

Growth Hormone Treatment and Prader-Willi Syndrome

Since the commercial release of recombinant human growth hormone (GH) in 1985, therapeutic use of this medication has been studied in a variety of medical conditions and genetic syndromes. Based on current medical knowledge, the Clinical Advisory Board of the Prader-Willi Syndrome Association (USA) has drafted and approved this policy statement to guide health care providers in the use of GH treatment in individuals with Prader-Willi syndrome (PWS). Currently, 60% of the individuals in the PWSA (USA) database are receiving GH therapy.

Current considerations regarding the use of GH treatment in PWS can be divided into the following categories:

1. GH treatment of infants/children with PWS to improve body composition abnormalities and improve linear growth
2. GH treatment of adults with PWS to improve body composition abnormalities and improve bone mineral density

Numerous studies indicate that GH deficiency occurs frequently in children with PWS and that treatment with GH is efficacious in improving the growth and body composition of these children¹⁻⁴. GH should not be a substitute for appropriate nutritional intake and physical activity.

GH treatment is FDA-approved for individuals with PWS. It is well-recognized that GH deficiency is a part of PWS and that provocative testing for GH deficiency is **not** indicated for children with PWS because: 1) the results can be influenced by obesity; 2) different testing protocols give widely discrepant results; 3) the diagnostic boundary for normal/abnormal GH result in response to testing is still debated; and 4) there is no ideal testing protocol.

GH Treatment of Infants and Children with PWS

Multiple studies have documented the benefits of GH therapy in individuals with PWS, including, but not limited to, improvements in lean body mass, decreased body fat, increased bone mineral density, and normalization of adult height¹⁻⁵. Further, GH treatment in infants and children with PWS has been shown to improve strength, agility, and motor development. Treatment with GH has also been shown to positively affect nitrogen balance and increase energy expenditure in individuals with PWS. Moreover, GH treatment may help preserve lean body mass during caloric restriction. There is evidence that beginning GH therapy prior to two years of age is beneficial because of the positive effects of this treatment on mental and motor development⁶⁻⁸.

The risks and benefits of GH treatment should be thoroughly discussed with the child's parents or guardians before making a decision to treat. At the same time, it should be stressed that GH therapy is only one treatment tool for their child and should be used in conjunction with appropriate nutritional intake and physical activity. GH treatment should not be viewed as a substitute for diet and exercise.

Treatment should commence using standard dose guidelines (0.18 – 0.3 mg/kg/week) given as a daily subcutaneous injection with careful monitoring of clinical status at regular intervals. Standard GH treatment includes dose initiation and adjustment based on weight. However, there is some evidence that lean mass is a better indicator of GH requirements and, therefore, monitoring clinical growth and IGF-1 levels is helpful in determining dose adjustments. The Clinical Advisory Board recommends that the GH dose in children with PWS be adjusted on an individual basis rather than by specific criteria. Clinical monitoring should include nutritional status, height, weight, and head circumference measurements; calculation of growth velocity; bone age; physical examination; and measurement of IGF-1, glucose, insulin, and thyroid hormone levels, as well as ensuring adequate nutrition for growth and brain development. If feasible, assessment of body composition is also helpful.

Children with PWS have an increased risk for spinal curvature abnormalities, including scoliosis and kyphosis. In general, these findings may first become apparent or more rapidly progress during periods of rapid growth. There is no evidence that GH itself causes these abnormalities⁹. Children with PWS, whether or not they are treated with GH, should receive a careful back examination at least annually. The decision to initiate or continue GH treatment in a child with spinal curvature abnormalities should be made in consultation with an endocrinologist and an orthopedic surgeon experienced in PWS, and after full discussion with the child's parents or guardians.

Children with PWS are prone to developing obesity and its associated complications, including glucose intolerance and type 2 diabetes mellitus. GH may induce insulin insensitivity. Therefore, children with PWS and GH deficiency should be carefully monitored for signs and symptoms of glucose intolerance during GH treatment, particularly if they are massively obese (e.g., >200% of ideal body weight) or have a family history of diabetes mellitus. Routine biochemical screening tests may include fasting blood glucose, urine glucose dipstick or HbA1c. If diabetes mellitus occurs as a result of GH therapy, the GH treatment should be stopped. If treatment is restarted, the dose of GH should be substantially reduced. If glucose intolerance occurs with GH therapy it can typically be treated with an oral hypoglycemic agent, such as metformin.

