

Growth Hormone for Adults with Prader-Willi Syndrome

By Barbara Y. Whitman, Ph.D

Even before all the studies have been completed, the benefits fully examined, and the impact of possible side effects evaluated, growth hormone (GH) replacement therapy has rapidly become standard of care for infants and children with Prader-Willi syndrome (PWS). GH was first approved by the FDA for use in children with PWS in the year 2000. For treated children, the apparent benefits are dramatic and non-trivial; in addition to increased height there is a normalization of cranial proportions and facial features, normalization of hand and foot proportions, and for most, a slim body. With early treatment, most no longer stand out from other children as “different”, nor are they readily identifiable as having PWS.

GH replacement for those whose short stature results from congenital, traumatic or surgical endocrine system failures is relatively recent. First utilized in the late 1950s, availability was exceedingly limited, as manufacture required human pituitary glands available only at autopsy. Biosynthetic growth hormone replacements were rushed to market when an excess of those treated with cadaver-derived hormone contracted Creutzfeld-Jacob disease, a fatal neurodegenerative disorder whose causal mechanisms have only recently been specified. Since the range and depth of studies usually required prior to FDA approval of a drug were incomplete when the use of biosynthetic agents became imperative, a compromise system of surveillance was set up to monitor safety and efficacy — the model currently utilized for many new drug releases.

Short stature has always been considered a characteristic of PWS. Studies indicate that despite normal length and weight at birth, the growth rate in children decelerates over time, so that the average final adult height is approximately two standard deviations below the mean for a non-affected population. That GH deficiencies were the probable basis for the short stature was documented as early as 1971, and subsequent evidence demonstrated the impact of GH on linear growth. In the late 1990s well designed, controlled scientific studies documented that GH therapy resulted in a significantly improved rate of linear growth when compared to those not receiving treatment.

More important, however, was the concomitant improvement in body composition (increased lean, i.e., muscle, mass, increased bone mineral density, and for many, a reduction in the amount of fat tissue); improved metabolism (higher resting energy expenditure, improved respiratory parameters); and increased energy and strength. Self-esteem, behavior, and attention were improved. As the children in those original studies are now reaching adulthood, unpublished data indicate that final adult heights

for individuals treated with GH as children are significantly taller than those not treated.

Unlike most long-term treatments for other chronic conditions, the side effects and safety concerns for GH therapy appear minimal to almost non-existent, in the absence of pre-existing morbid obesity and respiratory compromise. Most clinicians and researchers view the improved body composition and metabolism as far more valuable even than that of increased height.

As a member of one of the first U.S. teams researching GH intervention therapy for youngsters with PWS, I recall seeing the dramatically positive body changes evident at even the first six months’ follow-up visit following initiation of GH treatment. I remarked to my colleague on the project, Dr. Susan Myers, “We have to do an adult study to see if we get the same positive body composition effects.”

Growth Hormone Treatment for Adults

With the advent of puberty, the window of opportunity closes for increasing height through GH intervention due to a “capping” of skeletal growth potential. Further, GH levels normally decline with age in all populations. Entering adulthood already GH deficient presents significant health risks, including osteoporosis, increased body fat, decreased muscle mass, increased risks for heart and vascular disease, fatigue, social isolation and psychological depression. Thus in 1995 the FDA approved GH replacement therapy for those with either childhood or adult-onset GH deficiency. An area of research currently is the use of GH in a geriatric population, often with stunning results.

Recent studies indicate that adults with PWS continue to have the same GH deficiency that was present in childhood, with the same health risks attendant to non-PWS, GH-deficient adults. Most adults with PWS also are deficient in sex-steroid/sex hormone production, which further increases the health risks associated with GH deficiency. Thus, in addition to a possible improved body composition, the potential for improved long-term health strongly suggested the need to study GH therapy for adults with PWS.

Dr. Myers and I ultimately joined with several other teams of researchers to conduct a study of GH for 40 adults with PWS, ranging in age from 19 to mid to late 40s. That study and another conducted in Sweden are now completed and results are being published. So what can we understand from these studies at this point?

Significant improvement in body composition is observed in adults with PWS, both males and females, treated with GH replacement therapy. These include increased muscle mass,

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Before and After GH Therapy



Top: Al Heinemann with son Matt, who has PWS, just prior to adult GH therapy.

Bottom: Al and Matt in 2005 after a year on adult GH.



with PWS does not yet have full FDA approval, formal demonstration of GH deficiency through provocative GH stimulation testing is required, even for those who have been

and for many, a reduction in fat tissue. There also appears to be a small positive impact on bone mineral density; however, these effects are not as dramatic as those noted in children, probably because bone metabolism does not change as rapidly in adults as it does in children. Loss of fat tissue is particularly apparent in the trunk area, many show a waist and hip body form for the first time. Improvement in energy and strength as demonstrated in such measures as broad jumps, running, and arm curls showed improvement after only one month of treatment. Both attention and cognition showed improvement as well.

Unlike children, however, GH treatment for adults is not without some risk. Increased fluid retention, particularly in the feet and ankles, can initially occur and for some is sufficiently problematic to require discontinuing treatment. For some there may be a negative impact on glucose tolerance, leading to Type II diabetes. For some, the impact on scoliosis must be considered. Thus the risk/benefit ratio must be considered.

Obtaining GH Treatment for Adults

If a caregiver is considering this treatment for his/her adult with PWS, what is involved? Since GH replacement therapy for adults

on GH for a number of years during childhood. This timed procedure requires injecting a GH stimulating agent while fasting and measuring the peak level of GH secreted into circulating blood at specific points over a specified period of time. However, these procedures are neither straightforward nor simple. There is disagreement on what constitutes deficiency. Depending on the decision-making criteria employed, GH deficiency is defined as peak stimulated GH levels of less than 3–7 ng/ml. While a number of provocative agents are available, peak stimulated levels may differ depending on the agent used, resulting in a requirement for two or more tests. Further complicating the variability related to stimulating agents, variability can exist between analyzing laboratories. Thus, even true GH deficiency can be masked by both the provocative agent used or the analyzing lab employed, resulting in a denial of treatment. In addition, these tests are not without risk, so tolerating two such tests constitutes a major medical procedure. What happens when one test indicates decreased GH levels, while the other is borderline or above the cutoff?

Once GH deficiency is documented, your physician may want to obtain a number of medical tests both prior to initiating therapy and again at least annually as part of therapeutic monitoring. These include an x-ray for scoliosis, a DEXA scan for bone mineral density and body composition, a sleep test to rule out life-threatening (but treatable) apnea, and multiple blood tests, including a fasting lipid panel, fasting glucose, IGF-1, hemoglobin A1c, general chemistry profile with liver enzymes, and thyroid function tests.

Is It Worth It?

So one may ask, Is it worth it? One adult, in her mid-40s when her therapy was started, had shown enormous improvement on a number of physical measures. After 2 years of treatment, she was in danger of losing funding for her medication. She called her insurance company and said, "You can't take away my hormone — my brain is not confused any more!" Her hormone was continued. However, even with appropriate testing and documentation of GH deficiency in adults with and without PWS, obtaining coverage for GH therapy can be difficult in the United States.

Dr. Whitman serves on the PWSA (USA) Scientific Advisory Board. A version of this article including footnotes and list of references is available upon request from our PWSA (USA) national office and in the Members Only section of our website, www.pwsausa.org.