(a) levels [25]. However, lipoprotein(a) levels did not increase in the long term, but only rose transiently during the first 6 months of GH therapy. Three years of GH therapy not only led to a significant decrease of relative fat mass and abdominal fat distribution but also improved serum lipid profiles: as an index of the reduction of atherogenic risk during GH therapy, the ratio of LDL-cholesterol to HDL-cholesterol became normal in all patients [24].

Carbohydrate metabolism

Impaired glucose tolerance, as well as an early and more frequent manifestation of diabetes mellitus, was often described in individuals with PWS [1,26–29]. Although more recent studies revealed that insulin levels are low or normal [30–32], at least in children, there is concern about accelerated manifestation of diabetes mellitus during GH therapy [33]. This limitation could restrict the otherwise beneficial treatment with GH in PWS [15,16,34].

Insulin secretion during intravenous glucose tolerance testing [31] and oral glucose tolerance testing [32] was not only reduced compared with normal obese children, but also the pattern of insulin release was abnormal and delayed in children with PWS [35]. Mainly, the first-phase insulin secretion during oral glucose tolerance testing was reduced. These findings were previously ascribed to the hypothalamic GH deficiency [32]. It was subsequently shown that GH significantly enhances the first-phase insulin secretion in children with PWS [31,35], but the delay of insulin secretion in PWS remained unchanged during substitution with GH. It was speculated [32] that prolonged eating drive [36,37] or delayed gastric emptying, as well as impaired vagotone [32,38] accounted for the delayed and diminished insulin response to oral glucose load in PWS. Yet, in general, insulin resistance is not increased in this form of syndromal obesity, but rather insulin sensitivity is augmented in children with PWS [35], in contrast to simple obesity, and remains normal during GH treatment. As a consequence, no specific metabolic risk is induced by GH therapy [35]. Only in extremely obese patients with PWS, or in rapid weight gain, does the risk of manifesting diabetes seem to be increased. Therefore, in these patients, GH therapy should not be started. Regardless of GH therapy, carbohydrate metabolism in PWS must always be closely monitored, because excessive adiposity per se may disturb the metabolic balance. Body weight, height, body composition (by

skinfolds or DEXA) and fasting glucose, fasting insulin, HbA1c and IGF-I should be regularly assessed during GH therapy in PWS to monitor side effects and carbohydrate metabolism.

Respiratory problems

Respiratory problems are often present in PWS. They have been associated with muscular hypotonia and decreased lean body mass, the presence of throat dysfunction and anomalous architecture, narrow airways, hyperplasia of tonsils and adenoids, and obesity. Recently, the presence of central dysfunction has been recognized, implicating a defective hypothalamic control and hyposensitivity of chemoreceptors [39,40]. These disturbances have also been documented in very young patients and are independent of obesity [39]. The concomitant presence of sleep disturbances put these patients at high risk of sleep apnoea, both central and obstructive.

Recently, two case reports of death as a consequence of respiratory dysfunction in patients with PWS who were on treatment with GH were published [41,42]. Subsequently, three additional cases out of 318 GH-treated children with PWS were found in the KIGS (Kabi-Pharmacia International Growth Study) database and two more patients were reported from the USA and Canada. No details are yet available for the Canadian case; of the other six cases, five were obese, and four had documented respiratory problems before starting GH treatment, with nothing being known on the other two. Three cases seemed compatible with a diagnosis of sleep apnoea.

Epidemiology data on death rates in PWS patients are not available in public registries. However, in one study, a defined region in England and Wales was screened for patients with PWS and an overall death rate in this PWS population of about 3% per year was found [43]. The investigators compared this with an overall death rate in the population of England and Wales of about 1% per year, and only about 0.13% per year in those under 55 years of age. The comparison of the KIGS data with the conclusion of this article suggests that there are no excess deaths in the KIGS cohort. In addition, a group of experts is collecting cases of sudden deaths in patients with PWS [44]. They have evaluated the medical data of 21 PWS individuals, with ages at death ranging from neonatal to 68 years. Acute respiratory illness was common in the young children, as were obesity-related causes in the adult group [45]. This information seems to corroborate the suggestion that sudden death is not infrequent in PWS, and that a respiratory cause is not unexpected. At the present time, there is no suggestion that PWS patients treated with GH are at an increased risk of death compared with those not receiving GH therapy.

