Prader-Willi
SYNDROME ASSOCIATION | USA
SAVING AND TRANSFORMING LIVES

Package of Hope

www.pwsausa.org | (941) 312-0400

1032 E Brandon Blvd #4744, Brandon, FL 33511

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SYNDROME ASSOCIATION | USA
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Dear Parent,

Thank you for contacting PWSA | USA, and congratulations on the birth of your baby! We are grateful to have the opportunity to support your important role as the parent of a child with Prader-Willi syndrome (PWS). One of the main missions of PWSA | USA over the past 48 years is to bring families like yours the latest medical treatments, research information, and support.

We are pleased to provide this Package of Hope, which includes a variety of materials we believe will answer some of your questions and offer guidance on critical issues such as nutrition, medical concerns, and the use of Growth Hormone as a treatment for PWS. In addition, you will receive future materials and publications that will aid you on your journey.

First and foremost, remember that Prader-Willi syndrome is a condition your child has, not who your child is. We understand that you are probably trying to process the diagnosis and certainly worried about your child with PWS. In the beginning, the focus may have been on what's "different" about your baby but pause and take moments to enjoy and embrace the perfect beauty of YOUR child.

In the days, weeks, and years ahead, you will likely have new questions and face new challenges. Please call us at any time. We have counselors and parent mentors available to talk and to help. Our office is open Monday through Friday from 9-5, EST and our 24-Hour Support Phone Line is available 365 days a year at 941-312-0400. We are also available by email at info@pwsausa.org. Remember to visit our website frequently for new information, sign up for our newsletter – The Pulse and receive updated information at http://www.pwsausa.org/. If you are on Facebook, we invite you to "like" our page at http://www.facebook.com/PWSAUSA. We also offer several Facebook groups by age.

The services and resources offered by PWSA | USA are available because of the generosity of the families and friends of a loved one with PWS across the country who contribute regularly to support our organization. In many cases, our families actively raise money to support our work by conducting a fundraising event virtually, or in their local community. Our PWS Hope United peer-to-peer fundraising platform allows individuals to easily host events, such as walks, trivia nights, birthday fundraisers, golf tournaments and other fun events that provide vital funding for our work. As you are able, we hope you will join others who provide support for our research, programs, and services so that even more parents of children with PWS will benefit from our help in the future.

As we walk this journey together, we believe you will find hope in this package and in your beautiful child who is full of potential, personality, and love. Please share pictures and stories from your child's life with us. We love to hear what every child with PWS is doing and what they are accomplishing.

Sincerely,

Paige Rivard

Paige Rivard, MBA | CEO
Mom to Jake (12)

PWSA | USA Family Support Services

PWSA | USA's Family Support team provides support to individuals diagnosed with Prader-Willi syndrome, their families, and providers. They also educate medical providers, education professionals, and professional care givers about PWS and advocate for the comprehensive needs of the entire PWS community.

What We Do

New Diagnosis Support and Parent Mentoring

PWSA | USA offers comprehensive support and education to families at the time of diagnosis and provide information about PWS. Our Parent Mentoring Program is all about making connections with other "veteran" parents.

One of the most comforting parts of this journey is talking and meeting other families. Each of our mentors has shared similar experiences. We too have been comforted and nourished by our Parent Mentor. We have wept together, and we have laughed together. We are committed to ensuring that newly diagnosed families have the most up-to-date research materials, educational literature, counseling, nutrition, and medical information all within our Package of Hope, which we have been providing to families for well over a decade. We hand select our parent mentors with each family's specific needs in mind, to guide and support you throughout your child's lifetime. The compassion and caring from these very special connections can be a lifeline of HOPE.

Diet and Weight Management

Effective weight management is a crucial part of the care of a person with Prader-Willi syndrome. PWSA | USA supports families to manage weight effectively through appropriate meal planning, environmental supports, and other effective strategies.

Behavior Support

We provide behavior support to families, school districts, and residential providers by assisting with the development of positive behavior intervention plans, review of plans, and training implementation of best practices.

Consultations and Trainings

PWSA | USA offers consultations and trainings to residential providers, school personnel, and other support staff who need guidance or increased knowledge to support their client. Consultations may be provided in person, via telephone, or teleconference.

Peer Consultations

We facilitate consultations between PWSA | USA's volunteer medical consultants and an individual's medical team, emergency room physicians, or specialty clinicians.

Insurance/Medicaid/SSI Appeal Assistance

PWSA | USA provides support letters and guidance when appealing denials for Medicaid, Insurance coverage, Supplemental Security Income (SSI) and Social Security Disability Insurance (SSDI).

Residential Placement Support

PWSA | USA has created a Residential Care Database of agencies that provide residential services to individuals diagnosed with PWS. We support families through their search for the most appropriate provider for their loved one.

Grief and Bereavement Support

Grief is the response to loss, particularly the loss of someone or something that has died to which a bond or affection was formed. Most people associate grieving with the loss of life, but grief comes in many forms. Two types of grief sometimes experienced by parents of children who have a rare genetic condition are anticipatory grief and disenfranchised grief. Anticipatory grief is just that, grief experienced in anticipation of death. Parents who worry that their child's PWS diagnosis might shorten his or her life might be experiencing anticipatory grief. Disenfranchised grief might occur when a parent mourns the loss of the child they thought they were having. PWSA | USA has a certified grief counselor on staff to help you through your journey.

If you need support, you can contact our Family Support Team by calling (941) 312-0400 or emailing info@pwsausa.org.

PWSA | USA CHAPTER LIST

In partnership with state and regional Chapters, PWSA | USA is reaching more families and helping more individuals than ever before. Families turn to us for help navigating complex medical issues, support through the school years, securing safe residential care, and PWSA | USA Chapters help bring a local touch and extra support to families when they need it most.

Below you will find the contact information for every state Chapter. Please let us know if you would like someone from your state Chapter to reach out to you directly. If your state is not listed, please reach out to the Chapter in a neighboring state or contact PWSA | USA about forming a Chapter in your state or region.

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Quality of Life Issues

General health is usually good in individuals with PWS. If weight is controlled, life expectancy may be normal, and the individual's health and functioning can be maximized. The constant need for food restriction and behavior management may be stressful for family members. PWSA | USA can provide information and support.

Adolescents and adults with PWS can function well in group and supported living programs, if the necessary diet control and structured environment are provided.

To date, no medication or surgical intervention has been found that would eliminate the need for strict dieting and supervision around food. Bariatric procedures do not address the central lack of satiety and put the individual at risk for complications.

Studies show improvement in linear growth, fat mass, motor strength, respiratory drive, and bone density with the use of **growth hormone** in PWS. Precautions need to be taken prior to starting treatment including polysomnography, checking adrenal gland function, and following IGF1 levels.

What is Prader-Willi Syndrome?

Prader-Willi Syndrome is a disorder of chromosome 15
Prevalence: 1 : 12,000-15,000 (both sexes, all races)
Major characteristics: hypotonia, hypogonadism, hyperphagia, cognitive impairment, challenging behaviors

Major medical concern: morbid obesity

Cause and Diagnosis of PWS

- **PWS occurs from three main genetic errors.** Approximately 70% of cases have a non-inherited deletion in the paternally contributed chromosome 15. Approximately 25% have maternal uniparental disomy (UPD) - two maternal chromosome 15s and no paternal chromosome 15. Also, 2-5% have an error in the "imprinting" process that renders the paternal contribution nonfunctional; rarely, these imprinting defects may be inherited.

- **Diagnostic testing** Individuals who have a number of the clinical findings should be referred for genetic testing. DNA methylation analysis confirms diagnosis of PWS. FISH and DNA techniques can identify the specific genetic cause and associated recurrence risk. Patients who had negative or inconclusive tests with older techniques should be retested.

- **Recurrence risk** Recurrence is significant only for rare cases with imprinting mutations, translocations, or inversions. All families should receive genetic counseling.

Prader-Willi Syndrome is:

- A non-hereditary birth defect resulting from a disorder of chromosome 15
- A serious, life-long, and life-threatening medical condition
- Occurs in 1:12,000 to 1:15,000 births; both sexes, all races
- Characterized by
  - Hypotonia *(low tone)*
  - Hypogonadism *(underdeveloped sex organs)*
  - Hyperphagia *(uncontrollable hunger)*
  - Cognitive impairment
  - Challenging behaviors
- One of the most common conditions seen in genetic clinics
- The most common genetic cause of life-threatening obesity

A major medical concern is morbid obesity, however with early diagnosis and early intervention, many children can maintain a healthy weight.

Prader-Willi Syndrome Association | USA

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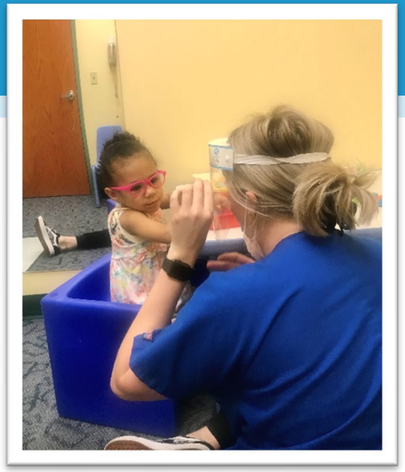
**PWSA | USA is a 501(c)(3) non-profit organization, is very grateful to our donors and invites support of our organization. All contributions are tax deductible to the extent allowed by law.*

We hope you find these materials helpful and that you consider a donation to PWSA | USA to assist in developing more good work(s) like this. Please see our website, www.pwsausa.org .

Medical Overview



A Diagnosis and Reference Guide on Prader-Willi Syndrome for Physicians and Other Health Professionals

Prader-Willi
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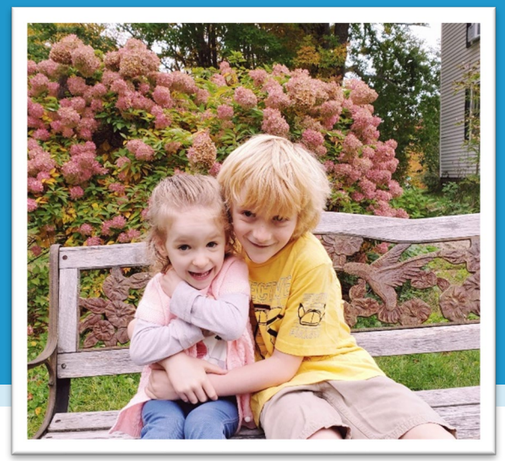


Life Threatening Medical Concerns

- **Anesthesia, medication reactions.** Unusual reactions to standard dosages of medications and anesthetic agents may occur because of metabolic differences and obesity seen in PWS. A narrow airway may be present. Use extreme caution in giving medications that may cause sedation; prolonged and exaggerated responses have been reported. Several genes for GABA receptor subunits are located in the PWS chromosome region and are missing in patients with the deletion. This decrease in GABA receptors in PWS could alter the response to GABA receptor agonist sedative agents (propofol, benzodiazepines).
- **High pain threshold.** Lack of typical pain signals is common and may mask the presence of infection or injury. Someone with PWS may have difficulty localizing pain or not complain of pain until infection is severe. Parent/caregiver reports of subtle changes in condition or behavior should be investigated for medical cause.
- **Respiratory concerns.** Risk may be increased for respiratory difficulties. Obesity, hypotonia, weak chest muscles, and sleep apnea are among possible complicating factors. Sleep studies for central and/or obstructive sleep apnea and hypoventilation should be obtained.
- **Lack of vomiting.** Vomiting rarely occurs. Emetics may be ineffective, and repeated doses may cause toxicity. This characteristic is of particular concern in light of hyperphagia and the possible ingestion of uncooked, spoiled, or otherwise unhealthful food items. The presence of vomiting may signal a life-threatening illness.
- **Body temperature abnormalities.** Idiopathic hyper- and hypothermia have been reported. Hyperthermia may occur during minor illness and in procedures requiring anesthesia. Fever may be absent despite serious infection.
- **Severe gastric illness.** Abdominal distention or bloating, pain and vomiting may be signs of life-threatening gastric inflammation or necrosis, more common in PWS than in the general population. Rather than localized pain, there may be a general feeling of unwellness. If an individual with PWS has these symptoms, close observation is needed. A CAT scan of the abdomen and/or endoscopy may be necessary to determine degree of the problem and possible need for emergency surgery.
- **Central adrenal insufficiency.** Studies suggest an increased incidence of CAI in individuals with PWS. Measurement of cortisol levels during a significant illness and supplementation of cortisol may be indicated.
- **Skin lesions and bruises.** Skin picking is common in PWS, causing open sores. In some situations, skin and rectal picking can be severe. Individuals with PWS also tend to bruise easily. Appearance of such wounds and bruises may wrongly lead to suspicion of physical abuse.
- **Hyperphagia (excessive appetite).** Insatiable appetite may lead to life-threatening weight gain, which can be very rapid and occur even on a low-calorie diet. Individuals with PWS must be supervised at all times in all settings where food is accessible. Those who have normal weight have achieved this because of strict external control of their diet and food intake. Water intoxication has occurred in relation to use of certain medications with anti-diuretic effects, as well as from excess fluid intake alone, producing lower electrolytes.
- **Obesity-related problems** include hypoventilation, hypertension, right-sided heart failure, stasis ulcers, cellulites, and skin problems in fat folds.

Potential Characteristics

Any infant with hypotonia should be tested for PWS. The following common characteristics raise suspicion of a diagnosis of PWS.

- Decreased fetal movement, infantile lethargy, weak cry
- Feeding problems and poor weight gain in infancy
- Excessive or rapid weight gain between 1 and 6 years of age; central obesity in the absence of intervention
- Distinctive facial features — dolichocephaly in infants, narrow face/bifrontal diameter, almond-shaped eyes, small appearing mouth with thin upper lip and down-turned corners of mouth
- Hypogonadism — genital hypoplasia, including undescended testes and small penis in males; delayed or incomplete gonadal maturation; and delayed pubertal signs after age 16, including scant or no menses in women
- Global developmental delay before age 6; mild to moderate cognitive disabilities or learning problems in older children
- Hyperphagia/food foraging/obsession with food
- Possible behavior problems — temper tantrums, obsessive/compulsive behavior; oppositional, rigid, possessive, perseverating, but also sweet and loving
- Sleep disturbances especially daytime sleepiness and sleep apnea
- Short stature for genetic background by age 15 if untreated with growth hormone
- Hypopigmentation — fair skin and hair compared with family, primarily in deletion subtypes
- Small narrow hands and/or feet for height/age. Straight ulnar border
- Osteoporosis — can occur much earlier than usual and may cause fractures; ensure adequate calcium, vitamin D, and weight bearing exercise; bone density test recommended
- Diabetes mellitus, type II — secondary to obesity; responds well to weight loss; screen obese patients regularly
- Dental problems — may include soft tooth enamel, thick sticky saliva, poor oral hygiene, teeth grinding, and infrequently rumination. Special toothbrushes can improve hygiene. Products to increase saliva flow are helpful.
- Speech articulation defects and dyspraxia
- Strabismus — esotropia is common; requires early intervention, possible surgery
- Scoliosis — can occur unusually early; may be difficult to detect without X-ray, kyphosis is also common in teens and adults

Resources for Health Care Providers

"Growth Hormone and Prader-Willi Syndrome, 2nd Edition" and the book "Management of Prader-Willi Syndrome" are available from PWSA | USA at www.pwsausa.org, as are many other publications for professionals and parents. Medical crisis support for professionals and parents is available at (941) 312-0400.

In the Event of Death

Reporting of Deaths
The Prader-Willi Syndrome Association | USA has created a research database of reported deaths of individuals with PWS. In the event of death of someone with PWS, please contact PWSA | USA: (941) 312-0400

Organ Donation for Research
When a child or adult with PWS dies, the family may wish to consider donation of organs for research. Prompt action is essential for tissue preservation. Families are advised to contact the Brain and Tissue Bank directly: 1-800-847-1539 (Maryland).






THE GLOBAL PRADER-WILLI REGISTRY WILL:

Generate new insights into PWS

Drive unmet research and treatments

Expedite the completion of clinical trials

Guide improved standards of care

Improve the lives of those affected by PWS

3 REASONS YOU SHOULD ENROLL IN THE REGISTRY

1 When you indicate in your contact preferences that you would like to learn more about clinical studies, you will be notified via email when you meet the eligibility criteria for a study.

2 As you complete each survey, you can immediately visualize the survey responses. This allows you to compare your responses with the greater PWS community.

3 Keep your medical records in one place! When you complete registry surveys, your responses will be available to you in the future so that your data is quickly at your fingertips.

Visit the Registry Today!
www.pwsregistry.org

Need help getting started?
email info@pwsregistry.org

V

REGISTRY DEMOGRAPHICS (2021)

GLOBAL PRADER-WILLI SYNDROME REGISTRY

1,846 total enrolled

208 new participants*

8,582 newly completed surveys*

*in the past 12 months

29% of registry participants have also participated in a **research study** or **clinical trial.**

91% of registry participants **HAVE USED GH**

more than **75%** of registry participants required a **feeding tube** in infancy

48% of registry participants ages 10 and up report **ANXIETY**

46% of registry participants over the age of 2 report having **SPINAL DEFORMITY**

14% of registry participants have been diagnosed with **HIP DYSPLASIA**

20% of registry participants report **THYROID ISSUES**

PARTICIPANTS BY COUNTRY

63 countries represented

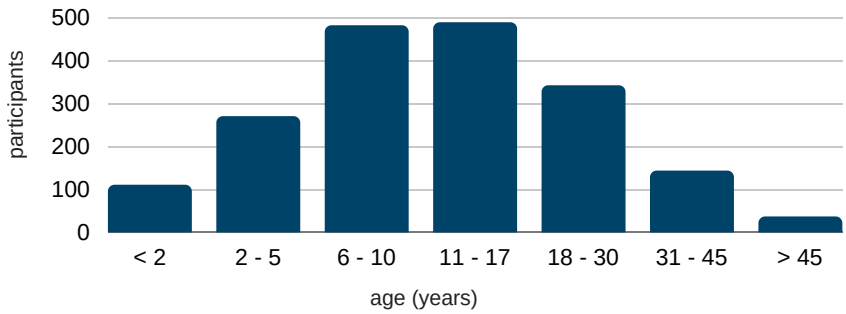

73%


9%

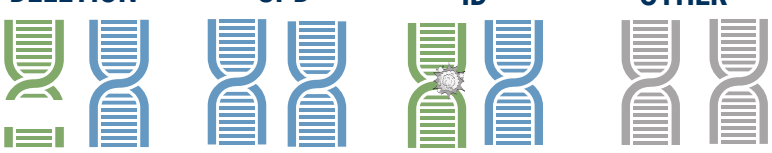

3%


3%

CURRENT AGE OF PARTICIPANT



GENETIC SUBTYPE OF PARTICIPANTS



56% **39%** **3%** **2%**

11% of registry participants **do not know** their genetic subtype.

WWW.PWSREGISTRY.ORG

The Child with Prader-Willi Syndrome:

Birth to Three

By
Robert H. Wharton, M.D.
Karen Levine, Ph.D.
Maria Fragala, P.T.
Deirdre C. Mulchahy Patch, M. S., CCC-SLP

With a Parent's Perspective
by Cinda Ball ©1999 and 2004

THE CHILD WITH PRADER-WILLI SYNDROME: BIRTH TO THREE

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(All are parents of a child with Prader-Willi Syndrome)

The children featured in this publication have Prader-Willi Syndrome.

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The Child with Prader-Willi Syndrome: Birth to Three
Revised 2011

Introduction

The first three years of life of children are filled with exciting and dramatic social, emotional, and physical development. While the pace of development of these skills varies from child to child, the dramatic social, emotional, and physical growth that occurs during these years causes them to be known as the “Wonder Years.” Infants and young children with Prader-Willi syndrome (PWS) likewise demonstrate significant developmental achievements in these early years that bring tremendous joy to their families. As these are such critical years of development, we would like to elaborate on some of these achievements. This booklet is intended to help parents as well as extended family members, Early Intervention workers, therapists, physicians, and other care providers of children from birth to three with Prader-Willi syndrome. We will provide an overview of these years with recommendations for optimum care and resources for more in-depth focus on specific areas.

Our goal is to provide parents and care providers with important information so that you have a better understanding of how Prader-Willi syndrome may impact your child, what interventions are available to help you maximize his or her overall development and natural talents, and how you may better prepare for your child’s and your family’s future, all while feeling more confident, optimistic, connected, and supported.

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A Parent's Perspective

by Cinda Ball 1999

My husband and I were told that our daughter had been diagnosed with Prader-Willi syndrome when she was 15 days old, the same day we brought her home from the hospital. For the first few weeks, we spent time searching for information about PWS on the Internet and telephone. Our fundamental questions were, "What does the syndrome mean?" and "What can we do for our daughter?" As we searched, we found reams of articles on the syndrome, but surprisingly little regarding what to do. So, in the following paragraphs, I will describe what we are doing to help our daughter.

As my husband and I sought to understand PWS and figure out how to best care for our daughter, we were faced with several major decisions. We needed to choose a pediatrician, figure out how to get her to gain weight, and combat the low levels of activity. Next, we searched for specialists. After seeing three and discussing their advice, we developed a basic approach to Avery's care. Our game plan includes therapy, stimulation, human growth hormone treatment, visits to specialists, and a lot of normal childhood activity.

Choosing her Physicians

Before our daughter was born, we had interviewed and chose the pediatrician in our neighborhood. After Avery's birth we talked to the doctors at the hospital, received recommendations for, and interviewed a couple of pediatricians with backgrounds in developmental delays and neurology. In the end, we chose our neighborhood doctor because of his openness, great common sense, and availability. He also assisted us by frequently weighing Avery, providing emotional support, tracking down information, and assessing the opinions of other specialists.

Feeding

Initially, our primary concerns were feeding the baby and trying to get her to gain weight. In the hospital she had been tube fed and then slowly taught how to suck from a nipple. We decided to keep her on the same feeding schedule that the hospital used every three to four hours.

For the first three months tactics included supporting and moving her jaw, moving the bottle in her mouth to stimulate a suck, tapping the bottom of the bottle, moving her to keep her awake, unwrapping her blanket or uncovering her feet, and playing music. We were aware of the need to balance ensuring that she received adequate amounts of milk without wearing herself out and burning up more calories than she consumed.

In the beginning, we also had a logbook on the counter in the kitchen, where we wrote down a target amount for her to drink for the day and how much she actually drank at each feeding. We also weighed her every two days. If she did not gain weight for two weigh-ins, we knew that she now needed more milk each day to continue to gain weight, and we would increase her target amount of milk. This way we had a good idea of how much she needed to drink to gain weight.

Activity

To address the low levels of arousal and activity, we held Avery as much as we could while she was in the hospital. We also massaged her and talked to her during feedings, diaper changes, and whenever she was awake. For the first four or five months I did range of motion exercises (moving baby's arms, legs, joints, etc.) a couple of times a day. Counting and singing while I moved Avery was fun and gave us an activity to do together in the newborn phase when there are not too many choices for play. We used black and white shapes, a mobile, and a Gimini playmate for visual stimulation and early swatting and reaching. Although our daughter did not develop at the rate of an average child, we found great excitement in each new movement and task she accomplished.

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Visits to Specialists

Soon after Avery came home from the hospital, we started searching for specialists. In hindsight we were intrigued with specialists who were practical and proactive. Although the specialists discussed similar information about PWS, their approaches to early action were dramatically different. One recommended watching the growth chart and starting growth hormone when weight and height lines crossed. The second doctor told us to love and care for our child and not do anything special other than some therapy until age two to four when feeding and behavior issues become apparent.

After these two appointments we felt as if we knew more about PWS, but still had not been given any practical advice about how to help our daughter now. The “Birth to Three” booklet was the first literature we read that described actions we could take to possibly improve the outcome for our child and the impact we could have with early intervention. When we spoke to Dr. Robert Wharton and the team he works with in Boston, we found the most proactive group that focused on what we can do now to improve future outcomes. Most regrettably, Robert Wharton, M.D. has since passed away.

We Develop Our Approach

After reading about PWS and visiting these specialists, my husband and I developed an approach to PWS and our daughter’s care. The thought behind our approach is one of planning for the worst and hoping for the future. While there are no magic bullets to cure PWS, there are many suggested actions to take that will not hurt our daughter but may help, such as therapy, nutrition planning and extra stimulation. For example, we are expecting her to have trouble with gross motor skills and speech development and are providing physical therapy and growth hormone medication now. These actions will benefit our child. As for hoping for the best, we believed Dr. Wharton and his colleagues when they told us that early diagnosis, early intervention, and treatments such as growth hormone appear to have created a second generation of children with PWS. Believing in his viewpoint has freed us from the psychological burden of knowing about the old outcomes of the syndrome and freed us to do what is most important – focus on our daughter and spend all of our moments with her productively.

What we do not know includes what characteristics of the syndrome our child will manifest, what is the power of early diagnosis and early intervention, what are the potential outcomes for our child, and what advances in the medical field will bring. From what we do know, there are clues about what to plan for, and from what we don't know, there is endless and tremendous hope that what we are doing will improve our child's life.

The Plan of Action

Based on our approach of planning for the worst and hoping for the best, our plan of action for Avery's care that includes therapy, stimulation, human growth hormone treatment, and regular family activities has taken shape. The role of the parent in therapy is fourfold: arranging the therapy, spending time coordinating and managing the social worker and therapists, participating in the therapy, and carrying over the therapy to our everyday care and play.

Early Intervention (EI) contacted us the day after we brought Avery home from the hospital and assigned us to an agency. The agency planned an at-home evaluation when Avery was seven weeks old that included four evaluators, our pediatrician, and us. During the evaluation, they tested reflexes, body movements, and responses to people, objects, and sounds. Based on the evaluation, we met with the agency and Early Intervention to make an individual Family Service Plan, or IFSP. The IFSP included an hour per week of oralmotor and speech therapy, feeding therapy, occupational therapy (OT) and physical therapy (PT). At about nine months we increased OT and PT to twice a week.

To make our daughter's time with the therapists as productive as possible, I spent time talking to our social worker and coordinating with the therapists. The therapists and I occasionally discussed what their goals were for Avery and what she would be trying to accomplish. Our three therapists talked once in a while and made brief notes in a logbook to coordinate the care and share observations about Avery's development.

I'll give an example of a situation where being close to the daily therapy and managing the situation helped Avery. After the first two months, our physical therapists started spending more time talking about and doing "healing work" instead of standard physical

therapy. Still being new at this, I was unsure about what a physical therapist should be doing with a five-month-old with low tone. By contacting our social worker, we were able to determine that we were not receiving the proper physical therapy and our therapist was changed. The therapists are fantastic and a tremendous resource, but in the end, it is the parents who are handling the child most and are ultimately responsible for the physical and emotional development. So, I do watch and ask the therapists about their work and handling and get their advice regarding what we can be doing at home. Then, as time permits, Avery and I have our own play sessions and incorporate the positioning and activities that the therapists use. Later we show the key things to Dad, babysitters, and grandparents. We spend as much time at floor play as possible and minimize downtime like stroller and car seat time. We do have those “sitting days” and I try to offer some kind of stimulation, even if it doesn’t include physical activity.

To work on speech development, we do oral-motor activities to help develop and use all of the proper muscles. Over time, this has included rubbing Avery’s face with a towel and using an Infandent finger toothbrush and Nuk baby toothbrushes to stimulate the gums, tongue, and mouth. Because a speech problem is likely, including speech delay and/or childhood apraxia of speech (often also referred to as speech dyspraxia), one strategy is to develop alternative methods of communication. We have made a photo book with pictures of familiar objects, pets, and people that we look through and talk about. In addition to hearing about signing with babies from the speech therapists, a book entitled, Baby Signs by Linda Acredolo and Susan Goodwyn was very informative. Other good sign language resources include Talking Hands. A Sign Language Video for Children by Small Fry Productions, and the website www.signwithme.com. Helpful information about childhood apraxia of speech or dyspraxia can be found on the website www.apraxiakids.org.

Sometimes it seems odd to spend so much time and effort trying to stimulate a child while many parents are trying to calm their children with baths and quiet voices. Stimulating takes creativity and persistence with a child who is less apt to respond. Some things that have helped us have been word and gesture games (with lots of hamming it up and overacting), singing, music, toys that make noise, and physical play. As a first-time mother whose nursery rhyme and song collection was limited to “Old McDonald’s Farm” tapes of children’s music and books with words and finger plays have been invaluable, particularly in the very early days when my daughter’s responses were minimal and play options were limited. The Gimini playmate was useful from months two through seven or so, when Avery was looking, learning to move against gravity, swatting, kicking, and rolling. Light toys with texture, fabric swatches of different textures, and rattles were big hits. One of our favorites is our weekly music class that has tapes and books for home use. We also play with instruments like bells, rhythm sticks and a tambourine. The music also seems to prompt more arousal and physical movement for Avery.

Watching a niece and a friend's child who are the same age as my daughter has given me new ideas for introducing more stimulation. If there are activities that these children enjoy doing that Avery cannot initiate on her own because of the gross motor delays, then I try to create the experience for her. For example, Avery can't get into the kitchen cabinets on her own, so I filled a container with plastic items, bottles, nipples, and pacifiers for her to play with. She also cannot get into the plants or flowers on her own yet, but occasionally I take her to them and let her explore and rip them apart.

Growth Hormone

At the time our daughter was born, one of the biggest decisions a parent of a child with PWS faced was whether to start using human growth hormone (HGH) and when to start.

After discussing it with our doctors, we read a lot of the available information, which at the time was not much. At that time we had two options: do not start HGH and possibly regret that decision five to ten years later, or start HGH and accept the possible unknown future side effects along with the benefits. For us, it was worth the unknown risk to start the treatment. We were particularly anxious to see the benefits of an improving muscle-to-fat-ratio and the potential impact of decreasing appetite and increasing the amount of calories burned. Today, there is sufficient evidence to support that growth hormone treatment can improve the health and quality of life of children with PWS. The questions that remain are largely individual ones - how early to begin treatment, and whether there are good reasons to stop treatment or not to use growth hormone in a particular child.

We started giving our daughter daily injections of growth hormone when she was six months old. The improvements in her tone and strength were noticeable within a month. She progressed to sitting independently quickly. While motor planning, like learning how to push to sit and using knees to transition to standing was difficult, her strength continued to improve. At two years old, her problem-solving and motor planning skills are much more fluid and she is walking and climbing vigorously. The HGH may have increased her attention, level of alertness, energy, and stamina. So far, we are extremely happy with the impact of the human growth hormone.

The Way It Is

We meet with a pediatrician specializing in PWS and an endocrinologist quarterly, and occasionally we see a psychologist. We have met with a speech therapist, physical therapist, and a nutritionist. It has been extremely helpful to talk to these specialists to get new ideas, ask questions, and get an indication of how Avery is doing. It has also been a good way to teach our regular therapists more about the specifics of PWS and Avery's situation.

I would have to imply by all this talk of therapy and play sessions that our life is clinical and scheduled. We do a great deal of "normal" childhood stuff like having play dates, visiting cousins and grandparents, swinging and walking, playing peek-a-boo, and going to birthday parties. Our other favorite daily activity is petting the cats.

Having an approach that my husband and I have discussed at length and worked out has made it easier for us to accept the fact that our daughter has and will continue to have Prader-Willi syndrome. It has helped us to be more relaxed about the daily childcare and more accepting of the curve balls. We know that whatever the outcome for our daughter is, we will probably never know if the causes lie purely in the genetics, the early stimulation, the therapies, or the HGH. Yet we feel better knowing that we have done all we can. So, as we plan for the worst, we have high hopes for the best for our daughter.

A 2004 Update

Key Principles to Help Your Child

Diane Spencer, formerly with Prader-Willi Syndrome Association | USA, notes it is natural and normal for parents to worry about the future of their newborn child. As we talk with the parents of children who have been newly diagnosed with PWS, a reoccurring question is "What does the future hold for my child?" None of our children come with guarantees so no parent really knows what the future holds. We suggest that with research and new management techniques, children with Prader-Willi syndrome can achieve beyond our expectations. The following letter, written five years after the previous article, instructs new parents how to spend their "worry energy" on some truly beneficial activities from the very first day that new little baby comes home with you."

Dear Parents of a Young Child with Prader-Willi Syndrome:

This letter is written to honor the memory of Dr. Robert Wharton. Dr. Wharton taught us four key principles for helping a young child with Prader-Willi syndrome:

- *Stimulate your baby*
- *Use Human Growth Hormone medication*
- *Follow the Food Rules*
- *Provide lots of Socialization*

These are the four key pieces of advice that Dr. Robert Wharton gave to my husband and me regarding our daughter. It is our relationship with Dr. Wharton and his advice that has transformed our lives. With Dr. Wharton's help, we went from fearing that our baby would have mild to moderate cognitive deficits, become obese, and have severe behavior problems, to contending with some learning disabilities, watching what our child eats and limiting some of her behaviors. Dr. Wharton was a developmental pediatrician who devoted much of his work to helping children with Prader-Willi syndrome. He had a knack for focusing on what could be done to help the child's quality of life. He cared for the children and families like no other and excelled at simultaneously comforting and motivating the parents.

Through his work with and devotion to PWS, Dr. Wharton developed strong beliefs about the syndrome. He believed that early diagnosis, human growth hormone treatment and early intervention brought a "Second Generation" of children with PWS. He thought that children who were born with PWS were lacking in survival skills: poor suck, weak cry, reduced movement. Dr. Wharton identified some key areas where intervention by doctors and parents would make an enormous impact on the child and his or her capabilities and happiness.

Stimulate

Dr. Wharton told us that he did not believe that mental retardation necessarily was a part of PWS. He believed that it was a result of the insufficient caloric intake due to the poor sucking instinct and a lack of stimulation due to the sleepiness and low arousal. He believed that if the babies received the proper number of calories and were awakened by the parents and caretakers and stimulated, that the level of cognitive deficits could be reduced or eliminated. (Research conducted in 2006 appears to indicate that morbid obesity prior to the age of four years can lead to cognitive impairment.)

Dr. Wharton noted that babies with PWS often do not “give back” the same way other babies do by smiling, giggling, and asking for more. This lack of response in babies can make many parents feel that their parenting is inadequate and that they are not bonding with their baby. He counseled that the low response is part of the syndrome but does not mean that the child is not bonding or loving. He suggested that parents need to be sensitive to the more subtle feedback given by their child with Prader-Willi syndrome and persistently and consistently interact with, stimulate, and play games with their child.

Human Growth Hormone

Dr. Wharton was an early advocate of human growth hormone medication (HGH). He advised us to give it to our daughter and we started her at 6 months of age. In addition to the obvious benefit of increasing the average height of the child, and Dr. Wharton believed even more strongly in the added benefit that HGH improves the ratio of fat to muscle imbalance. By improving the fat to muscle ratio, it helps to control weight, gives the child more strength and endurance, and helps close the developmental gaps between children with PWS and their peers.

Food Rules

Dr. Wharton said, “Your child lacks the ability to feel full. It is your job to give your child another very consistent signal that she is full. “He thought that children should be kept slim, because as soon as fat cells develop, they might be playing a role in signaling to the brain that the child is still hungry. The formula he gave us was 9 to 11 calories per cm of height. We developed Food Rules that we stick by. Here they are:

Food Rules Goal: To establish disciplined eating habits. It is not that one cookie will lead to obesity, but rather the establishment of habits and strict discipline that is critical.

- All snacks and meals should be eaten at the dinner table when at home
- Snacks away from home should be placed in a “snack bag” and be of a fixed quantity
- No extra snacks should be given to the child in order to keep the child quiet

- Provide all food on the plate or bowl at the beginning of the meal
- Do not provide second helpings unless the total amount of food to be served is divided into two servings
- If our child asks for more, calmly tell the child he/she is all finished eating, and then create a distraction or excitement to transition to the next activity
- No tasting off of other plates
- No tasting or snacking when child is present, unless one is sitting with her and eating from a plate
- For birthdays, special events, or cooking exercise at school, establish the rules you will always follow, and always follow them. For example, you may decide that your child may have one cupcake or cookie, preferably a small one, and no seconds.
- Make fewer exceptions and the child will ask for fewer exceptions

Our three other children also follow these food rules (although they do not follow the 9 - 11 calories per cm). The food rules have benefited us all. There is no begging in front of any candy display, no hassles over meals.

Socialization

Dr. Wharton and his wife, Dr. Karen Levine, believed that ultimately many of the children with PWS were not happy because they were naturally social children but did not socialize well. He suggested that children with PWS need extra help to learn to engage socially with their peers. Dr. Wharton and Dr. Levine told us about “floor time”, a way to play with children, engage, and teach them while you’re playing. He suggested a good resource for learning about floor time is the book, “How to Raise Children with Special Needs” by Stanley Greenspan. Getting your child together with other children, having more children if it’s a possibility and prompting your child to engage with other children are all things that can help lay the groundwork for more fulfilling and healthy socialization later in life.

Conclusion

So, the bad news is our children have Prader-Willi syndrome and will have it for every day of their lives. The good news is there are steps you can take that will help your child. For us, over the past six years, helping our daughter and doing everything that we

could do to help her develop and be more capable and happier made us feel better. Somehow, doing for your child cuts through the denial, creates acceptance of the diagnosis, and brings great pleasure to the present and hope for the future.

This letter is really a tribute to Dr. Wharton. We were blessed to have known him for almost six years and we want to spread his words and advice that we believe have been critical to improving our daughter's life. We hope that sharing this information can improve the lives of other children and bring hope to their families!

All our love and luck for a bright future, Another family with a child with PWS.

Please read the PWSA | USA Clinical Advisory Board Consensus Statement on Growth Hormone dated 2009, and the article titled, Consensus Statement/Clinical Practice Guidelines on PWS in the November 2008 issue of the Journal of Clinical Endocrinology and Metabolism, both available from the office of the PWSA | USA.

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Chapter 1
Pregnancy and Birth

Pregnancy

Prader-Willi syndrome is a congenital disorder, which means that the signs and symptoms exist because of a problem during early fetal development, namely at the time of conception. There is nothing that either parent did or didn't do at any time in their lives, however, that caused their child to have Prader-Willi syndrome. PWS is simply a part of the human condition and dates back to at least the 16th century.

The earliest recognizable indicators of PWS can usually be detected during pregnancy. Amniocentesis tests do not typically look for Prader-Willi syndrome, but PWS can be diagnosed in utero if it is specifically tested for. Almost all mothers, but especially those for whom the child with Prader-Willi syndrome represents at least a second sustained pregnancy, voice concern during the pregnancy that the child's kicking is not strong, and that the child does not seem to be active. This lack of forceful kicking is usually detected by the mother in the middle trimester and lasts for the remainder of the pregnancy.

In the last trimester additional more subtle differences may also appear. First, while the normal position in utero for a fetus prior to birth is headfirst, in approximately 20 percent of cases of children with Prader-Willi syndrome their position is bottom first or feet first, which is known as "breech." A smaller number of children also may have become stuck in an unusual position whereby their face or their brow is the presenting part at delivery rather than the crown or top of their head. Significantly decreased muscle tone and strength is what causes both the lack of strong kicking as well as the infant's not turning into the usual position for a delivery.

The vast majority of women go into spontaneous labor between 39 and 41 weeks of pregnancy. It is not infrequent that due to the lack of the baby's movement in utero, an obstetrician will want to deliver the baby prior to the due date, often by Cesarean section. When a pregnancy lasts longer than 42 weeks, the child is called postmature. In approximately 20 percent of cases, the pregnancies of woman carrying a child with PWS are in fact prolonged by at least 2 weeks. Therefore, mothers frequently may not go into labor themselves at the expected date of delivery, and instead obstetricians may need to initiate labor either through medication or by performing a Cesarean section.

It is worth reiterating that although the earliest signs of Prader-Willi syndrome can be detected during pregnancy, no activities, medications, drugs, type of work, stress, or other factors related to either parent's behavior have caused their child to have Prader-Willi syndrome.

The problems associated with PWS are caused by a spontaneous and random occurrence involving the child's 15th chromosome pair. Symptoms are due to a lack of expression of genes on a region of the paternally inherited chromosome number 15. The specific region is designated 15q11-q13. Genetic material in this region of chromosome 15 is expressed differently if inherited from the mother or father due to a normal process of genetic modification called "imprinting." In Prader-Willi syndrome, the paternally "imprinted" genes are not expressed due to one of three possible genetic alterations. Deletion of the 15q11-q13 region on the chromosome inherited from the child's father is the most common form, occurring in 70% of all cases. Uniparental Disomy, or UPD, accounts for 25% of cases, and occurs when the baby inherits both copies of chromosome 15 from the mother and is missing the paternal genes on Chromosome 15. The result has the same effect as a Deletion. An Imprinting Defect makes up the remaining 5% of cases. Further testing and genetic counseling are recommended for families who have a child with an Imprinting Defect and who wish to have more children.

The Newborn

As stated above, the newborn with Prader-Willi syndrome continues to have characteristics that have been noted in utero, namely diminished motor skills and arousal. The traditional concept of Prader-Willi syndrome suggests that the hypotonia or diminished motor tone is the most characteristic feature of the neonate. Diminished arousal and alertness should also be considered a "classic" or characteristic sign.

Frequently infants are given poor Apgar scores, a simple method to quickly assess the condition of a newborn immediately after birth, due to their apparent lethargy, poor muscle tone, and general lack of vigorous respiratory efforts. With respect to arousal, the newborn with Prader-Willi syndrome usually demonstrates a lack of alertness unusual for infants having just experienced the trauma of birth. Newborns with PWS characteristically do not cry following delivery nor do they demonstrate auditory alertness or visual attention. Instead, they typically lie on the examining table asleep. They are generally uninterested in and not capable of feeding.

Because of the dramatically decreased tone and arousal, infants with Prader-Willi syndrome are sometimes incorrectly diagnosed as having cerebral palsy or as having undergone a hypoxic injury (lack of oxygen to the brain) as a result of a birth trauma, or are thought to have some form of muscular dystrophy, or benign hypotonia. The application of these misdiagnoses has several implications for children and families.

First, by providing an incorrect diagnosis, a medical evaluation for the correct diagnosis may not be forthcoming, leading to an unfortunate delay receiving important medical and therapeutic interventions. Secondly, parents may look to errors in the birth process as the cause of or contributing factor to the problems they see in their infant.