Children with PWS have an increased prevalence of respiratory dysfunction, which may be related to obesity, hypotonia, or central respiratory drive abnormalities^{3,10}. Careful history and assessment of respiratory abnormalities should be evaluated prior to and during GH therapy. Individuals with sleep apnea, either before or after beginning GH therapy, should be evaluated by a pulmonologist, otolaryngologist, and gastroenterologist to determine if:

- 1) The apnea is mild or central in origin (in which case GH is not contraindicated).
- 2) If the apnea is severe and obstructive in origin, this needs to be addressed before GH is initiated.
- 3) There are confounding pre-existing conditions, such as morbid obesity, upper respiratory tract infection, adenoid/tonsillar hypertrophy, or gastroesophageal reflux that may exacerbate sleep-disordered breathing. In addition, some groups recommend that individuals with PWS have overnight polysomnography before and ~ 6-12 weeks after beginning GH treatment¹⁰ and if there is any worsening of clinical symptoms while on GH therapy.

GH Treatment of Persons who have Achieved Final Height and Adults with PWS

Recent studies indicate that adults with PWS also benefit from GH replacement therapy, with improvements in body composition, bone mineral density, and exercise capacity^{11,12}. Treatment doses are typically started at 0.2 mg/day and increased by 0.2 mg increments as necessary to maintain IGF-1 levels within the normal range for age and sex. The prevalence of GH deficiency in adults with PWS is not well-documented, but the problems surrounding provocative testing for GH deficiency are the same as described above for children. However, at this time in the U.S. insurance companies still require documentation of GH deficiency by provocative testing in adults with PWS.

References

1. Lee, P. D. K. : Endocrine and metabolic aspects of Prader-Willi syndrome. In Greenswag, L. R., Alexander, R. C. (editors): Management of Prader-Willi Syndrome, second edition. Springer-Verlag, New York, for the Prader-Willi Syndrome Association (USA), pp. 32-60, 1995.
2. Carrel AL, Myers SE, Whitman BY, Allen DB. Benefits of long-term GH therapy in Prader-Willi syndrome: A 4-year study. *J Clin Endo Metab* 87: 1581-5, 2002.
3. Haqq AM, Stadler DD, Jackson RH, Rosenfeld RG, Purnell JQ, LaFranchi SH. Effects of growth hormone on pulmonary function, sleep quality, behavior, cognition, growth velocity, body composition, and resting energy expenditure in Prader-Willi syndrome. *J Clin Endo Metab* 88: 2206-12, 2003.
4. Festen DA, Wevers M, Lindgren AC, Böhm B, Otten BJ, Wit JM, Duivenvoorden HJ, Hokken-Koelega AC. Mental and motor development before and during growth hormone treatment in infants and toddlers with Prader-Willi syndrome. *Clin Endocrinol (Oxf)*. 68:919-25, 2008.
5. Angulo MA, Castro-Magana M, Lamerson M, Arguello R, Accacha S, Khan A. Final adult height in children with Prader-Willi syndrome with and without human growth hormone treatment. *Am J Med Genet A*. 143:1456-61, 2007.
6. Festen DA, Wevers M, Lindgren AC, Böhm B, Otten BJ, Wit JM, Duivenvoorden HJ, Hokken-Koelega AC. Mental and motor development before and during growth hormone treatment in infants and toddlers with Prader-Willi syndrome. *Clin Endocrinol (Oxf)*. 68:919-25, 2008.
7. Myers SE, Whitman BY, Carrel AL, Moerchen V, Bekx MT, Allen DB. Two years of growth hormone therapy in young children with Prader-Willi syndrome: physical and neurodevelopmental benefits. *Am J Med Genet A*. 143:443-8, 2007.
8. Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M on behalf of speakers and contributors at the Second Expert Meeting of the Comprehensive Care of Patients with PWS. Recommendations for the diagnosis and management of Prader-Willi syndrome. *J Clin Endocrinol Metab*. 93:4183-97, 2008.
9. de Lind van Wijngaarden RF, de Klerk LW, Festen DA, Duivenvoorden HJ, Otten BJ, Hokken-Koelega AC. Randomized controlled trial to investigate the effects of growth hormone treatment on scoliosis in children with Prader-Willi syndrome. *J Clin Endocrinol Metab*. 94:1274-80, 2009.
10. Miller JL, Silverstein J, Shuster J, Driscoll DJ, Wagner M. Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. *J Clin Endo Metab* 91:413-7, 2006.
11. Mogul HR, Lee PD, Whitman BY, Zipf WB, Frey M, Myers S, Cahan M, Pinyerd B, Southren AL. Growth hormone treatment of adults with Prader-Willi syndrome and growth hormone deficiency improves lean body mass, fractional body fat, and serum triiodothyronine without glucose impairment: results from the United States multicenter trial. *J Clin Endocrinol Metab*. 93:1238-45, 2008.
12. Höybye C. Five-years growth hormone (GH) treatment in adults with Prader-Willi syndrome. *Acta Paediatr*. 96:410-3, 2007.