At this point it is important to note that the studies conducted in PWS patients to assess the impact of GH treatment on respiratory function showed positive results. The effects of GH treatment on respiratory function were investigated in depth in one study and an increase in ventilation at rest and inspiratory drive accompanied by a significant increase in CO_2 sensitivity was observed, which is a critical function in avoiding a fatal outcome of sleep apnoea episodes [46]. Positive effects on the respiratory function in PWS patients were also reported in another study [15]. However, the emergence of fatal outcomes of the known respiratory dysfunction in these patients, who are increasingly treated with GH, calls for heightened surveillance, which may require special investigations. Considering the prevalence of respiratory problems in PWS patients, inspection of the upper airways by an ENT specialist before onset of therapy and during treatment with GH may be useful, as may a polysomnography examination. This is especially relevant if snoring or increase in tonsil size occurs or if an upper airway infection is suspected, even in the absence of fever, since PWS children, due to their hypothalamic disturbance, sometimes do not develop fever during infection.

DAILY EXERCISE PROGRAM

Even though GH therapy had sustained beneficial effects on physical strength and agility, the reports of parents and care givers that children with PWS are more active while being administered GH [9,16,18,47] remained unproven. We

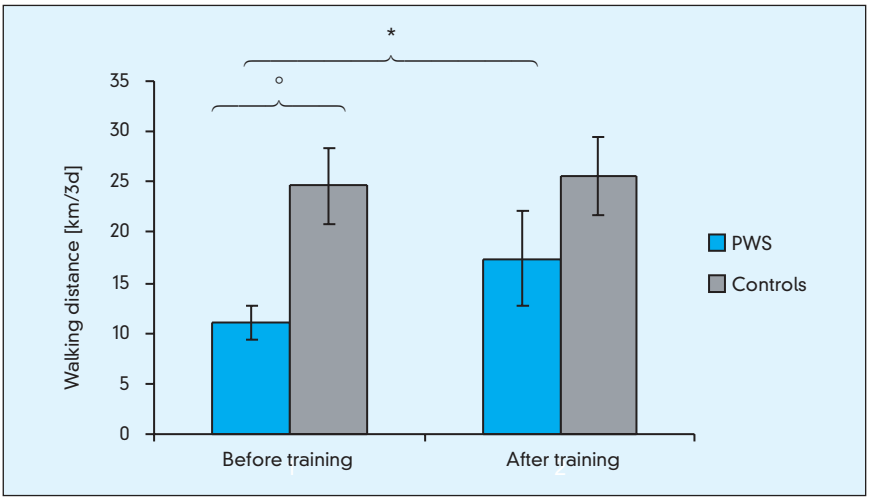

FIGURE 2 **Physical activity before the start and at the end of the training program of children with PWS (n=17) and controls (n=18) measured by means of pedometer registrations. Results expressed as means ±SEM. *p<0.05, significant difference within the PWS group tested by the Wilcoxon test, and °p<0.05, significant difference between the PWS and the control group, tested by the Mann-Whitney-U test.**

have recently measured spontaneous physical activity during GH therapy. We found that even while being administered GH, children with PWS are considerably less active than controls [48]. Thus, hypoactivity and a marked dislike of physical activity seem to be very essential symptoms of PWS. They are similar in importance to the lack of satiety and the ensuing hyperphagia.

To see if hypoactivity is the cause or the consequence of the reduced muscle mass we investigated whether muscles of children with PWS can be trained in the same way as those of healthy controls, using a training program for the calf muscle. After 3 months of training, both children with PWS and controls increased their local muscle mass by a similar and significant extent (Figure 2). From this it was concluded that reduced muscle mass, even during GH therapy, is a direct consequence of hypoactivity [48].

Moreover, and most promising, a significant increase in spontaneous physical activity was observed at the end of the training program in the children with PWS. Daily walking distance augmented from 45% to 70% compared with the baseline data of the controls. Furthermore, the training program led to a significant increase in physical capacity.