Lack of muscle tone with diminished strength are additional significant features of infants with Prader-Willi syndrome. If allowed, infants with PWS would tend to sleep through the night from delivery and maintain this pattern of increased sleep for the first six months of life. Infants are generally described as having a “rag doll” feel. This diminished tone, together with decreased arousal, contributes to sucking that is often not initially sufficient for successful feeding. Caregivers must awaken the infant for regular scheduled feedings, night and day. By the end of six months, however, infants generally begin to demonstrate increased periods of alertness and attention. It is likely that their level of arousal, or how awake they appear, while gradually increasing from the newborn period, will still be somewhat diminished. In addition to the features of low muscle tone and poor arousal, there are other features in the newborn that assist with diagnosis. First, although characteristic facial features may be too subtle to detect or may not be present at all, some individuals with PWS may have almond-shaped eyes with upslanting palpebral fissures (the separation between the upper and lower eyelids) that make the eyes look angled slightly upwards. They may also have a narrow forehead and a triangular shaped mouth. Additional features can be a high arched palate, strabismus (see section on strabismus), and a pale complexion. Boys will generally have a small penis and an undeveloped scrotum without the presence of descended testicles. This latter situation is known as cryptorchidism. This feature of hypogonadism will be more difficult to demonstrate in females who may reveal small, underdeveloped labia majora.

Infants with PWS are frequently diagnosed as “failure to thrive” because they often exhibit difficulty sustaining adequate weight gain. This difficulty with growth is associated with insufficient caloric intake caused by feeding difficulties and does not represent a metabolic disorder in the child. Infants generally demonstrate no appetite for their first several months. They tend not to awaken at night for feeding, nor do they cry during the day if they are not fed, or if a bottle is taken away prematurely. Waking to feed, alerting to visual and auditory stimulation, and crying because of discomfort require a level of alertness or arousal that the young infant with PWS does not yet have. These responses are generally described as “primitive responses” and “survival skills” as they alert parents to feed or otherwise respond to the infant. Their absence in the infant with PWS makes the parents’ role even more challenging since they must schedule all feedings, recognize and respond to their baby’s subtle behavior cues, and maximize their baby’s briefer periods of alertness.

In general, infants should be fed every 2 to 4 hours. Parents have found various strategies that can help keep their baby more awake and alert during feedings: gently scrunching the cheeks with your fingers and thumb to “awaken” the cheek muscles, unwrapping the baby from the blanket or unzipping the onsie to let the air awaken him, tapping the bottom of the feet, tapping the bottom of the bottle, and/or gently move the bottle around in the mouth. Special bottles and nipples, such as the Haberman, can make it easier for the baby to suck. Parents have found other nipples helpful as well, such as NUK silicone Orthodontic slow flow nipples or Gerber Nuk silicone orthodontic or slow flow nipples.

Bottle feedings can take a great deal of effort because muscle strength is generally weaker, and babies often have difficulty coordinating their suck, swallow, and breathing. A great many calories are expended simply during the feeding process. In order to take in more calories than are expended during feeding, a general rule of thumb is to limit the feeding process to no more than 45 minutes. Some pediatricians may recommend a calorie-boosting formula to augment breast milk or formula.

A high or cleft palate can interfere with feeding. The Haberman Feeder is a bottle and nipple system especially designed for impaired sucking ability. Many babies with PWS also appear to experience Gastroesophageal reflux disease (GERD), a condition in which the stomach contents (food or liquid) leak backwards from the stomach into the esophagus (the tube from the mouth to the stomach). A baby with reflux may be reluctant to feed due to discomfort and may benefit from treatment measures to reduce the reflux symptoms, including holding techniques and/or medications (See PWSA | USA’s booklet Nutrition Care for the Infant and Toddler with PWS).

If the baby is still not taking in sufficient calories for adequate growth, it may be necessary to use a nasogastric tube, or NG tube, to feed the infant until he or she has developed a sufficient suck. NG Tube feedings can occur alongside bottle feedings in order to ensure that the infant is receiving the proper caloric intake and is not tiring or burning off more calories than he or she is consuming. Another feeding option that may be used with infants who have continued difficulty bottle feeding is a Gastric tube, or G-tube. A G-tube requires a surgery to insert a tube directly into the infant’s stomach. Breast milk or formula is then poured directly into the tube. The G-tube will remain in place until the infant has developed a sufficient suck. Parents frequently report that they have the greatest success with a Mic-key button feeding tube.

Infants treated with recombinant human growth hormone generally improve their suck at a faster rate and experience greater success bottle-feeding than infants who are not treated with growth hormone. Some babies, though not many, are even able to breast feed. In addition, some families have found that the use of supplements, such as Coenzyme Q-10, L-Carnitime and Creatine help improve levels of alertness, energy and feeding.

Chapter 2

Early Intervention

As early as possible within the first few weeks of life, a referral for therapy services through the State's Early Intervention agency should be made. Early Intervention is a set of therapy services that are federally funded, through the Department of Public Health, for infants 0-3 years of age who have a developmental disability, such as Prader-Willi syndrome. Part H of the Individuals with Disabilities Act, (originally enacted as Public Law 99·457, The Education of the Handicapped Act Amendments), calls for a "statewide, comprehensive, coordinated, multidisciplinary, inter-agency program for all handicapped infants and their families." The Act further states that programs establish "developmental services… to meet a handicapped or toddler's developmental needs in any one or more of the following areas: physical development; cognitive development; speech and language development; psycho-social development; or self help skills." In short, it is your baby's legal right to receive intervention to help with his/her developmental difficulties.

Early Intervention Programs (EIP) are organized by area, much as school systems are, and enrolling in Early Intervention is similar to enrolling in Kindergarten. You can refer your child yourself or ask your pediatrician to refer. You can obtain the telephone number of the EIP in your area by calling your State Department of Public Health office. Following your call, the program will conduct a visit with you and evaluate your child to determine what services you and your child need. You and the EIP staff together then develop what is called the "Individual Family Service Plan" (IFSP), which is the program's contract to provide services for your child.

In some parts of the country local Early Intervention Programs will provide therapy services in the home on at least a weekly basis. In other areas, services are much less frequent and EIP programs will need to be supplemented by therapies funded through other sources, such as private health insurance. It is important for you the parent to be involved in your child's therapies to the greatest extent possible so that you can incorporate the beneficial therapy activities into daily life.

The Early Intervention “core therapies” for almost every child with PWS are Occupational Therapy, Physical Therapy, Speech and Language Therapy, and Social Skills Therapy. Other early intervention therapies can include Feeding Therapy, Oral Motor Therapy, Infant Stimulation Therapy, Music Therapy, Aquatic Therapy, and Behavior Therapy. The types of therapies, their frequency, and duration should be tailored to meet the individual needs of the child.

One to Six Months

The first six months of life for infants with PWS will almost always demonstrate significant positive developments with respect to sleep and arousal, their ability to sustain themselves nutritionally, motor development, and social interaction. Socially, by six months the child will appear increasingly bright, alert and visually attentive. The distant or sleepy appearance of the newborn will have likely improved, although it may not have resolved completely.

The excessive sleep behavior, a feature which leads to infants being described as “good babies”, generally resolves by six months such that the infant has increasingly longer periods of awake and alert time. Somewhat increased nap and/or sleep time, however, may be a persisting feature even into adulthood, although this symptom tends to decrease with growth hormone treatment. It may appear at this time that when awake, infants are fully alert and attentive. The increased attention and arousal brings opportunities for happy reciprocal baby play with parents and siblings.

Muscle tone will continue to gradually improve. The use of growth hormone typically promotes additional improvement in tone. Evidence of this increased tone can be seen in the child’s suck which, in almost all infants with PWS by six months of age, will be sufficient to sustain their nutrition and adequate growth.

The newborn’s apparent lack of interest in food usually resolves during the first six months and a more typical appetite develops. It is imperative that care providers understand the importance of helping the child achieve and maintain a healthy weight and not feed more than the appropriate amount of calories needed for the baby to grow and develop. This is especially important if the child has typically been underweight or appeared frail. Parents may generally rely upon the good advice of your regular pediatrician in regard to amount and types of foods to feed your baby, bearing in mind the importance of providing healthy fats, such as whole milk or soy milk, for good brain development. In general, babies under 1 year should have breast milk or formula.

Whole/soy milk should only be introduced at or after 1 year (some parents have found cow's milk to be problematic, causing too loose stools or diarrhea. Using soy, almond, or some other non-dairy milk product often resolves these intestinal issues).

Tasks

Infants with PWS develop attachments to their parents, siblings, and other family caregivers in the same ways as all babies and thrive on loving attention, cuddling, eye contact, play, smiles, and baby talk. Several small adaptations can ensure that infants with PWS have a full range of play experiences. For the young infant, an Occupational Therapist should provide therapy to improve overall strength and sensory input and integration. As the child approaches six months and older, the Occupational Therapist will focus on improving fine motor skills. If not already working with the child, a Physical Therapist should be introduced to the therapy regimen to begin to focus on the development of large or gross motor skills.

It will be beneficial to purchase lightweight toys (e.g., small, light rattles rather than bigger, heavier ones) that the infant can manipulate easily in spite of motor weakness.

Children with PWS will benefit from early intervention services provided by an occupational therapist who is well trained in sensory-integration therapy. Play therapy which incorporates the use of various textures, movements, body positions, sights, sounds, smells, and tastes will help improve the baby's overall sensory system. Two books on the subject of sensory integration are The Out-of-Sync Child, and The Outof-Sync Child Has Fun, by Carol Stock Kranowitz, M.D.

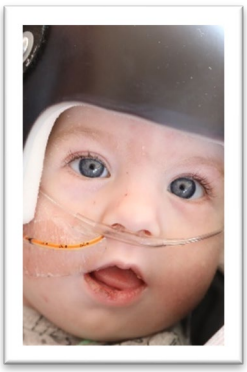
Due to low muscle tone, the infant will likely become easily "scrunched down" in some baby seating equipment. Prop the infant up with rolled towels or cushions such that he can sit and look around comfortably as he plays.

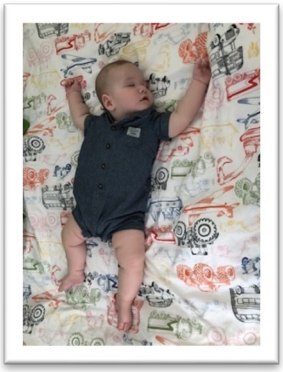
With respect to feeding, there are some simple activities a speech therapist can share with you to help improve your infant's mouth and tongue (oral-motor) coordination.

- First, you can begin mealtime with playful exercises called pre-feeding stimulation. Provide deep, firm touch and stimulation to the muscles in the cheeks, lips and tongue to help "wake up" muscles and develop strength and coordination.

- You can also use music with a rhythmic beat to help increase you child's arousal and rhythmic sucking pattern. Most children's music tapes and videos will work.
- Choose a nipple that helps your infant use his/her lips and tongue well but does not make him work too hard for the milk or formula. As previously mentioned, the bottle and nipple system called the Haberman Feeder has been quite successful for a number of families. For more information or to order the feeder, contact the Medela Company at (800) 435-8316 or www.medelabreastfeedingus.com
- Finally, give your child support at his cheeks and jaw so he or she can get a good seal.
- Read the booklet, Nutritional Care for Infants and Toddlers with Prader-Willi Syndrome available from PWSA | USA.

Babies with PWS eventually learn to develop techniques to communicate their wants and needs in essentially the same manner as all babies. Parents may, however, need to pay closer attention to the subtleties of their baby's communications and may need to work a bit harder to capitalize on, and even extend, the baby's awake and alert periods. You will likely need to awaken your baby after providing an adequate amount of time for napping or overnight sleep so that you and your baby can play. Babies learn through play and sensory exploration. The time you spend playing and providing opportunities to experience different kinds of sensory input is critically important to your baby's cognitive, social, emotional, and physical development. Typical games like peek-a-boo help develop your infant's attention and social interaction. When you play, try tickling your baby each time you say "boo" and use lots of intonation in your voice. Your infant will be able to hear, feel, and see the routine of "peek-a-boo." Help your baby shake light-weight rattles, grab crinkle-sounding toys, touch different fabrics, experience different textures, etc.






Chapter 3

Infant to Toddler

Six Months to Two Years

The child with PWS continues to achieve important social and developmental gains during this time period. Socially, the child will progress from just being socially alert to longer periods of social interactive play. Once the infant is alert for long enough to comfortably interact, eye contact and responsive smiles will emerge. The lower muscle tone generally impacts the muscles of the face and often makes early smiles more subtle. The child will continue to demonstrate his strong attachment to parents by showing interest in the parents' activities, need for parental attention, joy in testing parents with games of drop the spoon (or cup or plate!), hide and seek, and occasional displeasure at being left with less familiar adults. Some children may appear to lack some of the features associated with separation anxiety, and can appear quite content to spend prolonged periods in solo play. The ability to sustain themselves in play is occasionally viewed by families with some concern, however this characteristic seems to be simply a temperamental style often associated with PWS and is not associated with deficiencies in emotional development, intelligence or ability to learn new things.

The timing of success in achieving motor and speech milestones varies from child to child, and is usually accelerated with the use of growth hormone treatment. For example, the majority of children with PWS will walk independently between 18 and 30 months of age, although rarely, some children will not walk independently until they are three or four years old. These time frames are usually decreased with the use of growth hormone. Even without growth hormone treatment, however, muscle tone continues to improve over time, though continues to remain diminished irrespective of growth hormone treatment. Children with PWS demonstrate the same will to achieve developmental accomplishments as other children, namely the ability to communicate and move around their environment. However, motor accomplishments are more difficult to attain due to diminished muscle mass and tone, and difficulties with motor

planning skills (global praxis), which is the coordination between the brain and body to plan, sequence, and execute the steps involved in physical movement. All achievements that require improvements in strength, including holding up their heads independently, sitting, crawling, standing and ultimately walking will develop with time and practice, although generally later than seen in typical children.

Strength in the trunk and extremities will develop by placing increasing demands on those muscle groups. For young children this is accomplished gradually through supporting positions that require increasing amounts of strength. Strength alone, however, will not be sufficient to enable children to be successful with their motor milestones. Just as children require memory for such tasks as learning letters and numbers and remembering faces, so too do children require a memory for certain coordinated sequences of movements. Children with PWS frequently require additional practice for the learning associated with planning multiple-step motor activities. Their ability to make their bodies accomplish such tasks as crawling and walking requires sustained repetition for an activity to be truly learned and become automatic.

Expressive language (speech) is frequently the most impaired aspect of development in individuals with PWS. It generally lags behind receptive language (understanding) which develops in tandem with the child's cognitive development. The reason(s) why there are frequently problems with expressive speech are poorly understood but are undoubtedly due in part to oral motor difficulties (i.e., difficulty making the muscles in the mouth and tongue work together to formulate sounds and words). Many children with PWS are diagnosed with a specific speech disorder called Childhood Apraxia of Speech, also sometimes called Developmental Apraxia of Speech, Developmental Verbal Dyspraxia, or Oral-motor Speech Disorder. Speech delay and/ or dyspraxia often cause frustration for both the toddler and the family. In addition, the diminished expressive skills, plus delayed motor skills, make accurate developmental assessment of the child difficult and frequently leads to an underassessment of the child's cognitive level and potential. The actual cognitive level of the child is most apparent from what the child is able to understand rather than what the child is able to say or do with his or her body or hands.

Achievements in play in the first two years generally include the same types of play observed in other children. The usual baby activities such as peek-a-boo, smiling into the mirror, waving bye, and learning how to activate rattles and other noise making toys will all emerge during this period, although in some children they may emerge a few months later. Some baby toys will be too heavy for the child to manipulate but the infant and toddler will easily be able to manipulate lighter toys. The mild delays sometimes apparent in this period can be due to motor delays, longer time spent sleeping, and lowered arousal level and for some children, general developmental delay. Rate of development in this period, however, is not necessarily predictive of later rate. Delays in development of play activities do not necessarily indicate that the child will eventually demonstrate global developmental delays.

Appetite, apparently absent in the first few months of life, begins to appear with the development of oral motor skills sufficient to generate a strong suck. For the remainder of this time period (six months to two years) there are unlikely to be any features of hyperphagia, or the excessive appetite. Instead, children demonstrate the normal range of hunger and typical variety of tastes and interest in food as seen in other children. An increased interest in food or the hyperphagia symptom may appear, however, earlier than age two years. It is important to note that an early expression of the hyperphagia does not necessarily indicate that this symptom will be more severe later in life.

Children's sleep patterns will also change following the first six months of fairly sustained sleepy periods. Children will not only have increased periods of being awake, but their arousal, or level of alertness, will also increase. Growth hormone and supplements may also improve their level of arousal. In spite of this change, however, some children may fall from wakefulness into sleep rapidly and dramatically on some occasions, particularly while eating a meal, as well as at times where the child is experiencing a decrease in direct stimulation and attention (e.g., riding in a car). It is currently theorized that for some toddlers, falling asleep while eating may occur because of the increased pleasure the brain experiences while eating.

Some children with PWS develop constant strabismus (when the eye deviation or turning occurs all the time), intermittent or alternating strabismus (when the eye turn might be observed only occasionally), myopia (difficulty seeing far away), or amblyopia ("lazy eye"). Treatment for these eye symptoms can include patching, visual exercises, eye glasses, or surgery. More recently, some parents report having great success treating eye problems with Vision Therapy. Vision Therapy is performed by an optometrist who is specifically trained in Vision Therapy. More information about Vision Therapy can be obtained online or from an optometrist. A consultation with a pediatric ophthalmologist is recommended by age six months, and thereafter as recommended by the ophthalmologist, optometrist and/or pediatrician. It is worth noting that ophthalmologists often discount the merits of Vision Therapy, while parents with children whom have undergone Vision Therapy typically report good success.

A pediatric urologist should be consulted if your son's testicles have not descended into their scrotal position (cryptorchidism) by age one year. Some urologists suggest a five week course of HCG (human chorionic gonadotopin) treatment to pharmaceutically stimulate the testicles to descend. Though success has been reported by some families, the overall success rate of HCG treatments to permanently descend the testes is fairly low. Parents often report, however, that HCG shots have helped to increase the size of their son's penis and testicles, and make subsequent surgical intervention easier. One temporary side effect that should be noted is the premature and temporary growth of pubic hair. Patients who fail HCG treatment should undergo a common surgical treatment called an orchiopexy. Most pediatric urologists recommend an orchiopexy no

later than age eighteen months. Prior to any surgery, the surgeon and anesthesiologist should be informed that precautions must be taken when using anesthesia and other medications with an individual with Prader-Willi syndrome, especially a child. Information about anesthesia and medication use can be obtained from the Prader-Willi Syndrome Association | USA.

There have been occasional reports of epilepsy or seizures in individuals with PWS and a suggestion that infants with PWS may be susceptible to seizures, particularly febrile seizures caused by increased body temperature. While several systematic population surveys have failed to mention epilepsy as a specific feature of PWS, epilepsy is associated with other chromosome 15q11-13 defects. Parents who suspect their child may be experiencing seizure activity should consult a pediatric neurologist.

Tasks

To increase your child's capacity for social interaction, experiment with ways to increase your baby's excitement level. See what makes him look at you and widen his eyes happily. Try increasing your own emotional output, with happy excited facial expressions, interacting in "large type" yet in slow enough motion so your baby can respond to you. Try pretending to sneeze, with a long ("haa--haaa-haa") buildup before the funny "--CHEW" part. Try physical tickling games and rough and tumble games with facial expression and words ("Iiiii'm gonna GET you!) that build up in excitement. The more animated you are, usually the more animated and interactive your baby will be. Pause after playing excitedly and see if your baby will do something to indicate that he wants you to continue (eyes widen or smile, or searching your face, or waving his arms). Once you and your baby have some familiar games, just begin to start to play one and see if he or she will continue it. This is the beginning of initiating, which is often very challenging for young children with PWS.

Early Intervention services during this period work with the infant to help with the development of motor and speech skills and also serve as consultants to parents. For younger infants, Early Intervention may take place in the home. As children become increasingly social, around two years of age, the child can attend an Early Intervention playgroup in which speech and motor skills can be practiced in a fun, playful context with other children.

Speech and Language Intervention

Speech Therapy should begin in the first year of life, well before the child is able to actually speak, to minimize the child's frustration by helping him gradually learn to communicate wants and needs. The speech therapist should initially work on developing oral motor skills. In the second year of life, strategies to enhance verbal language development as well as on alternative augmentative forms of communication should be emphasized. At this age, we often use gestures with "silly" animated faces to introduce words to children. Adults naturally use many gestures and exaggerated sing-song intonation when talking to babies. These natural gestures such as waving "hi" and "bye", pointing, and exaggerated intonation are especially beneficial for the child with PWS. The use of gestures provides the child with PWS with an additional modality to facilitate attention and interest in speech and teaches him some ways to communicate before he has the ability to form words.

As the child grows older, speech therapists should be watchful of the characteristics associated with speech dyspraxia. Because speech dyspraxia is now considered common in children with PWS, it is generally recommended that the speech therapist treat the child "as if" he has speech dyspraxia. If the child has an undiagnosed and untreated speech dyspraxia, speech therapy is frequently very frustrating and unsuccessful. A nice resource for information about this specific speech disorder may be found online at www. apraxia-kids.org.

Songs, rhymes and finger plays are wonderful activities to help your child develop his ability to coordinate oral movements, sequence sounds, and learn new vocabulary words. The rhythm and repetitive nature of songs makes it fun and easy. When you first introduce songs, encourage your child to participate by clapping or imitating the gestures only. Then they can begin to "hum" or sing along. You can pause during the familiar and repetitive parts of the song to encourage your child to participate. Try, for example, the familiar favorite The Wheels on the Bus. Your child can gesture for "round and round." You can sing "the wheels on the bus go round", .. pause... to let your child join in. There is a wonderful compilation of songs on a CD titled, Time to Sing! produced by a speech language pathologist especially for kids who have speech problems. The CD, which features traditional songs that are played more slowly making it easier for kids sing along, may be purchased through the www.apraxia-kids.org website.

The use of some formal manual signs (e.g., American Sign Language) and picture communication systems are extremely beneficial to augment what the young child can communicate. It has been found that pairing teaching of augmentative communication such as gestures, signs and pictures while teaching verbal language actually helps children learn to talk sooner than when no augmentative systems are taught. Important early signs to teach include “more”, “all done”, a pointing gesture, “yes” and “no” gestures, and family names. Photos or sketches of daily and important events (e.g., family members, baby-sitters, trip to the zoo) are helpful, too. These photos can be placed in a book so you and your child can turn the pages, label pictures, and talk together about familiar people and places, or create a schedule with them. Eventually the child will begin to use the pictures as one means to request as well as comment about specific people or events. Pictures of favorite toys can be used so your child can point to the picture to make his choice while learning 10 say the name. Other signs or pictures to be taught will vary depending on what your child wishes to communicate.

Occupational Therapy Intervention to Improve Fine Motor Skills

Occupational therapy, to help improve fine motor skills such as grasping, pointing, pinching, etc. should continue. Therapy should focus upon improving the child’s sensory integration system, which involves the brain’s processing and organization of all sensory input including touch, taste, movement, body awareness, the pull of gravity, sight, and sound.

Physical Therapy Intervention to Improve Gross Motor Skills

Physical therapy in this period should emphasize activities to strengthen specific large muscle groups important for improving posture and gross motor skills. Placing your child on his or her tummy will help strengthen the arms, neck and shoulder muscles. Reaching for toys while lying on the stomach and putting weight on the forearms will also help strengthen these muscle groups as well as facilitate shoulder stability. Assisted reaching activities in sitting, assisted pull to sit during diaper changes and gentle resistance during rolling are activities that can be incorporated into play activities at home with songs and toys. As children with PWS often have difficulty organizing their bodies to perform fine and gross motor activities, therapy should be designed to give the child the idea of how to move his/her body to change positions.

Some children may need special equipment in order to achieve success at gross motor skills. Infant car seats may need to be adapted with rolls for better head control and adaptive seating may also be required to facilitate developmentally appropriate fine motor and other developmental activities. For more information about Physical Therapy, please read Physical Therapy for the Child with Prader-Willi Syndrome by Janice Agarwal, PT, available from PWSA | USA.

Play and Socialization Skills

At some point between one and two years the child will begin to enjoy pretend play such as with a doll or toy car or stuffed animals. This type of play is important to encourage as it will help language and communication develop more quickly.

Books are also an important activity for developing attention, listening skills, communication, and speech. Just as with the singing, establishing familiar favorites with predictable routines will facilitate your child's participation. In the classic, familiar favorite Good Night Moon, your child can join in by waving bye-bye or gesturing for "good night." Encourage your child to say the names of the pictures as you point and say "good night" or just say "night night" if that's easier. You and your child will quickly establish a library of favorites that will be a fun part of a daily routine and an important part of development.

Feeding and Mealtime Routines and Schedules

Regarding feeding during the six-to-twelve month period, the infant's continuing challenge of low muscle tone and oral motor coordination may make it difficult to transition from pureed baby food to chunky foods. Encourage your child to explore appropriate oral toys such as teething toys and his hands in his mouth. This is an important developmental experience for your child's oral motor and sensory skills. This activity helps to develop the movement patterns for chewing. In addition, make the transition from pureed to textured foods slowly. Pair new items and textures with familiar favorites. You can texture little by little. For example, gradually increase the amount of infant rice cereal so it has moist lumps. The benefits of infant rice cereal are that it is bland, has low risk in terms of causing an allergic reaction, is iron fortified, and is easy

to adjust the consistency, although some parents have found that it can cause constipation. Rice cereal should not be fed through a bottle. Children should receive food sufficient to meet their nutritional needs. As some children may be recovering from a period of poor weight gain experienced in the preceding period, parents may have a tendency to try to achieve “catch up” nutrition to ensure adequate weight gain. No child should be encouraged to eat past their own natural appetite, should one exist, however, or consume more calories than is healthy. The amount of food offered should be established in consultation with the child’s pediatrician, and the types of foods offered should be nutritious and contain healthy fats necessary for healthy growth and development. Answers to frequently asked questions about nutrition and feeding infants and toddlers with Prader-Willi syndrome can be found in the PWSA (USA) publication, Nutrition Care for Children with PWS, Infants and Toddlers by Janice Hovasi Cox, M.S., RD. and Denise Doorlag, OTR.

Children with PWS will benefit from the foundations of good parenting approaches appropriate for children in general with some additional strategies that are specific to Prader-Willi syndrome. Establishing structure and routine in daily life is important for all children and particularly important for the child with Prader-Willi syndrome. Structure and routines eliminate the unknown, reduce anxiety, and help children feel safe and secure. Continue to build upon the routines established in infancy. Children with PWS thrive in an environment that is rich with structure, routine, and predictability, so continue the feeding schedules with mealtime and snack schedules, nap, playtime, and bedtime schedules.

Two to Three Years

During this period, exciting gains continue in the areas of socialization, communication, and ambulation. Many children with PWS will begin walking and talking in this period. Play becomes complex, with toddlers beginning to play pretend and to imitate their parents and siblings. Children in this age range will begin to enjoy looking at books and television or videos (welcome to the age of Barney!).

Although typically less so when treated with growth hormone, toddlers will generally be late to attain developmental milestones such as sitting up, crawling and walking. Therapies begun in infancy should continue throughout this phase of life. Occupational therapy should continue to address fine motor control and sensory integration issues. Physical therapy should continue to focus upon increasing muscle strength and improve coordination and motor planning skills. During these first few years of life, the infant’s

mind will likely be “ahead” of his body and he may be ready to learn more about his environment than his body will “allow.” Parents can assist by helping the child explore, maneuver, and have fun with his environment. For example, using your hand over his hand, help your child pick up the blocks, stack them, and knock them down. Speech and language therapy should continue to help improve articulation, word acquisition and language skills. Social Skills Therapy should begin during this phase of life to help the child participate in more cooperative play.

During this period mild behavioral differences may begin to emerge. While children with PWS at this age seem to generally have a reasonable eating pattern, there are often subtle appetite differences. Some children may show increased interest in food and/or may have mildly elevated appetites. Some children with PWS instead of exhibiting the typical fussy toddler eating behavior instead may be described as “serious eaters.” Although most toddlers will not search for food when none is in view and will not tantrum if they do not receive what they believe to be sufficient amounts of food, most will finish most or all food on their plates and eat most if not all foods offered to them. The appetite of toddlers with PWS may vary from one day to the next and they may have clear likes and dislikes. The more indiscriminate eating pattern of toddlers with PWS probably reflects the beginning of the hyperphagia – insatiable appetite – stage. The excessive appetite typically begins sometime around the age of 2 years. However, it is not infrequent that parents will report their toddler’s appetite became extremely high overnight and they were sure the “PWS Appetite” had begun, only to find that in the next day or two their child’s appetite was back to its status quo. These temporary spikes in appetite may simply reflect a growth spurt. Care should be taken to ensure that calories provided to the child are adequate, not too few and not in excess of what is needed for healthy growth. It is recommended that the parents begin to increase their focus to teach their child healthy food choices and amounts and develop healthy eating habits.

It is during this period that families should begin implementing the Principles of Food Security developed by PWS specialists Janice Forster, M.D. and Linda Gourash, M.D. Families and care providers of someone with Prader-Willi syndrome can significantly improve everyone’s daily life by adhering to PWS Specialists Linda Gourash, M.D. and Janice Forster’s, M.D. Principles of Food Security: No Doubt; No Hope; No Disappointment. No Doubt about when meals and snacks will be served, plus No Hope that extra food can be obtained equals No Disappointment that extra food was not obtained, and it is disappointment that generally fuels a behavior problem.

The tantrums and behaviors typically associated with the “terrible twos” are also seen in children with PWS during ages two to three years. Other children with PWS do not experience behavioral difficulties beyond the norm during this period. For children with PWS who do exhibit increased behavioral difficulties, these may be caused by frustration related to their difficulty to verbally communicate. As the child’s verbal skills improve, especially with the aid of speech therapy, this type of behavioral difficulty lessens.

One of the parts of the brain that is impacted by Prader-Willi syndrome regulates the control of emotions. Most children with PWS have a very low tolerance for frustration and can quickly experience a loss of emotional control. In addition, most children with PWS experience higher-than-normal levels of anxiety which leaves them feeling vulnerable to changes in plans and unable to calmly respond to unexpected situations. Parenting techniques that incorporate and emphasize positive reinforcers, consistent routines and structure are beneficial for all children, and absolutely critical for the child with PWS. Children with PWS respond very poorly to criticism and punishment, but respond extraordinarily well to positive praise. Structure and routines create an overall sense of predictability and safety. It is important to establish consistent routines and schedules, including consistent bedtime, naptimes, and wake up times; consistent snack and meal times; consistent therapy and play times; etc. Consistency in terms of parental behavior is equally important. The adage, “Say what you mean and mean what you say” provides a helpful guideline. For example, if you tell your child, “You will need to stop in five minutes and clean up your toys” then you must help the child stop and clean up in five minutes. Or, if you tell your child he or she may only eat one more item, then don’t allow your child to eat beyond that one item, especially if the child proceeds to tantrum. Give positive attention for successful behaviors, and ignore or gently limit negative or detrimental behaviors. Brief (not more than a minute) “time out” periods in a safe area such as a playpen for difficult tantrums will be helpful for the child as well as for the parent. Further, increasing ways for the child to express him/herself will diminish behavioral challenges. Introducing simple signs such as “more”, “all done”, and “no” will help children who do not yet have words for these concepts.

Providing calm and consistent structure and limits now will help reduce tantrum behavior in the future. Remember, though, that all young children tantrum on occasion - it is a child’s “job” to push limits, and it is a parent’s job to teach the child what those limits are.

Many children with PWS exhibit excessive-repetitive behaviors which can cause concern for their parents. Common behaviors include pulling at or playing with strings, repeatedly putting things in containers and then taking them out, collecting and needing to carry a large number of toys such as dolls or stuffed animals, and lining up items or toys. Unless these behaviors begin to interfere with the daily life of the child with PWS, they probably don’t need to receive intervention, other than to limit the amount of time the child spends doing them. Gently gain your child’s attention, and encourage a transition to some other activity.

Socially, children with PWS, like other children at this age, are particularly charming and delightful to be around. All children up to the age of about three years engage in parallel play, meaning they “play” by themselves while sitting next to a playmate who is also playing by himself. At this age, young children with PWS will interact and play

appropriately with other children and adults, and play with typically developing children will generally be quite successful. After the age of about three years, typically developing children begin to shift into cooperative play, which incorporates more complex and sustained interactions with other children. For various reasons, including problems with speech problems and/or auditory processing delays, some children with PWS may need assistance to transition from parallel to cooperative play. Play dates and opportunities for more one-on-one social opportunities, including therapeutic play groups, may be beneficial to the social development of the three year old. For children with significant motor delays, play in smaller groups will be beneficial to avoid getting "trampled" by large groups of more mobile children.

Social interaction and symbolic play can be expanded through highly animated fun play sessions with you. Some toddlers with PWS are apt to play alone unless you get them to play with you. Pick toys or activities your child already likes (e.g., bubble play, Sesame Street or Barney figures, etc.) and make the play very interactive. Add pretend elements from the child's everyday life (e.g., going in the car, being at the park, etc.) to act out in play. Get the child as involved as he can be as you play. The goal here is first and foremost to have fun, and along the way, for your child to learn about turn taking, pretending, and about emotions and sharing of agendas, all of which will be helpful later in conversational skills, behavioral regulation, and friendships. The book, The Child with Special Needs, (Addison Wesley, 1998) by Stanley Greenspan, M.D. has many helpful tips about this type of play he calls "floor time."

Some children, especially those not treated with growth hormone, continue to appear more sleepy or lethargic during this period. This may be due to a combination of lower levels of arousal and also low muscle tone which causes the child's face and posture to appear more like someone who is sleepy. Growth hormone medication, Creatine and/or L-Carnitine Fumarate supplements may help reduce excessive daytime sleepiness. Many children with PWS exhibit underlying sleep disorders which interfere with quality, restful sleep. A sleep study is recommended for all children with PWS which assesses for potential obstructive and/or central sleep apneas, brain wave activity, respirations, sleep stage architecture, and slow wave sleep. Narcolepsy is occasionally diagnosed in persons with PWS and can be managed with medication.

The rate of learning in young children with PWS varies, with some children developing generally like their age mates with the exception of speech and motor areas and others showing delays in all areas. Although verbal expression as well as gross and fine motor skills will still exhibit some delay, careful developmental evaluation can help provide a better understanding of the child's learning capabilities. The best indicators of a child's level of cognitive development is the words the child understands, and how the child plays with pretend toys such as dolls, cars, or trucks. In this period a careful evaluation of a child's learning strengths by a developmental psychologist or an educational

therapist will be helpful to determine at what level a child is thinking. The person evaluating the child with PWS must be skillful in the assessment of young children who have speech and motor delays. This professional can also supply suggestions regarding helpful activities to enhance learning.

Therapeutic Interventions

Infants and children with PWS can benefit from regular play dates and playgroup experiences in addition to special therapies and early intervention. Through these experiences toddlers learn social skills, language skills, develop early friendships and have lots of fun! Differences in motor or language skills amongst groups of toddlers are generally easily accommodated in small playgroups.

Early Intervention services are very important in this period and should include physical therapy, occupational therapy, speech therapy, social skills play groups, and a developmental educator. Additionally, an Early Intervention play group provides a beneficial learning and social environment. In addition to providing direct therapy, therapists should also serve as consultants to the parents, teaching parents how to incorporate the therapeutic interventions into playful activities to do at home between sessions. It is the impact of these many parent-child interactions and play periods that reinforces and supports the progress made in each therapeutic hour of therapy, and facilitates the child's development.

Physical therapy will continue to be important to assist with strength, endurance, coordination, postural stability, and motor planning development. Due to low muscle tone, children with PWS tend to have excessive foot pronation. Corrective dynamic ankle foot orthotics (DAFOs), or SureStep orthotics, or soft inserts, heel cups or UCBs (University of California Berkeley inserts) can assist in earlier and more stable walking. Additionally, weighted down toy grocery carts or baby carriages can be used for stability during walking. Additional information about physical therapy issues and interventions is available from PWSA | USA.

Occupational therapy will help improve hand strength, finger strength and dexterity, motor planning, coordination, and should address sensory integration issues. For children not treated with growth hormone, and sometimes even for those who are, lightweight toys are easier for play and cognitive stimulation. Use toys that teach the "cause and effect" concepts, such as lightweight rubber squeaky toys and Busy Boxes. Provide assistance if the buttons and knobs are too difficult for the child to activate. Toys can be attached by very short ties to the highchair or play table for the child who is not yet mobile.

There are several important goals for speech therapy during this period. First, for children with significant oral motor problems, working with the child to enhance control of the muscles of the mouth and tongue, through a variety of exercises and games, will help with articulation and pronunciation. Secondly, continuing to use a “total communication” approach, teaching simple signs and gestures, using pictures, as well as building verbal vocabulary all help to allow the child to communicate what’s on his or her mind. A helpful on-line resource for therapeutic speech interventions is www.apraxia-kidsorg.

Low saliva production is a common symptom of PWS. Low saliva production looks like stringy, thick saliva that produces “crusties” around the corners of the mouth and can interfere with clear sounding speech and articulation and can cause a host of oral hygiene problems. Products that are made to reduce dry mouth symptoms, such as Biotene products made by Smith Kline Beecham, can be quite helpful. Biotene toothpaste can be purchased in the toothpaste isle of most grocery stores, or in the local pharmacy.

The Principles of Food Security should begin to be implemented during this time. Access to food should be restricted which may include locking the refrigerator and food pantries. Schedules and routines for meals and snacks should be created. More information about specific strategies may be found in the DVD The Principles of Food Security: Practical Management for the Child and Adult with Prader-Willi Syndrome available from the Prader-Willi Syndrome Association | USA.

Regarding other activities for parents to do with their toddlers, all of the regular family and parent-child activities are highly appropriate and beneficial for toddlers with PWS. While having PWS impacts children’s motor and speech development and may make behavioral challenges more difficult, in general, toddlers with PWS are more like than different from toddlers without PWS. They are sociable, playful, mischievous, communicative, impatient and loving little people just as are all toddlers are. Cuddling in bed, going to the playground or the beach, family outings, shopping, playing with siblings, grandparents, cousins and neighbors, reading books together, watching videos and television for appropriate amounts of time, doing arts and crafts together, playing with dolls and trucks, are all highly appropriate and help toddlers develop in every way.

Chapter 4

Brothers and Sisters and Family Life

Parents often wonder how having a child with Prader-Willi syndrome will impact other children in the family. Research studies have shown that siblings of children with developmental disabilities do not necessarily or automatically have greater difficulties than other children. Further, several studies have found that siblings, especially older sisters, of children with disabilities are more likely to go into the “helping professions” such as education or medicine. Siblings learn very early a different and invaluable set of values around what is important - that children are loved and lovable not for their competitive accomplishments but for who they are. Siblings also learn to celebrate even small achievements in others, and to value differences.

Parents should be aware of some of the more common negative experiences of siblings. Siblings can feel envious, jealous, angry or resentful of the amount of time parents spend attending to and assisting their sibling with PWS. Siblings can feel left out, fear the disability is contagious or inherited, feel embarrassed or lonely, feel the parents love the disabled sibling more, and may desire to be “sick” themselves to get more attention. It is important for parents to help the sibling understand that these feelings are normal and understandable. To the extent possible, spend some individual time each week playing or “hanging out” with the sibling, and create a special activity or routine devoted solely to the sibling without PWS.

While older siblings can be great helpers and even love to help take care of their new baby sister or brother, care should be taken not to overly depend upon the help of your other child(ren) or place demands upon older siblings that are not age appropriate.

Siblings should be given matter-of-fact explanations about aspects of their brother or sister with Prader-Willi syndrome that may be confusing to them. For instance, they may see neighborhood children of the same age who are walking or talking more. The young sibling (three to five years) can be told something like “He needs help to make his leg muscles/ mouth muscles stronger.” At the same time things that the sibling can do can

be discussed. It is often helpful to use the term “PWS” casually in conversation so it is a word or phrase the sibling and the child with the syndrome is comfortable with even before they have a full understanding of what it is.

Managing meals and snacks to accommodate the differing dietary needs of each individual family member can be a challenge, especially as the child with PWS grows older. Families often report, however, that having a child with PWS has “forced” them into a healthier overall lifestyle that places greater emphasis on exercise, family time, and eating healthier snacks and meals. Many families have found they can share the same type of meal, but make modifications to the meal to be served to the child with PWS. For example, everyone can enjoy a spaghetti dinner but fewer noodles, less sauce and more meat or cottage cheese (for protein) would be served to the child with PWS.

Young siblings may not understand the insatiable appetite that their brother or sister with Prader-Willi syndrome experiences. Siblings may try to “sneak” food to their sibling with PWS, thinking that they are being underfed, and may be angry at parents for denying food for the child with PWS. A matter-of-fact explanation that “Mikey has a special diet” and “Junk food could make him sick” or other such explanation may be helpful. If the child with Prader-Willi syndrome is showing clear signs of a strong appetite, it may also be helpful to explain that “Her brain makes her feel hungry but eating more wouldn’t be healthy for her body”’ and then maybe to add something like “Like how you feel with your Halloween candy, like you want to eat more candy even though it could make you feel sick.” Of course, these explanations can be helpful to the young child with Prader-Willi syndrome as well as the siblings.

Chapter 5

Parental Adaptation

The initial characteristics of infants with Prader-Willi syndrome have significant consequences for parents. The infant's difficulty achieving an aroused and alert state significantly interferes with their ability to interact socially with their parents. For mothers, traditionally the "nurturers", this difficulty connecting to their child is often compounded by the mother's inability to nourish her newborn through either the breast or bottle. Mothers and fathers therefore need to develop other strategies to foster solid emotional attachment. Parents should remain alert for signs of the child's own personality and work to understand the child's inherent rhythms. Fortunately, infants with PWS welcome holding, communicating through songs and glances, and respond to the loving intervention of their parents. In spite of the challenges, infants and young children with PWS have many delightful qualities that enable parents to become strongly bonded and feel effective and competent as their sleepy infant develops into a sturdy, playful and communicative toddler.

Learning that a baby has PWS often feels overwhelming to parents. A combination of disbelief, guilt, anger, fear, and grief are common and typical feelings, and will likely recur at various stages throughout the child's development. For most parents, however, feelings of well being will emerge as they bond with their baby and create typical, day-to-day schedules and routines.

Some parents will want to learn as much as possible about Prader-Willi syndrome as soon as the diagnosis is confirmed. For these parents, contacting other parents of young children with PWS either through Early Intervention, PWSA | USA and their local PWS organization will be helpful. Other parents may at first decide not to investigate much about PWS, or to talk much about it. Parents should remember that there is no one right way to cope or feel, and that different people use different coping strategies to manage their feelings of grief and stress in order to proceed with the job of parenting their child.

Couples who have different styles of coping may find it helpful to discuss their differences openly with each other. Taking care of the marital relationship is extremely important – as important as taking care of the child. Of particular challenge to parents with a child who has PWS is the fact that spouses may very well be at a different emotional places; while one parent may be closer to the realm of “acceptance” and ready to make an action plan, their spouse may be fully involved in denial or feeling more anger or depression. While one spouse may be ready to connect with a PWS support group or other parents, their spouse may not be ready to deal with the syndrome. It is important to remind ourselves that we must allow our own process to proceed at its own pace and we must tolerate and support our partner’s process as it proceeds at its own pace. Understanding that the grief we feel is chronic may provide us greater motivation to seek out ongoing support systems and help us develop patience and a deeper understanding of ourselves and our spouse who is also experiencing chronic grief. It is imperative, however, that parents do become knowledgeable about Prader-Willi syndrome as quickly as possible so that they can provide their child with the appropriate and helpful therapies, medications, and home and school environments that will enable their child to experience a happy and healthy childhood.

While these are broad generalizations, it can be helpful to keep in mind that generally men are able to talk about their thoughts about a given situation, whereas women will talk about their feelings. Asking one’s husband to share his thoughts on a subject may yield better results than asking him to share his feelings. Men are generally “doers” or “fixers” and are often quick to try to “fix” a situation someone may wish to simply share with him. It can be helpful to preface a conversation with a “fixer” by stating clearly at the beginning of the conversation, “I’m not looking for you to do anything about what I’m about to share with you. It will be helpful to me for you to just listen.”

Fathers who are overwhelmed by feelings of grief often look for solace or relief by working longer hours at their workplace. Mothers who are overwhelmed by feelings of grief may be more emotional (feeling a roller coaster of sadness, anger, anxiety, fear, hopelessness, etc), withdrawn, or overly focused upon the welfare of her child to the exclusion of everything else. Extreme care should be taken to attend to, understand, and comfort your spouse as you comfort and care for yourself and your family as a whole.

One unnecessary burden some parents experience is blaming or being blamed by the other parent, or being blamed by extended family members for “causing” the child to have Prader-Willi syndrome. In almost all cases, there is no known cause for Prader-Willi syndrome. Remember, nothing either parent did or didn’t do at any time in their lives, including during pregnancy, caused their child to have PWS. There are some rare instances where a specific type of Prader-Willi syndrome may be passed from parent to child, and therefore it is recommended that parents seek out the

guidance of a genetic counselor if they intend to have more children and are concerned about the possibility of having another child with PWS.

More helpful information about how to improve the marital relationship and family dynamics can be found in the article, Laughter Through Tears: Creating a Strong, Supportive and Healthy Marriage and Family available from PWSA | USA.

It may be reassuring to know that over time, parents can absolutely once again experience happiness and well being both within themselves and with their child and family. Parents may find it helpful to talk with their physician, their child's doctor, or a mental health professional for some extra support while coping with the initial adjustment. Most parents report that while the unexpected and initially devastating shift in their lives has brought them sadness and challenges they did not anticipate, having a child with PWS has also eventually brought them to experiences, people, and feelings that they deeply appreciate and would not otherwise have known.

Following is a partial list of some valuable resources and support services available to parents, extended family members and care providers. Please contact the national Prader-Willi Syndrome Association | USA at 941-312-0400 or visit www.pwsausa.org to learn more about any of these resources, or to receive the most current list of resources, books, DVDs and other materials.

Support Services

Parent Mentors and Grandparent Mentors are available through the Prader-Willi Syndrome Association | USA to provide in-person and/or telephone support to new parents and grandparents.

Online Support Groups are available for parents and care providers through the Prader-Willi Syndrome Association | USA. These “eSupport Groups” are separated by age of the child with PWS, i.e., Birth to Five Years; Six to Twelve Years, Teens, Adults. Additional eSupport Groups are also available for Military families, Siblings, dually diagnosed PWS and Autism, Spanish Speaking families, and more. Visit www.pwsausa.org and search for the eSupport Group(s) that interests you.

Additional Articles, Books and DVD Resources

The Early Years - A collection of articles regarding young children with Prader-Willi syndrome. Prader-Willi Syndrome Association | USA.

My Grandchild has Prader-Willi Syndrome: Now What? By Barbara McManus and Michele Leightman. Booklet written by grandparents for grandparents. Prader-Willi Syndrome Association | USA. Updated 2010.

The Genetics of Prader-Willi Syndrome: An Explanation for the Rest of Us. Prader-Willi Syndrome Association | USA. Updated 2004.

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Physical Therapy for the Child with Prader-Willi Syndrome, by Janice Agarwal, PT. Prader-Willi Syndrome Association | USA. Updated 2010

Nutrition Care for Children with PWS, Infants and Toddlers. Prader-Willi Syndrome Association | USA. Updated 2004

Nutritional phases in Prader-Willi syndrome. Miller, J.L., Lynn, C.H., Driscoll, D.C., Goldstone, A.P., Kimonis, V., Dykens, E., Butler, M.G., Shuster, J.J. & Driscoll, D.J. American Journal of Medical Genetics Part A. 155(5):1040-1049. May 2011

Red Yellow Green: System for Weight Management, by Karen Balko, RD. Available for purchase from Prader-Willi Syndrome Association | USA. Updated 2005.

Cookbook for the PWS Diet, by Donna Unterberger. Prader-Willi Syndrome Association | USA. Cookbook is filled with low-fat, low-sugar recipes designed to be used by the whole family. Updated 2003.

See Me, Hear Me, I'm Here, Too. Prader-Willi Syndrome Association | USA. A book about siblings, for siblings, and by siblings. Updated 2006.

Sometimes I'm Mad, Sometimes I'm Glad – A Sibling Booklet, by Sarah Heinemann as told to her mother, Janalee Heinemann. Prader-Willi Syndrome Association | USA. Updated 2005.

Prader-Willi Syndrome Medical Alerts Booklet, Prader-Willi Syndrome Association | USA. Important pocket-size resource for parents to give to their child's doctor, ER staff, caregiver, etc. Updated 2022.

Growing Up with Prader-Willi Syndrome: Personal Reflections of a Mother, by Janalee Heinemann. A collection of articles and tips for managing family life on a practical level. Prader-Willi Syndrome Association | USA. Updated 2003.

Nobody's Perfect, Nancy B. Miller, Ph. D.

The Seven Principles for Making Marriage Work, John M. Gottman, Ph.D. and Nan Silver

Laughter Through Tears: Creating a Strong, Supportive and Healthy Marriage and Family, by Janalee Heinemann, M.S. and Lisa Graziano, M.A., MFT. Prader-Willi Syndrome Association | USA.

Food, Behavior & Beyond: Practical Management for the Child and Adult with Prader-Willi Syndrome. DVD featuring Linda M. Gourash MD, developmental Pediatrician and Janice L. Forster, MD, child and adolescent Neuropsychiatrist. Prader-Willi Syndrome Association | USA. Available with Spanish subtitles. Updated 2005.

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Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome

Cheri L. Deal, Michèle Tony, Charlotte Höybye, David B. Allen, Maïthé Tauber, Jens Sandahl Christiansen, and the 2011 Growth Hormone in Prader-Willi Syndrome Clinical Care Guidelines Workshop Participants

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Context: Recombinant human GH (rhGH) therapy in Prader-Willi syndrome (PWS) has been used by the medical community and advocated by parental support groups since its approval in the United States in 2000 and in Europe in 2001. Its use in PWS represents a unique therapeutic challenge that includes treating individuals with cognitive disability, varied therapeutic goals that are not focused exclusively on increased height, and concerns about potential life-threatening adverse events.

Objective: The aim of the study was to formulate recommendations for the use of rhGH in children and adult patients with PWS.

Evidence: We performed a systematic review of the clinical evidence in the pediatric population, including randomized controlled trials, comparative observational studies, and long-term studies ($>$3.5 y). Adult studies included randomized controlled trials of rhGH treatment for $\geq$ 6 months and uncontrolled trials. Safety data were obtained from case reports, clinical trials, and pharmaceutical registries.

Methodology: Forty-three international experts and stakeholders followed clinical practice guideline development recommendations outlined by the AGREE Collaboration (www.agreetrust.org). Evidence was synthesized and graded using a comprehensive multicriteria methodology (EVIDEM) (http://bit.ly.PWGHIN).

Conclusions: Following a multidisciplinary evaluation, preferably by experts, rhGH treatment should be considered for patients with genetically confirmed PWS in conjunction with dietary, environmental, and lifestyle interventions. Cognitive impairment should not be a barrier to treatment, and informed consent/assent should include benefit/risk information. Exclusion criteria should include severe obesity, uncontrolled diabetes mellitus, untreated severe obstructive sleep apnea, active cancer, or psychosis. Clinical outcome priorities should vary depending upon age and the presence of physical, mental, and social disability, and treatment should be continued for as long as demonstrated benefits outweigh the risks. **(*J Clin Endocrinol Metab* 98: E1072–E1087, 2013)**

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Abbreviations: BMI, body mass index; ENT, ear, nose, throat; GHD, GH deficiency; HbA1c, glycated hemoglobin; PWS, Prader-Willi syndrome; RCT, randomized controlled trial; rhGH, recombinant human GH; SDS, SD score.

Prader-Willi syndrome (PWS) is a rare genetic disorder (OMIM #176270) characterized by hypotonia, poor feeding in infancy, hyperphagia with evolving obesity, hypogonadism, decreased adult height, and cognitive and behavioral disabilities (1, 2).

The birth incidence of PWS is difficult to ascertain, but data from several studies suggest that it is at least 1 in 25 000 live births. PWS is genetically heterogeneous; in approximately 65–70% of patients, PWS results from a deletion of the paternally inherited chromosomal 15q11.2–q13 region (DEL15); in 25–30%, from maternal uniparental disomy for chromosome 15 (UPD15); whereas approximately 1% of patients have imprinting defects (ID) or translocations involving chromosome 15 (2, 3).

The therapeutic rationale for the use of recombinant human GH (rhGH) is derived from our understanding of the comorbidities seen in PWS, which resemble those seen in association with GH deficiency (GHD) (eg, reduced muscle strength, altered body composition, low energy expenditure, and reduced growth, even in the presence of obesity). Although the etiology of impaired GH secretion in PWS remains controversial due to the common occurrence of obesity, the serum levels of IGF-I are reduced in most children (4–6) and adults (7) with PWS, and excess body fat is seen in even nonobese affected children (8, 9). Reduced GH responses to a variety of GH secretagogues, as well as decreased 24-hour spontaneous GH release, have been documented in 58–100% of affected children (10). Information regarding GH secretory pattern in adult patients with PWS is more limited and suggests more variability, with many potential explanations (7, 11–13).

Short-term rhGH treatment of children with PWS was first reported in 1987 (14). It has been used by many members of the international medical community and advocated by parental support groups since its approval by the Food and Drug Administration in 2000 for use in children with PWS, based on short-term growth data and subsequently for its effects on body composition. However, the use of rhGH therapy for this condition represents a unique therapeutic challenge that includes treating individuals with cognitive disability, varied therapeutic goals that are not focused exclusively on increased height (15), and concerns about potential life-threatening adverse events (16).

Prior expert consensus documents discuss the general care of patients with PWS, including some discussion of rhGH therapy in children and adults with PWS (17, 18), although many questions remained, particularly about the effects on functional outcome and on long-term body composition changes. Recent pertinent publications have since appeared (19–29), and the Growth Hormone Research Society therefore held a Consensus Workshop to systematically review the literature and grade the available evidence (30, 31) and provide concise recommendations for the use of rhGH in this context with adherence to the Principle of Respect for Persons (32) as the guiding ethical principle for rhGH use in PWS (ie, provision of care and protection of patients who do not have autonomy).

The objective of the workshop was to evaluate the effects of rhGH therapy in pediatric and adult patients with PWS and provide evidence-based guidelines for its use, summarized herein.

Workshop Methodology

Forty-three experts (pediatric and adult endocrinologists, clinical and basic geneticists, epidemiologists, a nutrition specialist, an orthopedic surgeon, a psychiatrist, health technology assessment specialists, a bioethicist, a health economist, and a patient advocate; see author list in *Acknowledgments*) participated by invitation from the scientific committee (see author list). Clinical representatives from 5 manufacturers of rhGH also submitted their PWS-specific safety data.

Prior to the workshop, an extensive literature review based on a multicriteria methodology (30, 31) was performed to identify relevant available data concerning rhGH treatment for patients with PWS. For clinical evidence in the pediatric population, randomized controlled trials (RCTs) (20–26, 33–41), comparative observational studies (42–48), and long-term studies (>3.5 y) (5, 49–58) were included. Adult studies included RCTs of rhGH treatment for ≥ 6 months (7, 29, 59, 60) and uncontrolled trials (61–64), because data were more limited. Safety data from pharmaceutical registries (phase 4 trials)[1] and sponsored clinical trials (phase 3) were reviewed. Data on disease, therapeutic context, and economic, ethical, and societal aspects were also included to reflect a broad international context. Details on approach, evidence tables, and data summaries are available in Supplemental Table 1, sections A and B (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org) and on the workshop web site (http://bit.ly/PWGHIN; Ref. 65).

The level of evidence was evaluated using the scoring procedure based on the Oxford Centre for Evidence-Based Medicine (CEBM) Level of Evidence scale (66). Strength

[1] National Cooperative Growth Study (Genentech), Genetics and Neuroendocrinology of Growth International Study (Lilly), Kabi International Growth Study (Pfizer), GH Moniter (EMD Serono), Nordinet and ANSWER (Novo Nordisk).

of evidence (Supplemental Table 1, section C) was graded independently by 2 of the authors (C.L.D. and M.T.) using the EVIDEM Quality Assessment instrument (30, 67), and a quality grade on a 4-point scale (low to excellent) was then assigned to each publication. In the rare cases of disagreement, the study was re-examined jointly.

Synthesized information by criteria was then provided to workshop participants before the workshop discussions as follows: 1) for validation of content; and 2) to provide background information to answer relevant questions concerning GH and PWS (Supplemental Table 2).

Based on 2 days of structured talks and breakout sessions, participants formulated and categorized levels of recommendations using the following system:

A. Evidence or general agreement that a given procedure of treatment is beneficial, useful, and effective.
B. Weight of evidence is in favor of usefulness or efficacy.
C. Usefulness or efficacy is less well established by evidence or opinion.
D. Evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful.

To each recommendation, a CEBM level of evidence score was assigned to reflect the origins of the data that led to the recommendation.

Overview of Evidence Quality

Multiple pediatric RCTs with rhGH have reported statistically significant effects in patients with PWS on growth, body composition, resting energy expenditure, motor development (infants and children), muscle strength, exercise tolerance, bone health, and lipid profiles (20–26, 33–41, 50). Overall, these trials have been performed in small populations, and durations were short compared to the length of rhGH treatment in the real-life setting; quality grade ranged from low (10 publications) to high (1 publication). There is only 1 placebo-controlled study (35) and 1 controlled dose-response study (34) in the pediatric population, although the adult trials include placebo-controlled groups (7, 29, 59, 60). Most patients had genetically confirmed diagnoses. Methodological issues were noted in several studies, including incomplete reporting of patient numbers, lack of discussion of randomization methods, rare inclusion of intent-to-treat analyses, limited statistical details (*P* values only), and minimal information about important confounders (eg, socioeconomic status, degree of adherence to diet, exercise plan). Only 2 studies reported individual patient responses (26, 33).

It is difficult to criticize the validity of these studies based on flawed methodologies because the effects are consistent at least in the short term (1-y data), as demonstrated by recent meta-analyses in children and adults (19, 28). There are data regarding clear benefits to rhGH treatment in infants, childhood, adolescence, transition to adulthood, and in young adulthood, but there are less long-term data available after the fourth decade.

Summary of Recommendations

The workshop participants established 15 recommendations dealing with rhGH use in PWS, as shown in Table 1.

Considerations specific to each recommendation are briefly summarized here.

Baseline Evaluation of the GH-IGF Axis Before rhGH Treatment

Previous expert opinions (17) have suggested that GH testing is not necessary in children with PWS, although some countries require it in order for treatment reimbursement. It was agreed that over 50% of infants and children with PWS are, or will become, GH deficient by standard testing protocols (4, 10, 26, 38, 50, 68–72). No consensus was reached concerning the frequency of testing in cases where GH sufficiency is initially documented. Determining the presence of GHD after attainment of adult height may be beneficial, however, because reports from dynamic testing in adults suggest that GHD is not universal, and many countries require testing before treatment of adults with GHD (28). It is not known whether GH secretory status predicts metabolic response to rhGH treatment. Furthermore, within a research context, and in order to increase our understanding of genotype-phenotype relationships, GH testing may be desirable. Because serum IGF-I is a useful biomarker for monitoring compliance with treatment as well as sensitivity to GH, all participants agreed that baseline IGF-I levels should be determined.

Additional Considerations Prior to Starting rhGH Treatment

All participants agreed that evaluation of patients before beginning treatment should ideally include a complete assessment coordinated by a multidisciplinary team with expertise in PWS, as summarized in Table 2. This stems from the importance of diagnosing and treating comorbidities that may impact on GH safety as well as on GH response.

Table 1. Summary of Clinical Care Guidelines for rhGH Therapy in PWS

I.	After genetic confirmation of the diagnosis of PWS, rhGH treatment should be considered and, if initiated, should be continued for as long as demonstrated benefits outweigh the risks. (Recommendation level A; level of evidence 1)
II.	GH stimulation testing should not be required as part of the therapeutic decision-making process in infants and children with PWS. (Recommendation level A; level of evidence 3)
III.	Adults with PWS should have an evaluation of the GH/IGF axis before rhGH treatment. (Recommendation level A; level of evidence 4)
IV.	Before initiation of rhGH therapy, patients with PWS should have a genetically confirmed diagnosis and expert multidisciplinary evaluation. (Recommendation level A; level of evidence 5)
V.	Exclusion criteria for starting rhGH in patients with PWS include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis. (Recommendation level A; level of evidence 4)
VI.	Scoliosis should not be considered a contraindication to rhGH treatment in patients with PWS. (Recommendation level A; level of evidence 2)
VII.	Infants and children with PWS should start with a daily dose of 0.5 mg/m^2 · d sc with subsequent adjustments toward 1.0 mg/m^2 · d every 3–6 mo according to clinical response [*] and guided by maintenance of physiological levels of IGF-I [**]. (Recommendation level A; level of evidence 1[*] or 5[**])
VIII.	Adults with PWS should receive a starting dose of 0.1–0.2 mg/d based on age, presence of edema, prior rhGH exposure and sensitivity, and concomitant oral estrogen use. Subsequent dosage titration should be based on clinical response, age-, and sex-appropriate IGF-I levels in the 0 to +2 SDS range. (Recommendation level A; level of evidence 2)
IX.	Selection of patients with PWS for rhGH therapy and dosing strategy should not depend on the genetic class of PWS (DEL15; UPD15; ID). (Recommendation level A; level of evidence 2)
X.	IGF-I levels in patients with PWS on rhGH treatment should be maintained within the upper part of normal range (maximum + 2 SDS) for healthy, age-matched normal individuals. (Recommendation level B; level of evidence, 3 [adults] or 5 [children])
XI.	Clinical outcome priorities should vary depending on age and on the presence of physical, mental, and social disability. (Recommendation level A; level of evidence 1)
XII.	Monitoring of rhGH treatment in patients with PWS should address specific benefits and risks of treatment in this population and the potential impact of other hormonal deficiencies. (Recommendation level A; level of evidence 3)
XIII.	Patients with PWS receiving rhGH must be followed carefully for potential adverse effects during GH treatment. (Recommendation level A; level of evidence 1)
XIV.	Treatment with rhGH must be in the context of appropriate dietary, environmental, and lifestyle interventions necessary for care of all patients with PWS. (Recommendation level A; level of evidence 4)
XV.	Cognitive impairment should not be a barrier to treatment with rhGH for patients with PWS. (Recommendation level A; level of evidence 4)

Recommendation levels: A, evidence or general agreement that a given procedure of treatment is beneficial, useful, and effective; B, weight of evidence is in favor of usefulness or efficacy; C, usefulness or efficacy is less well established by evidence or opinion; and D, evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful. Levels of evidence: 1, systematic review of randomized trials; 2, randomized trial or observational study with dramatic effect; 3, non-RCT/follow-up study; 4, case-series, case-control, or historically controlled studies; and 5, mechanism-based reasoning.

Product labeling information for all of the rhGH preparations commercially available (regardless of approved diagnosis) lists several contraindications to rhGH use, including acute critical illness, severe obesity or severe respiratory impairment, active malignancy, active proliferative or severe nonproliferative diabetic retinopathy, and hypersensitivity to the product. Workshop participants acknowledged these exclusion criteria and felt that active psychosis should also be included. Psychiatric illness is now increasingly recognized in patients with PWS (73).

Careful attention should be given to the clinical criteria used to define severe pediatric obesity because there are no clear definitions as in adults (body mass index [BMI] $>$ 40 kg/m^2). Workshop participants felt it prudent to consider obesity in the pediatric population with PWS as "severe" if a child with a BMI over the 95th percentile manifests complications of obesity such as sleep apnea, nonalcoholic fatty liver disease, or abnormalities of carbohydrate metabolism. Because treatment with rhGH decreases insulin sensitivity, uncontrolled diabetes mellitus, regardless of the presence or absence of diabetic complications such as retinopathy, demands attention before initiation of rhGH therapy in patients with PWS.

Children with PWS have a high incidence of both central apnea and obstructive apnea (74–77). Marked obesity or intercurrent respiratory tract infection (often underdiagnosed because of the absence of fever), can exacerbate obstructive apnea and may even lead to sudden death (78–82). Because rhGH therapy can theoretically lead to lymphoid tissue growth in children due to increased IGF-I effects (83), patients and parents must be fully informed about the potential association between rhGH therapy and unexpected death during the pretreatment consenting process, and polysomnography should be performed before starting therapy. rhGH therapy is contraindicated in children with breathing difficulties until ear, nose, throat (ENT) evaluation and treatment of respiratory-compromising obesity has been achieved. Therapy should not be initiated dur-

Table 2. Multidisciplinary Evaluation of Pediatric and Adult Patients with PWS Before Starting rhGH Treatment[a]

Evaluation	Testing/Interventions
Endocrine examination to document anthropomorphic status: weight, length/height, BMI (and if possible, waist circumference and skinfold thickness), pubertal status, and presence of additional endocrine deficiencies	Bone age determination in infants and children Evaluation of hypothyroidism (TSH, free T_4, free T_3) and commencement of replacement if appropriate Determination of IGF-I level and, if possible, GH response to provocative testing, particularly in adult individuals Evaluation of metabolic status if age ≥ 12 y and obesity: HbA1c, fasting insulin and glucose; consider oral glucose tolerance test if family history of diabetes, acanthosis nigricans or ethnic risk factors Evaluation of cardiovascular risk profile as per guidelines for obese individuals:[b] fasting total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol Assess for hepatic steatosis as per guidelines for obese individuals:[b] AST and ALT levels, abdominal ultrasound, and biopsy where appropriate Body composition evaluation if available (dual-energy x-ray photon absorptiometry or bioelectrical impedance) Consider need for evaluation of adrenal function on an individual basis
Genetic evaluation and counseling	DNA studies to confirm PWS
Referral to dietician	Nutritional evaluation and advice including use of food diary, control of food environment, diet composition, and caloric intake
Assessment of developmental and cognitive status	Age-appropriate psychomotor testing
Assessment of motor function if possible	Physiotherapy and occupational therapy referral
ENT referral if history of sleep-disordered breathing, snoring, or enlarged tonsils and adenoids are present	Tonsillectomy and adenoidectomy where indicated
Referral to pneumologist/sleep clinic	Sleep oximetry is mandatory before starting rhGH in all patients, preferably completed by polysomnographic evaluation
Scoliosis evaluation and referral to orthopedic surgeon if indicated	Spine x-ray
Family instruction on rhGH treatment including benefits and risks of the treatment and importance of careful monitoring	Procurement of legal guardian consent and patient assent/consent according to age and cognitive status

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] Adapted and modified from A. P. Goldstone et al: Recommendations for the diagnosis and management of Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2008;93(11):4188 (17), with permission. © The Endocrine Society.

[b] For guideline references in obesity, see Refs. 127–129.

ing an acute respiratory infection, but it need not be interrupted during subsequent episodes of respiratory infection unless indicated because of the onset of breathing difficulties.

Scoliosis in PWS is not a contraindication to rhGH treatment; its occurrence is common (up to 30–80% depending on age), but neither its incidence nor its rate of progression is influenced by rhGH therapy (21).

The potential role of the GH-IGF axis in cancer incidence and/or progression has received a great deal of recent attention (84) despite the safety record, to date, of rhGH treatment. The recent SAGhE study publications do not specifically address rhGH use in patients with PWS, and a true appreciation of dose-related risks of rhGH will require better and longer surveillance protocols because all observational studies are subject to bias (85–88).

The potential development of central adrenal failure, which may not be clinically relevant except during intercurrent illness and/or surgical intervention, was also discussed. Investigations have not uniformly documented a high incidence of central adrenal failure in PWS (89–91). No consensus was reached concerning the need for adrenal axis testing before initiation of rhGH, but families and clinicians should remain vigilant and not hesitate to use stress doses of glucocorticoids as clinically indicated.

Age at Treatment Initiation

According to observational data, rhGH treatment is usually initiated at a mean age of 7 years, as reported by Takeda et al (92). Increasingly, rhGH treatment is initiated earlier (10, 17, 71). Published data support benefits of rhGH treatment when started between 4 and 6 months of age (25, 34), but some experts are currently treating from as early as 3 months. No consensus was reached on age of rhGH start, although all agreed to the benefits of treating before the onset of obesity, which often begins by 2 years of age.

Dosing

Infants and children

Evidence for efficacy in infants and children is based on trials using a dosage of 1.0 mg/m^2 · d achieved within approximately 1 month of starting treatment (50). Given that patients with PWS exhibit variable degrees of GHD and that salutary outcomes in RCTs were associated with doses of 1.0 mg/m^2 · d (higher than the dose of rhGH routinely used in congenital GHD) or higher, it is unknown whether similar outcomes could be replicated with rhGH doses that result in consistently normal IGF-I levels. IGF-I levels and IGF-I/IGFBP-3 ratios rise to above 2 SD in some patients on this dosage, theoretically presenting some risk (26, 35, 38, 40, 51, 84, 93, 94). The efficacy of doses lower than 1.0 mg/m^2 · d administered over a long period of time is unknown; however, it has been suggested that the efficacy of lower doses of rhGH on body composition is decreased (50, 51). Infants and children with PWS should start with a daily dose of 0.5 mg/m^2 · d sc to minimize side effects, with subsequent adjustments toward 1.0 mg/m^2 · d; there was disagreement as to how rapidly this should occur (3–6 mo). If not using body surface area-based calculations (recommended), it was felt prudent to base dose calculations on a nonobese weight for height in cases where overweight for height (BMI = 85th to 95th percentile) or obesity exists, particularly when starting rhGH therapy. There was a difference of opinion regarding the timing and frequency of IGF-I measurement before increasing dosage to 1.0 mg/m^2 · d in the pediatric population with PWS. Notably, patients with PWS appear to be highly sensitive to GH in terms of IGF-I generation (95), and standard rhGH dose often results in IGF-I levels outside the normal range. Because lymphoid hyperplasia is related to the levels of IGF-I (96), this might increase the risk of sleep apnea (81).

Adults

In adults with PWS, rhGH doses tested in placebo-controlled and open-label trials have varied between 0.2 and 1.6 mg/d sc, depending on the time period under rhGH treatment, weight, and induced IGF-I levels. This dose range gives an acceptable side effect profile (29, 59, 61–64, 97), as well as beneficial effects on body composition, psychological and behavioral problems, quality of life, and heart function and results in IGF-I levels within the range of age-matched controls (59, 61, 63, 64, 97, 98). It was unanimously concluded that in adults with PWS, the optimal IGF-I level, ie, the level where the rhGH treatment will have clear beneficial effects and at the same time the lowest possible risk of adverse events, will be a value similar to 0 to +2 SD score (SDS, z-score) for age-matched controls.

Monitoring and Potential Side Effects

There was unanimous agreement that rhGH therapy should be supervised by pediatric or adult endocrinologists, ideally those experienced with the care of patients with PWS. Periodic monitoring of the safety and efficacy of the treatment is mandatory (Table 3).

In the past, rhGH therapy dose adjustments in children were routinely performed based on growth response and/or weight (or body surface area) increases. Epidemiological data suggesting a potential link between IGF-I levels and some adverse events (77, 84, 86, 99) have motivated investigators to consider maintaining IGF-I levels within the physiologically normal range (0 to + 2 SDS), an approach shown to be feasible in other conditions, such as rhGH treatment of children with idiopathic short stature or small for gestational age, where pharmacological doses are used (100, 101). Workshop participants felt that for the pediatric age range, IGF-I levels in patients with PWS on rhGH treatment could therefore safely be maintained within the upper part of normal range (+1 to +2 SDS) for healthy, age-matched normal individuals. For the adult population, where discontinuation of treatment because of side effects is more frequently noted, an IGF-I of 0 to +2 SDS was suggested.

Table 4 summarizes the side effects that should be routinely monitored. Although rhGH therapy has a favorable safety profile, the postulated association between unexpected death and rhGH treatment in children with PWS deserves special attention not only in the consenting process and pretreatment evaluation, but also during treatment (16, 83, 98, 102). During rhGH treatment, changes in breathing (particularly during sleep) should be promptly reported and evaluated by repeat oximetry and/or polysomnography within the first 3 to 6 months of starting therapy. Longer-term rhGH therapy has been associated with improvement in respiratory function in chil-

Table 3. Multidisciplinary Evaluation of Pediatric Patients[a] with PWS During rhGH Treatment[b]

Regular clinical assessment of height, weight, BMI, pubertal status, scoliosis, IGF-I, and side effects every 3–6 mo
Clinical assessment of body composition every 6–12 mo by 1 or more of the following: waist circumference, skinfold thickness, dual-energy x-ray absorptiometry (or other available technique for determining body fat and lean body mass)
Yearly bone age determination, particularly during pubertal age range
IGF-I determination every 6–12 mo
ENT assessment and sleeping oximetry, or ideally, repeat polysomnography within the first 3–6 mo
If development or worsening of sleep-disordered breathing, snoring, or enlargement of tonsils and adenoids, ENT assessment, polysomnography, and IGF-I measurement are mandatory.
Fasting glucose, insulin, and HbA1c; if obese and/or older than 12 y and/or acanthosis nigricans and/or family history of diabetes/ethnic risk factors, oral glucose tolerance test
X-ray ± orthopedic assessment if concern or doubt about scoliosis progression
Monitoring for hypothyroidism yearly or if symptoms occur
Lipid profiles and liver function tests and/or liver ultrasound according to family history, age, and weight status as per clinical guidelines for non-PWS patients, with referral to gastroenterologist if nonalcoholic fatty liver disease is suspected
In cases of acute illness and suggestive symptomatology, obtain critical blood samples for measurement of cortisol and ACTH levels, if possible, and assess adrenal glucocorticoid response to provocative testing where indicated
Continued contact with nutritionist, physiotherapist/occupational therapist, speech therapist, and psychologist (determine frequency on a case-by-case basis)
If marked deterioration in behavior with or without overt psychiatric symptoms, psychiatry assessment

[a] Applicable to adult patients with PWS, with the exception of the radiological evaluations (bone age monitoring, scoliosis monitoring).

[b] Adapted and modified from A. P. Goldstone et al: Recommendations for the diagnosis and management of Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2008;93(11):4188 (17), with permission. © The Endocrine Society.

dren and adults, primarily due to improvements in respiratory muscle function as indicated by increases in peak expiratory flow (35, 50, 97). Data concerning rhGH effects on central respiratory drive are few and are difficult to interpret because of multiple confounders (74, 103). No data are available concerning rhGH treatment and sleep apnea in adults with PWS.

There was a consensus to include an evaluation of diabetes risk (determination of glycated hemoglobin [HbA1c], fasting glucose, and insulin) in patients with PWS who are obese and/or who are older than 12 years or who have a positive family history of diabetes. Further studies are needed to refine these recommendations because insulin sensitivity and risk of metabolic syndrome in patients with PWS may vary depending upon degree of obesity, adipose tissue distribution, genetic background risk, and use of antipsychotics (104–108).

Tolerability

Tolerability of rhGH by pediatric and adult patients with PWS is high, according to the workshop participants involved in RCTs (7, 24, 25, 29, 35, 36, 38, 41, 59–64, 97). However, relatively few adults with PWS have been studied, and insufficient data are available to judge whether adverse effects of rhGH, death due to other causes, or personal choice accounted for treatment cessation. For

Table 4. rhGH Potential Side Effects to Monitor[a]

Changes in physical features and body proportions (face, hands, feet) or bone growth
Peripheral edema
Joint pain
Sleep apnea/disordered breathing: snoring, respiratory pauses, excessive daytime sleepiness
Pseudotumor cerebri/benign intracranial hypertension: headache, visual changes, nausea, dizziness
Slipped capital femoral epiphysis: hip and/or knee pain, gait disturbance
Insulin resistance: elevated fasting insulin
Decreased T_4 level (requires measurement of T_3 to differentiate from true central hypothyroidism)
Scoliosis (recent data suggest no causal relationship or exacerbation of progression)
Long-term surveillance on, or after, cessation of rhGH
Glucose intolerance/type 2 diabetes mellitus particularly in obese patients or patients with positive family history
Epilepsy (no known relationship, but should be reported)
De novo neoplasia (no known relationship, but should be reported)
Stroke, intracranial bleeding

[a] Shown are the reported side effects of GH treatment primarily in the pediatric population with or without PWS. No published data are available concerning GH treatment in adults with PWS on joint pain, sleep apnea, epilepsy, intracranial hypertension, neoplasia, and stroke/intracranial bleeding. Furthermore, none of the studies in PWS adults (longest follow-up, 5 y) have reported breast tenderness/enlargement, unexpected death.

children with PWS treated with rhGH and followed in phase 4 postmarketing surveys, the reported rate of side effects leading to treatment cessation in trials overall is low (109). The enthusiasm of parents of PWS children for rhGH therapy suggests that early cessation is lower than in other rhGH-treated patients with conditions like idiopathic short stature, Turner syndrome, and children who are born small for gestational age.

Clinical Outcome Variables and rhGH Nonresponsiveness

In untreated children with PWS, auxological and body composition parameters tend to deteriorate over time, so if these continue to improve or to stabilize, treatment is usually continued until adult height or near-adult height is reached. However, if adult height attainment is used for the decision to stop rhGH therapy in adolescents with PWS, it is important to note that these patients often experience premature adrenarche and obesity, causing early closure of growth plates (110, 111).

For adults with PWS and GHD, treatment duration depends on primary clinical outcome (body composition, lipid metabolism, physical and psychosocial functioning) and occurrence of side effects (impairments of glucose metabolism, edema, heart disease) (62).

Controlled studies of continuous treatment through childhood, adolescence, and the transitional period into adulthood are not available in PWS, yet there is a strong likelihood of continued benefit by inference from non-PWS organic GHD and observational studies in PWS.

It was agreed that psychomotor development should be the priority during infancy, with body composition and growth becoming important during childhood and adolescence. The data on cognitive benefits of rhGH treatment in the pediatric setting are limited, but should positive effects be extended, this would likely become a top treatment priority (25, 26, 35, 112). The workshop participants concluded that metabolic outcome variables should become the important priority in adults with PWS, although muscular hypotonia, mental retardation, and psychosocial dysfunction should continue to receive attention throughout the life span. The ultimate goal is an improvement in the patient's well-being.

The definition of nonresponsiveness to rhGH is arbitrary because there is a continuum in GH response. Many other anthropomorphic and biochemical parameters plateau after some years of treatment but deteriorate subsequently if rhGH is stopped. Response criteria to rhGH will vary according to age, pubertal status, degree of growth retardation, and duration of therapy. Workshop participants felt that a successful first-year pediatric response to rhGH treatment includes a Δ height SDS > 0.3, a first-year height velocity increment of ≥ 3 cm/y, or a height velocity SDS $\geq +1$. Workshop participants acknowledged the difficulty of having alternative, easily measurable, robust, validated, affordable clinical endpoints other than the initial growth response. When possible, attempts should be made to document favorable changes in psychomotor progress and development, body composition, strength and exercise tolerance, and quality of life for both patients and caregivers, and findings should be reviewed with all involved in the decision to continue treatment. Parameters that define the sustained success of therapy include adult height SDS, adult height SDS minus height SDS at start of rhGH, adult height minus predicted height at start of treatment, and adult height minus target height (based on sex-corrected mean parental height). Emerging data on genotype-phenotype correlations relevant to specific outcome measures targeted with rhGH therapy need to be repeated in additional cohorts before firm conclusions can be drawn (12, 102, 106).

Use of Adjunct Therapies

Nutritional management remains the mainstay of treatment of patients with PWS, even during rhGH therapy. Regular contact with a dietitian knowledgeable about PWS is essential, initially to calculate desirable caloric increases during the failure-to-thrive period often observed in infants with PWS. Once the failure-to-thrive period is over, caloric requirements vary according to the nutritional phase of the patient and are typically approximately 80% those of children and adults without PWS (113). This entails surveillance of vitamin and trace element intake to ensure that recommended daily allowances are achieved. When hyperphagia begins, or if weight percentiles are increasing (usually ages 2–4 y), close supervision must be maintained to minimize food stealing. Locking the kitchen, refrigerator, and/or cupboards is often necessary. As members of the treating team, dieticians must regularly reinforce adherence to diet, environmental control, and programmed physical activity (114–116).

In some children, particularly those who have inadequate dietary, environmental, and/or lifestyle interventions, unacceptable weight gain may occur during therapy. All attempts should be made to sensitize the family as to the increased risks for obesity-related health concerns and to explain that rhGH therapy should not be viewed as a weight loss solution.

Recent studies in adolescent and adult patients with PWS (90% untreated with rhGH) using cyclic, intensive

exercise and nutritional restriction successfully led to BMI reductions during the period of participation in the study (up to 6 y) (117). Long-term, rigorous exercise and strict nutritional control have not been tested against rhGH therapy at any age.

Multiple pharmacological approaches in PWS aimed at increasing energy expenditure and weight loss have not been successful in limited short-term trials and are summarized in Table 5. The workshop participants agreed that surgical strategies to achieve weight loss have not been

Table 5. Adjunct Therapies Attempted in PWS

Pharmacological Strategies	Mechanism of Action	Limitations/Adverse Events	Refs.
Sibutramine	Noradrenergic reuptake inhibitor Induces satiety without reducing metabolic rate	Modest weight loss efficacy Poor long-term compliance Hypertension	Padwal et al, 2007 (130)
Orlistat	Inhibits pancreatic lipase	Modest weight loss efficacy Poor long-term compliance Gastrointestinal side effects	Butler et al, 2006 (114)
Bupropion and naltrexone	Bupropion: activates central melanocortin pathways in the arcuate nucleus (α-MSH and β-endorphin secretion); decreases hunger and increases energy expenditure	Ineffective individually, some suggestion that combination therapy may be more effective at weight loss, no published clinical trials in PWS	Greenway et al, 2009 (131)
	Naltrexone: opioid inhibitor; blocks β-endorphin inhibition of α-MSH release (normal feedback disrupted); decreases hunger and increases energy expenditure	Multiple side effects: nausea, dry mouth, headache, dizziness, fatigue, constipation, insomnia, possibility of alteration of mood and depression	Lee and Fujioka, 2009 (132)
		Contraindicated in acute hepatitis or liver failure	Padwal, 2009 (133) Plodkowski et al, 2009 (134) Zipf and Berntson, 1987 (135)
Antiepileptics (topiramate)	Antiseizure drug also used in migraine treatment	No published clinical trials in PWS	Shapira et al, 2002 (136)
	Modulatory effects on Na+ channels, GABAA, and AMPA/kainate receptors Affects food-seeking behavior	Multiple side effects: fatigue, difficulty concentrating, paresthesia, somnolence, ataxia, dizziness, nephrolithiasis, word-finding difficulty, mild confusion, sedation	Smathers et al, 2003 (137)
Somatostatin analogs	Inhibits ghrelin secretion Limits the release of insulin Decreases hyperphagia	No benefits on weight or appetite in PWS Decreased insulin secretion Impaired glucose tolerance Risk of cholesterol gallstones	De Waele et al, 2008 (138) Haqq et al, 2003 (139) Haqq et al, 2003 (140) Tan et al, 2004 (141) Tzotzas et al, 2008 (142)
Rimonobant	Blocks endocannabinoid receptor CB1 in central and peripheral nervous systems and other key cells involved in body energy metabolism	Efficacious weight loss Lack of compliance in adults with PWS due to high risk of psychiatric side effects (mood disorders, suicide)	Motaghedi et al, 2010 (143)
Anorexigens gut hormones (eg, exenatide)	Incretin mimetic: GLP-1 receptor agonist Increases insulin secretion	Lack of efficacy in subjects with PWS	Purtell et al, 2011 (144) Sze et al, 2011 (145)
CoQ10	Involved in the production of ATP in the mitochondria	No observed weight loss effects in PWS Possible benefits on psychomotor development, but masked by the natural development	Eiholzer et al, 2008 (45)

(*Continued*)

Table 5. Continued

Pharmacological Strategies	Mechanism of Action	Limitations/Adverse Events	Refs.
Restrictive bariatric surgery (gastric banding or bypass)	Several surgical procedures Induces weight loss by altering the digestive tract so that nutrients and fats are not absorbed by the body (stomach reduction and/or bypass)	Contradictory efficacy results Limited weight reduction long term	Buchwald, 2005 (120) Antal and Levin, 1996 (119)
		Numerous postoperative issues	Marinari et al, 2001 (122)
		Weight regain 1 to 5 y after surgery	Papavramidis et al, 2006 (123)
		Frequent complications from the resulting intestinal malabsorption (ie, nutritional deficiencies)	Marceau et al, 2010 (121)
		Postoperative respiratory and infectious complications Gastric perforation Death	Scheimann et al, 2008 (118)

Abbreviations: AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; GABAA, γ-aminobutyric acid$_A$; GLP-1, glucagon-like peptide-1.

successful long term (initial weight loss followed by weight regain) and have been associated with frequent complications (intestinal malabsorption, infectious complications, gastric perforation, and death), and should therefore be discouraged (118–123).

Additional studies are required to ascertain the safety, efficacy, and tolerability of alternative pharmacological approaches to weight loss in PWS either alone or in combination with rhGH. Thus, there is insufficient evidence to support the use of currently available obesity management medications or bariatric surgery in conjunction with rhGH treatment for weight reduction in patients with PWS, and indeed, some may be contraindicated.

Issues of Consent/Assent

There are differences in national legal regulations dictating when a child reaches the age of consent (eg, 18 y in many countries). Informed assent of a child is required in circumstances where he or she is beginning to make more complex decisions; this requires that the child is capable of some degree of understanding and appreciation of the clinical reasoning.