In summary, a short training program is sufficient to significantly improve local body composition, to significantly increase spontaneous physical activity, and to lead to a significant and sustained improvement of physical capacity [48]. We suggest a personal and regular physical training program for individuals with PWS, including a workout of a variety of different muscles. This new approach in the treatment of PWS opens up a complementary therapeutic option in addition to dietary control and GH treatment.

HYPOGONADISM

Hypogonadism in PWS is generally also attributed to hypothalamic dysfunction. However, histologic abnormalities of testes, exaggerated luteinizing hormone and follicle stimulating hormone responsiveness to luteinizing hormone releasing hormone as well as an impaired gonadal response to gonadotropins suggest the existence of a primary disorder of the testes, possibly in most cases as a consequence of cryptorchidism. Although hypogonadism is clearly documented in PWS, the replacement of sex hormones in puberty remains controversial – an

aspect that is not well covered in the literature. Most authors recommend androgen replacement in males, because of its beneficial effects, such as complete virilization, increasing muscle mass and higher activity level, but it was commonly believed that it may lead to more aggressive behaviour and aggravate temper tantrums. However, there are no studies of behaviour during sex steroid substitution. In young women with PWS, estrogen substitution may prevent osteoporosis, although an increase in obesity is feared, but has not yet been scientifically assessed in these patients [10]. In our experience, a careful substitution of gonadal function at an appropriate age (bone age of 13 in boys and 11 in girls), as routinely performed in other types of hypogonadism, is well tolerated and has only positive effects for the patients and their families.

PSYCHOLOGICAL COUNSELING OF THE FAMILIES

Because hyperphagia and hypoactivity persist even during GH therapy, limiting energy input and enhancing energy output continue to be the most important aims in the care of children with PWS. In most instances, the parents have to assume the responsibility for these tasks. They have to impose these measures on the child with PWS, who is mentally retarded and often behaviourally disturbed. This task is so time consuming and energy draining that most parents and families are at risk of exhausting themselves. Therefore, these families have to be provided with assistance. They have to learn that admitting that one's resources are exhausted and accepting professional help is nothing to be ashamed of.

CONCLUSION

Thus, GH therapy, limitation of nutritional input as well as daily conduction of a well-defined exercise program, substitution of gonadal function and giving psychological counseling to the parents and families are today the most important tools to improve body composition and well-being of children with PWS.

REFERENCES

►1 Cassidy SB.
Prader-Willi syndrome.
J Med Genet 1997; 34: 917-923.

►2 Laurance BM, Brito A, Wilkinson J.
Prader-Willi Syndrome after age 15 years.
Arch Dis Child 1981; 56: 181-186.

►3 Zellweger H.
Diagnosis and therapie ind the first phase of PWS. In: Holm V, Sulzbacher SJ PPL (eds) The Prader Willi syndrome. Baltimore: University Park Press; 1981, 55-68.

►4 Greenswag LR.
Adults with Prader Willi syndrome: a survey of 232 cases.
Develop Med Child Neurol 1987; 29: 145-152.

►5 Stadler DD.
Nutritional management. In: Greenswag LR, Alexander R (eds) Management of Prader-Willi syndrome. New York: Springer-Verlag New York, Inc; 1995, 88-114.

►6 Schoeller D, Levitsky L, Bandini L, Dietz W, Walczak A.
Energy expenditure and body composition in Prader-Willi syndrome.
Metabolism 1988; 37: 115-120.

►7 Brambilla P, Bosio L, Manzoni P, Pietrobelli A, Beccaria L, Chiumello G.
Peculiar body composition in patients with Prader-Labhart-Willi syndrome.
Am J Clin Nutr 1997; 65: 1369-1374.

►8 Eiholzer U, Blum WF, Molinari L.
Body fat determined by skinfold measurements is elevated despite underweight in infants with Prader-Labhart-Willi syndrome.
J Pediatr 1999; 134: 222-225.

►9 Eiholzer U, Gisin R, Weinmann C, et al.

Treatment with human growth hormone in patients with Prader-Labhart-Willi syndrome reduces body fat and increases muscle mass and physical performance.
Eur J Pediatr 1998; 157: 368-377.

►10 Eiholzer U.
Prader-Willi syndrome. Effects of human growth hormone treatment. In: Savage MO (ed) Endocrine development. Basel: Karger; 2001, 1.