Even in cases of cognitive disability in an older child or adolescent with PWS, it is optimal that legal guardians remain surrogate decision-makers, but that physicians strive to obtain the patient's assent for rhGH therapy, even if the patient has limited decision-making capacity. An adult patient with intellectual disability due to PWS may be capable of consenting to rhGH treatment if he/she is able to understand and appreciate his or her clinical circumstances. In circumstances in which an adult patient does not have the capacity to consent, a surrogate decision-maker is appropriate, guided by country- and state-specific guardianship laws (124). This assent/consent process fosters a doctor–patient relationship based on partnership, mutual trust, understanding, and respect (32, 125, 126).

It is not known to what degree the cognitive impairment of the individual with PWS plays a role in physicians' lack of recommendation for rhGH use, whether because of perceived difficulty in obtaining truly informed consent or because of physicians' views on healthcare priorities. All participants felt that cognitive impairment should not be a barrier or a contraindication to discussion of rhGH treatment with the patient and caregivers.

Issues of Fair Access to rhGH

According to several PWS support associations, access to the option of rhGH therapy is currently unevenly provided, even in countries with drug approval for this indication. Members of the workshop felt that several factors currently contribute to differences in the availability of the option for rhGH therapy for patients with PWS: 1) a lack of parental awareness of treatment options and general impediments to healthcare; 2) inadequate numbers of physicians willing and qualified to prescribe rhGH and to regularly assess treatment response and potential adverse events; and 3) inability to pay for rhGH either through personal wealth or by participation in a healthcare system that supports rhGH treatment and monitoring costs for PWS.

In considering efficiency and best distribution of healthcare resources among desirable interventions for patients with PWS, a long list of important interventions must be considered, such as occupational and physical therapy, speech and language therapy, social skills ther-

Table 6. Areas Regarding rhGH Use for PWS Requiring Prioritized Attention in Future Studies[a]

Top 10 areas for further research	
i.	Effects of rhGH therapy in adults with PWS on quality of life
ii.	Long-term post-treatment effect of rhGH on mortality and morbidity using registries
iii.	The optimal timing and dosage of rhGH treatment initiation in early life
iv.	The effect of rhGH interruption at completion of growth
v.	Effects of rhGH on behavior and cognitive function across the age range
vi.	Impact of rhGH treatment on activities of daily living and well-being as defined by WHO
vii.	Influence of IGF-I titration on clinical effects
viii.	Effect of rhGH on glucose metabolism/diabetes risk, mainly long-term effect
ix.	Effects of rhGH therapy on sleep and sleep-disordered breathing in PWS adults
x.	RCTs investigating combination approaches to treatment
Additional areas for future research	
xi.	Effects of GH/IGF-I on nasopharyngeal tissue and mainly whether adenotonsillectomy changes the course or may avoid potential side effects of rhGH on sleep disorders and obstructive sleep apnea
xii.	Dose-response relationships investigating efficacy of physiological (rather than pharmacological) dosing
xiii.	Effects of rhGH treatment in children and adults on visceral adiposity and ectopic fat, eg, muscle, liver, and pancreas
xiv.	Effects of rhGH on timing of development or severity of hyperphagia
xv.	Effects of rhGH on bone maturation and premature pubarche
xvi.	Effects on structural brain development
xvii.	Scoliosis and slipped capital femoral epiphysis in children
xviii.	Is there hypersensitivity to rhGH in PWS?
xix.	Thyroid function before and after rhGH
xx.	Effects on cardiac function
xxi.	Effects of rhGH on lipid metabolism
xxii.	Effects of rhGH on water retention
xxiii.	Intracranial hypertension (difficult to assess in young children)

[a] All participants were asked to discuss areas for future investigation within breakout groups. All participants were then asked to order the areas, by priority, using a secret ballot.

apy, weight management therapy and behavioral therapy, ophthalmological and orthopedic interventions, and neurological, psychiatric, and endocrine care (replacement therapies for sex hormones, GH, L-thyroxine, cortisol). Although rhGH therapy is costly (92), compared with the cost of the provision of all of these services, the cost of rhGH may be relatively modest. However, a true understanding of the healthcare burden of treating individuals with PWS requires long-term health outcome research studies.

Future Directions

At the end of the meeting, workshop participants were asked to individually rank, in order of importance, areas needing further research that had been discussed during breakout sessions. It is not surprising that continued surveillance of long-term effects of rhGH treatment was considered the top priority, particularly with regard to glucose metabolism and diabetes risk, as well as sleep and sleep-disordered breathing. The impact of rhGH treatment on quality of life, not only of patients but also of their families, was also ranked as an important aspect of treatment response that needs additional documentation. Most of the attendees who were not physicians saw an important place for future clinical trials combining rhGH with other therapeutic approaches, particularly those targeting hyperphagia and behavior. The top 10 areas that received the highest priority scores can be seen in Table 6.

Conclusion

It is hoped that this PWS Workshop Summary will give patients, caregivers, and physicians a framework with which to optimize care. More importantly, it is hoped that it will help harmonize the healthcare access of the pediatric and adult populations with PWS, not just with regard to rhGH treatment but also with regard to the need for lifelong follow-up of these patients by multidisciplinary teams with experience in PWS. Finally, we stress the importance of the ethical framework in which healthcare specialists working with patients with PWS should practice and which should emphasize principles of informed consent/assent, respect for persons, and distributive justice.

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Growth Hormone and Prader-Willi Syndrome:
Second Edition

A Reference for Families and Care Providers

Donald G. Goranson, Jr., Editor

Prader-Willi
SYNDROME ASSOCIATION | USA
SAVING AND TRANSFORMING LIVES

VIII

GROWTH HORMONE AND PRADER-WILLI SYNDROME: SECOND EDITION

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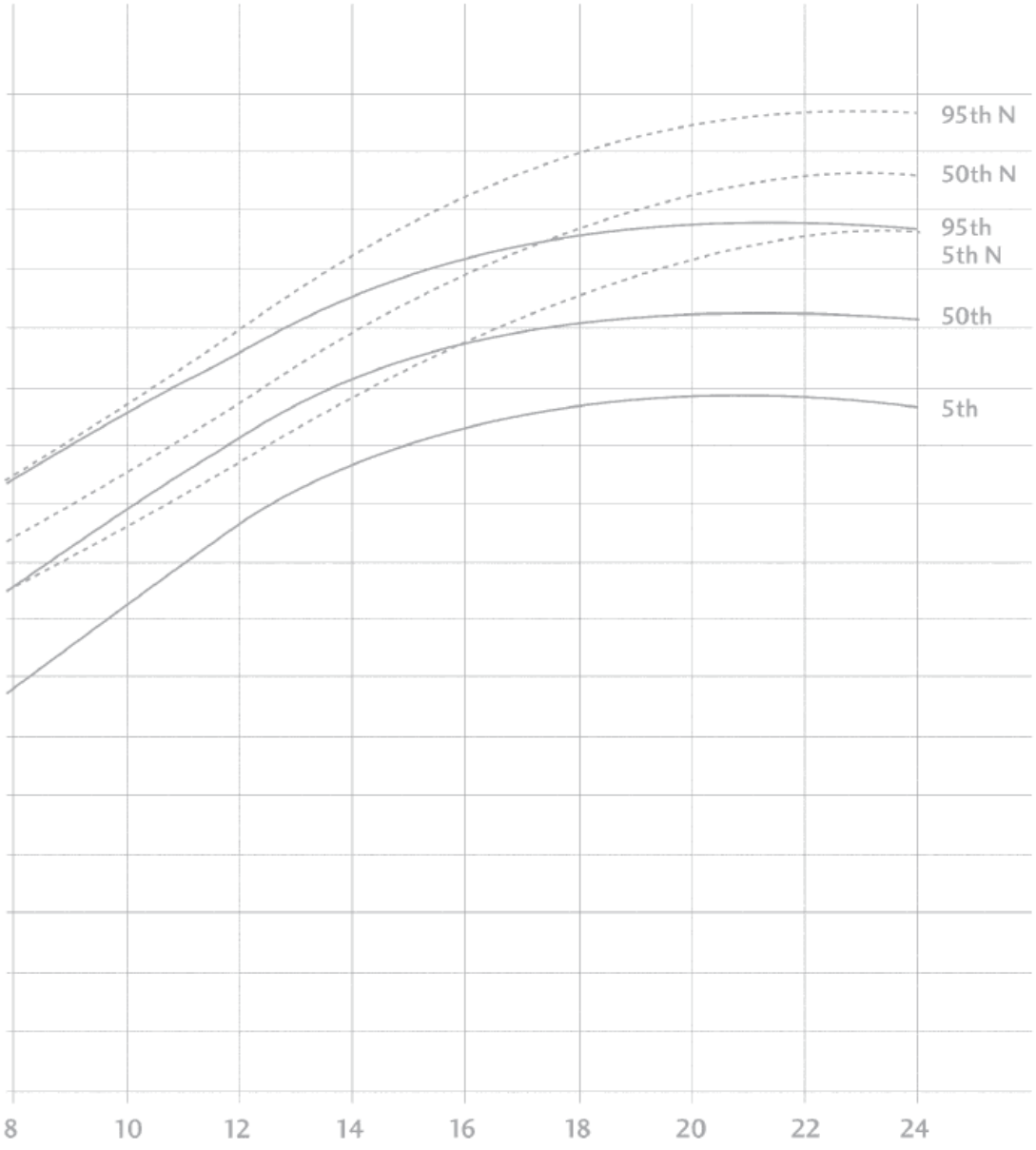
All the children featured in this publication have Prader-Willi Syndrome.



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APPENDIX

About This Publication

EDITOR — The second edition of this publication was edited by Don Goranson, a recent retiree, who worked in the communications industry for 42 years. Goranson began his career in radio as a broadcast journalist; moved into newspapering and held the positions of reporter, assistant city editor and managing editor with a company that published both daily and weekly newspapers; and then rounded out his career in the Office of Communications of the Connecticut State Department of Education as Publications Unit Coordinator. Goranson served for seven years as vice president of PWSA | USA, for six years as a member of the Board of Directors of PWSA | USA and is a former president of PWSA | USA's Connecticut Chapter. He served as both consulting editor and production coordinator of the first edition of Growth Hormone and Prader-Willi Syndrome — A Reference for Families and Care Providers, published in 2001. Married to Margaret Goranson, Don and Peg make their home in Bristol, Connecticut, and are the parents of David, a 42-yearold with Prader-Willi syndrome. Our goal is to provide parents and care providers with important information so that you have a better understanding of how Prader-Willi syndrome may impact your child, what interventions are available to help you maximize his or her overall development and natural talents, and how you may better prepare for your child's and your family's future, all while feeling more confident, optimistic, connected, and supported.

DESIGNER — Design and layout of this publication are the work of Andrea Wadowski of Burlington, Connecticut. Ms. Wadowski's graphic design was also featured in the 2001 edition of this publication.

SPECIAL THANKS — We wish to extend a heartfelt word of thanks to Linda Keder of Silver Spring, Maryland, a freelance editor, and past editor of the PWSA | USA national newsletter The Gathered View, who researched and wrote the first edition of this book in 2001. It is through Ms. Keder's efforts that the standards were established for this second edition.

FUNDING — Financial support for this project was provided through unrestricted educational grants from the RGK Foundation of Austin, Texas, and Eastside High School of Taylors, South Carolina. The grant from East Side High School comes from a student-sponsored Spirit Week fund-raising project that designated PWSA-USA as beneficiary.

PHOTOS — We wish to thank the unnamed families who generously shared photographs of their children and adults, and their experiences with growth hormone treatment.

DEDICATION — This publication is dedicated to the committed people whose efforts have brought us to this point of knowledge about growth hormone treatment — the research scientists who conducted growth hormone studies, the children, and adults with PWS and their families who willingly participated, and all who advocated for acceptance of this new treatment to improve the lives of people with Prader-Willi syndrome.

EDITOR'S NOTE — While the information in this booklet is believed to be accurate at the time of publication, it is not intended to be a substitute for medical advice, which should be obtained from qualified professionals.

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Merlin G. Butler, M.D., Ph.D, Professor of Psychiatry, Behavioral Sciences and Pediatrics and a certified geneticist at Kansas University Medical Center, Kansas City, KS; and Chairperson of the Scientific Advisory Board of PWSA | USA.

Kathryn Clark, RN, CS, MSN, Pediatric Nurse Practitioner, Department of Pediatric Endocrinology, at the University of Michigan, Ann Arbor, MI.

Debra Hanley, of Kingston, NY, parent of a daughter with Prader-Willi syndrome.

Janalee Heinemann, MSW, Director of Research and Medical Affairs of PWSA | USA and Vice President of the International Prader-Willi Syndrome Organization (IPWSO).

Jennifer Miller, M.D., M.S., endocrinologist and Assistant Professor, Division of Pediatric Endocrinology, University of Florida, Gainesville, FL; and a member of the Clinical Advisory Board of PWSA | USA.

Harold J. P. van Bosse, M.D., surgeon, Department of Pediatric Orthopedic Surgery at Shriner's Hospital for Children, Philadelphia, PA.

Barbara Y. Whitman, Ph.D, Professor of Pediatrics at Saint Louis University School of Medicine, St. Louis, MO; and a member of both the Scientific Advisory Board and Clinical Advisory Board of PWSA | USA.

1. Introduction and History

"Sean was unable to run for more than a few steps without experiencing pain, shortness of breath or without his little heart beating rapidly, nor could he hop, skip, jump, kick or climb anything with any agility… Most of this has changed rapidly after starting GH… Sean is now able to play on a Challenger Little League Baseball team, and he can run all the bases without a complaint. That is about the best part of all — Sean can play normally with other children… The additional strength helps in areas of self-care as well… I can't begin to tell you how good it feels when your child accomplishes even one small thing other people take for granted."

— Mother of a 5-year-old

Doctors, researchers and parents continue to report many dramatic changes and positive outcomes from the use of human growth hormone (GH) in individuals of all ages with Prader-Willi syndrome (PWS). In the 10 years since the initial distribution of the First Edition of this publication in 2001, the use of GH has become standard care for those with PWS when prescribed by an experienced endocrinologist. In children, human GH can help with height, weight, body mass, strength and agility, and also may help with cognitive development. In addition, reports on the use of a low dose of human GH in the adult PWS population have shown positive results in the areas of bone strengthening and the promotion of leaner muscle mass and greater energy.

Prior to 1990, there were no scientific studies to show the use of human GH to be a good idea for children born with Prader-Willi syndrome. While some children with PWS did get treatment, others were denied treatment because it could not be proven that they had a growth hormone deficiency. Even if a doctor prescribed GH, the family's health insurance plan might refuse to cover the cost because it was considered an "experimental" treatment in children with PWS. For those families the cost of the medication — and the promise of a better life for their child — was simply out of reach.

Pioneering some of the earliest reported work in this area were Dr. Moris Angulo, of Winthrop University Hospital in Mineola, New York, who currently serves on the Clinical Advisory Board of PWSA | USA, and Dr. Phillip Lee of Baylor University in Texas, a past member of the Scientific Advisory Board of PWSA | USA. Dr. Lee, who reported on the use of GH with a handful of patients in 1987 at a PWS meeting in Houston, is also credited with organizing the first PWS GH symposium, held at the 1999 PWSA | USA conference in San Diego. Dr. Angulo, meanwhile, made a major presentation in Jerusalem, Israel in October 1989 documenting GH deficiency in five children with PWS.

Reports of the first “controlled” studies of GH therapy in individuals with Prader-Willi syndrome began to appear in medical journals in the 1990s. At the 1998 national conference of PWSA | USA, Dr. Martin Ritzen of Sweden reported impressive results from the first major study to compare children with PWS who were treated with growth hormone therapy with a similar group of children who were not treated. Not only did GH treatment increase height and growth rate dramatically, it was shown to reduce body fat and to increase muscle mass and bone size.

As more study results poured in, support mounted for GH treatment to be approved specifically for children with PWS. Doctors experienced in treating growth disorder in PWS began to agree that Prader-Willi syndrome causes a true deficiency of growth hormone secretion, probably originating in the hypothalamus portion of the brain. An international consensus statement signed by 21 endocrinologists worldwide was published in July 2000, stating that “GH testing and treatment should be made available to all children with PWS” and that “consideration should be given to eliminating the need for … testing before treatment.”

By the time the July 2000 consensus statement was published, the U.S. Food and Drug Administration (FDA) had already taken action. In June 2000, the FDA approved an application from Pharmacia Corporation (since acquired by Pfizer), the makers of Genotropin® brand recombinant growth hormone, to market and promote its product for the treatment of growth failure due to Prader-Willi syndrome. For families in the United States, this FDA decision removed one of the last barriers to obtaining growth hormone for their children. Because Prader-Willi syndrome is an approved “indication” for GH medication, children with PWS in this country can now be considered for GH treatment based solely on their genetic diagnosis and growth pattern, rather than on the results of GH deficiency testing.

Approximately 10 years later the FDA approved a second growth hormone treatment specifically for children with growth failure due to Prader-Willi syndrome. This latest product approval — in April 2010 — involves Omnitrope®, manufactured and distributed by Sandoz, Inc. Please review Appendix C for additional product information.

There is no longer any doubt that growth hormone treatment can improve the health and quality of life of children with PWS. The questions that remain are largely individual ones — how early to consider treatment, when there are good reasons to stop treatment or not to use GH in a particular child, and to what extent GH treatment will benefit an adult with PWS. PWSA | USA does not endorse a specific age to begin growth hormone therapy, nor does the national organization recommend particular doses. Decisions regarding GH should be made by an experienced endocrinologist. Please see Appendix G for the full text of the June 2009 PWSA | USA Clinical Advisory Board consensus statement on GH treatment.

Although human GH treatments do not decrease appetite, these therapies — together with early intervention — have helped to create a whole new generation of children with PWS who are taller, slimmer, more active and alert, and who are living much longer and healthier lives. This publication is intended to help both families and care providers understand the issues involved so that they can make decisions in the best interests of the child or adult with PWS.

"It has done wonders for his self-esteem. Little things, like opening the car door and buckling his seat belt, are no problems for him now."

— Parent of a 6-year-old

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2. Prader-Willi syndrome and Growth Hormone

A Different Pattern of Growth

Children with Prader-Willi syndrome (PWS) grow and develop in ways that are different from other children. This is because their bodies don't make enough of certain hormones that are needed for normal growth. While there are individual variations, the following history is common for children with PWS who do not receive hormone treatment.

In infancy and early childhood — Most children with PWS are born with normal weight and length but are described as "floppy infants" because of their low muscle tone (hypotonia). Statistics show that 30 percent of these infants are born with low birth weights. Newborns typically have trouble feeding and gaining weight, and they often must be fed through a tube for a time in order to survive and grow. They gradually gain strength and eventually begin to reach their major milestones (sitting up, walking, etc.), although somewhat later than other children their age. As young children with PWS continue to develop, their body fat seems to grow at a much greater rate than their

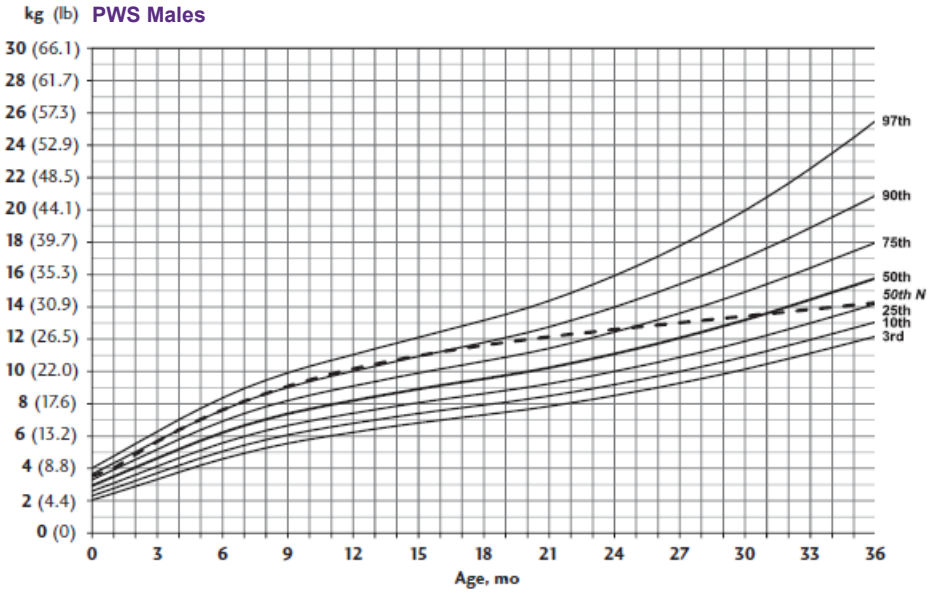
muscle and height. Although they are eating well, they continue to be weaker and less active than other children. The toddler or preschool child with PWS often begins to desire more food than his or her young body can use, and excess weight can build quickly.

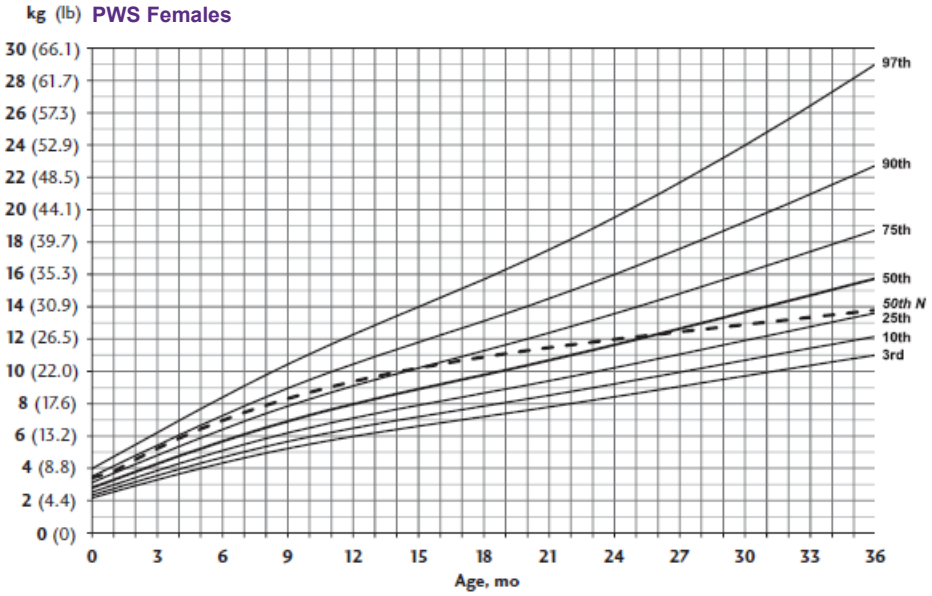
A group of 10 U.S. researchers, six of whom serve on either the Scientific Advisory Board or the Clinical Advisory Board of PWSA | USA, published five sets of standardized growth curves for infant boys and girls with PWS in April 2011. These data and growth curves, representing 186 non growth hormone-treated white infants between 0 and 36 months of age, were published in Pediatrics, the official journal of the American Academy of Pediatrics, and are reprinted with permission on pages 10-14 of this publication.

Included in the five sets of growth curves, representing 108 boys and 78 girls, are data analyzed for weight, length, head circumference, weight/length and body mass index (BMI). All information was compared to the 50th percentile national growth data released in 2003 by the Centers for Disease Control and Prevention. Of additional interest, the researchers reported that “No significant differences in growth measurement were seen when comparing the data among infants (boys or girls) with PWS having the 15q11-q13 deletion or other genetic defects, including maternal disomy 15.”

PWSA | USA Scientific Advisory Board Chairperson Merlin G. Butler, M.D., Ph.D., of the Kansas University Medical Center, offers the following context-setting statement in behalf of the group of researchers: “We encourage the use of these growth standards (by the clinician and dietitian) when examining infants with PWS and evaluating growth for comparison purposes, monitoring for growth patterns, nutritional assessments, and recording responses to growth hormone therapy commonly used in infants and children with PWS.”

Weight of Infants with PWS
Compared with Normal Weight for Age

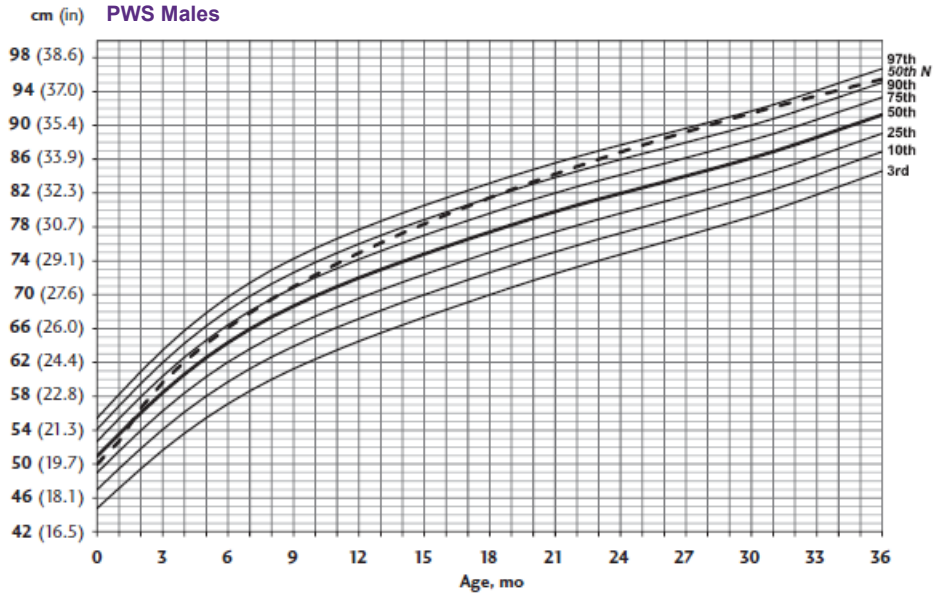


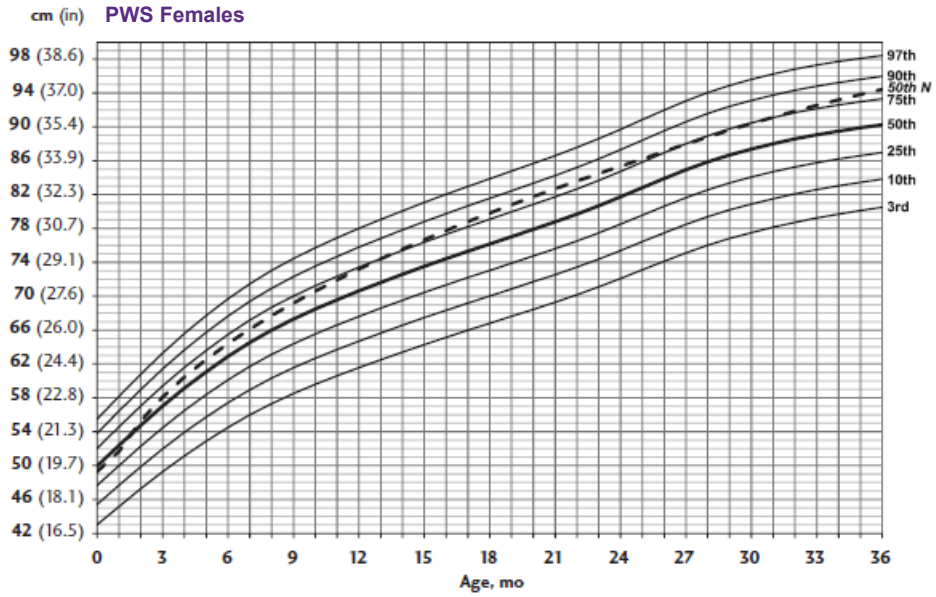


Standardized curves for weight of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line).

"Growth Standards of Infants with Prader-Willi Syndrome," by Merlin G. Butler, et al., are reproduced with permission from *Pediatrics* (the journal of the American Academy of Pediatrics), Vol. 127, May 2011, Pages 687-695, Copyright 2011 by the AAP.

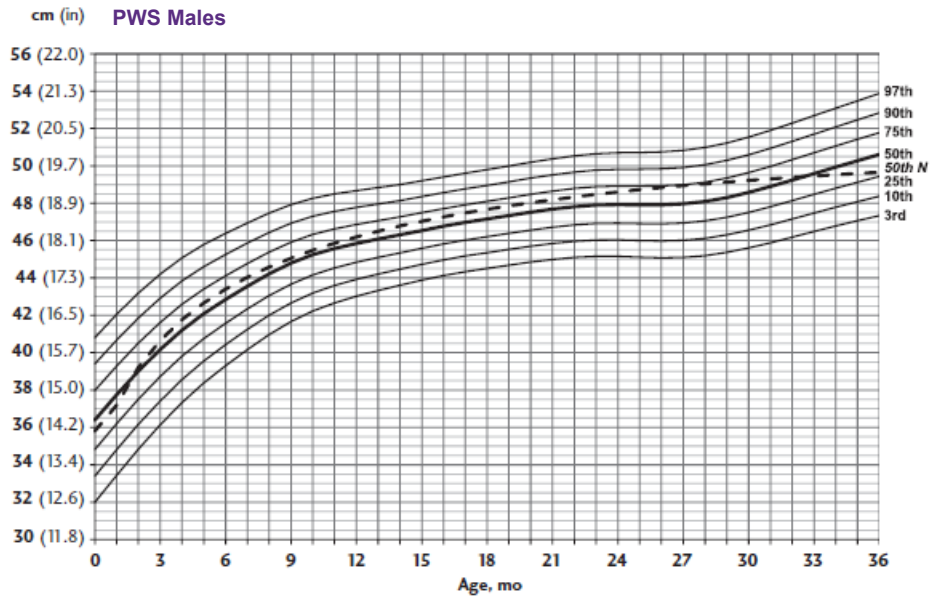
Length of Infants with PWS
Compared with Normal Length for Age

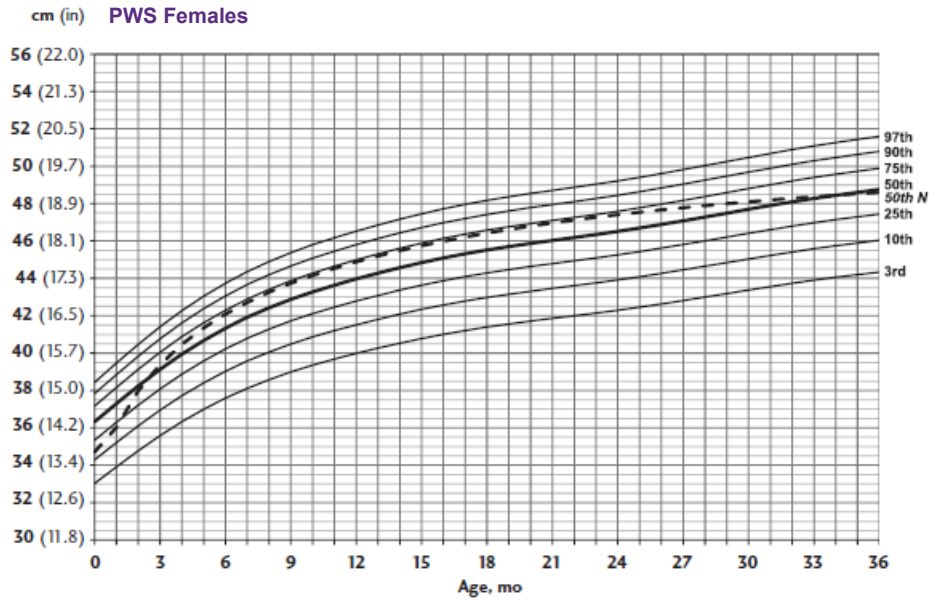




Standardized curves for length of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line).

Head Circumference of Infants with PWS Compared with Normal Head Circumference for Age





Standardized curves for head circumference of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line).

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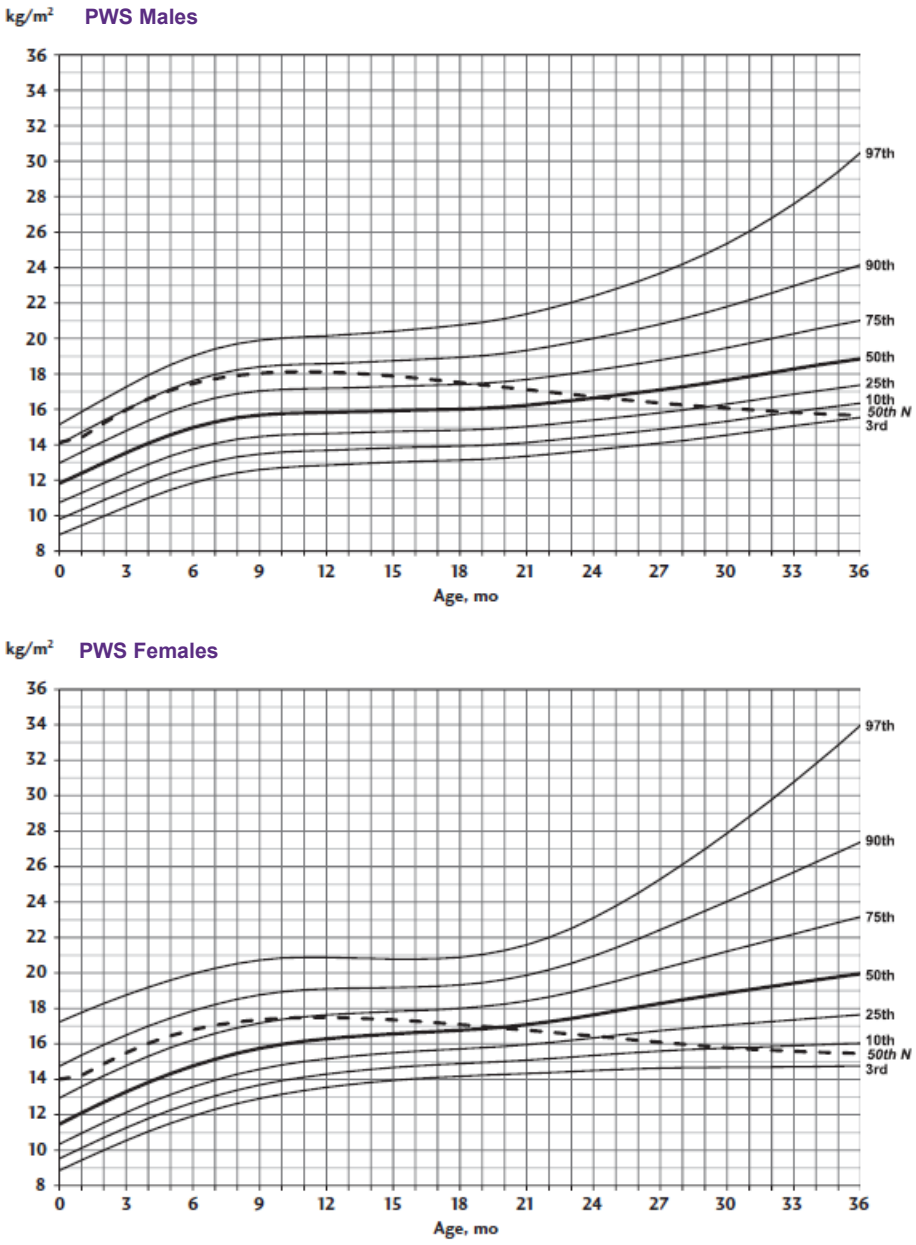
BMI of Infants with PWS
Compared with Normal BMI for Age



Standardized curves for BMI of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line).

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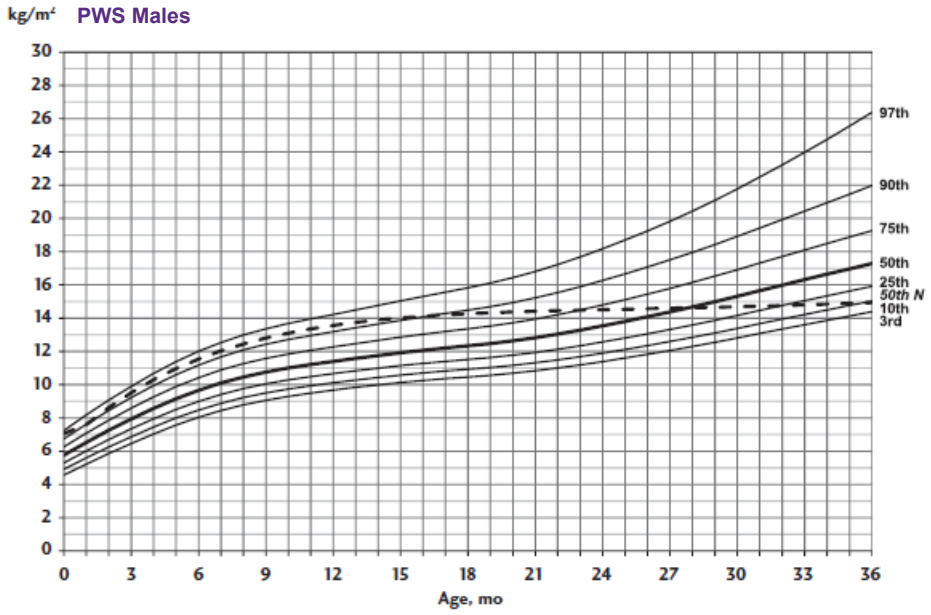
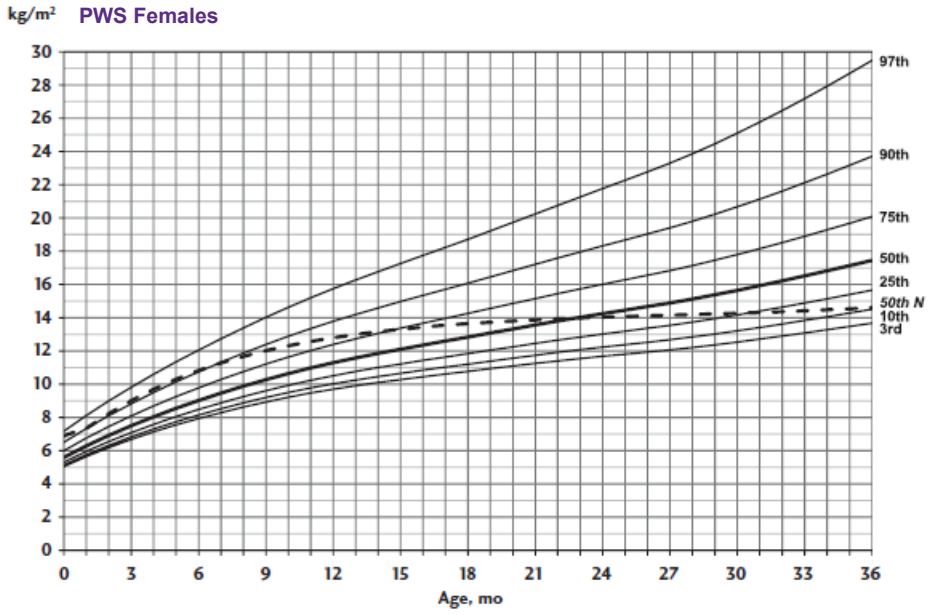
Weight/Length of Infants with PWS Compared with Normal Weight/Length for Age





Standardized curves for weight/length of male (upper) and female (lower) infants with PWS (solid line) and normative 50th percentile (broken line).

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In later childhood and beyond — Through the school-age years, a common physical profile usually becomes apparent in the child with PWS who has not received the benefits of human growth hormone therapy. He or she is likely to have short stature (compared with that of classmates and other family members), small hands and feet, poor muscle development and excess fat, especially in the middle of the body. Studies of body composition have found that children and adults with PWS tend to have more than twice the amount of body fat as others their age — often measuring around 40 to 50 percent of their total body weight.

At the usual time of puberty, the differences between children with PWS and their peers become even more obvious. Without growth hormone treatment, teens with PWS do not experience the typical adolescent growth spurt and all the bodily changes that occur with sexual development. Height measurements taken on a number of children with PWS show that at least half are growing at a rate far below average as early as age 2 and that most end up below the 5th percentile after adolescence. This means that adults with PWS are shorter than nearly all other adults. (See height charts on page 18.)

Note: These are not the only characteristics of Prader-Willi syndrome. For a more complete overview of PWS, see Appendix A.

What Causes These Growth Problems?

Researchers strongly suspect that the part of the brain called the hypothalamus is the main source of the growth differences in PWS. A tiny part of the central brain, the hypothalamus connects the body's two key systems for survival and maintenance — the nervous system and the endocrine system. In addition to playing a key role in growth and sexual development, the hypothalamus regulates appetite, metabolism, body temperature, mood, and other functions that we know are affected in people with PWS. It is likely that one or more of the genes that are missing (or not functioning) in people with PWS supply essential instructions to this part of the brain.

To understand growth and growth hormone treatment in Prader-Willi syndrome, it is helpful to have a basic understanding of how the hormone — or endocrine — system normally works. The endocrine system is made up of all the glands that produce and release hormones into the bloodstream. Just below the hypothalamus, and directly attached to it, is the pituitary gland. Called the "master gland" because it receives messages from the hypothalamus and relays them to the other endocrine glands, the pituitary makes and releases many hormones. Among these are growth hormone (GH) and the hormones for sexual development and reproduction (LH and FSH). If the pituitary does not make or release enough of these hormones, then the organs that depend on them cannot do their jobs.

How Growth Hormone Works

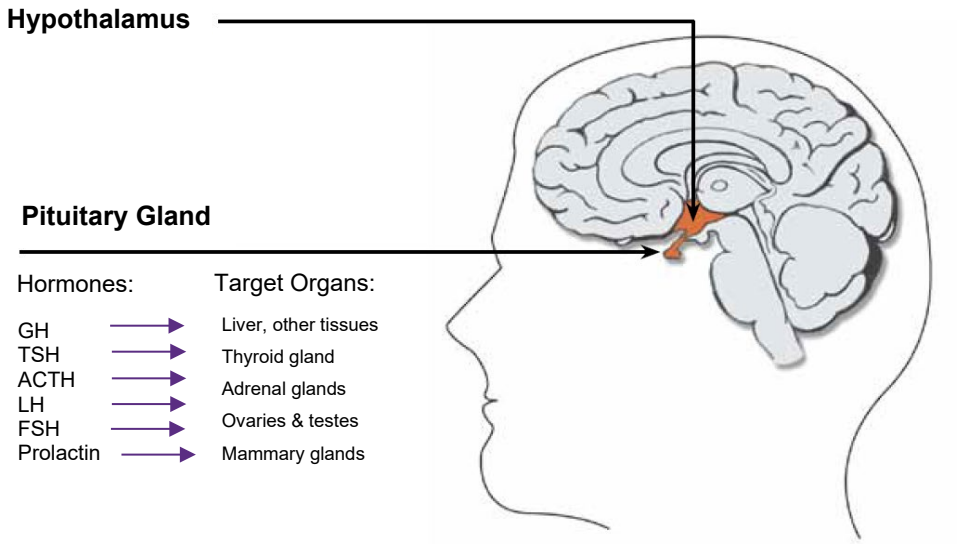
The growth hormone process begins when the hypothalamus sends a chemical messenger called growth hormone releasing hormone (GHRH) to the pituitary gland. This signals the pituitary to release growth hormone, which it does in small spurts throughout the day, but especially during the first hours of sleep.

GH travels throughout the bloodstream to target cells with GH receptors that are programmed to respond. There are GH receptors in many organs in the body, but the most important of these is the liver. Growth hormone does not directly cause most of the growth in bones and body tissue. It signals the liver to make and release the substances that do — the insulin-like growth factors. The main one of these is a protein called insulin-like growth factor-I (one), or IGF-I. It is IGF-I that stimulates new cell growth in the cartilage near the ends of the skeletal bones (called the epiphyses) and in the muscle tissues.

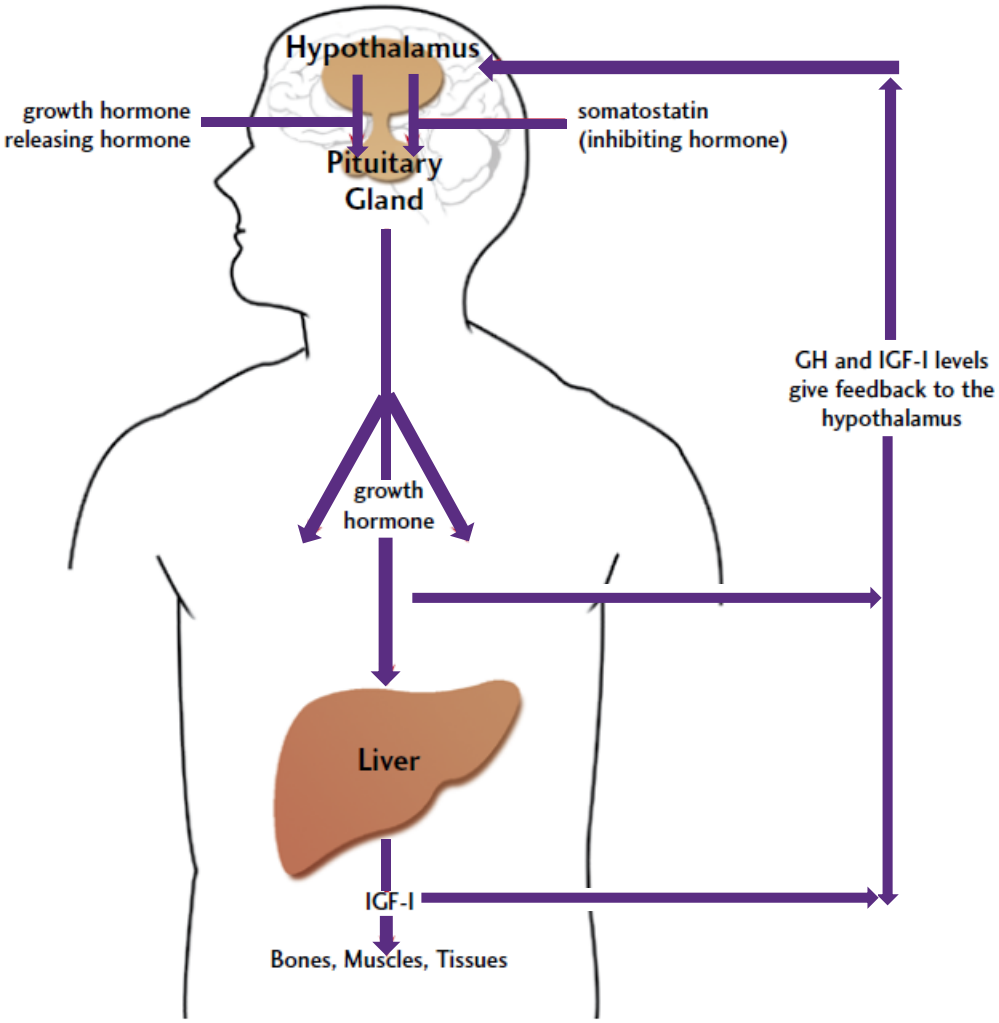
The body's growth system also has checks and balances. For example, when there is a high level of GH or IGF-I in the system, the hypothalamus receives the message and produces a different hormone called somatostatin, which tells the pituitary to stop releasing GH into the bloodstream.

Growth Problems and Treatment

Growth can be adversely affected if there is a problem at any level of the process: in the work of hypothalamus, the pituitary gland, the liver or the feedback system to the hypothalamus. When the pituitary gland doesn't make or release enough growth hormone, or when the growth hormone that is made is not effective in the body,



Growth hormone (GH) is one of six major hormones produced and stored in the front (anterior) lobe of the pituitary gland. Pituitary hormones are released into the bloodstream and travel to their target organs, where they stimulate additional action or hormone release.

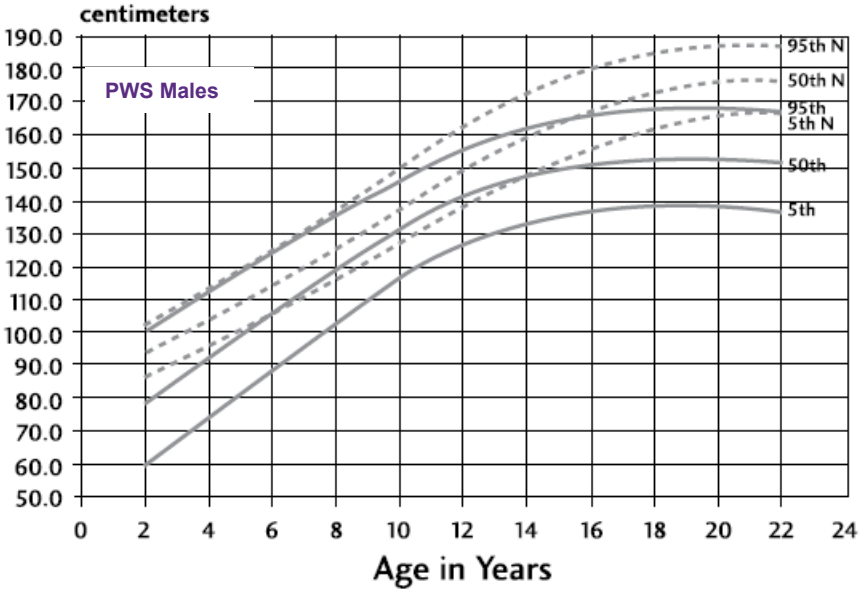


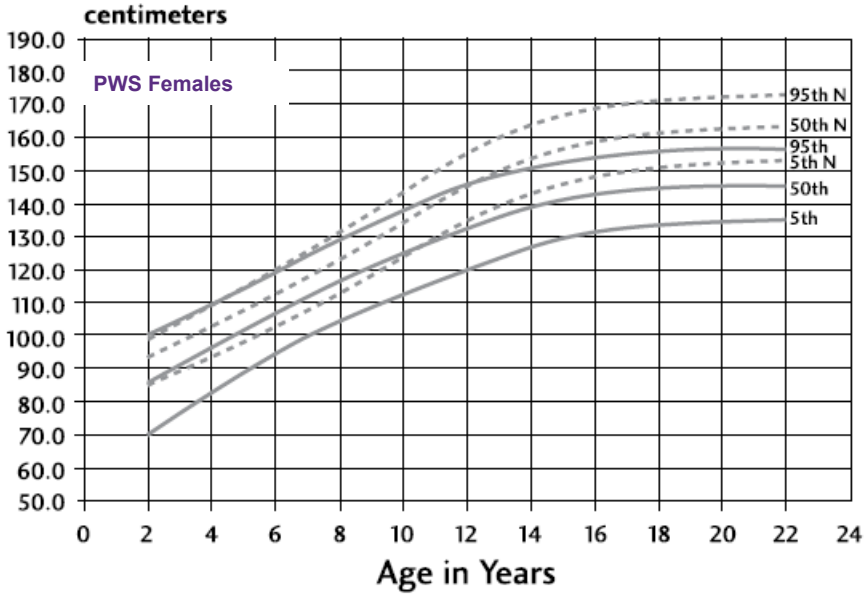
Signs of growth hormone deficiency (GHD) will begin to appear. These include many of the growth-related characteristics seen in people with PWS — short stature and slow growth rate, poor muscle development, increase in central body fat, reduced activity level, etc.

Growth also is affected by other parts of the endocrine system, such as the thyroid and reproductive hormones (which might also be deficient), as well as by an individual's diet, sleep, exercise level, etc. The human growth process and regulation is very complex, and scientists have learned that it is possible to replace or supplement growth hormone when the body does not produce enough.

Growth hormone treatment is the addition of synthetic growth hormone to the body to make up for what the pituitary gland fails to produce. GH must be given as an injection because it is a protein hormone that would be destroyed by digestion if taken in pill form. Pharmaceutical representatives report that a noninjectable form of human GH is not likely to become available in the foreseeable future.

Heights of Individuals with PWS Compared with Normal Heights for Age





Standardized curves for height of Prader-Willi syndrome (PWS) male and female patients (solid line) and healthy individuals (broken line). (M.G. Butler and F.J. Meaney) Reproduced by permission of Pediatrics, Vol. 88, p. 853-860, copyright 1991

GH therapy became widely available in 1985, when the first manufactured form of growth hormone was approved for sale in the United States. GH has since been proven safe and effective in correcting problems in growth and body regulation caused by GH deficiency. Giving growth hormone treatment to someone who needs it is no different than giving insulin to a person with diabetes or thyroid hormone to someone with thyroid deficiency.

The Need for Growth Hormone Treatment in PWS

For a time, there was considerable debate among researchers about whether children with PWS have a true growth hormone deficiency (GHD). This was an important question because GH treatment had only been approved for children with GHD and a few other rare conditions. Testing for GHD has been a controversial issue, however, because the body's level of GH is difficult to measure and may show different results on different tests.

Studies of children with Prader-Willi syndrome confirm that PWS causes a true disorder of GH secretion, resulting in absolute or functional growth hormone deficiency. However, while the widely accepted tests for GH can measure deficiency when it is severe, they may miss the cases where it is a functional or evolving deficiency. That is why GH deficiency testing is no longer required for children with PWS.

Clinical trials of GH in children with PWS clearly demonstrate that many of the growth-related problems outlined at the start of this section can be corrected, at least partially, if GH treatment is started early enough. It has also been demonstrated that adults with PWS — even those who never had GH treatment as children — can benefit from GH therapy.

Sections 3, 4 and 5 of this publication will discuss in greater detail the benefits and risks of using GH, as well as some of the vital information needed before starting GH treatment in the infant, child, or adult with PWS. The Appendix includes additional information and resources regarding Prader-Willi syndrome and growth hormone, including the text of the 2009 PWSA (USA) Clinical Advisory Board consensus statement on PWS and growth hormone, announcement of the two FDA approvals of GH treatment products Genotropin® and Omnitrope® specifically for PWS, summaries of GH clinical trials in children and adults with PWS, and a glossary of terms.

"The most important benefit is self-esteem. She is very aware that she is bigger now and growing. It has been a positive social factor in her grade one integration and special-needs class."

— Parent of a 6-year-old

"Growth hormone makes a huge difference in Ian's quality of life.… He continues to grow and improve his strength, alertness, level of activity and endurance."

— Parent of a 4-year-old

3. Effects of Growth Hormone Treatment in Children with Prader-Willi syndrome

Reports from a number of research groups around the world have confirmed what was suspected in the late 1980s: growth hormone treatment (GHT) offers many benefits to children and adults with Prader-Willi syndrome (PWS). Studies on GHT use in infants and adults have been positive, but answers are still evolving. How young do you start GHT? Is there an age when you stop GHT? These are just two of the questions with no clear answers to date, but you are invited to contact PWSA | USA for updates. Information in this section addresses the benefits and potential side effects of GHT. Results of some of the major studies are outlined in greater detail in Appendix E.

Benefits of GH Treatment

Measured Improvements

The following physical changes have been documented in various research studies, and the most dramatic results are reported in the first year of GH treatment. Studies in the United States and other countries followed children beyond one year of treatment and reported some additional improvements.

- **Increased height and growth rate** — Treated children grow in height at double or more the rates before treatment. For example, some study participants grew five or more inches during the first year of treatment, compared with two inches a year or less prior to GH treatment. A child treated with GH measures higher on the normal growth curves than before treatment and continues to grow along that higher curve as long as GH therapy is continued. Depending on the starting age of treatment, a child's final height can be closer to that of others in the family.

- **Increase of hand and foot sizes to normal proportions** — GH treatment enables hand and foot sizes to catch up with height growth in just one year. Without GH treatment, people with PWS typically have small hands and feet for their body size, which can affect motor skills.

- **Little change in body fat** — Excess fat is characteristic of PWS, but data from a recent study shows that there was no real difference in the fat levels of children with PWS who had received growth hormone treatment for a period of six years. This was especially true for children whose parents were unable to provide proper structure. According to Barbara Y. Whitman, Ph.D., professor of pediatrics at Saint Louis University School of Medicine, “It was disappointing that there wasn’t that much difference in accumulation or percentage of fat, but there was significantly improved muscle mass and better bone density and height.”

- **Decrease in body mass index (BMI)** — BMI, which is a measurement of obesity based on weight and height, declines with GH treatment, and increases when treatment is stopped.

- **Increase in muscle development** — Improvements have been shown in measured size of muscles and in muscle as a percent of body weight. Muscle growth does not quite reach normal levels, although it is significantly improved. Young, underweight children in one study gained weight because of the increased muscle.

- **Improved respiratory function** — GH-treated children can breathe better, due to stronger respiratory muscles and improved response to build-up of carbon dioxide (CO2).

- **Improved physical performance** — Studies document improvements in physical performance with GH treatment due to increased muscle strength and respiratory function. Children are able to run faster, jump farther, lift more weight and do more sit-ups than those who were not treated with GH.

- **Increase in resting energy expenditure (REE)** — At least one study records an improvement in REE after two years of treatment. REE is the level of calories a body burns while at rest, which is most of the day’s calorie usage, or the individual’s basic rate of metabolism. REE is raised by adding muscle and increasing physical activity.

- **Improvement in cholesterol levels** — Studies show that total cholesterol decreases in treated children, while their HDL (high-density lipoprotein, or so-called “good cholesterol”) levels rise.

- **Increase in bone mineral density (BMD)** — Researchers have found that BMD increased at a faster rate in children who were treated with GH for one year than in those who were not treated. Continued increases after two years of treatment suggest that GH therapy may help to avoid osteoporosis (thinning of the bones), which is a concern for adults with PWS.

- **Improved head circumference** — One study of children with PWS who received growth hormone treatments from infancy for a period of six years shows a much more normal head circumference. This result may serve as an index for better brain growth.

Parent Observations

Parent reports collected during several of the studies suggest that GH treatment may bring a number of real-life benefits for children with PWS and their families:

- **Improvement in alertness and activity level**
  Treated children seem to have more energy and stamina for daily activities.

- **Improvement in motor skills and athletics**
  Parents seemed most impressed by their children's new muscle strength and abilities. Some reported that their children were able to try new sports or other physical activities; others reported better strength and independence in everyday tasks, such as climbing bus steps and carrying groceries.

- **Subtle behavior improvements**
  A behavior survey conducted periodically as part of the U.S. growth hormone study suggests that GH treatment may have positive effects on depression, obsessive-compulsive behaviors, and skin-picking in children with PWS.

- **Improved size and appearance**
  It is obvious from the photos throughout this publication that children treated with GH begin to look more like other children their age. In addition to fostering better self-esteem, parents note practical benefits, such as being able to buy clothing off the rack to fit their children.

Areas of No Changes

None of the studies on GH treatment in children with PWS has documented either an improvement or a worsening in any of the following:

- **I.Q. (intelligence quotient)**
  Although some parents say their children seem more focused or alert with GH treatment, none of the studies measured changes in I.Q. or suggested that GH treatment might affect I.Q.

- **Behavioral problems such as temper outbursts**
  Because behavior is such a concern in PWS, the U.S. research study on GH specifically surveyed parents on behavior before and throughout the GH treatment period. Neither this nor any other study found an increase in problem behaviors because of GH treatment, but one report noted that behavior seemed to become worse when treatment was stopped. Families of physically aggressive children may have cause for concern about their child gaining size and strength with GH treatment. These families are advised to seek help from a behavior specialist, whether or not their child begins GH treatment.

- **Appetite and food-seeking behaviors**
  Although some parents have reported that their child's appetite either increased or decreased while on GH treatment, none of the studies of children with PWS documented a change in appetite and food seeking behaviors. Even for the children on GH who could eat extra calories, diet restrictions remained necessary.

- **Bone age**
  GH treatment does not appear to speed up bone age advancement. (If bone age advances too quickly, the period of growth potential becomes shorter.) Many children with PWS have delayed bone age, which is associated with growth hormone deficiency.

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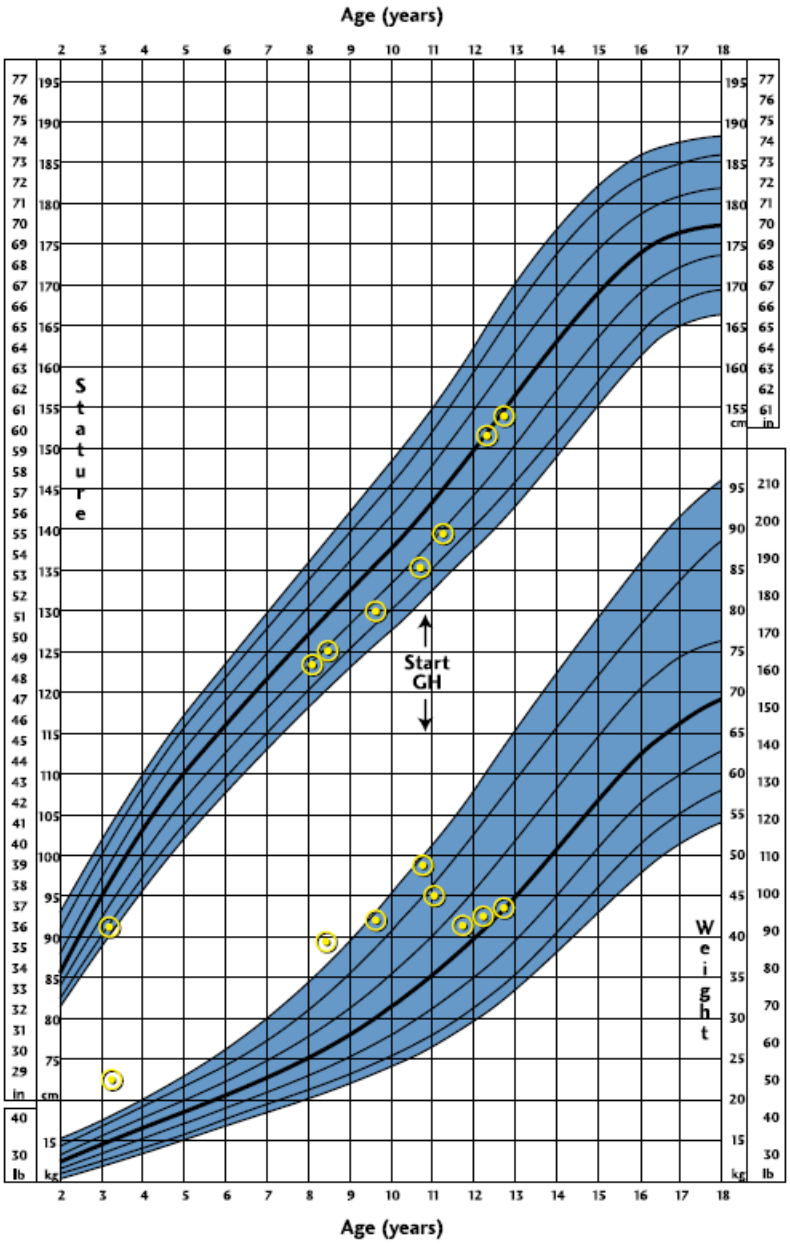
Growth Chart of a Boy with PWS Who Began GH Treatment at Age 10



(Courtesy of Dr. Aaron Carrel, University of Wisconsin–Madison)

Note: Points show the height (stature) and weight of the boy pictured on page 21 at various ages. Shaded areas represent the ranges of height and weight for normal, healthy children. Lines on each growth curve represent the 5th, 10th, 25th, 50th (bold line), 75th, 90th and 95th percentiles.

Side Effects

Editor's Note: Please review Appendix G — PWSA | USA 2009 Consensus Statement — and Appendix I — PWSA | USA Precautions Statement — for additional comprehensive information on possible side effects and standard warnings about growth hormone treatments.

As with any medication, GH therapy may cause undesirable side effects in some cases. The risks and benefits of GH treatment, therefore, should be thoroughly discussed with the child's or adult's physicians prior to making a decision to proceed. The most common side effects are minor, such as changes in the skin at the injection site, e.g., occasional bruising, slight bleeding, tiny bumps on the skin, or an indentation at the injection site (from overuse of that site or a particular injection method). Some of these effects can be avoided or corrected with a change in injection procedures or devices.

Although the studies of children with PWS found no widespread side effects of GH treatment, they noted some individual experiences that required attention. These reactions to GH treatment are rare, but they do sometimes occur:

- **Headaches**
  Some children get headaches during GH treatment, probably due to the pressure of extra fluid in the body. This symptom usually occurs within the first eight weeks of the initiation of GH treatment. The headaches sometimes have stopped on their own, but in some cases, it was necessary to lower the child's dosage and raise it more gradually. Rarely, headaches can be severe and may be accompanied by vomiting and vision disturbances due to fluid pressure in the brain. This condition may be called intracranial hypertension or pseudotumor cerebri. Although the symptoms seem very serious, they go away when GH treatment is stopped. The child often is able to restart GH at a lower dose and work up gradually to the higher dose without this problem recurring.

- **Swelling in the feet and legs (edema)**
  Edema, due to fluid build-up, has been reported in a few cases during the beginning of treatment. This is more common in the adult population with PWS. This problem can go away on its own, or the GH dose may need to be decreased in order to resolve it.

- **Increased levels of insulin**
  Low levels of insulin are found in children with PWS before GH treatment, and those levels can rise significantly during treatment. Insulin is a hormone produced by the pancreas that is needed to use and store carbohydrates and reduce glucose levels in the blood. Although the increased insulin usually stays

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within normal levels, cases have been reported in which a GH-treated child became resistant to insulin and developed Type 2 diabetes. In each case, this occurred after significant weight gain (obesity interferes with the body's insulin receptors), and the diabetes disappeared when GH treatment was stopped, and insulin levels decreased. Children with PWS and GH deficiency should be monitored carefully for signs and symptoms of glucose intolerance during GH treatment, particularly if they are massively obese or have a family history of diabetes mellitus. If diabetes mellitus occurs while on GH therapy, the GH treatment should be stopped. If restarted, the GH dose should be substantially reduced.

- **Decreased levels of thyroid hormone (thyroxine)**
  Some children with PWS developed thyroid deficiency after they started GH treatment and required oral thyroid hormone replacement.

- **Respiratory dysfunction**
  A careful history and assessment of respiratory abnormalities should be evaluated prior to and during GH therapies. Individuals with sleep apnea should be evaluated by a pulmonologist, otolaryngologist, and gastroenterologist before and shortly after beginning GH treatments. (Please See Appendix J — Recommendations for Evaluation of Breathing Abnormalities Associated with Sleep in PWS.)

- **Progression of scoliosis (sideways curvature of the spine)**
  Children with PWS have an increased risk for spinal curvature abnormalities, including scoliosis and kyphosis, believed to be caused by weak muscles and loose joints. Although rapid growth can cause a scoliosis curve to worsen, PWS studies found no significant difference in curve progression between the children with scoliosis who were treated with GH and those not receiving GH treatment. Several children in the studies, however, did require treatment of their scoliosis — either a back brace or surgery, depending on their degree of curve. Detection and monitoring of scoliosis are important for all children with PWS, whether or not they are receiving growth hormone treatments. Decisions to initiate or continue GH treatments in a child with spinal curvature abnormalities should be made in consultation with an endocrinologist and an orthopedic surgeon experienced in PWS.

- **Elongation of lower face**
  Also described as a "high mid-face," this subtle change in proportion of the face after GH treatment has been noted by several PWS researchers. The lower jaw tends to be more responsive to GH treatment than the upper jaw, which may account for these facial changes. There is no appearance of deformity from this change in the jaw, but it may affect teeth alignment and plans for orthodontic treatment (braces).

- **Acromegaly**
  This is the term for extreme overgrowth caused by too much growth hormone in the body, a rare condition usually caused by a tumor on the pituitary gland. This condition causes distorted growth of the brow, jaw, and other body parts, as well as damage to internal organs and processes. Acromegaly is a risk for anyone who receives an excessively high dose of GH over a period of time. It is particularly important to avoid giving dosages meant for a growing child to a teen or adult whose growth plates have closed. Periodic bone age x-rays are usually done to guard against this possibility.

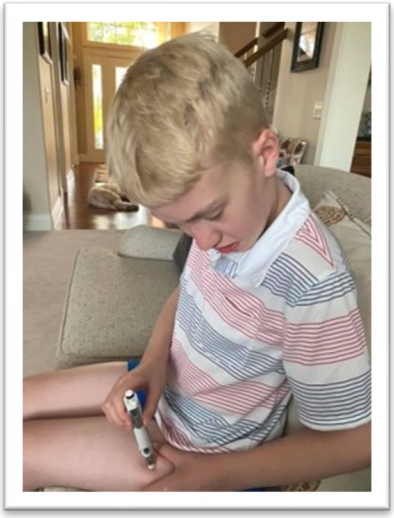
Standards Warnings

The patient literature about growth hormone discusses several other possible side effects of GH treatment. None of the following occurred in any of the PWS research studies, and the most serious of these are considered to be extremely rare.

Arthralgia, myalgia, carpal tunnel syndrome — Various types of joint and muscle pain have been reported with GH use, more commonly in adults with GH deficiency who experience them at the beginning of treatment. Usually, such pain disappears within a few months.

Tumor/cancer spread — When growth is stimulated, abnormal and malignant growths may also respond. If a child has an active tumor or cancer, growth hormone therapy is not advisable. A child who once had cancer but has been in remission for a period of time might still be considered for treatment. The risks and benefits need to be thoroughly discussed with the child's physicians. There is no evidence that GH causes cancer.

Slipped-capital femoral epiphysis (SCFE) — This term describes a condition almost like a break in the top of the thigh bone (femur). The cartilage in the area of bone growth (called the epiphyseal plate or growth plate) slips from the top of the femur for reasons not well understood. This injury has occurred very rarely with GH treatment, and obesity seems to put an individual at greater risk. Symptoms of the problem include hip pain and stiffness, knee pain and limping. Since this injury requires surgical correction, an orthopedic surgeon should be consulted if these complaints arise.



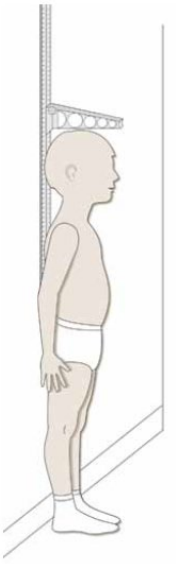
4. What is Involved in Growth Hormone Treatment?

This section provides a question-and-answer look at some of the key aspects of GH treatment beginning in childhood. Additional information on growth hormone and treatment considerations is available from a number of sources listed in Appendix C.

Who Determines the Need for GH Treatment?

To decide whether a child or adult needs to be treated with growth hormone, a family normally sees a specialist called an endocrinologist. Endocrinologists are doctors who specialize in the body's hormones, including growth hormone, sex hormones, insulin, thyroid, etc. There are pediatric endocrinologists, who specialize in treating
children, and adult endocrinologists, who treat adults and possibly adolescents. Since there are a number of medical issues in Prader-Willi syndrome (PWS) that involve the hormone system, an endocrinologist who is familiar with PWS and who can work with the child or adult on all of these issues would be the best choice. If a family has health insurance benefits through an HMO (health maintenance organization) or other type of managed care plan, a referral from the pediatrician or regular doctor usually is needed in order to see an endocrinologist.

How is the need for growth hormone evaluated?



The endocrinologist will likely review the medical history and growth of the child (often before age 2), ask about the child's diet, take information about other family members' heights and growth patterns, and examine the child. The child's growth may need to be monitored for a period of time before the endocrinologist can determine whether there is "growth failure due to Prader-Willi syndrome." (In June 2000, the FDA approved use of GH treatment for this condition.)

Endocrinologists take careful measurements of a child's height using a wall mounted ruler or a special measuring board for children under 2- to 3 years old. Typically, the child is measured several times at the same visit to ensure accuracy. Results are recorded on standard growth charts to determine how the child's height compares with others of the same age. Many children with

PWS start out growing along the normal curve but then, at around age 2, begin growing more slowly and drop lower and lower on the standard growth charts. Children with growth failure usually are significantly shorter than their peers or shorter than would be expected for their family. (Note: Standard growth charts for various ages are available on the U.S. Centers for Disease Control's Web site: www.cdc.gov/growthcharts/.)

Other tests that might be done as part of a GH evaluation include a blood test to check the level of thyroid hormone (low thyroid levels can affect growth and GH treatment), a hand x-ray to determine bone age, a physical exam for scoliosis (curvature of the spine), and a sleep study to check for obstructive sleep apnea (often corrected by removing the tonsils and adenoids) and central sleep apnea, or hypoventilation. The hand x-ray is compared with a set of standard x-rays for different ages and can tell the doctor how much bone growth potential the child has left. (Children with growth hormone deficiency typically have a bone age that is younger than their actual age.) If scoliosis is suspected, a back x-ray should be taken and examined by an orthopedic specialist to determine the exact degree of curve and the need for monitoring or treatment.

If a child with PWS is found to have growth failure, and there are no conditions that would create serious risks (such as cancer), he or she would be eligible for treatment with growth hormone without further testing. Children with Prader-Willi syndrome no longer need blood tests to prove they have growth hormone deficiency before they can be treated with GH.

In 1996, the FDA approved the use of GH replacement therapy in adults, but unlike the 2000 FDA authorization affecting children with PWS, adults are required to undergo diagnostic blood studies to formally establish growth hormone deficiency. Although linear bone growth would no longer be a concern, reports on the use of a low dose of GH in the adult PWS population have shown positive results in the areas of bone strengthening and in the promotion of leaner muscle mass and greater energy.

At what age are children assessed for GH treatment?

A child with PWS can be assessed for GH treatment at any age. Clinical experience suggests that GH treatment can be beneficial for an individual with PWS as early as 2- to 3 months of age (McCandless, et al., 2011). Treatment intended to increase height needs to begin before the normal age of puberty, and earlier treatment (often prior to age 2) seems to offer the best opportunity for improvements in body composition and acquisition of motor milestones.

Short stature may not be apparent in the earliest years of life because infants with PWS often are born with normal length; however, there may be other signs of growth failure or GH deficiency that call for very early treatment. GH treatment has been safely used in infants with growth hormone deficiency for many years. Studies confirm that GH treatment can improve muscle and motor development in infants with PWS.

Growth failure does not always mean that a child must drop below normal range for height or length but, rather, that his or her own pattern of growth fails to keep pace with normal growth speeds. Thus, a shorter child might grow at a normal speed and be considered to have normal growth, and a taller child with poor growth would be of greater concern.

Are there any children who should not be treated with GH for medical reasons?

Because GH treatment stimulates growth throughout the body, children with diagnosed active cancer or tumors that could worsen are not good candidates for GH therapy.

Children with diabetes or glucose intolerance need to be closely monitored if they are treated with GH, since GH therapy is known to increase insulin resistance.

The Clinical Advisory Board of PWSA | USA, in its June 2009 consensus statement (see Appendix G), cautions that children with PWS have “an increased prevalence of respiratory dysfunction.” A sleep study is recommended before the start of GH treatment in all infants, children, and adults with PWS, with a follow-up study six to eight weeks later. If sleep apnea worsens, it is recommended that it be managed by the appropriate standards of care (American Academy of Pediatrics, 2002), including seeing an otolaryngologist to evaluate the airway and making efforts to lose weight if the child is obese. It is up to the discretion of the treating endocrinologist to determine if GH treatment should be temporarily discontinued until the sleep study improves.

How is GH administered?

One of the challenges of growth hormone treatment is that the patient’s family or caregivers must learn to give injections at home. Like insulin, GH is a protein (not a steroid) hormone that must be injected through the skin in order to reach the bloodstream and be effective in the body. Also, like insulin shots, the GH injections are usually given just under the skin (subcutaneously) rather than in the muscle. The shots are given with a very fine needle and typically are not painful. They can be given

in a number of different areas of the body — the abdomen, the top and sides of the thigh, the buttocks, and in larger children the back of the upper arm. The injection should be given in a different spot each night to prevent skin problems.

The reason for rotating injection sites is that repeated injections at the same site may cause atrophy (loss of fat/ muscle). Atrophy can lead to depressions (a cosmetic issue) and scarring, which can inhibit the absorption of medication and a diminished therapeutic response. It is adequate to rotate back and forth between two sites, such as the thighs, buttocks, and right and left abdomen. Even within a 2-inch by 2-inch single site, one can make an imaginary grid of quarter-inch squares to move across.

Growth hormone shots usually are given nightly or six times a week by the parent, caregiver, or the child him or herself. Nighttime is recommended because the largest natural spurt of growth hormone release occurs in the first few hours of sleep, so it is closest to the body's natural cycle. Over the years, experience has shown that daily shots gave more effective results than injections only three or four times a week. Families also generally find it easier to make the injection part of the regular bedtime routine rather than to alternate injection days.

How do families learn to give the injections?

Family members and caregivers who will be giving the GH injections must be trained in how to mix the medication (if necessary), how to prepare and give the injection, and how to properly handle and store the GH product and injection equipment. A number of different pen-type syringes are available that make injections simpler for the parent or caregiver and less worrisome for the child who dislikes needles (see Appendix C).

When families start their children on growth hormone treatment, they are normally provided with personal training, printed information, and telephone numbers to call in case they have questions or need help. They usually have an opportunity to practice using the syringe or injection pen and to give their child the first injection under the supervision of a nurse. The growth hormone supplier also might provide an instructional video for review at home. It is important to follow the manufacturer's directions since each type of injection method requires somewhat different procedures.

Although the thought of giving a child an injection may sound frightening, children and their parents usually learn and adjust to the routine quickly. Getting through the first injection at home is often the hardest part. It helps to remember that most GH shots are virtually painless. Also, since many children with PWS have a high pain tolerance, they are less likely than others to feel the injection.

Information from the Human Growth Foundation and the MAGIC Foundation can help families understand GH treatment better and prepare themselves and their child to get started on a positive note (See Appendix C). Both of these organizations have e-mail discussion lists for parents who want to ask questions or share information and support concerning GH treatment.

Are there different kinds of GH?

Although growth hormone medication is sold by a number of companies in the United States under different product names, the basic protein ingredient is the same in nearly all GH products for injection. Because it is based on the human gene for growth

hormone, manufactured GH is identical in structure and chemistry to the growth hormone produced in the body. The generic name for the major GH products now in use is somatropin, rDNA origin, for injection. The “rDNA” (recombinant DNA) means that it is produced by combining DNA material from different sources through genetic engineering.

While the GH protein molecule itself is the same from product to product, there is an increasing variety of medication forms and injection methods available. In its basic, manufactured form, GH is a freeze-dried white powder that must be mixed with liquid, called a diluent. Some manufacturers now have pre-mixed forms of GH and/or pens that simplify the mixing process. As with other types of medicines, GH products may contain inactive ingredients as preservatives. These additives vary among the different products, and some might cause minor reactions in some people. Most GH products require refrigeration before mixing and use, but a few can be left at room temperature until the powder is reconstituted.

FDA approval of two GH products for Prader-Willi syndrome (Genotropin® and Omnitrope®) has opened the door for doctors to prescribe all equivalent products for that use as well. Doctors might recommend a particular medication based on any of the following: the doctor’s familiarity or experience with different GH products or delivery systems, requirements or preferences of the patient’s insurance company or managed care organization, cost differences, ability of the family to learn and use a particular medication mixing and injection method, or the child’s history or sensitivities. Families should discuss their concerns and needs with the doctor to ensure that the best treatment is chosen for their child’s situation. (See Appendix C for information on the various GH manufacturers and their products.)

How is a child's dose of GH determined?

There are some commonly accepted dosage ranges for GH treatment in infants, children and adults, but endocrinologists may vary in choosing a starting dose. In the United States, individual dosages of GH are expressed in milligrams (mg) of the protein powder form of GH to be given, either per injection or per week.

For infants with Prader-Willi syndrome, the dosing is based on body surface area. The typical starting dose is 1 mg/m2 per day. In older children, beginning doses are typically calculated based on weight alone, or ideal body weight if the child is significantly overweight. Most endocrinologists adjust doses in older children after monitoring growth velocity, weight and IGF-1 (Insulin-like Growth Factor-1) level. The largest dosage is given at the time of puberty, when children normally have their last big growth spurt. For adults, there are standardized dosing regimens for beginning GH treatments. The adult dosage then is subsequently titrated based on IGF-1 levels. (See Appendix G for additional information on GH dosing.)

What about follow-up after treatment begins?

Once growth hormone treatment has begun, regular follow-up exams must be scheduled to evaluate results, check for side effects, and adjust the child's dosage when needed. Endocrinologists typically check patients a minimum of every four to six months when they are on GH treatment. At each checkup, the child will be carefully measured for growth and generally examined. Periodically, the follow-up visits may also involve tests for:

- thyroid levels (blood test);
- insulin or glucose levels (blood test);
- IGF-1 and IGFBP-3 levels (blood test);
- bone age (x-ray);
- scoliosis (physical exam or x-ray);
- secondary sexual characteristics (physical exam); and
- sleep apnea (sleep study).

It is important for families to follow through with these scheduled follow-up visits and to contact the doctor between visits if there are any problems with the treatment. GH treatment and follow-up is a team effort, and the child's or adult's family is a key part of the team. It is the family that must carry out the day-to-day treatment and be alert for any changes in the child that may need medical attention.

In addition to the family and the endocrinologist, other professionals may need to be involved as the child responds to GH treatment. Since calorie needs may change with increased growth, a consultation with a dietitian should be considered to ensure that the child is receiving proper nutrition. Any specialists that the child normally sees on a regular basis (e.g., eye doctor, dentist, orthopedist, physical therapist, etc.) should be made aware that the child is starting growth hormone treatment. Knowing that there will be a period of rapid growth may affect how often those professionals will need to monitor or treat the child in their area of specialty.

How does scoliosis affect GH treatment?

Orthopedic specialists recommend that children be monitored for scoliosis as soon as then begin sitting. Children with diagnosed scoliosis can be treated with GH if an orthopedic surgeon is involved to monitor the child's curve frequently, and to treat any significant curve progression that requires bracing or surgery. Frequent back x-rays (as often as every 4 to 6 months) may be necessary. Back curves measuring between 20 and 40 degrees are often successfully treated with a brace, but curves that advance to more than 40 degrees in a growing child generally require major surgery to stabilize the spine. Unfortunately, doctors are unable to predict which mild curves will progress with growth.

Treatment with GH also can have positive effects on the spine—strengthening back muscles and increasing bone density — which may improve the child's outlook for scoliosis treatment. The endocrinologist and orthopedic specialist should coordinate care and keep each other informed of changes in the child's condition or treatment. While scoliosis is a major concern, the prevalence of scoliosis has been found to be the same in individuals with PWS regardless of GH treatment. Therefore, scoliosis should no longer be considered a contraindication for GH treatment.

When does GH treatment end?

Treatment at childhood dosage levels of GH stops when the growth plates near the ends of the bones have closed. This means that the cartilage where growth occurs has all solidified into bone, and there is no more growth potential. In the past, children always ended their GH treatment at that point. However, research has shown that growth hormone deficiency (GHD) can cause problems beyond the growing years — poor body composition, reduced energy and physical performance, osteoporosis (thinning bones), and disorders of sleep and mood.

Studies of adults with GHD have found that a low dose of GH can help these problems, leading the FDA in 1996 to approve use of GH for adults with growth hormone deficiency. Adults with PWS may need to have documented growth hormone deficiency in order to be treated with growth hormone. (The FDA approval for GH use in Prader-Willi syndrome only covers children.) Children who have been on growth hormone treatment through their final years of growth typically stop GH injections for a period of three to six months, then take a GH stimulation test to determine if they have growth hormone deficiency, as defined for adults. GH stimulation tests check the level of GH in the blood before and after the person is given a substance known to cause release of growth hormone (e.g., insulin, arginine, clonidine, or glucagon). GH treatment in adults is provided at a much lower dosage level than in children. As with children, GH dosing for adults needs to be individualized, with close monitoring by specialists for unwanted side effects.

What are the cost and insurance issues?

Growth hormone is a very expensive medication, often costing $50,000–$60,000 a year at the highest dosage levels. Most families could not even consider GH treatment without excellent insurance coverage or other outside funding. If a family's insurance policy has an annual or a lifetime cap on benefits, the cost of one child's GH treatment over a long period of time could leave insufficient plan benefits for another family member who may need expensive care.

It is important for families to read carefully their insurance policies and any "riders" that amend the policies to find out what prescription drug benefits are provided, what is required to obtain them for GH treatment, and what limits have been set on either

prescription drug benefits or total benefits payable. Because of rising prescription drug costs, insurance companies and managed care plans often try to limit their coverage in a number of ways. For example, a plan might specifically exclude or require special authorizations for expensive medications such as GH. Some provide coverage of "injectable" drugs under a different section of the plan that requires higher co-payment by the family. Others might set annual limits on how much they will pay for drugs, or they might require a higher co-payment from the family after a certain level is reached.

"Seems to be displaying more 'mature' behavior. More accepting of chores. … Almost no more nail biting or picking at skin around fingernails."

— Parent of a 9-year-old

"Food is a lot more manageable. If we have a high calorie [meal] she doesn't immediately gain two pounds. If she gains weight, she can lose it."

— Parent of a 4-year-old

If a family's plan appears to cover GH treatment, but the initial insurance claim is rejected, an appeal can be filed for reconsideration of the claim. Every health plan has a process for submitting appeals and grievances, and each growth hormone company has a program to assist its patients with obtaining insurance coverage, if needed. It is important to keep detailed notes of phone calls and copies of any documents related to an appeal or complaint.

If the family's current plan does not provide adequate benefits to cover GH treatment, other insurance options need to be explored. Finding an insurance policy that covers GH treatment can be difficult and may affect parents' employment options, since most insurance plans are provided through employers. (Information on Medicaid and State Children's Health Insurance Programs, which provide health insurance for families with lower incomes, is available on the Centers for Medicare and Medicaid Services of the U.S. Department of Health and Human Services Web site: www.cms.gov.)