►11 Eiholzer U, l'Allemand D.
Growth hormone normalises height, prediction of final height and hand length in children with Prader-Willi syndrome after four years of therapy.
Horm Res 2000; 53: 185-192.

►12 Wollmann HA, Schultz U, Grauer M, Ranke M.
Reference values for height and weight in Prader-Willi syndrome based on 315 patients.
Eur J Pediatr 1998; 157: 634-642.

►13 Prader A, Largo R, Molinari L, Issler C.
Physical growth of Swiss children from birth to 20 years of age.
Helv Paediatr Acta 1989; 43[Suppl 52]: 1-125.

►14 Eiholzer U, l'Allemand D, van der Sluis I, Steinert H, Ellis K.
Body composition abnormalities in children with Prader-Willi syndrome and long-term effects of growth hormone therapy.
Horm Res 2000; 53: 200-206.

►15 Carrel A, Myers S, Whitman B, Allen D.
Growth hormone improves body composition, fat utilization, physical strength and agility in Prader-Willi syndrome: a controlled study.
J Pediatr 1999; 134: 215-221.

►16 Lindgren AC, Hagenas L, Muller J, et al.
Growth hormone treatment of children with Prader-Willi syndrome affects linear growth and body composition favourably.
Acta Paediatr 1998; 87: 28-31.

►17 Davies HA, Evans S, Broomhead S, et al.
Effect of growth hormone on height, weight, and body composition in Prader-Willi syndrome.
Arch Dis Child 1998; 78: 474-476.

►18 Myers SE, Carrel AL, Whitman BY, Allen DB.
Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength and agility, and growth in Prader- Willi syndrome.
J Pediatr 2000; 137: 42-49.

►19 Eiholzer U, Bachmann S, l'Allemand D.
GH treatment as part of a comprehensive therapy design for children with PWS.
Int Growth Monitor 2000; 10: 2-8.

►20 Lee P, Hwu K, Henson H, et al.
Body composition studies in Prader-Willi syndrome (PWS): effects of growth hormone (GH) therapy. In: Ellis KJ, Eastman JD (eds). Human body composition. Newark: Plenum Press; 1993, 201-206.

►21 Davies PS, Joughin C, Livingstone MBE, Barnes N.
Energy expenditure in Prader-Willi syndrome. In: Cassidy SB (ed) [H61]. Berlin: Springer, 1992, 181-187. Nato ASI Series.

►22 Brambilla P, Manzoni P, Sironi S, et al.
Peripheral and abdominal adiposity in childhood obesity.
Int J Obes Relat Metab Disord 1994; 18: 795-800.

►23 Lindgren AC, Hagenas L, Muller J, et al.
Growth hormone treatment of children with Prader-Willi syndrome affects linear growth and body composition favourably.
Acta Paediatr 1998; 87: 28-31.

►24 l'Allemand D, Eiholzer U, Schlumpf M, Steinert H, Riesen W.
Cardiovascular risk factors improve under 3 years of growth hormone therapy in Prader-Willi syndrome.
Eur J Pediatr 2000; 159: 835-842.

►25 Nolte W, Radisch C, Armstrong VW, Hufner M, von Zur MA.
The effect of recombinant human GH replacement therapy on lipoprotein(a) and other lipid parameters in adults with acquired GH deficiency: results of a double-blind and placebo-controlled trial.
Eur J Endocrinol 1997; 137: 459-466.

►26 Prader A, Labhart A, Willi H.
Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus und Oligophrenie nach myotonieartigem Zustand im Neugeborenenalter.
Schweiz Med Wochenschr 1956; 86: 1260-1261.

►27 Parra A, Cervantes C, Schultz RB.
Immunoreactive insulin and growth hormone responses in patients with Prader-Willi syndrome.
J Pediatr 1973; 83: 587-593.

►28 Illig R, Tschumi A, Vischer D.
Glucose intolerance and diabetes mellitus in patients with the Prader-Labhart-Willi-syndrome.
Mod Probl Paediat 1975; 12: 203-210.

►29 Tze WJ, Dunn HG, Rothstein R.
The endocrine profiles and metabolic aspects of Prader-Willi syndrome. In: Holm VA, Sulzbacher SJPPL (eds). The Prader Willi syndrome. Baltimore: University Park Press; 1981, 281-291.