Realizing that health insurance coverage is a major issue that may prevent a child from getting needed treatment, growth hormone manufacturers may supply the medication at no cost or at reduced cost for a period of time to eligible patients who are working to

obtain insurance coverage or other funding. (See Appendix C for the patient assistance programs of the various GH manufacturing companies.)

"Sarah's muscle strength and ability to run, jump, catch, etc., have improved dramatically since starting growth hormone treatment."

— Parent of a 6-year-old

"After only two months she sleeps less and is more active. … Started standing on her own and trying to take steps, seems more brave."

— Parent of a 4-year-old

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5. Questions, Wisdom, and Survey Data from our Families

How can I find an endocrinologist to assess my child?

Ask your child's pediatrician or internist for suggestions. If you have a chapter of the Prader-Willi Syndrome Association in your state or region, ask members of that group for suggestions also. Call several doctors and ask about having your child with PWS assessed for GH treatment. Ask how much experience they've had working with children with PWS. If you are unable to find a doctor with lots of experience in PWS, call PWSA | USA at (941) 312-0400 for information to share with your endocrinologist.

Can an insurance company require that my child be tested for growth hormone deficiency (GHD) before they will cover GH treatment?

Health insurance plans are allowed to set their own requirements for coverage, but usually they will follow the U.S. Food and Drug Administration's (FDA) approvals. It should not be necessary for a child with PWS to be tested for growth hormone deficiency since the FDA's decision regarding Prader-Willi syndrome, effective June 20, 2000. The FDA approved Pharmacia Corporation's (now Pfizer) application to market and promote their existing GH product, Genotropin®, for "long-term treatment of pediatric patients who have growth failure due to Prader-Willi syndrome." In April 2010, the FDA approved a second growth hormone treatment specifically for children with growth failure due to PWS. This latest product approval involves Omnitrope®, manufactured by Sandoz, Inc. In creating these specific "indications" for children with PWS, the FDA recognized that GHD testing is not a reliable determinant of whether a child with PWS needs GH treatment. Those with PWS only need to show signs of

growth failure and have a genetic diagnosis of PWS to qualify for GH treatment under these special Orphan Drug Act approvals. A letter from your doctor to the insurance company might help. For more information, see PWSA | USA's announcement of the FDA ruling, reprinted in Appendix F.

What happens if my child stops GH treatment?

People who stop taking growth hormone will not lose their height gains, but they will gradually lose the other physical benefits that GH produces, i.e., muscle development, fat reduction, increased energy level, etc., and will most likely gain weight. If your child is benefiting from GH therapy but needs to stop because of a side effect, it may be possible for him or her to continue treatment at a lower dosage level, or to stop treatments and then restart them after the problems are understood and addressed. Even a low dose can improve body composition. There is generally no problem with stopping and restarting GH treatment, but risks and benefits of treatment should be discussed with your child's doctor.

My child says the GH shots hurt. What can I do?

Although most children become accustomed to the injections, some children are more sensitive or find that certain injections hurt. Work with your endocrinologist's office to analyze what is causing the problem. There are many things that could cause discomfort, including the size of the needle, the type of injection device being used, the preservative in the medication, the temperature of the medication, the area of the body used for the shot, and the procedure used in giving the shot and removing the needle. If you cannot find a way to reduce the discomfort by changing one or more of these things, you can try rubbing a frozen spoon on the injection site prior to giving the dose. This will provide a quick numbing effect. You can also talk to your doctor about trying a cream to numb the skin prior to giving the shot.

Many children interpret fear as pain. A very small reward given after each shot, such as a sticker, can help to make the routine more positive. Too much anticipation, or randomness in a routine, can build up worry about an injection. Resisting, crying or stalling are all normal coping behaviors and can even become part of the "routine" for some children. Some families find that giving the injection after the child is asleep decreases stress for everyone. This is a difficult choice to make, and you may want to talk with your health care provider if this seems like your best option. Finally, if the time

after the injection seems to be normal, do not worry too much if the child does not like receiving shots. This may be nothing more than normal child behavior.

Are there natural GH supplements that my child could take instead of getting shots?

There are no oral forms of growth hormone and, although many nonprescription supplements and pills are being promoted today as growth enhancers or GH releasers, they are not effective for the needs of children with PWS. Since these supplements are not regulated by the Food and Drug Administration, there is no way of knowing their actual content, effects, or safety.

Some GH manufacturers are trying to develop alternative ways to deliver GH to the body, and we may eventually see forms of synthetic growth hormone that can be taken orally or through the nostrils. If these products do come to market, they will be prescription drugs regulated by the FDA.

"I feel growth hormone has helped Kristine progress a great deal. … She moves around better than before, is talking more, communicates a great deal more."

— Parent of a 2-year-old

Parent Wisdom

Getting Started

Parents often are the best sources of solutions and answers to the little questions that arise when starting GH treatment. For example, parents from several e-mail discussion lists offered the following bits of wisdom:

- "At first, my wife and I did the shots together. This way we made sure we were doing everything correctly. The first few times you have to read and re-read the instructions to make sure you do everything correctly. Expect to be nervous the first few times. I promise you; it gets easier."

- “Put the baby on the floor, not the bed. The bed is too soft and it’s too easy for him to move around. Have one parent hold his arms and legs to keep him from moving. The shot doesn’t seem to bother him, but kids are active!”

- “Mikey was only 21 months old when he started on GH. We just told him he was going to get a shot every night. My hubby holds Mikey down while I give the shot. We have the injector pen with the needle cover, so I never actually see the needle go in. That helps me a lot! Mikey is very used to the shot now. After we finish the counting and we pull the needle out, he says, ‘All done!’”

Travel Tips

Since most GH products must be refrigerated, traveling with a child on GH treatment can pose some interesting problems. A travel bag usually comes with the first GH prescription from the supplier. It can hold a small ice pack, the GH medication and some injection supplies. After a certain amount of time, however, the medication needs refrigeration or a fresh ice pack, so planning ahead is critical. Ask the GH supplier about specific temperature requirements for your product. Following are some parent tips for traveling with supplies of GH:

- “Most hotels can get you a refrigerator for your room. This is especially helpful for longer hotel stays. Otherwise use four zip-lock bags and put the pen in an ice chest or the ice bucket. Don’t count on one zip-lock bag keeping the pen dry in an ice chest. They leak.”
- “Most places will have a refrigerator somewhere. Carry some extra reusable ice packs and ask the hotel desk or restaurant to freeze them for you. Put them in a labeled bag. When your GH travel bag needs a fresh ice pack, stop at the desk or restaurant and ask them to switch packs for you. When they know it’s for a child’s medication they’re usually accommodating.”
- “Keep an empty water or soda bottle with a screw cap to store the used needles or syringes until you can dispose of them safely.”
- “Don’t ever use baggage check for medicines when traveling by plane!”

“Her behavior has definitely changed — some good, some bad — but it is a more normal behavior.”

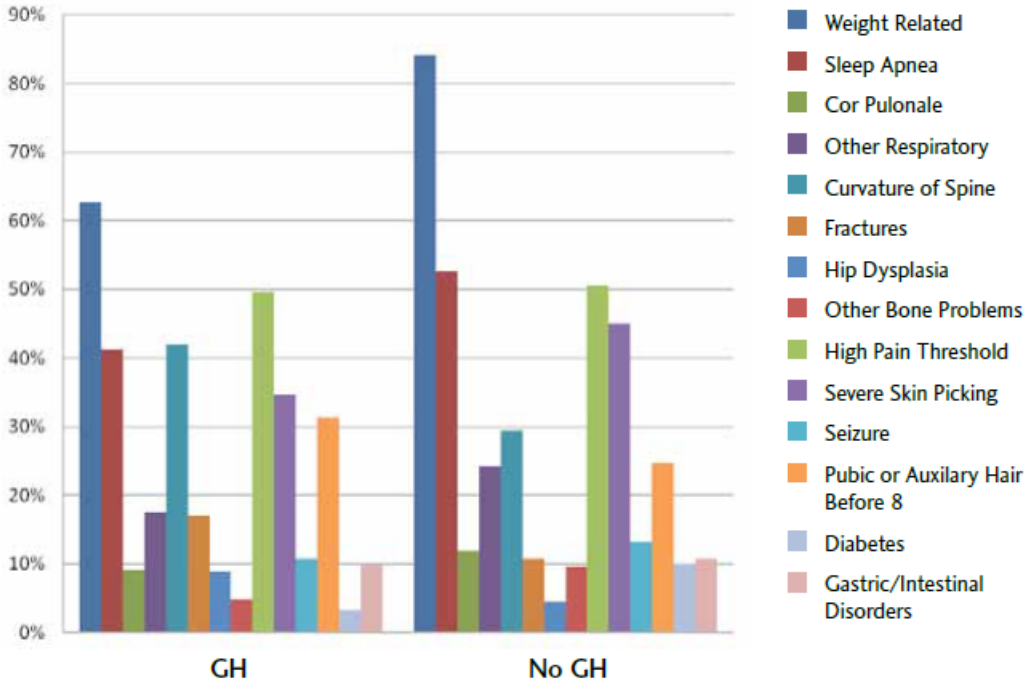
— Parent of a 6-year-old

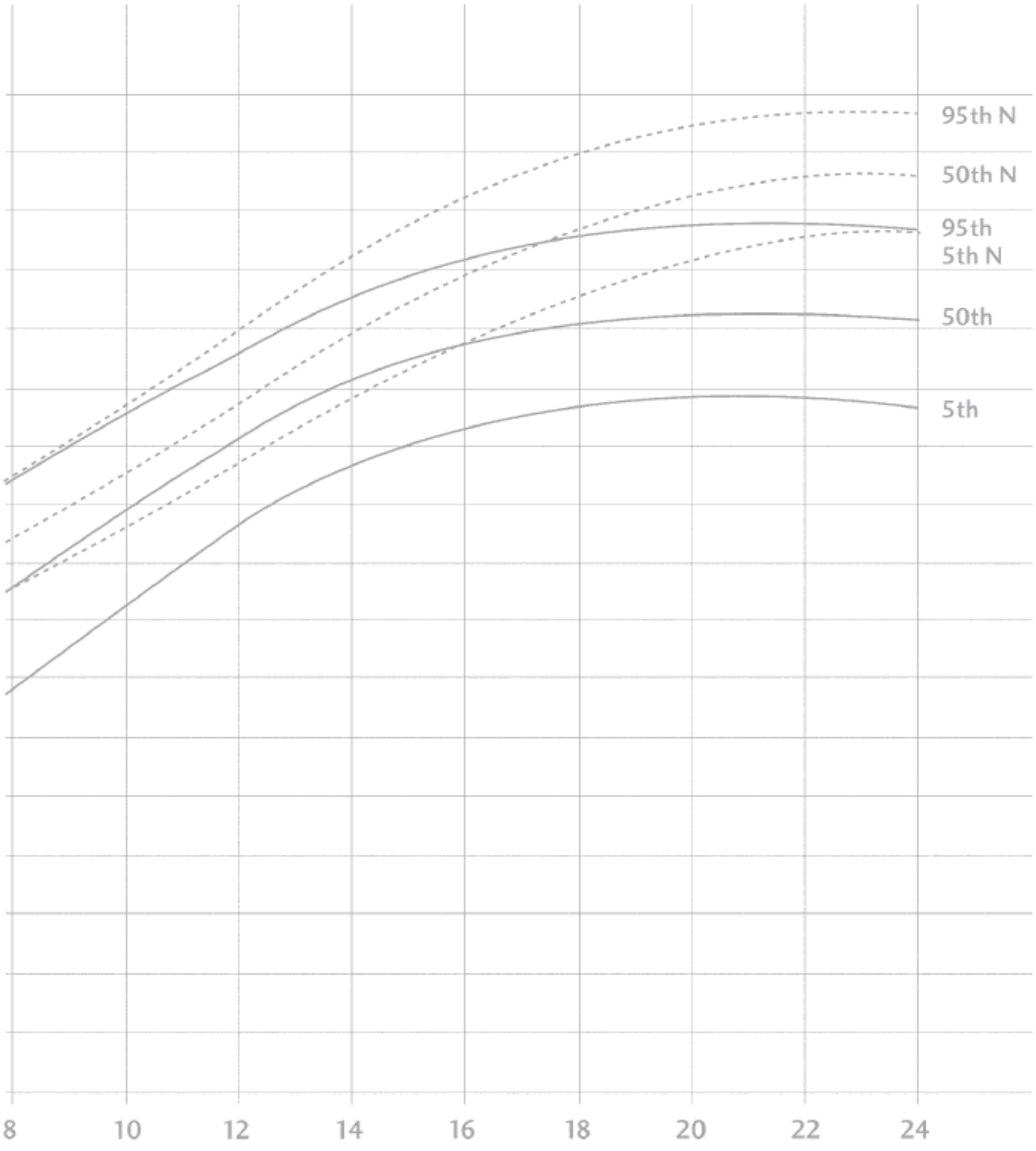
Survey Data

Beginning in October 2004, PWSA | USA has been collecting data from the parents and/or guardians of children with Prader-Willi syndrome (PWS) who have been receiving growth hormone treatments. The online survey is available on the PWSA | USA website; the quick link is www.pwsausa.org/population found under “Support: Registration of People with Prader-Willi Syndrome”.

The detailed chart of collected data, below, reflects information from 643 of the 1,868 parents and/or guardians who had responded to the survey up to April 2011. Of the 643 respondents who have children with PWS between the ages of 6 and 18, 393 reported having children who had been receiving growth hormone treatments either continuously, or for varying periods of time. The accompanying survey chart details the relationships in more than a dozen medical categories of those who had both received and NOT received growth hormone treatments.

PWS Ages 6 to 18 With and Without Growth Hormone Treatment





1032 E Brandon Blvd #4744, Brandon, FL 33511 | Phone: (941) 312-0400 | www.pwsausa.org

APPENDIX

A. **Overview of Prader-Willi Syndrome**

B. **Information Resources on Prader-Willi Syndrome**

C. **Information Resources on Growth Hormone Use and Products**

D. **Glossary of Terms**

E. **Growth Hormone Studies of Children and Adults with PWS**

F. **Historic June 2000 Announcement from PWSA | USA of FDA Genotropin® Approval**

G. **Growth Hormone Treatment and Prader-Willi Syndrome: PWSA | USA Clinical Advisory Board Consensus Statement, June 2009**

H. **Bibliography on PWS and Growth Hormone**

I. **PWSA | USA Growth Hormone Precautions Statement, February 2011**

J. **Recommendations for Evaluation of Breathing Abnormalities Associated with Sleep in Prader-Willi Syndrome, December 2003**

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Appendix A:
Overview of Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a complex and uncommon genetic disorder that affects about one in every 12,000 to 15,000 people. It is a lifelong condition that can be life-threatening.

Genetics

PWS is caused by several different genetic errors on chromosome 15, all of which result in the loss of certain genes normally expressed only from the chromosome 15 received from the father. The most common forms are:

- Deletion — some genes are missing from the chromosome 15 inherited from the father (about 70 percent of cases)
- Maternal uniparental disomy (UPD) — the child received two chromosome 15s from the mother and lost the one from the father (about 25 percent of cases)

The remaining 3 to 5 percent involve rare errors that can be inherited. PWS usually is not passed down from parent to child, and there is no known way to prevent it. Genetic testing, including prenatal testing, is now available to confirm all cases of PWS and to identify the specific genetic cause and the risk of having another affected child.

Physical Characteristics

Although not present in every person with the syndrome, the following are common:

- short stature
- small hands and feet
- hypotonia (low muscle tone in resting muscles) and poor muscle development
- excess fat, especially in the central portion of the body
- narrow forehead, almond-shaped eyes and thin, down-turned lips
- light skin and hair, compared with other family members (especially in those with the chromosome 15 deletion)
- lack of complete sexual development in adolescence (e.g., small genitals, delayed menses)

Major Challenges of PWS

Although children and adults with PWS have many wonderful qualities, they and their families face significant challenges throughout life:

- **Early growth and development** — Infants often require assisted feeding efforts, including tube feeding, to avoid failure to thrive. Major milestones (sitting up, walking, forming sentences, etc.) usually are delayed, and early intervention therapies often are needed to help develop motor, speech and learning skills.
- **Learning** — The child with PWS usually has some degree of learning and attention difficulties, requiring special education support throughout the school years.
- **Physical ability** — Weaknesses in muscle tone, strength and motor planning skills make it difficult to gain coordination and speed for normal childhood activities and competitive sports. Since regular exercise is essential for weight control, sports modifications and alternate activities must be found and encouraged.
- **Weight control** — From early childhood, people with PWS require fewer calories than average to maintain reasonable weight, but they usually develop a greater-than-average appetite. Scientists suspect that PWS affects the brain's appetite control center, preventing the person with PWS from feeling full after eating. Until there are more effective medications to reduce appetite, those with the syndrome need other people to restrict their access to food so that they won't overeat. This requires careful meal planning and vigilance at home, day care, school, work, recreation and all other daily environments.
- **Behavior** — There are common behavior difficulties in people with PWS besides the urge to overeat. These may include obsessive-compulsive actions, changeable moods, sleepiness and underactivity, resistance to change, temper outbursts and skin-picking. Dealing with these behaviors requires consistent strategies and supports and sometimes medication. In spite of these potential problems, children and adults who have Prader-Willi syndrome are sweet and loving most of the time.

Major Medical Concerns

Conditions that are common in PWS and might require medical treatment include:

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- obesity and its resulting problems, including Type 2 diabetes;
- respiratory weakness, of particular concern in infants and those with obesity;
- sleep apnea (periods of not breathing during sleep);
- osteoporosis (thinning of bones) in adults;
- scoliosis and kyphosis (abnormal curves of the spine); and
- strabismus (crossed eye).

Growth hormone therapy offers a number of health benefits for individuals with PWS, including improvements in height, body composition, respiration, physical activity level and bone density.

Additional Cautions

In monitoring health, families and care providers should be aware of these common characteristics in people with PWS:

- reduced sensitivity to pain;
- temperature instability;
- absence of normal vomiting reflex; and
- sensitivity to normal doses of some medications.

For more information on Prader-Willi syndrome, see information resources in Appendix B.

Appendix B:
Information Resources on Prader-Willi syndrome

Prader-Willi Syndrome Association | USA

PWSA | USA is a national membership organization for families, professionals, and service providers, and is a major source of information and research support on Prader-Willi syndrome in the United States. PWSA | USA supports research and offers information, crisis assistance, publications, and multimedia products; a bi-weekly newsletter, The Pulse; and bi-annual National Convention for families, service providers, and medical and scientific professionals. PWSA | USA also has a network of state and regional chapters, a Scientific Advisory Board, Clinical Advisory Board, Professional Providers Advisory Board, and an Adults with PWS Advisory Board. To learn more about PWSA | USA, please use any of the following points of contact:

PWSA | USA
1032 E Brandon Blvd #4744,
Brandon, FL 33511
Phone: (941) 312-0400
Website: http://www.pwsausa.org

The PWSA | USA website contains an extensive amount of information on issues such as medical, genetics, school support, research, crisis support and general health care guidelines for individuals with PWS, as well as links to other sources of information and support.

Appendix C:
Information Resources on Growth Hormone Use and Products

Human Growth Foundation
997 Glen Cove Ave., #5
Glen Head, New York 11545-1593
Toll-free: 800-451-6434
Local: 516-671-4041
Fax: 516-671-4055
E-mail: hgf1@hgfound.org
Website: http://www.hgfound.org

The Human Growth Foundation (HGF) is a nonprofit membership organization of parents and professionals interested in growth disorders. HGF offers publications, a quarterly newsletter, an annual conference and e-mail discussion lists concerning growth issues in children and adults. HGF's website contains a number of informative articles about growth and deficiency treatment.

The MAGIC Foundation for Children's Growth
(Major Aspects of Growth in Children)
6645 W. North Ave.
Oak Park, Illinois 60302
Toll-free: 800-362-9423
Local: 708-383-0808
Fax: 708-383-0899
Website: http://www.magicfoundation.org

The MAGIC Foundation is a nonprofit membership organization providing support and education regarding growth disorders in children and adults. It offers brochures, newsletters (print and online, for members only), national networking, including an e-mail discussion list for families of children with GH deficiency, and an annual convention. MAGIC's website has many free brochures on various aspects of growth and deficiency treatment.

American Association of Clinical Endocrinologists (AACE)
AACE updated its "Medical Guidelines for Clinical Practice for Growth Hormone Use in Growth Hormone-Deficient Adults and Transition Patients" in 2009. These guidelines contain a great deal of information on the use of growth hormone and appear under AACE Guidelines on the AACE website: http://www.aace.com

Growth hormone manufacturers' websites
Manufacturers of synthetic growth hormone have helpful websites with general information about GH, as well as specific information on their products.

(See listings on pages 44-47.)

GROWTH HORMONE PRODUCTS

Following is information about the major synthetic growth hormone products available for sale in the United States in 2011 and the companies that produce them. These seven brands are identical to human growth hormone in molecular structure and are prescribed interchangeably. The products are nearly identical in composition, efficacy and cost, varying primarily in the formulations and delivery devices. There are a number of variations in product lines, especially in final formulations (diluents and preservatives used) and in the mixing and injection methods offered. GH injection devices and options continue to change. Manufacturers' websites should be checked for the latest information.

All of these manufacturers offer patient support programs, including insurance assistance and provision of medication for the uninsured and underinsured.

GH Product
Genotropin®

Manufacturer
Pfizer, New York, NY
http://www.pfizer.com

GH information website
http://www.genotropin.com/

Special product features
Double-chamber cartridge allows GH powder and liquid to be mixed without use of syringes

Genotropin Pen® — with a needle guard to hide needles from view, customizable Geno-Caps® and a userfriendly digital dose display; 5 or 12 mg multidose unit; allows click-dialing of a day's dosage

MiniQuick® — premeasured disposable syringes. An ideal travel choice, it's prefilled and portable. Requires no refrigeration for up to three months before reconstitution. Available in 10 dosage strengths. Preservative free.

Genotropin Mixer®, featuring a standard syringe system with flexible dosing.

Patient support program
"The Pfizer Bridge Program" — 800-645-1280. Assistance with insurance.

GH Product
Humatrope® (Somatropin rDNA)

Manufacturer
Eli Lilly and Company, Indianapolis, IN
http://www.lilly.com

GH information website
http://humatrope.com

Special product features
HumatroPen™ — multidose unit; allows click-dialing of day's dosage (user first injects liquid diluent into powder cartridge with a separate syringe unit). 6, 12 and 24 mg. pens

Patient support program
800-545-5979 or 800-847-6988
"Humatrope Reimbursement Center"
"Humatrope Access Program"

GH Product
Norditropin®

Manufacturer
Novo Nordisk Pharmaceuticals, Inc., Princeton, NJ
http://www.novonordisk.com

GH information website
http://www.novonordisk.com/therapy_areas/growth_hormone/public/default.asp
http://www.norditropin-us.com/parents/nordiflex.asp
http://www.norditropin-us.com/flexpro/index.html

Special product features
FlexPro® — premixed, multidose GH pen can be used with FlexProPenMate®. Can be personalized with skins and charms. Smaller pen for child's smaller hand. 5, 10 or 15 mg.

FlexProPenMate® — an automatic needle insertion accessory with hidden needle

NordiFlex® — prefilled, multidose GH pen, can be used with NordiFlexPenMate®. Available in 30 mg.

NordiFlexPenMate — an automatic needle insertion accessory with hidden needle

Patient support program
888-NOVO-HGH (668-6444)

"NordiCare" — Reimbursement Hot Line assists with insurance coverage and claims submission.

"JumpStart" — Provides 28-day, no-charge supply of Norditropin cartridges to qualified patients working to access insurance benefits.

"Patient Access Program" funds medication for patients with limited/no insurance coverage.

GH Product
Nutropin®

Manufacturer
Genentech, Inc., South San Francisco, CA
http://www.genentech.com/

GH information website
http://www.nutropin.com/index.jsp

Special product features
Nutropin AQ NuSpin® — Liquid GH from a prefilled, automatic device. Available in 5, 10 and 20 mg.

Nutropin AQ Pen® — Liquid GH from a cartridge, delivered by a device. Available in 10 and 20 mg.

Nutropin AQ® with vial and syringe — liquid GH for use with a syringe. Available in 10 mg.

Nutropin Vial and Syringe — GH in dry powdered form, to be mixed with a special fluid for use with a syringe. Available in 5 and 10 mg.

Patient support programs
866-NUTROPIN (688-7674)

“Nutropin GPS (Growing Patient Support) — assistance with insurance, free nurse hotline, injection training

Genetech Access to Care Foundation — Help for uninsured patients

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GH Product
Omnitrope®

Manufacturer
Sandoz, Inc., Princeton, NJ
609-627-8500
http://www.sandoz.com/index.shtml

GH information website
http://www.omnitrope.com

Special product features
Omnitrope® — liquid GH injection pen available in 5 and 10 mg.
Omnitrope® — 5.8 mg vial for reconstitution for use with syringe.

Patient support program
OmniSource — provides insurance assistance, injection training, and the
Sandoz Patient Assistance Program — assists in obtaining Omnitrope to uninsured and underinsured patients: 877-456-6784

GH Product
Saizen®

Manufacturer
Merck, Rockland, MA
800-283-8088
http://www.merck.de/en/index.html

GH information website
http://www.howkidsgrow.com

Special product features
Easy Pod® — fully automated injection device for GH delivery
Cool.click™2 needle-free pen — injects GH through the skin with a blast of air

Patient support program
“Connections for Growth” — 800-582-7989

GH Product
Tev Tropin®

Manufacturer
Teva Pharmaceuticals, USA, North Wales, PA
888-TEVA-USA (838-2872)
http://www.tevabiologics.com/

GH information website
http://www.tev-tropin.com/

Special product features
Tev-Tropin® — Reconstitute dry powder with diluent for use with a syringe
T-Jet® Device — needle-free device for use with Tev-Tropin®

Patient support program
“Growth Solutions” — injection training and education, as well as insurance and reimbursement assistance: 866-TEV-TROP (838-8767)

Appendix D:
Glossary of Terms

The following are definitions of some of the terms used in this publication and in the clinical research summaries.

BIA
Bioelectrical impedance analysis; use of an electrical charge to measure fat in the body (fat tissue resists electricity); considered to be less accurate than DEXA scan

Body composition
Proportions of body weight made up of fat, muscle, bone, etc.

Bone age
Stage of development of the bones, evaluated by comparing a hand x-ray to a series of reference x-rays for specific chronological ages; used to determine skeletal growth potential

Bone mineral density (BMD)
Thickness, strength of internal bone structure

BMI
Body mass index, a formula used to determine obesity; calculated by dividing a person's weight (in kilograms) by the square of their height (in meters)

CAT scan
Computerized axial tomography, now known as computed tomography or CT scan; a type of x-ray that films cross sections of the body to measure masses and body composition

Centimeter (cm)
A metric unit of linear measurement equal to 0.39 inches (1 inch = 2.54 cm)

Control group
Participants in a study who receive no treatment; used to compare results with the treated group

CT scan
Computed tomography, a type of x-ray that films cross sections of the body to measure masses and body composition; also referred to as CAT scan

DEXA scan
Dual-energy x-ray absorptiometry, a low-level x-ray used to measure body composition and bone density

Endocrine
Referring to the body's system of hormones and the glands that produce and release them into the bloodstream

Endocrinologist
A medical doctor who specializes in disorders of the endocrine system also called the growth plate

Epiphysis
The layer of cartilage at the ends of the skeletal bones where new cell growth occurs in children; when the epiphysis "closes," all cartilage has hardened into bone and no further growth is possible; also called the growth plate

Fat-free mass
The portion of body that is not fat, including muscle, bone and water

GH
Growth hormone, a protein hormone made and stored in the pituitary gland and released into the bloodstream in response to GHRH; also called somatotropin

GHD
Growth hormone deficiency, a lack of sufficient growth hormone in the body

GHRH
Growth hormone releasing hormone, the messenger hormone sent by the hypothalamus to the pituitary gland, prompting it to release growth hormone

GH stimulation test
Measurement of GH in the bloodstream following administration of one or more substances known to stimulate growth hormone release; also called provocative GH testing

Height velocity
The rate of height growth, usually measured in centimeters per year

hGH
Human growth hormone produced in the pituitary gland, as distinguished from the synthetic form

Hypothalamus
The part of the brain that connects the nervous system and the endocrine system; the hypothalamus is connected to the pituitary gland and gives it the commands to make and release growth hormone

IGF-I
Insulin-like growth factor-I, a protein hormone produced by the liver in response to growth hormone; IGF-I directly causes growth in skeletal and muscle cells; IGF-I is also called somatomedin-C

IGFBP-3
IGF binding protein-3; the substance that carries IGF-I throughout the body to promote growth

IU
(also written as mU) International unit; a weight measurement equal to 0.33 milligrams (1 mg = 3 IU)

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Kilogram (kg)
A metric unit of weight measurement equal to 2.2 pounds (1 pound = 0.45 kg)

Linear growth
Growth in height

Liver
The major target organ for GH; in response to GH in the bloodstream, the liver produces IGF-I and releases it to promote growth in bones and muscles

Meter (m)
A metric unit of linear measurement equal to 39.37 inches or 100 centimeters

M2
Meters squared; a computation of body surface area based on a person's weight and height; sometimes used to calculate GH dosage, especially when weight is high for the person's height

Pituitary gland
The "master" endocrine gland that makes and releases growth hormone into the body as well as a number of different hormones that stimulate the other endocrine glands; the pituitary is connected to and controlled by the hypothalamus

Pulmonary function
Breathing, lung function

Recombinant Growth Hormone (rGH)
A biosynthetic hormone that is identical to human growth hormone, but it is synthesized in the lab

Resting energy expenditure (REE)
Metabolic rate (calorie usage) during rest

SD
Standard deviation; a unit of measure to describe how much a given number is below (-) or above (+) the average for a certain group; 2 SD is the difference between the 50th and the 3rd percentile on a growth chart

Skinfold thickness
A physical measurement of body fat, using a tool called calipers to determine the thickness of flesh at specific areas of the body

Somatropin (rDNA origin)
The medical name for synthetic growth hormone products that are identical in molecular structure to human growth hormone

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Appendix E:
Growth Hormone Studies of Children and Adults with PWS

EDITOR'S NOTE: This summary of methods and findings is presented alphabetically by country. Please consult the bibliography in Appendix H for complete citations.

Participants:
17 prepubertal children, ages 3-12, with projected final height <3rd percentile for Germans

Study Description:
Eight children received GH treatment at a starting dose of 0.075 IU/kg/day for one month, followed by an increase to 0.15 IU/kg/day (up to a maximum dose of 8 IU/day) for the next 11 months. The remaining nine children received no GH treatment during the year. Measurements were taken for both groups at the start and at one year.

Results:
- Height velocity increased significantly (+5.5 SD) for the treated group and decreased for the controls
- GH treatments result in height increase (+1.07 SD) without acceleration of bone age advancement
- IGF-I and IGFBP-3 levels in the blood also increased significantly
- No differences found between the groups in weight and body composition (measured as skinfold thickness and waist: hip ratio)

SWEDEN, DENMARK, AND NORWAY

Two Years of Growth Hormone Therapy Improves Body Composition in Adults with Prader- Willi Syndrome (Rasmus Sode-Carlson, et al., Presented in May 2010 in Taipei, Taiwan at International Prader-Willi Syndrome Organization 7th Scientific Conference)

Participants:
46 adults with PWS (25 women and 21 men); median age, 29 years

Study Description:
This Scandinavian study was undertaken in an effort to confirm and substantiate the results of three previous studies that adults with genetically verified PWS experienced beneficial effects of growth hormone treatment upon body composition. Only one of the three earlier studies had the optimal randomized controlled design.

The patients in this project were randomized to treatment with GH or placebo for 12 months. During the following 12 months all patients were treated with GH according to their IGF-I value. Body composition was measured yearly by dual x-ray absorptiometry.

Results:
In this first large-scale, long-term placebo-controlled study the improvement in body composition by GH treatment in adults with PWS was confirmed. No side effects were observed. Based on our two-year results, findings persist during long-term therapy.

Growth Hormone Treatment of Children with Prader-Willi Syndrome Affects Linear Growth and Body Composition Favourably (Lindgren, et al., Acta Paediatricia, January 1998)

Participants:
29 prepubertal children, ages 3-12 years

Study Description:
Children were observed for six months, followed by random assignment to treatment (15 children) or control group (14). A non-PWS control group — 10 normal, obese children, ages 5-12 — was also studied. The GH treatment group received 0.1 IU/kg/day. Diet was controlled throughout the study to keep energy intake at same level per kg of body weight.

Results at One Year:

- Increase in height velocity (+6.0 SD), from 4.1 cm/yr to 11 cm/yr
- 25% reduction in fat mass in treated group (measured by BIA, DEXA and CAT scan of thigh)
- 30% increase in fat-free mass in treated group
- Increase in fasting insulin levels and IGF-I levels in treated group
- No severe progression of scoliosis in either PWS group
- No difference found between the treated and untreated PWS groups in progression of bone age or puberty, in bone mineral density, or in calorie intake

Study Continuation in Sweden:

Nine children from the treatment group in the first year of the study continued treatment at 0.1 IU/kg/day for a second year. Another nine children from the untreated PWS control group began GH treatment at a dose of 0.2 IU/kg/day. After one year, both groups stopped GH treatment for six months, then were restarted, all at the lower dose of 0.1 IU/kg/day. Treatment was continued through five years from the start of the original study.

Results at Five Years:

- At both dosage levels (0.1 and 0.2 IU), BMI decreased significantly during the first year of treatment, then increased again during the six months without treatment, with a significant rise among those who had been treated only one year and at the higher dose of GH
- At both dosage levels (0.1 and 0.2 IU), height increased significantly during the first year of treatment
- Fasting insulin levels increased in both groups with GH treatment, and rose above normal levels in the higher dose group (two children developed Type 2 diabetes after rapid weight gain and stopped GH treatment in order to resolve it)
- After five years of GH treatment, participants maintained above-average growth rate for their age, and four children reached their final heights within ± 2 SD of their target heights

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SWITZERLAND

Treatment with Human Growth Hormone in Patients with Prader-Labhart-Willi Syndrome Reduces Body Fat and Increases Muscle Mass and Physical Performance (Eiholzer, et al., European Journal of Pediatrics, Vol. 157, 1998)

Participants:
12 children, ages 0.6 - 14.6 years

Study Description:
All were treated with GH at a dose of 24 IU/m2/week for one year. Effects were compared for three groups of the participants: Group 1 — overweight and prepubertal (six children, ages 3.8 - 7.0 years), Group 2 — underweight and prepubertal (three children, ages 0.6 - 4.1), and Group 3 — pubertal (three children, ages 9.2 - 14.6). Body composition was measured by DEXA in the two older groups.

Results:

- In all groups, height velocity, hand and foot length, and arm span increased, but the changes were smaller in the oldest group
- Body fat decreased (percent fat dropped 14 points for Group 1 and 4 points for Group 3), but did not reach normal levels
- The youngest, underweight children gained weight for height because of the increased muscle mass, while the overweight groups had a decrease in BMI, weight for height and skinfold thickness

- Muscle mass increased in all groups, but less dramatically in the oldest group
- Physical performance improved in four children who were tested

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THE NETHERLANDS

Efficacy and Safety of Long-Term Continuous Growth Hormone Treatment in Children with Prader-Willi Syndrome (van Wijngaarden et al., Journal of Clinical Endocrinology and Metabolism, Vol. 94, 2009)

Participants:
55 children with a mean age of 5.9 years

Study Description:
Investigate effects of long-term continuous GH treatment on body composition, growth, bone maturation, and safety parameters during four years of continuous GH treatment (1 mg/m2 · d). Data were annually obtained on fat percentage (fat%) and lean body mass (LBM) by dual-energy x-ray absorptiometry, height, weight, head circumference, bone age, blood pressure, and fasting IGF-I, IGF binding protein-3, glucose, insulin, glycosylated hemoglobin, total cholesterol, high-density lipoprotein, and low-density lipoprotein. SD scores were calculated according to Dutch and PWS reference values (SDS and SDSPWS).

Results:
Four years of continuous GH treatment in children with PWS improves body composition by decreasing fat%SDS and stabilizing LBMSDS and head circumferenceSDS and normalizes heightSDS without adverse effects. Thus, long-term continuous GH treatment is an effective and safe therapy for children with PWS. Fat%SDS was significantly lower after 4 years of GH treatment ($P < 0.0001$). LBMSDS significantly increased during the first year ($P = 0.02$) but returned to baseline values the second year and remained unchanged thereafter. Mean ± SD height normalized from –2.27 ± 1.2 SDS to –0.24 ± 1.2 SDS ($P < 0.0001$). Head circumference SDS increased from –0.79 ± 1.0 at start to 0.07 ± 1.1 SDS after 4 yr. BMISDSPWS significantly decreased. Mean ± SD IGF-I and the IGF-I/IGF binding protein-3 ratio significantly increased to 2.08 ± 1.1 and 2.32 ± 0.9 SDS, respectively. GH treatment had no adverse effects on bone maturation, blood pressure, glucose homeostasis and serum lipids.

Randomized Controlled Trial to Investigate the Effects of Growth Hormone Treatment on Scoliosis in Children with Prader-Willi Syndrome (van Wijngaarden et al., Journal of Clinical Endocrinology and Metabolism, Vol. 94, 2009)

Participants:
91 children with PWS with median age of 4.7 years

Study Description:
The aim was to study the effects of GH treatment on the onset of scoliosis and curve progression. The prevalence of scoliosis in children with Prader-Willi syndrome (PWS) is 30–80 percent, depending on age. Although reports about effects of GH treatment on scoliosis in children with PWS are limited, scoliosis is generally considered a contraindication for GH treatment. We conducted a multicenter, randomized, controlled GH study in infants and prepubertal and pubertal children. Infants and prepubertal children were randomized into a GH-treated group (1.0 mg/m2 · d) and a control group for 1 and 2 yr, respectively. Pubertal children were randomized to receive somatropin 1.0 or 1.5 mg/m2 · d. Yearly, x-rays of the spine were taken, and height, weight, truncal lean body mass (with dual energy x-ray absorptiometry), and IGF-I were measured.

Results:
GH-treated children had similar onset of scoliosis and curve progression as randomized controls (P = 0.27–0.79 and P = 0.18–0.98, respectively). GH treatment, IGF-I SD score (SDS), and catch-up growth had no adverse effect on the onset of scoliosis or curve progression, even after adjustment for confounders. Height SDS, truncal lean body mass, and IGF-I SDS were significantly higher in GH-treated children than in randomized controls. At baseline, a higher IGF-I SDS was associated with a lower severity of scoliosis. Scoliosis should no longer be considered a contraindication for GH treatment in children with PWS.

Mental and Motor Development Before and During Growth Hormone Treatment in Infants and Toddlers with Prader-Willi Syndrome (Festen, et al., Clinical Endocrinology, Vol. 68, 2008)

Participants:
43 infants with PWS

Study Description:
In an effort to evaluate psychomotor development in infants with Prader-Willi syndrome who are receiving growth hormone treatments, 29 of the 43 participants were randomized into a GH group (n=15) receiving 1mg/m2/day GH or a non-GH treated control group (n=14). At baseline and after 12 months of follow-up, analysis with Bayley Scales of Infant Development II (BSID-II) was performed. Data were converted to percentage of expected development age (%ed), and changes during follow-up were calculated.

Results:
Both mental and motor development improved significantly during the first year of the study in the GH group vs. the control group: median interquartile range change was +9.3% (-5.3 to 13.3) vs. -2.9% (-8.1 to 4.9) ($P<0.05$) in mental development and +11.2 % (-4.9 to 22.5) vs. -18.5% (-27.9 to 1.8) ($P<0.05$) in motor development, respectively.

UNITED KINGDOM

Effect of Growth Hormone on Height, Weight and Body Composition in Prader-Willi Syndrome (Davies, et al., Archives of Disease in Childhood, Vol. 78, 1998)

Participants:
25 children, ages 4-10

Study Description:
Children were observed for six months, followed by six months of GH treatment at a dose of 20 IU/m2/week in daily injections. Testing was done at start, six months and 12 months for height, weight, skinfold thickness and body composition (through measurement of total body water, using stable isotopes).

Results:

- Height velocity doubled, increasing height by an average 5.7 cm
- Percent body fat rose before GH treatment, and declined with treatment (from an average 36.7% at 0 months to 40.6% at six months and to 32.5% at 12 months)
- Skinfold thickness decreased
- Percent fat-free mass increased from 59.4% to 67.5%

UNITED STATES

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 U.S. Multi-Center Trial (Mogul, et al., Journal of Clinical Endocrinology and Metabolism, January 2008)

Participants:
38 adults with PWS (25 women and 13 men); mean age of 30.5 years

Study Description:
Growth hormone (GH) replacement in children with PWS has well-defined benefits and risks and is used extensively worldwide. The objective of this project was to evaluate the effectiveness and safety of GH in GH-deficient genotype positive PWS adults at four academic medical centers over a 12-month period with six-month dose-optimization and six-month stable treatment periods. Human recombinant GH was initiated at 0.2mg/day with monthly 0.2mg increments to maximum 1.0mg/day, as tolerated.

Results:
LBM increased from 42.65([se]2.25) to 45.47[2.31]kg (P≤.0001) and %fat decreased from 42.84[1.12] to 39.95[1.34] % (P=.025) at a median final dose of 0.6mg/day in 30 study subjects who completed 6-12 months of GH. Mean fasting glucose, 85.3[3.4]mg/dl, HbA1C5.5[.2]%, fasting insulin 5.3[.6]µU/ml, AUC-insulin 60.4[7.5] µU/ml. HOMA-IR[.2] were normal at baseline in 38 study initiators, including 5 diabetics, and remained in normal range. Total T3 increased 26.75%: 127.0[7.8] to 150.5[7.8]ng/dl (P=.021) with normalization in all subjects, including 6(20%) with baseline T3's≥2SD's below mean. Mildly progressive ankle edema was the most serious treatment emergent adverse event (5 patients). This study demonstrates that GH improves body composition, normalizes T3, and is well tolerated without glucose impairment in PWS genotype adults.

Final Adult Height in Children with Prader-Willi Syndrome with and without Human Growth Hormone Treatment (Angulo, et al., American Journal of Medical Genetics, Part A., 143A, 2007)

Participants:
21 individuals (8 females and 13 males), ages 15-20, who received growth hormone treatments and attained final adult height after 7.9 + 1.7 years; and 39 individuals (26 females and 13 males), ages 18-25, identified through the same database and who reached adult height without receiving growth hormone treatment.

Study Description:
The objective of this study was to compare adult heights attained in separate groups of males and females with Prader-Willi syndrome. One group of subjects had received growth hormone treatments; the second group had not received growth hormone treatments. Subjects were included in the study if they had reached adult height, determined as the height attained when the bone age reached 16 years for males and 14 years for females, and when growth velocity had reached a plateau (<2cm/year).

Results:
Data revealed that the administration of growth hormone to children with Prader-Willi syndrome restores linear growth and final adult height without significant adverse

events. In contrast, children with PWS who had not received growth hormone treatments had a significant decrease in growth velocity, with a mean final adult height under 2 standard deviations below the relevant population mean, and a higher risk for type 2 diabetes mellitus.

Long-Term Growth Hormone Therapy Changes the Natural History of Body Composition and Motor Function in Children with Prader-Willi Syndrome (Carrel, et al., Journal of Clinical Endocrinology and Metabolism, Vol. 95, 2010)

Participants:
48 children (21, ages 6-9; and 27, ages 5-9)

Study Description:
To assess the impact of hGH therapy begun early in life on the natural history of PWS, we compared height, body composition and strength in similar-age children with PWS naïve to hGH with those treated with hGH for 6 years. Twenty-one subjects (aged 6-9 yr) treated with hGH for 6 years (beginning at 4-32 months, mean 13 ± 6 months) were compared with 27 children of similar age (5-9 yr) prior to treatment with hGH. Percent body fat, lean body mass, carbohydrate/lipid metabolism, and motor strength were compared using analysis of covariance.

Results:
PWS children treated with hGH demonstrated lower body fat (mean, 36.1 ± 2.1 vs. 44.6 ± 1.8%, $P < 0.01$), greater height (131 ± 2 vs. 114 ± 2 cm; $P < 0.001$), greater motor strength [increased standing broad jump 22.9 ± 2.1 vs. 14.6 ± 1.9 in. ($P < 0.001$) and sit-ups 12.4 ± 0.9 vs. 7.1 ± 0.7 in 30 sec ($P < 0.001$)], increased highdensity lipoprotein cholesterol (58.9 ± 2.6 vs. 44.9 ± 2.3 mg/dl, $P < 0.001$), decreased low-density lipoprotein (100 ± 8 vs. 131 ± 7 mg/dl, $P < 0.01$), and no difference in fasting glucose or insulin.

Conclusions:
hGH treatment in children with PWS, begun prior to 2 years of age, improves body composition, motor function, height and lipid profiles. The magnitude of these effects suggests that long-term hGH therapy favorably alters the natural history of PWS to an extent that exceeds risks and justifies consideration for initiation during infancy.

Growth Hormone Improves Body Composition, Fat Utilization, Physical Strength and Agility, and Growth in Prader-Willi Syndrome: A Controlled Study (Carrel, et al., Journal of Pediatrics, 134 (2), 1999)

Participants:
54 children, ages 4-16

Study Description:
All were observed for six months; then 35 children were treated with GH at a dose of 1 mg/m2/day, and 19 were untreated controls for one year. In the second year, the control group also received GH treatment, all at the same initial dose. Comprehensive testing was done on all subjects, including behavioral surveys, diet records and bone x-rays, in addition to blood tests and measurements of height, weight, body composition, resting energy expenditure and physical performance.

Results:

- Treated children increased height, growth velocity and muscle mass during the two years, although growth rate slowed in the second year
- Head, hand, and foot measurements approached normal averages during treatment, and the lower facial height exceeded average
- Treated children improved in running speed, sit-ups, broad jump and weight-lifting tests, compared with the control group
- Improvements in pulmonary function and physical performance during the first year were maintained during the second year, with further increases in arm strength and running speed
- Body fat decreased by an average 8 percentage points after one year of treatment, but did not decrease further during the second year
- 70% had mild scoliosis at the start of the study, and progression of the curves was similar in the treated and untreated groups
- Total cholesterol and LDL decreased, and HDL increased after one year of growth hormone treatment
- Resting energy expenditure started below average and increased in both groups, but more so in the treated children
- Bone mineral density started within normal ranges and increased at a greater rate in the treated children than in the controls
- GH treatment caused no deterioration in behavior and appeared to reduce depression, obsessive/compulsive symptoms and skin-picking

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Growth Hormone and Mortality in Prader-Willi Syndrome (Abstract By Phillip D. K. Lee, MD, FAAP, FACE www.GGHjournal.com June 2006)

The administration of growth hormone (GH) has numerous benefits for individuals with PWS including a decline in the fat percentage of lean body mass, and improvement in body composition, agility and muscle strength. In the almost 20 years since the introduction of the use of GH in PWS, very few bad effects have been reported. However, two children with PWS who were receiving GH died in 2002. This led to a discussion about the safety of GH in PWS and ultimately resulted in the drug company,

Pfizer, applying a warning label to its GH prescriptions. This warning stated that GH should not be used in those with PWS who are severely obese or have severe breathing problems. In 2004, other drug companies added the same warning to their GH drugs. This led to a tremendous amount of concern in the PWS community, as denying GH to individuals with PWS can be very damaging to their health and lifestyles.

Unfortunately, premature death in PWS has been a problem since long before GH was used as a treatment. Deaths are often due to cardio-respiratory illness, and none of the reported 190 deaths reported to PWSA | USA since 1977 appear to be related to GH. Since May of 2006, 18 children and two adults worldwide with PWS died while receiving GH. Some of these deaths were due to causes completely unrelated to GH, such as drowning in a bathtub. Many of the deaths were in individuals who were significantly overweight, and almost all of the cases were not receiving the dose on the medication's label.

Some have suggested that GH can cause death in individuals with PWS with breathing problems. For individuals who appear to have died because of severe breathing problems, it is noted that these problems were present before GH treatment even began. In five out of six cases examined, cases of those with breathing problems, GH treatment did not make these types of conditions worse. Special analysis of sleep problems need not be standard for every individual being treated with GH. However, if an individual has a history of excessive daytime sleepiness or extreme breathing problems during sleep, a sleep analysis is recommended before GH treatment.

The concerns about GH and death in PWS are ultimately invalid for the following reasons: 1) deaths in infants with PWS are usually due to feeding aspiration, have nothing to do with GH treatment and should be closely monitored; 2) deaths in older children and adults with PWS are very often associated with obesity, and the insulin resistance associated with obesity may be increased by GH; this deserves special attention; 3) tub drowning deaths have nothing to do with GH and should be addressed separately; 4) most of the deaths during GH treatment occurred with doses below the recommended amounts; doses should not be limited and should be well-monitored; 5) clinical follow-up is crucial to preventing deaths which are attributed to GH treatment, as almost all of the reported deaths occurred within the first 18 months of treatment; and 6) sleep analysis should not be required for GH treatment unless the patient has an outstanding history of breathing problems which merit further examination before treatment begins. *(This opinion is not held by most PWS experts who believe a sleep study should be done. See Appendix G, Growth Hormone Treatment and Prader-Willi Syndrome: PWSA | USA Clinical Advisory Board Consensus Statement, June 2009.)*

GH as a treatment for those with PWS has led to improvements in height and appearance in addition to providing "a new outlook on life." Further population studies and more thorough follow-up with patients will add to our knowledge of GH and will lead

to a better understanding of how to best administer GH while sparing the seemingly unnecessary association between deaths in PWS and this life-altering treatment.

Appendix F:
Historic June 2000 Announcement from PWSA | USA of FDA Genotropin Approval

Dear PWSA | USA Member:

As we have all been aware, for years there has been no medication specifically approved for individuals with Prader-Willi syndrome (PWS). Now, finally, there is some good news. We are pleased to inform you that the U.S. Food & Drug Administration (FDA) has just determined that PWS is an “indication” (eligible condition) for treatment with GenotropinTM (somatropin rDNA for injection), which is a form of growth hormone manufactured by Pharmacia Corporation. Previously approved to treat “growth hormone deficiency” in children and adults, Genotropin is now the only treatment approved specifically for “growth failure in children with PWS.”

This does not mean that there is a problem if your child is on another brand of growth hormone. In general, growth hormone therapy has been approved for some time – but now, Genotropin specifically has been approved for treating PWS. Genotropin’s approval for PWS was issued by FDA under the Orphan Drug Act. (This designation is only given to treatments for which the potential patient population is under 200,000. Orphan Drug status entitles Pharmacia exclusivity in marketing the drug for this purpose for the next seven years.) FDA approval should make it easier for families to appeal to insurance companies for coverage and should help with Medicaid coverage. Also, under the FDA ruling, growth hormone deficiency testing will no longer be required for children with PWS and growth failure who are being considered for GH treatment.

Results from the studies submitted to the FDA reveal that growth hormone treatment improves growth and body composition in children with PWS, including stimulating skeletal growth, decreasing the amount of body fat and increasing lean body mass (muscle). Given the many issues faced by families affected by PWS, we believe the increased availability of growth hormone will be of benefit to many members of our community by helping to reduce some of the major medical problems often inherent in this syndrome. Please note that you should consult with your physician as to whether growth hormone therapy is appropriate in your particular case, since it may not be beneficial for every child with PWS.

By the end of the year PWSA | USA will publish a new booklet for parents and guardians, designed to help you make informed decisions about growth hormone treatment. When it is available, we will inform you through our newsletter, The Gathered View. Meanwhile, you can refer to the enclosed consensus statement and log on to our website at www.pwsausa.org. If you would like more information specifically about Genotropin or its use in PWS, please feel free to visit the Genotropin website (www.genotropin.com) or call 1-800-645-1280.

It is a new era for Prader-Willi syndrome with many encouraging things on the horizon! We are enclosing further “cutting edge” information on growth hormone therapy and will do all we can to keep you informed of all new treatment options.

Sincerely,
Janalee Heinemann, MSW
Executive Director, PWSA | USA

EDITOR’S NOTE: In April 2010 the FDA approved a second growth hormone treatment specifically for children with growth failure due to Prader-Willi syndrome. This latest product approval involves Omnitrope®, manufactured by Sandoz, Inc. See Appendix C for additional product information.

Appendix G:
Growth Hormone Treatment and Prader-Willi Syndrome: PWSA | USA Clinical Advisory Board Consensus Statement, June 2009

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 percent 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 2 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 abnormalities3,10. 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.

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Appendix I:
PWSA | USA Growth Hormone Precautions Statement, February 2011

We advocate a sleep study before the start of growth hormone (GH) on infants, children and adults with Prader-Willi syndrome (PWS), and then a follow-up study 6-8 weeks later. If there is worsening of obstructive sleep apnea (OSA) while on GH, temporarily stopping the GH is recommended until the cause is understood. Frequently, the OSA can be corrected by removing the adenoids and tonsils or lowering the dose of GH (in the face of an abnormally high IGF-1). We also recommend taking precautions during bouts of upper respiratory infections.

There are reports and discussions in the medical literature about adrenal hypofunction in PWS. Single measures of cortisol levels will not be helpful and adrenal challenge tests may be warranted. Please consult an endocrinologist for input and advice before starting growth hormone treatment.

Infants with PWS may have gastroesophageal reflux disease (GERD), which causes obstructive hypopneas/apneas. If an evaluation is positive for GERD, an anti-reflux medication may be prudent before starting GH.

Studies have shown that in most individuals with sleep-disordered breathing due to PWS, GH can actually improve (or at least does not worsen) the apnea (Haqq, et al., 2004; Miller, et al., 2006; Festen, et al., 2006). Withholding GH from those with sleep apnea may be detrimental on several levels. Therefore, the recommended approach is that children with PWS be monitored closely when starting GH to make sure they do not worsen.

The FDA has a statement warning that there could be an increased risk of death associated with GH due to a recent study in France indicating that there may be a slightly increased risk of death in certain individuals treated with GH. PWS is not one of the groups mentioned as being at increased risk; they specifically mention idiopathic short stature and isolated GH deficiency.

Jennifer Miller, M.D., M.S. – Endocrinologist, PWSA | USA Clinical Advisory Board member

Merlin G. Butler, M.D., Ph.D. — PWSA | USA Scientific Advisory Board Chairperson

Daniel J. Driscoll, M.D., Ph.D. — PWSA | USA Clinical Advisory Board Chairperson

Appendix J:
Recommendations for Evaluation of Breathing Abnormalities Associated with Sleep in Prader-Willi Syndrome

PWSA | USA Clinical Advisory Board Consensus Statement December 2003

Problems with sleep and sleep disordered breathing have been long known to affect individuals with Prader-Willi syndrome (PWS). The problems have been frequently diagnosed as sleep apnea (obstructive [OSA], central or mixed) or hypoventilation with hypoxia. Disturbances in sleep architecture (delayed sleep onset, frequent arousals, and increased time of wakefulness after sleep onset) are also frequently common. Although prior studies have shown that many patients with PWS have relatively mild abnormalities in ventilation during sleep, it has been known for some time that certain individuals may experience severe obstructive events that may be unpredictable.

Factors that seem to increase the risk of sleep disordered breathing include young age, severe hypotonia, narrow airway, morbid obesity and prior respiratory problems requiring intervention such as respiratory failure, reactive airway disease and hypoventilation with hypoxia. Due to a few recent fatalities reported in individuals with PWS who were on growth hormone therapy (GH) some physicians have also added this as an additional risk factor. One possibility (that is currently unproven) is that GH could increase the growth of lymphoid tissue in the airway, thus worsening already existing hypoventilation or OSA. Nonetheless, it must be emphasized that there are currently no definitive data demonstrating that GH causes or worsens sleep disordered breathing. However, to address this new concern, as well as the historically well documented increased risk of sleep-related breathing abnormalities in PWS, the Clinical Advisory Board of the PWSA | USA makes the following recommendations:

1. A sleep study or a polysomnogram that includes measurement of oxygen saturation and carbon dioxide for evaluation of hypoventilation, upper airway obstruction, obstructive sleep apnea and central apnea should be contemplated for all individuals with Prader-Willi syndrome. These studies should include sleep staging and be evaluated by experts with sufficient expertise for the age of the patient being studied.

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2. Risk factors that should be considered to expedite the scheduling of a sleep study should include:
    a. Severe obesity — weight over 200 percent of ideal body weight (IBW).
    b. History of chronic respiratory infections or reactive airway disease (asthma).
    c. History of snoring, sleep apnea or frequent awakenings from sleep.
    d. History of excessive daytime sleepiness, especially if this is getting worse.
    e. Before major surgery, including tonsillectomy and adenoidectomy.
    f. Prior to sedation for procedures, imaging scans and dental work.
    g. Prior to starting growth hormone or if currently receiving growth hormone therapy.

Additional sleep studies should be considered if patients have the onset of one of these risk factors, especially a sudden increase in weight or change in exercise tolerance. If a patient is being treated with growth hormone, it is not necessary to stop the growth hormone before obtaining a sleep study unless there has been a new onset of significant respiratory problems.

Any abnormalities in sleep studies should be discussed with the ordering physician and a pulmonary specialist knowledgeable about treating sleep disturbances to ensure that a detailed plan for treatment and management is made. Referral to a pediatric or adult pulmonologist with experience in treating sleep apnea is strongly encouraged for management of the respiratory care.

In addition to a calorically restricted diet to ensure weight loss or maintenance of an appropriate weight, a management plan may include modalities such as:

- Supplemental oxygen
- Continuous positive airway pressure (CPAP) or BiPAP
- Oxygen should be used with care, as some individuals may have hypoxemia as their only ventilatory drive and oxygen therapy may actually worsen their breathing at night.
- Behavior training is sometimes needed to gain acceptance of CPAP or BiPAP.
- Medications to treat behavior may be required to ensure adherence to the treatment plan.

If sleep studies are abnormal in the morbidly obese child or adult (IBW>200%) the primary problem of weight should be addressed with an intensive intervention — specifically, an increase in exercise and dietary restriction. Both are far preferable to surgical interventions of all kinds. Techniques for achieving this are available from clinics and centers that provide care for individuals with PWS and from the national parent support organization (PWSA | USA). Behavioral problems interfering with diet and exercise may need to be addressed simultaneously by persons experienced with PWS.

If airway-related surgery is considered, the treating surgeon and anesthesiologist should be knowledgeable about the unique pre- and postoperative problems found in individuals affected by Prader-Willi syndrome (see “Medical News” article regarding “Anesthesia and PWS” written by Drs. Loker and Rosenfeld in The Gathered View, vol. 26, Nov. — Dec. 2001 or visit www.pwsausa.org). Tracheostomy surgery and management presents unique problems for people with PWS and should be avoided in all but the most extreme cases. Tracheostomy is typically not warranted in the compromised, morbidly obese individual because the fundamental defect is virtually always hypoventilation, not obstruction. Self-endangerment and injury to the site are common in individuals with PWS who have tracheostomies placed.

At this time there is no direct evidence of a causative link between growth hormone and the respiratory problems seen in PWS. Growth hormone has been shown to have many beneficial effects in most individuals with PWS, including improvement in the respiratory system. Decisions in the management of abnormal sleep studies should include a risk/benefit ratio of growth hormone therapy. It may be reassuring for the family and the treating physician to obtain a sleep study prior to the initiation of growth hormone therapy and after 6-8 weeks of therapy to assess the difference that growth hormone therapy may make. A follow-up study after one year of treatment with growth hormone may also be indicated. Members of the Clinical Advisory Board are available for consultation with physicians and families through the Prader-Willi Syndrome Association | USA.

Prader-Willi Syndrome Association | USA
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MILESTONES

1956	Prader-Willi syndrome (PWS) is first described in a published article by Swiss doctors Prader, Willi and Labhart
	Human growth hormone is first isolated by scientists
1958	The first growth hormone injection is given to a human, using growth hormone extracted from the pituitary of a cadaver (deceased person)
1972	The chemical structure of human growth hormone is discovered
1985	Use of human growth hormone from cadavers is halted after several patients develop a deadly brain disease (Creutzfeldt-Jakob disease, or CJD) from contaminated extract
	The first synthetic (manufactured) growth hormone is approved by the U.S. Food and Drug Administration (FDA) for treatment of children with growth hormone deficiency
1987	The first article on the effect of growth hormone treatment in PWS is published in a medical journal
1992	The first major presentation on growth hormone treatment in PWS is given at a PWSA | USA conference
1996	The FDA approves GH for treatment of adults with growth hormone deficiency
1997	Results of the first controlled scientific studies on GH treatment in PWS (in Europe) are published
1999	Results of the first U.S. controlled study of GH treatment in PWS are published
2000	The FDA approves the first GH treatment specifically for children with growth failure due to PWS (Genotropin®/Pfizer)
2010	The FDA approves a second GH treatment specifically for children with growth failure due to PWS (Omnitrope®/Sandoz)

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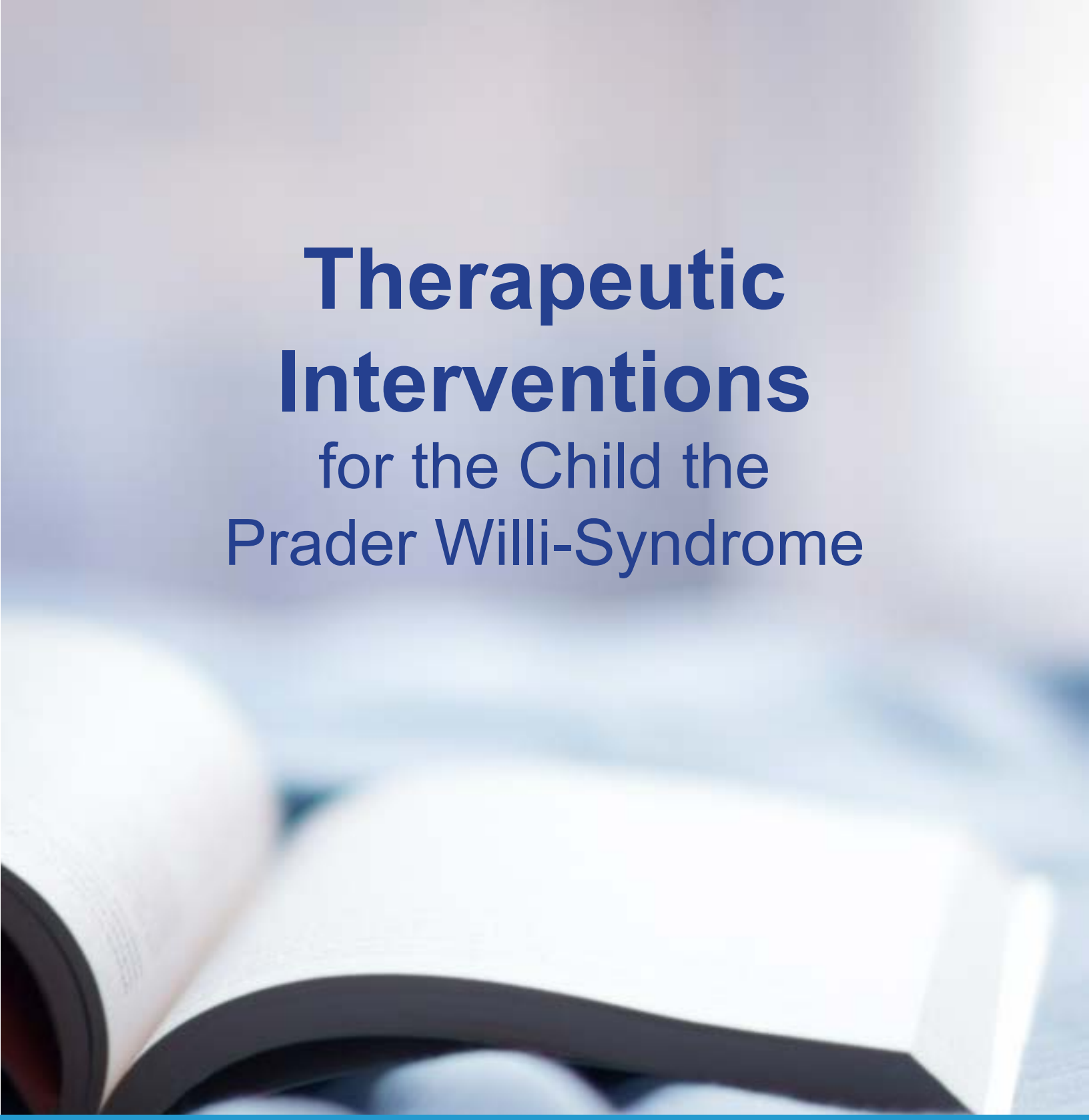
RGK Foundation
1301West 25th Street
Suite 300
Austin, Texas 78705-4236

Together We Are Saving Lives

Prader-Willi
SYNDROME ASSOCIATION | USA
SAVING AND TRANSFORMING LIVES



Therapeutic Interventions

for the Child the Prader Willi-Syndrome

Prader-Willi
SYNDROME ASSOCIATION | USA
SAVING AND TRANSFORMING LIVES

Written by:
Janice Agarwal, PT, CNDT

THERAPEUTIC INTERVENTIONS FOR THE CHILD THE PRADER WILLI-SYNDROME

Working Together
To Change Lives!

Published by Prader-Willi Syndrome Association | USA

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Acknowledgements

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And to Stacey Hiller and Kate Schuppert, friends first, therapists and sounding boards second. Limitations in my descriptions are not reflections of their skills and dedication to their patients.

Special thanks to Rebecca Gibson and Jessica Hearn who helped with illustrations, and Jessica Hearn for editing my book.

Janice Agarwal, PT, CNDT

Chapter 1: What is a Pediatric Physical Therapist?

A pediatric physical therapist specializes in the examination, evaluation, treatment, and management of infants, children, and adolescents with developmental, neuromuscular, and skeletal disorders. Physical therapists collaborate with patients' families and other medical, educational, developmental, and rehabilitation specialists to promote the participation of children in daily activities and routines in the home, school and community. Physical therapy treatments improve gross and fine motor skills, balance and coordination, and strength and endurance. In addition, physical therapy treatments enhance learning opportunities and sensory processing/integration.[2]

All physical therapists currently must earn a graduate degree (either a master's degree or a clinical doctorate) from an accredited physical therapy program before taking a national licensure examination. A physical therapist must also be licensed in each state in which the therapist practices. Physical therapists are trusted health care professionals with extensive clinical experience who complete a thorough examination and then prevent or treat conditions that limit the body's ability to move and function in daily life.

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Chapter 2: What is Early Intervention?

Early Intervention (EI) is a systematic program of therapy, exercises, and activities designed to address developmental delays that may be experienced by children with Prader-Willi syndrome or other disabilities. These services are mandated by a federal law called the Individuals with Disabilities Education Act (IDEA). The law requires that states provide EI services for all children who qualify, with the goal of enhancing the development of infants and toddlers and helping families understand and meet the needs of their children. The most common EI services for infants with Prader-Willi syndrome are physical therapy, speech and language therapy, occupational therapy, and social services.

Private and public health insurance programs cover payment for physical therapy, but the services and reimbursement may vary and families should be familiar with the benefits provided by the policy or program. In addition, provision of pediatric physical therapy is required legislatively by the following acts of congress:

The Individuals with Disabilities Education Act (PL 105-17, IDEA)

IDEA is a federal law that supports the provision of public education for all children regardless of the nature or severity of their disability. Part C of IDEA is an optional federal program that supports Early Intervention for infants and toddlers (birth to three years). All states currently participate in Part C.

IDEA includes provisions for pediatric physical therapy for children from birth to twenty-one years of age who are eligible for Early Intervention (Part C) or special education and related services (Part B) programs. IDEA interacts with other legislative mandates, such as the Americans with Disabilities Act, Section 504 of the Rehabilitation Act, and the Technology-Related Assistance for Individuals with Disabilities Act.

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The Americans with Disabilities Act

ADA protects the rights of all individuals with disabilities.[25]

Section 504 of the Rehabilitation Act

Section 504 requires the provision of reasonable accommodations, including physical therapy, for persons with disabilities.

When Should Early Intervention Start?

Early Intervention (EI) should begin any time shortly after birth, and should usually continue until the child reaches age three. An amendment to IDEA in 2004 allows states to have EI programs that may continue until the child enters, or is eligible to enter, preschool. Although it's never too late to start, the sooner EI begins, the better.

How Does Early Intervention Benefit Infants?

The first years of life are a critical time in a child's development. All young children go through the most rapid and developmentally significant changes during this time. During these early years, they achieve the basic physical, cognitive, language, social, and self-help skills that lay the foundation for future progress. These abilities are usually attained according to predictable developmental patterns. Because children with Prader-Willi syndrome face delays in all areas of motor development, EI is highly recommended.

Development is a continuous process that begins at conception and proceeds stage by stage in an orderly sequence. There are specific milestones in each of the five areas of development (gross and fine motor abilities, language skills, cognitive development, social development, and self-help skills) that serve as prerequisites for the stages that follow. Most children are expected to achieve each milestone at a designated time, also referred to as a "key age," which can be calculated in terms of weeks, months or years. Primarily due to hypotonicity (see Chapter 4, "Basic Issues for All Children with PWS"), infants with Prader-Willi syndrome will likely experience delays in certain areas of development. On their own timetable, however, infants with Prader-Willi syndrome will achieve each of the same milestones in the same order as other children. Remember, in monitoring the development of a child with Prader-Willi syndrome, it is more useful to look at the sequence of milestones achieved, rather than the age at which the milestones are reached.

Each service type provided in Early Intervention (EI) addresses specific aspects of an infant's development.

Physical Therapy

Physical therapy (PT) focuses on motor development. For example, during the first three to four months of life, an infant is expected to gain head control and the ability to pull up to sitting position with no head lag and enough strength

in the upper torso to maintain an erect posture. Obtaining this milestone and others will be delayed in infants with Prader-Willi syndrome, but with appropriate physical therapy these milestones will eventually be achieved.

Speech and Language Therapy

Speech and language therapy (ST, SPT, or SLP) focuses on the many pre-speech and pre-language skills that must be acquired before an infant says his or her first words. These skills include the ability to imitate and echo sounds; turn taking skills (learned through games like “peek-a-boo”); visual skills (looking at the speaker and objects); auditory skills (listening to music and speech for lengthening periods of time, or listening to speech sounds); tactile skills (learning about touch, exploring objects in the mouth); oral motor skills (using the tongue, moving the lips); and cognitive skills (understanding object permanence and cause and effect relationships).

As infants with Prader-Willi syndrome may not say their first words until two or three years of age, speech and language therapy during this early time period is crucial to help infants with Prader-Willi syndrome develop the skills needed to say their first words. While many children may have delays with speech they often have normal receptive skills for understanding speech.

For more information, see the American Speech-Language-Hearing Association at www.asha.org.

Occupational Therapy

Occupational therapy (OT) focuses on fine motor skills, activities of daily living (ADL’s), and sensory development. These skills include opening and closing things, picking up and releasing toys of various sizes and shapes, stacking and building, manipulating knobs and buttons, experimenting with crayons, etc. As infants with Prader-Willi syndrome will need to learn to feed and dress themselves and learn skills for playing and interacting with other children, occupational therapy during early development is crucial.

For more information, see the American Occupational Therapy Association, Inc. at www.aota.org.

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How Does Early Intervention Benefit Parents?

Programs for Early Intervention (EI) offer parents support, encouragement and information. Therapists teach parents how to interact with their infant and toddler while meeting their child's specific needs and enhancing development.

Parents and families have the primary role in their child's development. EI therapists collaborate with the family to implement an individualized program for the child. Families are supported through coordination of services, advocacy, and assistance to enhance the development of their child. For example, pediatric physical therapists help parents with:

- *Positioning* during daily routines and activities
- *Adapting toys for play*
- *Expanding mobility* (movement) options
- *Using equipment effectively*
- *Teaching safety for the home and community*
- *Providing information* on the child's physical and health care needs
- *Easing transitions* from early childhood to school and into adult life
- *Safe movement* throughout the home

Who Pays for Early Intervention?

The evaluation to determine whether your child is eligible for EI is free of charge if performed by a state-authorized entity. No child deemed eligible can be denied services based on ability to pay, but insurance companies may be billed and/or a sliding scale payment may be required, depending on the state in which you reside. Check with your state's EI center for information about authorized service providers and financial obligations. Frequently, there is little or no cost to parents for these services.[20]

How Do I Sign Up for Early Intervention Services?

Parents can refer their own child. They can also get a referral for Early Intervention (EI) from their pediatrician, or find a local agency by visiting the website of the National Early Childhood Technical Assistance Center (www.nectac.org). Each state has its own set of laws governing EI services. Once a referral has been made, the program staff must schedule and complete an initial evaluation within a specified time.

Once the assessment is completed, a caseworker is assigned to coordinate the various services for which the infant and family qualify. EI services are individualized to meet the specific needs of each infant. The caseworker, therapists, and family will determine the duration, frequency, and location of services and will set goals based on developmental

milestones.

These will be recorded in a document called the **Individualized Family Service Plan (IFSP)**. The IFSP describes the process of planning, decision-making, and implementation of EI services for children and their families. This IFSP is periodically reviewed so that goals can be re-assessed by the whole team as the child progresses.

What Happens After Age Three?

Children age out of Early Intervention at age three. Children are re-evaluated by their school district to be approved for special education and continued speech, physical, and occupational therapy services administered through a preschool. The Individualized Education Program (IEP) is mandated by the Individuals for Disabilities Act to meet the needs of any individual with disabilities or special needs.

For more detailed information, visit this IEP guide on the Department of Education's website: www2.ed.gov/parents/needs/speced/iepguide/index.html

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Chapter 3: APTA and IDEA Fact Sheet

APTA, American Physical Therapy Association
1111 North Fairfax Street
Alexandria, VA 22314-1488

Phone: 800-999-2782, ext 3254

Fax: 703-706-8575

Email: pediatrics@apta.org

Website: www.pediatricapta.org

IDEA, the Individuals with Disabilities Education Act

Implementation of IDEA Part C is the responsibility of each state through a lead agency appointed from education, health, human services, public health, or another related state agency.

Part C requires that multiple agencies work together and collaborate on meeting the needs of infants and toddlers and their families in their states and communities.

Eligible children have a developmental delay or a medical diagnosis that has a high probability of a developmental delay.

States define the eligibility criteria for developmental delay by addressing the child's development in cognitive, physical, communicative, social/emotional, and adaptive (self-help) domains.

Eligible infants and toddlers are entitled to Early Intervention (EI) services in natural environments where children live, learn, and play (their own homes).

EI services are provided, as necessary, to meet the developmental needs of the child and needs of the child's family related to the family's ability to enhance the child's development.

IFSP, the Individualized Family Service Plan

Parents are an integral part of the process and development of the IFSP and must be notified of their rights, including the right to due process.

Under IDEA, Early Intervention Child Find mandates evaluation and assessment, service coordination and development of an IFSP that must be provided free of charge. *EI services are free except when federal or state law provides for a system of payments by families, including a schedule of sliding fees.*

With parental consent, local agencies may access other funding sources, such as the state's Medicaid program. Additional rules and requirements pertaining to funding may be determined by the state.

The inability of parents to pay or utilize personal insurance must never prevent the delivery of EI services.

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Chapter 4: Physical Therapy

Physical therapists use their knowledge and skills specifically related to motor and self-care function, assistive technology, and medical/ health care science to provide a unique contribution to the IFSP team.[2] Physical Therapists provide service by collaborating with the team, exchanging information with the family, and integrating interventions into everyday routines, activities, and locations.

How to Start Pediatric Physical Therapy

The process begins with an interview to identify the child's needs, usually while a newborn is still in the hospital, and continues with a physical and developmental evaluation of the child. This evaluation may include assessment of muscle and joint function, mobility, strength and endurance, cardiopulmonary status, posture and balance, and sensory motor and neuromotor development.

Basic Issues for All Children with PWS

Children with Prader-Willi syndrome exhibit low tone (hypotonicity), decreased muscle strength, delayed motor planning, dyspraxia, delayed gross motor skills, scoliosis, and decreased sensory awareness (such as oral motor deficits).

Hypotonicity

Hypotonicity (low muscular tone) is seen as excessive floppiness and inactivity. The child feels more flexible and difficult to handle. This is noticeable because considerable support may be necessary to stabilize the head and trunk during feeding, dressing, bathing, and carrying the child. This will often lead to difficulty in exploring their environment or bringing their hands or objects to their mouth. Movement is how children learn. If a child loses even a few months of this movement and exploration their cognitive and physical development can be adversely affected.

Hip subluxation may occur when the child's thigh and pelvic muscles are hypotonic. Legs are abducted (like doing the splits) and externally rotated (pigeon-toed). If you or your therapist are concerned about hip subluxation, speak with your pediatrician. An x-ray may be warranted.

Muscle Strength

Muscle strength is the amount of force a muscle can produce with a single maximal effort.16 Building muscle strength helps with body alignment and makes performing everyday actions easier. *Children with low muscle tone have the potential to strengthen their muscles.*

Motor Planning

Motor planning is the brain-body communication that allows one's brain to make a plan of action and have one's body carry it out.

Dyspraxia

Dyspraxia is difficulty in planning, sequencing, and carrying out unfamiliar actions in a skillful manner. Dyspraxia leads to poor motor planning.

Praxia is the ability to interact successfully with the physical environment to plan, organize, and carry out a sequence of unfamiliar actions, and to do what one intends, wants, and needs to do in an efficient, satisfying manner.[14]

Gross Motor Skills

Gross motor skills are movements that involve large muscle groups for crawling, walking, running, and other activities. Motor skills involve the movements of muscles in the body. Fine motor skills are movements of smaller muscles for actions such as grasping objects. Gross and fine motor skills usually develop together since most activities use both large and small muscle groups.

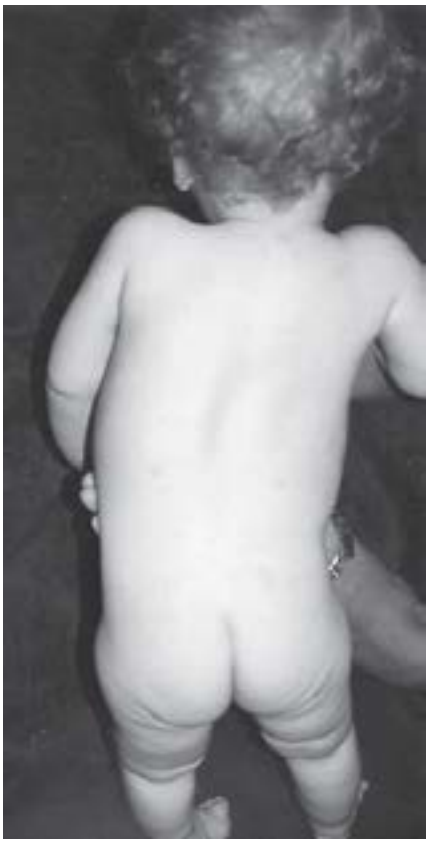
Scoliosis

Scoliosis is an abnormal lateral (sideways) curve of the spine. Scoliosis may be noted with infants who are encouraged to sit before their back muscles can properly sustain an upright posture symmetrically using muscles on both sides of the back. For many children with Prader-Willi syndrome, however, scoliosis occurs before they come up to sit. This type of infantile scoliosis will often resolve when parents, working with therapists, are able to aggressively strengthen their children's back and trunk (core) muscles. Physical therapists should strongly recommend that infants with scoliosis be placed in a functional compression bracing suit to assist with sensory-motor, neuro-motor, or musculoskeletal deficits.

These suits help a child develop and use postural control and movement mechanisms to perform daily activities in the most efficient and least energy consuming manner, and build a symmetrical and stable foundation for strengthening the core muscle

groups. The suits are often made of a Lycra material to provide a steady stretch tension while also guiding the internal soft tissue structures with compression. This compression provides deep pressure sensory information to the proprioceptive feedback system (see “Sensory Awareness” below), resulting in improved limb and body awareness, improved core muscle and joint stabilization, and increased activation and use of muscles.

If your child has scoliosis, work with your physical therapist to learn about the best type of compression brace for your child.



Young children with PWS often have infantile scoliosis, which can usually be resolved with therapy and bracing. As a child’s trunk strength increases, the muscles can correct the curve. This child had a thirty-three degree scoliosis that decreased to seven degrees with one year of therapy and bracing.

Sensory Awareness

As described by A. Jean Ayers, OT, in *Sensory Integration and the Child*: Sensory experiences include touch, movement, body awareness, sight, sound, and the pull of gravity. The process of the brain organizing and interpreting this information is called Sensory Integration (SI). Sensory Integration provides a crucial foundation for later, more complex learning and behavior.

For most children, Sensory Integration develops in the course of ordinary childhood activities. Motor planning ability is a natural outcome of the process, as is the ability to adapt to incoming sensations. But for some children, Sensory Integration does not develop as efficiently as it should. When the process is disordered, a number of problems in learning, development, or behavior may become evident.[4]

All children with Prader-Willi syndrome have Sensory Integration deficiencies. These weaknesses are manifested through poor motor skills, poor sucking, poor vocalization, poor body awareness, behavioral issues and cognitive development. Basic treatment strategies are described later in this book.

Work with your OT, PT, and SPT to address sensory awareness and develop a plan for the early years. Update the plan as children enter school to provide strategies to help them develop and be successful at all ages and in any environment.

PWSA | USA’s website (http://www.pwsausa.org) has several articles on sensory integration deficiencies and strategies.

Chapter 5: Physical Therapy Intervention

The goal of physical therapy is to facilitate normal development of gross motor skills, not to artificially accelerate the rate of gross motor development. It's important not to put too much emphasis on *when* our infants achieve their milestones, and to focus instead on *how well* our infants achieve each stage of development. These stages need to be achieved in the correct sequence, so that each subsequent stage can be built on the solid foundation of the prior stage. Although almost all of our infants will eventually obtain motor skills (regardless of the speed or order in which they are acquired), developing motor skills in the proper order ultimately translates into better strength and coordination.

Unfortunately, many parents, physical therapists, and insurance companies assume that the value of physical therapy is only measured by the speed with which a child achieves motor skills. Nothing can be further from the truth. How quickly a child goes from lying to sitting, and later to standing, does not address the underlying issues of hypotonia, lax ligaments, decreased strength and endurance, and decreased sensory motor awareness. If pushed too quickly, children with Prader-Willi syndrome will learn inefficient compensatory muscle movement patterns because they do not have a solid foundation in strength and coordination. If these compensatory patterns are not addressed properly, they will develop into significant orthopedic and functional problems.

One example would be how an infant learns to sit up independently, widely considered an important "milestone." An infant who develops trunk muscles and sits before developing neck, chest, and shoulder muscles will be able to sit up, but once up, will not be able to hold his head upright, will not be able breathe efficiently (limiting lung expansion), and will not be able to rotate his trunk to help look around. This will lead to further difficulty when the infant learns to stand. Physical therapists help infants develop neck, chest, and shoulder muscle strength before working on trunk strength. Physical therapists will first work with a prone (on his stomach) infant to build muscles to support

lifting his neck so he can look around, then on chest wall muscles to help support his shoulder blades and shoulder joints, then shoulder and arm muscles to allow him to prop up, then finally on trunk, waist, and pelvic muscles. Developing support level-by-level keeps a child's spine and pelvis in proper alignment as he incrementally builds strength to hold each spine segment in place before he moves upright. If weak when upright, a child will not be able to use his arms and shoulders for support and protection when he falls. If weak when upright, a child will try to develop the muscles he needs for neck and chest strength, but these muscles will develop poorly (with compensatory movements). Appropriate physical therapy can minimize problems with trunk posture and facilitate correct muscle development. More advanced motor skills can then be built upon a proper foundation.

Treating injury is different from facilitating normal development. After an injury, children with PWS have difficulty maintaining correct motor development. If treatment of an arm or leg fracture requires immobilization or causes any decrease in activity level, it is imperative that therapy be started as soon as medically allowable to let the child relearn how to use the limb and correct the compensatory movements that will have developed due to the immobilization. Although normal tone children will almost automatically resume normal activity after an injury, children with PWS may not.

lex loves to ski. Instructors that have the necessary knowledge and equipment can provide amazing results. A family ski trip that includes a child with PWS is now a reality.

Instead, our children will take the easy way out and continue to use the compensatory movements learned during recovery. It is difficult but important to revert back to previously learned "normal" ways of movement. Children with PWS need to move through each stage of the developmental sequence in proper order without skipping ahead: rolling, pivoting, sitting, crawling, and so forth. Children develop postural control in stages, using sight as the dominant sense to achieve and maintain an upright position. The following are some of the milestones that our children need to master and the order in which they should be achieved. Parents and caregivers are encouraged to attend physical therapy sessions to learn exercises and techniques that can be carried over at home to help infants and children reach their milestones.

Normal Development in the First Year

Infants without delays follow a developmental progression that starts at birth. As the infant grows and his neurological system matures, gross motor skills will develop.[6]

First Three Months

The infant becomes increasingly alert and wants to look around and hold his head up to watch you talk or look at lights and movement. He begins to develop strength and coordination in his neck and upper back muscles.[6]

When prone (on his belly), he is able to move his head more efficiently. His upper extremity control increases and he is able to prop up on his forearms. While watching activities around him, he will start to shift weight side to side.