►30 Eiholzer U, Stutz K, Weinmann C, Torresani T, Molinari L, Prader A.
Low insulin, IGF-I and IGFBP-3 levels in children with Prader-Labhart-Willi syndrome.
Eur J Pediatr 1998; 157: 890-893.

►31 Lindgren AC, Hagenas L, Ritzen EM.
Growth hormone treatment of children with Prader-Willi syndrome: effects on glucose and insulin homeostasis.
Horm Res 1999; 51: 157-161.

►32 Schuster DP, Osei K, Zipf WB.
Characterization of alterations in glucose and insulin metabolism in Prader-Willi subjects.
Metabolism 1996; 45: 1514-1520.

►33 Cutfield WS, Wilton P, Bennmarker H, et al.
Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment.
Lancet 2000; 355: 610-613.

►34 Hauffa BP.
One-year results of growth hormone treatment of short stature in Prader-Willi syndrome.
Acta Paediatr Suppl 1997; 243: 63-65.

►35 l'Allemand D, Eiholzer U, Schlumpf M, Torresani T, Girard J.
The carbohydrate metabolism is not impaired after 3 years of growth hormone therapy in children with Prader-Willi syndrome.
Horm Res 2003, in press.

►36 Ritzen EM.
Endocrine physiology and therapy in Prader Willi syndrome. In: Cassidy SB (ed). Prader Willi syndrome and other 15q deletion disorders. New York: Springer Verlag; 1992, 153-169.

►37 Lindgren AC, Barkeling B, Hagg A, Ritzen EM, Marcus C, Rossner S.
Eating behavior in Prader-Willi syndrome, normal weight, and obese control groups.
J Pediatr 2000; 137: 50-55.

►38 Zipf WB, O'Dorisio TM, Cataland S, Dixon K.
Pancreatic polypeptide responses to protein meal challenges in obese but otherwise normal children and obese children with Prader-Willi syndrome.
J Clin Endocrinol Metab 1983; 57: 1074-1080.

►39 Schlüter B, Buschatz D, Trowitsch E, Aksu F, Andler W.
Respiratory control in children with Prader-Willi syndrome.
Eur J Pediatr 1997; 156: 65-68.

►40 Menendez AA.
Abnormal ventilatory responses in patients with Prader-Willi syndrome.
Eur J Pediatr 1999; 158: 941-942.

►41 Nordmann Y, Eiholzer U, l'Allemand D, Mirjanic S, Markwalder C.
Sudden death of an infant with PWS – not a unique case?
Biol Neonate 2002; 82: 139-141.

►42 Eiholzer U, Nordmann Y, l'Allemand D.
Fatal outcome of sleep apnoea in PWS during the initial phase of growth hormone treatment. A case report.
Horm Res 2002; 58[Suppl 3]: 24-26.

►43 Whittington JE, Holland AJ, Webb T, Butler J, Clarke D, Boer H.
Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK health region.
J Med Genet 2001; 38: 792-798.

►44 Schrander-Stumpel CT, Sijstermans H, Curfs L, Fryns JP.
Sudden death in children with Prader-Willi syndrome: a call for collaboration.

Genet Couns 1998; 9: 231-232.

►45 Schrander-Stumpel CT, Curfs L, de Greef S, Sastrowyto P, Fryns JP.
Prader-Willi syndrome: causes of death and guidelines for possible prevention.
Genet Couns 2003; in press.

►46 Lindgren AC, Hellstrom LG, Ritzen EM, Milerad J.
Growth hormone treatment increases CO(2) response, ventilation and central inspiratory drive in children with Prader-Willi syndrome.
Eur J Pediatr 1999; 158: 936-940.

►47 Eiholzer U, Malich S, l'Allemand D.
Does growth hormone therapy improve motor development in infants with Prader-Willi syndrome?
Eur J Pediatr 2000; 159: 299-301.

►48 Eiholzer U, Nordmann Y, l'Allemand D, Schlumpf M, Schmid S, Kromeyer-Hauschild K.
Improving body composition and physical activity in Prader-Willi Syndrome.
J Pediatr 2003; 142: 73-78.