Around Four Months

As the infant gains control of his head, he will *roll over accidently* as he reaches for a toy.[6]

Early movement at this age may start as “creeping” (pushing his body around on his stomach), scooting or crawling on one leg while dragging the other, or a combination of rolling and squirming on his stomach, back, or bottom. Shortly after this form of locomotion, most infants progress to hands-and-knees crawling. Most don’t start crawling until around eight months, when they are more independent with sitting.

Around SIx Months

The infant has good control of his head and displays strong control against gravity. When placed into a seated position, the infant will balance himself by *propping up* on both arms.[6]

Shortly after this, infants will *move into and out of sitting without help* using both hands to move and then *sit independently* while mouthing or playing with a toy.

Around One Year

This is the time when an infant/toddler tries to pull himself up to a stand, then *cruise along furniture*, then *take a few steps*. This is the age when nothing is safe because kids get into everything![6]

Infants with PWS: Year 1 (Before Walking)

Our children with Prader-Willi syndrome are often delayed in comparison to the normal pattern of development. Without interference their gross motor skills do develop in sequence, but not with the strength, balance, coordination, and motor planning control required to allow them to learn higher skills successfully. We must encourage their natural curiosity to reach out, explore objects, and interact with the environment.

Development takes effort, so we might as well make it fun.

The following are just ideas; your PT will establish an individualized program to treat your infant's strengths and weaknesses based on a detailed professional assessment. In accordance with the prescribed program, your PT will give you very specific instructions on wonderful ways to work with your child — however, this section provides a few general ways in which you can interact with your infant at home to encourage proper development at each stage of the process. Each developmental milestone will build on a previously developed skill as your infant learns many new movements and prepares himself for higher activities. Playing with your infant at home will make it possible for your infant to explore his surroundings and develop gross motor and cognitive skills.

A child lying prone on a stable pillow or boppy will raise his head to view objects and reach for toys while strengthening his neck, shoulders, and back.

Head Control

Head control is the first movement that an infant achieves and is necessary for sitting, crawling, and walking. Head control requires strength and coordination of neck muscles to allow the infant to flex (bend) forward, backwards, and side-to-side. An infant will first develop head control and good postural tone on the ground while prone (on his stomach), then while supine (on his back), and later in sitting.[6]

Intervention: Start in Prone

Due to the risks of SIDS (sudden infant death syndrome), all work done in prone needs to be monitored carefully.

Staying prone means staying on one's belly. Infants first develop head control and postural tone while on the ground, mostly when they are prone. An infant develops very strong shoulders when learning to prop up and look around. Infants should be allowed to slowly work to lift their heads up, to come up on their shoulders, and later, to come up on all fours and crawl. Strong shoulders mean:

- **Easier future development of fine motor skills** such as writing, playing with small toys, and developing soft and strong grips.

- **Better development of protective "righting reactions,"** or catching themselves with their extended arms, needed to protect heads when infants fall forward, sideways or backwards. Without proper strength in their shoulders

and trunks, they may walk but will have difficulty with advanced movements involving balance coordination.

- A strong stable shoulder girdle, which is required later for accurate speech sounds.

Infants with hypotonia often abduct their arms and legs from the trunk to increase their stability. Try placing a hypotonic child on his stomach over a small pillow, leg, or boppy and bringing his arms over the pillow. Place their hands on the ground to provide some weight bearing and give your child a chance to work on his spinal muscles and neck by encouraging him to look up at interesting objects or towards sounds.

Children that don't have proper strength in their shoulders and trunk may walk but will have difficulty with more advanced movements due to fear of falling and hurting themselves, otherwise known as postural instability.

One of the other issues that is improved with infants spending time on their bellies is a stronger pulmonary system. The rib cages of babies are set very high. As they develop strong trunks and abdomens, we see their rib cages start to drop and elongate, and breathing becomes deeper and more oxygen rich. Many of our children have unanticipated problems because of their pulmonary limitations. We want to give them every chance to increase their pulmonary function.

Pull to Sit:
Place the infant on your lap and gently, with hands on his shoulders, raise him to sit upright. Do not let their head drop back. This is a fun way to sit with your child and play.

Intervention: Pull-to-Sit

Another important way to develop head control is in the pull-to-sit position. Place the infant on his back (either on the floor or on your lap). Place both of your hands behind his shoulders, providing as much support as required so that the baby's head does not drop back. If the neck is very weak, place a hand behind his head rather than his shoulders. Slowly raise the child from the ground towards you. As the infant's neck gets stronger, you can do this by holding his hands and gently pulling the infant up to sit. This should only be done when the infant shows that he can bring his own head forward.

As you place your child back onto the ground, realize that this is a wonderful time to encourage him to look from side to side. If he

Pull to Sit (advanced):
When your child has more head control, you grab his elbows and slowly pull to sit. This requires strength in neck, shoulders, and core.

cannot move his own head fromside to side, you can gently place your fingertips on his head and help him while he follows a toy with his eyes. You can also help your child bring his hands and feet to hismouth so he can start exploring his own body. This also encourages the strengthening of the abdominal muscles (belly).

Encourage a child on his back to explore his feet and bring his hands to hismouth to strengthen his arms, legs, and core. This facilitates good sensory and body awareness.

Intervention: Sitting

Place the infant in an upright sitting position on your lap, facing you. With your hands behind his shoulders and his head initially supported by your knees (until he can hold it up himself), move him from side to side.

Rolling

Rolling an infant from back to belly or belly to back requires some head control and the ability to rotate the body from hips to shoulders. Rolling is one of the first abilities that allows an infant to move around.[6] Often, infants with PWS have difficulty initiating this movement.

Rolling SIde-to-Side:
To roll an infant to the left, gently grasp his right leg and draw it across his body to encourage him to twist and roll over his left side to his belly. Reverse the motion to return him to his back, and do the same with the other leg. This can become a fun game with your child and it dramatically improves his vestibular system.

Intervention: Place the infant on his back on the floor. Show the infant a bright toy. As he focuses on the toy, move the toy to one side. As the infant follows the object with his eyes, he will be encouraged to roll. If he cannot roll independently, gently hold onto his opposite leg and help him roll onto his side, and then over onto his stomach. Repeat for each side. This can become a fun game to play with your child!

Sitting

The ability to maintain a sitting position requires an infant to have developed
equilibrium reactions and protective reactions forward, side-to-side, and backwards.[9]

Propping Up

Equilibrium and righting reactions: Righting reactions can be broken into several different reflexes that serve to keep the head in a normal position, right the body to a normal position, and adjust the body parts in relation to the head and vice versa. The majority of the righting responses should be built into the nervous system before three years of age. The equilibrium reactions develop in childhood as well and are for

the purpose of maintaining or regaining control over the body's center of gravity.[21]

Intervention: If an infant has difficulty maintaining his balance, his equilibrium reactions can be improved by playing in sitting and challenging his balance in all directions. This should be done in a very safe environment with pillows all around, and the adult must be careful not to let the infant fall and hurt himself. If the infant falls to the side while in sitting, you need to try to teach him to use his hands for balance. Start by placing one of his hands out to the side. Gently shift him off balance to that side so that he needs to use that arm to maintain sitting balance. Try the same procedure on the other side.

Initially an infant sits by propping himself up with both hands in front. As his balance and upright posture improve, he maintains the sitting position by placing a hand to one side or the other as needed to keep upright. Eventually, the infant will be able to hold himself in a good sitting position without the use of hands for balance.[6]

Alex is just learning to move from prone to a sit. He has propped himself up on both hands for posture.

Creeping and Crawling

Creeping is moving around on one's stomach. Some define it as squirming on one's stomach or rolling to obtain objects.

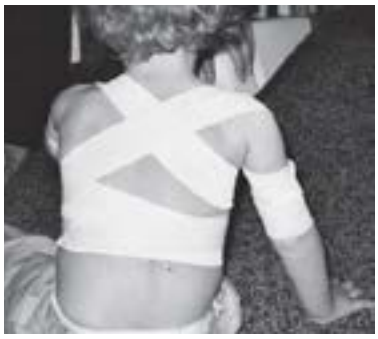
Some people prefer to call this "commando-crawling."

Crawling is raising one's stomach off the ground and moving around on arms and knees. Initially, it may start as scooting. This is when the child brings both arms forward simultaneously, followed by both legs. Eventually, this will progress to use of alternating arms and legs, usually once the infant sits well without support. He will also learn to rotate from a sitting position to his hands and knees. Their arms, legs, and back muscles need to be strong enough to keep him from falling on the floor as he does this.

It is vital that infants and toddlers not be placed too frequently in car seats, infant walkers, bouncy seats or other positions that limit their time on the floor on their stomachs. Belly time and experience bearing weight on the palms of their hands is vital to correct fine motor development, pencil grasp for writing, and attainment of fine motor skills to button and zip while dressing later in life.

Alex is transitioning from creeping on his belly to crawling. His legs are abducted to provide increased stability.

Babies that are left on their backs for long periods of time often become bottom shufflers and do not go through the normal developmental stage of crawling. They transition into walking without having attained the necessary strength that they should have developed in their shoulders and back during crawling, nor all of the strength of their arms and hands as well as the sensory motor experience that are crucial to fine motor development in their adolescent years.



Work with your therapist to place tape on your child to encourage correct posture and provide shoulder stability to allow him to be more active.

Intervention

Up until this time, infants have been working on head, neck, shoulder, and back control while on their stomachs by propping up on a rolled up towel to allow placement of weight on their arms. As strength increases, their ability to look around and to reach out and touch objects becomes easier. Placing toys outside their reach and then putting your hands under their stomachs gives them just enough support to move toward the toy. Once the toy has been retrieved, you can gently remove your hand from their abdomen to allow them to fall back down to the ground. When infant are ready to do this on their own, they will become more vocal and will start pushing objects away. This is an important time — this is when infants develop the neural connections to learn how to push up on all fours. A parent or therapist coming to their infant's "rescue" to help them do what they need to learn to do by themselves robs infants of this needed opportunity. Postural control, balance, locomotion, and manipulation all come together in crawling.

Pull to Stand

Once an infant has developed the strength, coordination, and balance to move freely on the floor by crawling, he will begin to pull up to stand.

High Kneel Position

Intervention

Initially this will start with your child coming into a high kneel position on both knees, facing a sturdy piece of furniture, such as a coffee table. If your child is unable to assume this position, you can place him in this position yourself. Then position yourself behind them with your hands on his hips to keep him upright and gently shift him to one side, placing all of his weight on one knee, so that you can pick up the non-weight-bearing leg to assist him up into a standing position. You may need to keep your hands on his hips to guide him as he pulls himself up to the standing position.

As infants pull up to stand, they gain further strength and control in their trunk and leg muscles. Soon they develop enough strength and balance to cruise

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along furniture, and nothing is safely out of their reach! This is a great time to work with your therapist to see if your child will need foot orthotics to correct any weaknesses that will lead to future problems in standing and walking.

If your infant has difficulty moving, you can help him improve his standing balance by gently shifting his weight from side to side and encouraging him to learn to balance weight on each leg. Place your hands at his hips as you shift his weight from one leg to the other.

Encourage cruising along furniture by placing a toy just of out of reach along the edge of a couch or coffee table. With both of your hands on your child's hips as he supports himself while facing the piece of furniture, allow him to shift his weight to the leg farthest from the toy so that he can move his front leg closer to his intended goal. Once he places that foot down, shift his weight to his front leg and allow him to bring his trailing leg up to meet it. Once your infant has perfected this sidewise shuffling movement, he will soon be able to move around the furniture independently.

Alex is learning to pull up to stand. His therapist is using both hands on his hips to encourage weight shifting from one foot to the other to he can start cruising along furniture. The straps will help him move with less support.

Walking

As your child begins to walk, confirm with your therapists whether orthotics are required at this point. Children with PWS typically learn to walk with their feet wide apart, their knees stiff, and their feet turned out. Locking their knees, widening their base, and rotating their feet are strategies they will naturally use to increase stability. This very inefficient pattern will eventually develop into problems with the knees and feet. Infants will also find it difficult to move up to a narrow base of support, which is required to run and jump and play with their peers. Orthotics are sometimes recommended to eliminate this inefficient walking pattern.

Intervention

Place your child in a standing position behind a small push toy (with handles) that is very stable. Stand behind the infant with your hands on his hips for support. Move the object several inches forward and allow him time to shift his weight to one side, pick up a foot, and take a step forward. Repeat this as he continues to move the object forward. As his balance and posture improve, offer him less support. Try to make walking a fun and purposeful activity. Allowing an infant to hold a large ball or object will give him some confidence in walking around the room.

Children with PWS: Year 1-3 (After Walking)

Once your child is walking, you may find that your therapists decrease his physical therapy to one session per week. They may also increase his occupational therapy to two or three sessions per week as he starts to refine motor movements. This is a great time to make sure that your therapists are all communicating with each other to get the best carryover.

For example, your physical therapist should work with your occupational and speech therapists as to determine which sitting device will provide the greatest stability for your child's trunk when he is working on fine motor or oral motor activities.

Once children begin to walk, we want to refine how they walk and expand their gross motor skills. This process can involve lots of fun activities and exercises. For example:

- **Walking up and down stairs,** first with both feet meeting on each step, and then with alternating feet
- **Jumping down from a two-inch platform,** slowly increasing the height
- **Jumping on a trampoline** while you are holding both of their hands
- **Catching large balls** and throwing them back at you (this challenges their balance)
- **Starting to run**
- **Standing on one foot**
- **Kicking a ball**
- **Walking obstacle courses**
- **Walking on thick mats**
- **Balance beams** or walking on painted lines

Children will need good balance control for daily functional activities such as dressing, picking up objects, moving from indoors to outdoors, navigating uneven surfaces like grass or sand, and walking up and down hills.

Things parents can do to make these activities more fun:

- **Visit playgrounds** so they can play on the slides, climb the ladders, and swing!
- **Take them to mommy and me classes** or gym classes
- **Hippotherapy –** therapy on a horse

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Children with PWS: Year 3-5 (Preschool)

Most children with PWS walk independently by the time they are in preschool. During the preschool years, normally-developing children continue to build gross motor skills such as running a bit faster while swinging their arms, jumping off small steps, climbing, skipping, catching and throwing, hopping (first on two feet, then on one foot), and riding a tricycle. Children with PWS, however, continue to have difficulty with these skills due to their hypotonicity and obstacles related to muscle strength, motor planning, sensory awareness, and the delayed development of earlier gross motor skills.

Alex is climbing a rope ladder. Climbing adds shoulder and arm strength to existing back muscles and builds legs. Climbing also encourages alternating arm and leg movements, builds confidence, and can be fun! Placing small toys at the top can be a fun reward.

Children with PWS: Year 6-12 (Grade School)

At this age, injuries become more common. Please remember that any injury should be followed with therapy as soon as is medically allowable. The period after an injury is also a great time to reassess a child for scoliosis and determine if orthotics will be of benefit.

Children with PWS can receive therapy services in school; however, be aware that due to the cutbacks in state funding of local schools, this has become more and more difficult to obtain in recent years. Still, if your child is having difficulty with balance and walking to and from classes, he should be eligible for continued help. In-school therapy is a great opportunity for your child's professionals to continue to help him refine gross motor skills such as running, hopping, and throwing and catching balls. It is also an excellent time to continue to work on the vestibular system (balance), the proprioceptive system (body awareness), and some more advanced movements.

Hippotherapy (therapy on a horse) stimulates muscles, mobilizes joints, increases sensory motor interpretation, and develops balance and equilibrium reactions. It also improves cardiopulmonary function, which may lead to improved speech production.

Even if your child is unable to obtain services in school, you should be able to find other ways to help him become more active through weekend and after-school programs. Many communities have clubs that may offer adapted team sports and other individual and group activities dedicated to children with disabilities. These sorts of activities can not only help your child continue to develop physically and learn discipline, but can also provide a great opportunity for you to meet other parents and find out what other community resources are available. Many organizations

work with a sliding fee scale to accommodate families with financial constraints. When your child has developed sufficient skills and confidence, he or she might also enjoy participating in the Special Olympics. (Registration for the Special Olympics begins at age eight.) And of course, there are many activities that can be done right at home as well. Here are just a few of the age appropriate activities you may be able to find near you:

- **Adapted team sports** (football, basketball, baseball, soccer, bowling, etc.)
- **Swimming**
- **Karate or tae kwon do**
- **Dance**
- **Tennis**
- **Running or walking programs**
- **Exercise, yoga, or Pilates**
- **Horse riding**
- **Special Olympics** (begins at age eight)
- **Backyard games** (tag, capture the flag, leaf-pile jumping)
- **Playing on play sets**
- **Video game fitness programs** for Wii, Playstation, or Xbox

Alex playing soccer. He started playing on our town teams. He was never the best, but he always tried the hardest!

Although riding a horse is great, any animal willvdo! We are an active family and include Alex in everything.

As our children grow older we need to encourage them to be active with our families. Hiking, biking, and swimming are just a few activities. While some adjustments may be required, the more we ask from our children the more they will give (all of our children).

Adolescents with PWS

As with younger children, if an adolescent with PWS sustains an injury, you should be sure to follow recovery with therapy as soon as possible — and remember to continue to screen periodically for scoliosis. If your child is heavy, it may be necessary to have them x-rayed in order to properly identify any signs of scoliosis.

Some adolescents do well in both group and individual activities such as those listed in the prior section, as well as in more specialized group classes like low impact aerobics or Zumba. The primary goals in choosing activities are for the kids to have fun while working to maintain core strength, build strong lungs and hearts, and manage weight.

Encouraging active lifestyles in general will also help control weight. The release of endorphins induced by exercise is an additional benefit; this can allow an adolescent to relax following a period of activity, and may help moderate poor behavior, promote healthy sleep habits, and ultimately lead to a better mood and more positive self-image.

Adults with PWS

Adults have similar needs to adolescents, but may have additional issues following the transition from a family home to a group home.

Ideally, group homes should provide regular, organized exercise time that is fun and motivational. If funding allows, bring in an exercise instructor to add variety and to assess the exercises led by group home coordinators. Local health clubs or colleges may be able to provide volunteer or low cost instructors.

Other ideas include:

- **DVD's for yoga, Pilates, or dance.** Kids and adults alike love to dance to jazz, swing, hip hop, and Zumba (Latin dancing).
- **Wii-Fit, Xbox Kinect, and other physically interactive video games.** Both Wii and Xbox offer a variety of fun activities. Some programs allow players to store weight and body mass information, then track weight loss as added motivation. It's also fun to design your own Wii avatar and watch it move as you move.
- **Swim classes at a local YMCA or school.** Supervised swimming is fun for all ages and is a treat of an activity.
- **Exercise equipment.** For overweight adults, machines that offer lower impact on joint, such as ellipticals and stationary bikes are preferred.

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Chapter 6: Sensory Integration

Sensory integration is “the organization of sensory input for use.”4 This system enables the body to synthesize, organize, and process incoming sensory information received from the body and the environment to produce purposeful, goal-directed responses.

Sensory dysfunction is the ineffective neurological processing of information received through the senses, causing problems with learning, development, coordination, and behavior.[4]

Sensory integration theory is based on the understanding that neural plasticity (the ability to change) and sensory integration occur in a specific developmental order and that brain functions integrate the sensory and motor experiences.

Four main sensory systems play a role in the growth and development of the child: vestibular, proprioceptive, tactile, and oral motor.

Vestibular System

Vestibular receptors are in the semicircular canals of the inner ear. Improvements in vestibular function are often associated with improvements in hearing. Vestibular receptors provide information about movement, gravity, and changing of the head position, which helps us to stabilize our eyes when we are moving and tell us if objects around us are moving or remaining still. These skills affect balance, posture, righting reactions, muscle tone, seeing, attention, and regulation of behavior.[11]

The vestibular system is one of the first sensory systems to develop in utero and is functional at birth. Children born with abnormal tone (decreased fetal movement) will have vestibular dysfunction and should start vestibular intervention as soon as possible to stimulate vestibular development (to catch up). Initially, that is as simple as rocking our babies over and over again. Placing your child in a mechanical rocking chair with

padding on both sides to support their head is a lovely way to start.[17]

What We see when the vestibular system is weak[14]

- Hypotonia. Because of low muscle tone, many of our children feel squishy when we squeeze their bodies and arms. If you shake their arms or legs, you will see their hands or feet flopping in an uncontrolled manner. They also don't help you when you are picking them up — it's like picking up a sack of flour.

- Clumsiness. We all know these children. Almost anything they touch falls, anything that can be broken will be broken, and any opportunity to spill or drop something will lead to a mess. They are also incredibly messy with feeding, get food all over their mouth and face, and really don't know they are doing this. They are the proverbial "bull in a china shop."

- Difficulty learning new activities.

- Frequent falls. These are the children that seem to fall over their feet. They don't have the protective reactions to extend their arms in front of them to prevent their heads from hitting the ground when they fall. We need to be vigilant with this because the fear of falling will prevent our children from attempting new tasks or refining very simple milestones such as running, climbing stairs or hills, jumping, etc.

- Unpredictable behavior. This starts to declare itself as our children reach the toddler stages and older. They can get upset at the simplest of things. They are easily distracted and taken off tasks. They have frequent tantrums.

- Overly impulsive.

- Poor attention. Vestibular input gets the brain ready to act, think, and participate. Without a vestibular system to help our children understand where they are in time and space, they often appear lost.

- No handedness, delayed emergence of dominance, right/left confusion.

- Tends to take longer periods of time to accomplish age-appropriate tasks.

What we do to strengthen the vestibular system

To lessen the fear of movement or positional change, start at very slow, tolerable speeds. A child will become upset due to sensory overload if over stimulated. Before, during, and after vestibular stimulation, the child should be assessed for overstimulation. Please work with your therapists closely as you start this therapy.

- Swinging. In a well-supported seat that provides head control. Linear activities strengthen motor development and will help with balance and extensor muscle tone.

- Rocking. Linear (back and forth) activities in a chair or on a rocking horse without head support. The sooner we start this the better, for newborn and up, even adults. Rocking chairs, rocking horses, or other rocking animals are great

ways to build vestibular function and help to calm a child who is upset. Many amusement parks have animals or cars that allow the child to rock forward and back.

Vestibular therapy starts at birth! Swings and rockers will dramatically improve balance, posture, righting reactions, muscle tone, vision, speech, attention span, and behavior. Encourage all family members and therapists to engage in fun vestibular activities.

- Bouncing. On large balls, air mattresses, or old spring mattresses. This is a wonderful way to work on the vestibular system and will immediately result in a more upright posture with better head control. With bouncing, as with other activities, we see a cascade of overlapping effects on several sensory systems.

Bouncing stimulates the proprioceptive system by compressing joints and developing better posture, which allows more appropriate swallowing and better control of fine motor activities. Blow up mattresses are wonderful tools for all children, allowing jumping, falling, and walking with balance. If you prop the mattress up against a wall, a child will have fun running and bouncing off of it. These are great ways to challenge your children in a safe environment.

- Games. Such as hop scotch, ball catch, soccer, baseball, hockey, and tag. All of these will depend on the balance system, and learning them early will help to refine it. These games cause our children to learn to shift their weight onto one leg to kick a ball, learn hand-eye coordination to play catch, and learn to control a stick held in their hands to play baseball or hockey. Physical games also force children to learn to maintain their balance while rotating their bodies and shifting their weight to accommodate for the movements of weighted objects.

Children love to be pushed and pulled. We raised and taped the flaps to provide shoulder and trunk support. He loved to be scooted all over the floor and progressed to a laundry basket.

- Scooter boards. Scooters — small square flat boards with four wheels — are an excellent tool to begin learning the balance required to ride wheeled vehicles. A child can lie or sit on the scooter and be pushed in multiple directions, travelling by spinning or in straight lines. These scooters help children to learn to maintain trunk and head control while using arms and legs to move about. With a group of kids, it's fun to set up mini scooter races. Kids should become familiar with linear travel (back and forward, or side to side) before working on spinning.

- Trikes and bikes. Significantly more advanced. A trike allows us to see if our children can maintain balance and look forward while their hands and feet are steering and pedaling (dissociate head and extremity movements). For many of our children, the greatest problem here is distractibility. Parents need to be reminded that getting a child with vestibular issues to ride a bike is fantastic, but not to fret if it cannot be done safely. Not all kids will ride bikes. If finances permit, a tandem bicycle can allow parents and caregivers to actively provide the benefits of biking with a safety net for moments of distraction. On a tandem, the child in back can talk to the person in front and let us know what is happening around us. Wonderful compromise!

- Rolling and sledding down hills. Initially, parents may have to deal with the sensory issue of our children not liking the feel of grass. Please start early with brushing and playing in sand and grass to overcome this issue. Rolling sideways down hills is a fun activity for any kid. Although many hypotonic children find it difficult to engage the stomach and back muscles needed to keep rolling down the hill, it's worth the dirt and grass stains on clothing to encourage vestibular strength and balance and build awesome memories. On snow this becomes even more fun, and it's faster!

Sledding down a hill after a big snowstorm!

- Roughhousing or wrestling. Many fathers love the idea of wrestling with their kids, but are scared to roughhouse because they feel children with disabilities are too fragile. Our kids love roughhousing and wrestling! They are not too delicate, and they will actually benefit from rough but careful play. Touch stimulates proprioception, rolling stimulates vestibular, giggling stimulates oral motor, and so on. I remember telling this to an audience of Dads. Many of them agreed they would love to play on the floor with their kids but that they were afraid to hurt them. Well, several years later, one of these Dads, a lawyer, came up to me to thank me. He told me how his 15-year-old son now waits at the door for them every day to come home from work so that they can wrestle together. Both look forward to this everyday and both are doing extremely well! So, getting on the floor or on a mattress and wrestling can be a safe and positive developmental activity, as well as a fun event for our kids.

- Sliding down a slide. Slides are a wonderful way to learn protective reactions. Our kids need to develop strong protective reactions to protect their heads if they fall. Always be there to hold your child so that they are not afraid to slide, then let them go down faster and faster with their arms in front of them. It will be fantastic training.

- Somersaulting. Our kids come into this world with such poor head control that we wince at the thought of somersaulting. Once children can walk and have good head control, placing them in a gym class with thick mats and someone to help them control the complete motion is great for the vestibular system and for confidence. This is safe if done in moderation with control and supervision.

- Spinning. On a swivel chair, Sit-and-Spin, scooter board, or tire swing. Spinning is initially very scary for many of our kids. Going around just once or twice and stopping to give them a cuddle will allow them to slowly accept spinning. Our goal is to get our children to ask for more and more. Once they get over the initial fear of something that feels different, hypotonic children crave spinning. I love watching kids spin themselves and then try to walk a straight line before falling. Once children get used to spinning, higher-level activities are obtained more easily as children have fewer and fewer fears.

- Walking, running, hiking, and swimming.

- Aerobic, dance, or Zumba classes. Kids love to dance. They love to feel the rhythm and the music. It really doesn't matter if they can keep the proper steps — just that they have fun. With repetition, the steps may actually come!

- **Wii-Fit and Xbox Kinect** provide a variety of fun activities. Both now have a number of games/programs that track names, ages, fitness levels, and calories burned. They are fun and can be played in all types of weather with minimal space.

- Amusement park rides — The more the merrier! Amusement rides challenge our kids while providing so much fun. You can use these rides to see how developed their vestibular system has become. If your child can handle the tea cup rides and asks for more, you've done a great job training their vestibular system. Try these rides only if you know your child has great head and trunk control.

Calming Vestibular

Calming vestibular movements involve slow, rhythmic, linear swinging or rocking, or very gentle bouncing motions. Begin by rocking your child in a chair or placing him (with adequate props for alignment and support) in mechanical rockers/ swings. This should be started as soon as an infant is born, and I highly encourage it forever! Rocking will become a favorite activity to calm a child who feels stressed, needs to relax, or for other reasons needs to calm hinmself down. In a classroom where rockers may not be available, a child can

Rocking is Forever! Rocking has a very calming affect and should be encouraged daily.

bounce lightly on a large therapy ball when learning difficult or tedious material without disturbing the rest of the classroom.[14]

Proprioceptive System

The proprioceptive system receives sensory stimuli from receptors in all muscles, joints and connective tissue and sends it to our central and peripheral nervous systems (our brains and spinal cords). Without our needing to think about it, this system processes information about our body's position in space, the position of our body parts, their relation to each other, our balance, and our position relative to other people and objects (body awareness). It tells us how much force we need to contract our muscles and allows us to grade our movements. By reassuring us that we are where we think we are, proprioceptive input can have a powerful calming and organizing effect.[14]

What we see when the proprioceptive system is weak

- Biting and chewing objects, fingers, or nails. Often this is done out of boredom or during highly stressful times when children are trying to cope with their surroundings. It is a way of selfstimulating as an effort to not act out.

- Exerting too much or not enough pressure when handling objects. This can be seen when petting or holding a small animal. With incorrect proprioceptive input, children are not able to tell the difference between soft and hard touch and may pet or hold too hard. This can also be seen when holding a pencil or utensil. Objects are held so hard that a child's hand fatigues.

- Grinding teeth. This is often noted in the evening. Please discuss this with your dentist. A night guard to prevent significant damage to teeth and prevent temporomandibular joint syndrome (TMJ) may be recommended.

- Mushy speech. A child needs to be aware of the position of tongue and jaw to make controlled sounds and speech. Without this awareness, speech may not be intelligible.

- Walking next to or gently touching walls. Children have to be touching something all the time! With poor body awareness, continuing to touch walls after balance should be well developed is a crutch to add security when walking. It also gives them a better awareness of what is around them and how close objects are, and can calm anxieties due to poor balance or protective reactions.

- Seeking activities involving weights. Heavy work, jumping, crashing, pushing, and pulling. All of these activities put stress on the joints and give children more proprioceptive awareness, which makes them feel better, so of course, children will crave these activities.

- Poor writing. Working hard at writing, or difficulty with coloring between or within lines, stopping writing on target, forming letters, or staying on lines. Children will press down very hard to get more input into their hands.

What we do to strengthen the proprloceptive system

-Gross motor activites.

- Brushing, rolling, deep massage. In the shower or tub, use a cloth or sponge to rub arms and legs vigorously. Hand massagers are great to use on your child as well, or the child can feel and benefit from the vibration by using the hand massager to massage you! You may also want to learn the Wilbarger Brushing Protocol, a technique used in occupational therapy to address issues such as sensory seeking or defensiveness. It helps provide internal organization with tactile and proprioceptive stimuli. The program needs to be taught and supervised by an experienced OT — please speak with your OT for more information.[16]

Encourage your therapist to utilize weighted vests. The benefits include increased body awareness, balance, and orientation, and decreased impulsivity.

- Digging in the garden. This is especially fun if you dig for treasures that have been previously buried in the ground.

- Carrying heavy items. Books or luggage, or watering flowers with heavy watering cans. Weight lifting. Sleeping under blankets or quilts that have pennies or washers sewn in to add weight.

- Pushing or pulling heavy objects. Laundry baskets, light furniture, heelbarrows, or weighted wagons.

- Make a human burrito or sandwich. Firmly press on your child's arms, legs, and back with pillows, or make a "burrito" by rolling him up in a blanket.

- Tug of war with blankets or ropes.

- Catching and throwing weighted balls, beanbags, and cushions.

- Crawling through tunnels or boxes on the floor.

Climbing increases overall body awareness and encourages strengthening, and is also fun.

- Animal walks. Crab, bear, penguin, or other silly animals. Wheelbarrow walking (the adult holds the child's legs like wheelbarrow handles while the child walks on his hands while facing the ground).

- Walking, biking uphill, running obstacle courses, or toning exercises with a backpack filled with a small amount of weight.

- Hammering nails into logs or tees into Styrofoam. Pounding and rolling Play-Doh or clay.

- Hanging from monkey bars with supervision.

- **Jumping** on a trampoline, old mattress, or air mattress. Start by holding a child's hands while he jumps.

- Karate. This is also great for balance and strength and can be fun for the entire family.

- Pillow fights or squishing between pillows.

- **Pouring** beans, sand, or water from one container to another. With simple bowls, spoons, or buckets and small items to bury and dig back out, sand boxes can provide endless therapy and amusement for a young child. If you are planning this activity outdoors, you can use bird seed so if it spills, it will be eaten!

- Swimming or extra bath time. Swimming is an activity your child can enjoy lifelong. Many communities and schools offer swim lessons and have swim teams.

- Tumbling on the floor or in the grass.

Tactile System

The tactile system provides information about the environment by the sense of touch. Stimulation of the tactile system is received by receptors in the skin, which is the largest organ of the body. The system has two components. The first is the protective system which senses if touch is harmful due to pressure, temperature and pain; the other is the discriminative system which senses the difference between harmful and beneficial touch.[15]

What we see when the tactile system is weak

- Desensitization to cuts and bruises, pain, and temperature. It is very important that we be vigilant to injuries or changes and the possibility of heat stroke or frostbite.

- Does not like having hair or teeth brushed. Gingivitis and damage to the roots of teeth are frequent complaints. Work carefully with your dentist. Quarterly visits for cleaning are recommended.

- Flicks or shakes hands, rubs face.

- Licks or chews on lips.

- **Picks at skin** or hangnails.

- Sloppy handwriting, eating, and dressing.

Jumping on a trampoline provides excellent joint and muscle stimulation and encourages balance and cardiopulmonary function, but it needs to be CLOSELY supervised.

What we do to strenghten the tactile system

- Brushing, rolling, deep massage. In the shower or tub, use a cloth or sponge to rub arms and legs vigorously. Hand massagers are great to use on your child as well, or the child can feel and benefit from the vibration by using the hand massager to massage you! You may also want to learn the Wilbarger Brushing Protocol, a technique used in occupational therapy to address issues such as sensory seeking or defensiveness. It helps provide internal organization with tactile and proprioceptive stimuli. The program needs to be taught and supervised by an experienced OT — please speak with your OT for more information.[16]

- Deep pressure and joint compression. Deep massages, tight clothing. Work with your therapists to learn different techniques to help you.

- Dress up boxes with gloves, shoes, hats etc.

- Massage hands. This is also an excellent technique to calm a fidgety child when you need for him to relax. We often use this during shows, long plays, or movies. Adding a massage of the feet is also encouraged.

- Painting, finger painting or with brushes. Sitting or standing both encourage sensory activities, posture stabilization, and fun!

- Pet care — brushing, grooming, petting.

- Rubber or latex gloves (doubled) filled with corn, rice, flour, etc. Children love to play with these. Use them when you need your child to be quiet or attentive during school, at a play, or at events that require long sitting.

- Scavenger hunts. Look for toys in objects like Play-Doh or sensory play materials.

- Sensory toys. Let kids fidget with Koosh balls, slinkies, colorful paperclips, plastic pop beads, therapy tubing, or elastic bands. Have several so that they can be rotated.

- Sensory buckets filled with pinto beans, rice, etc. Hide objects or cards in the buckets for treasure hunts.

- Sitting on padded seats, beanbag chairs, or air cushions.

- Playing musical instruments, piano, bells, drums, rhythm sticks.

- Temperature variation. Discuss the difference between cool and cold, warm and hot.

- Warm beds before going to sleep.

- Sew washers or pennies into bedding to create weighted blankets. Initially, infants will need to learn to accommodate to this new weight, but once they adjust, they will find it easier to sleep.

Oral-Motor System

Eating is the most sensory-intensive activity. Oral-motor issues such as sucking and chewing difficulties are due to weak lip, cheek, and tongue muscles and lack of jaw stability. A child's lack of early hand-to-mouth and toy-to-mouth play also contributes to increased sensory deficits.15

Oral-motor input plays a large part in maintaining a child's/individual's level of sensory arousal:

- Oral function is connected to posture and respiration.

- Oral-motor control relies on proper stabilization of the head, neck, and trunk.

- Suck-swallow-breath synchrony plays an important role in a child's arousal levels.

- Oral-motor input (sucking) induces a calming and self-regulating state to allow an infant to learn about sensory input.

- Oral-motor input can help a child calm or alert themselves so that they can

play and interact with their peers.

- Eating is the most sensory intensive activity. Oral diets will consist of a variety of tastes, textures, and temperatures and will encourage sucking, blowing, biting, crunching, chewing, and licking.

Parents can work with speech and occupational therapists to devise plans to stimulate oral-motor activity. PWSA | USA's website **(http://www.pwsausa.org)** has updated articles on sensory integration and treatment ideas for oral motor deficiencies.

Oral-motor treatment will aid in increased oral-motor and gross motor function in the following ways:

- Sucking can promote increased trunk flexion.

- Blowing can promote trunk extension.

- Biting can promote jaw, neck and shoulder, and pelvic stability.

- Crunching and chewing can promote balance/stability and mobility in the jaw, neck, shoulder, and pelvis.

What we see when the oral-motor system is weak

- Difficulty sucking or blowing through a straw.

- Grinding teeth.

- Inappropriate use of tongue and lips.

- Poor suck and swallow.

- Prefers to eat only sour, pungent, salty, or bland.

Alex kissing a giraffe. Actually, the giraffe is very gently retrieving a very small piece of food on Alex's lips.

What we do to strenghten the oral-motor system

- **Blowing.** Bubbles or whistles, playing musical instruments, making tooting sounds.

- **Sucking.** Hard candy, citrus fruit wedges, lollipops. Using a straw to suck up applesauce or jello.

- **Tugging, biting, pulling.** Licorice, beef jerky, fruit leather, a straw, or soft rubber tubing.

- **Sour/tart.** Cranberries, tart lemon/lime wedges, Warheads® or sour candies, sour sprays/powders.

- **Cold or frozen.** Grapes, popsicles, frozen peas or carrots, flavored ice cubes crushed into ice chips.

- **Chewy.** Bagels, dried fruit, fruit rollup, end of a straw.

- **Crunchy.** Pretzels, vegetables, popcorn, apples, rice cakes.

- **Spicy.** Hot salsa, red cinnamon jellybeans, gum or Altoids®.

- **Warm.** Soup, oatmeal, tea, cider.

Blowing, sucking, and chewing activities can significantly improve a child's ability to calm himself, attend to difficult tasks, keep control of body movements, and support his airflow for speech. Sucking and blowing activities in particular help develop breathing and the support posture needed to sit upright. The longer the straw and the thicker the liquid, the more work it takes to suck the liquid. Sucking also helps calm a child down, and deep breathing helps relaxation. Blowing or sucking through a straw or other tool also requires watching, so these activities can also strengthen the eye muscles used to focus sight.

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Chapter 7: Calming Techniques

Many activities can be calming, help relax the nervous system, and reduce exaggerated responses to sensory input. Calming activities and techniques include[15]:

"Sucking and blowing activities in particular help develop breathing and the support posture needed to sit upright."[14]

- **Warm or tepid bath.**
- **Deep-pressure massage,** back rub, deep brushing or roller; massaging a child's hands or feet during activities that require him to sit for long periods of time.
- **Snuggling** in a sleeping bag, beanbag chair, or large pillow.
- **Firm pressure** or skin-to-skin contact, bear hugs.
- **Swinging** back and forth.
- **Slow rocking** in a rocking chair, in an adults lap or a hammock.
- **Neoprene vest,** Lycra/spandex clothing, weighted vest.
- **Tube socks or pillows filled with dried beans.**
- **Lavender, vanilla, or soothing smells.**
- **Sucking hard candies or lollipops.**
- **Fidget** toys.
- **Hugging** a teddy bear, self hug, or adult hug.
- **Stretches.**
- **Hideout,** fort, or quiet corner.
- **Reduced noise and light levels** (turn off the TV, radio, and lights).

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Chapter 8: Organizing Techniques

Organizing techniques provide sensory input that satisfies a child's immediate needs so that he can focus on tasks or activities. These may include:

Deep-Pressure Massage

- Sucking. Hard candy, long curly straws, lollipops, pacifiers, or chew toys. Please discourage sucking on shirts or fingers by providing a replacement object.

- Chewing. Gum, hard licorice, gummy bears, or similar sugar-free candies, bagels, or firm bread.

- Vibration. Wiggle pen, toy massager, vibrating toys or pillows.

- Proprioceptive activities can be both calming and organizing. Placing a weighted toy or vest on a child's lap can help HIM calm down and listen to a teacher. Placing your hands on HIS shoulders and firmly pushing downwards will also relax and calm down a child. A big long hug will also relax. If you see a child start to become disorganized or upset, starting with a hug may prevent a tantrum.

- Carrying a weighted ball or heavy object from room to room or pushing a heavy object will also help a child calm down and stay focused.

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Chapter 9: School and Childcare Strategies

Both calming and organizing activities need to be utilized as part of an Individualized Education Program (IEP). Teachers, aides, and care providers need to know how to take advantage of sensory input to help a child learn.

- Visual information is easier to organize than verbal information. Make a picture chart for daily activities.

- Use the sensory systems to teach new activities. Including visual and tactile (and taste if appropriate) input with new activities will increase the chances or greater learning potential.

- Minimizing visual clutter decreases distractions and allows better focus.

- Defined workspace. Children should be near the front of the classroom where it's easier to maintain focus on the teacher, rather than near a door or in the middle or back of a class where the distractions are greatest.

- Encourage the child to be in the front of lines. If the line leader position is rotated among students, then the back of the line is a good second choice, as it will have fewer distractions than the middle.

- Allow time to switch from one activity to another. As much as possible, keep to a routine and announce transitions well before they need to occur.

- Building movement and sensory activities into the day helps a child remain in a calm state.

- Allow time for self-soothing behaviors. Have a rocking chair available for calming time.

- Provide a quiet corner, room, or place for child to go and relax (for instance, a bean bag chair to read quietly).

- Use weighted vests, hats, bean-filled socks to help calm a child down. If you know that a child will be placed into a new situation or needs to really focus on a task, placing a weighted object on his lap will set them up to successfully

stay calm and learn.

- Use color-coded folders to keep order.

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Chapter 10: Sleep Strategies

Calming strategies help a child get to sleep:

- Warm bath or shower.

- Predictable bedtime routines. Predictable bedtime routines. Bedtime should be the exact same time every night. Children prefer the routine and will develop a better sleeping pattern.

- Massage or joint compression prior to bed. Back rubs and brushing.

- Weighted blankets. Blankets with weights sewn into them, heavy quilts, horse blankets.

- Body pillows, sleeping bags.

- Swaddle an infant.

- Different types of pajamas. Try tight or loose, cotton or silky, to determine what your child prefers.

- Bed tent to block out distractions. Dark blinds to cut down on the light.

- Neutral color on the walls.

- Organized room, clean and uncluttered.

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Conclusion: Sensory Diets -- A Daily Plan for Sensory Stimulation

People of all ages, with or without Prader-Willi syndrome, rely on various types of sensory stimulation to stay alert, focused, and organized. Many of these sensory activities take place unconsciously or unintentionally, such as chewing gum during a meeting or a class, doodling during a telephone call, or tapping a pen against the table while working out a difficult crossword puzzle.

A sensory diet is an activity plan that provides this kind of sensory input in a regimented and intentional fashion to help individuals (like those with Prader-Willi syndrome) who may have particular difficulty with tasks that the rest of us take for granted to stay focused and organized. Such a plan will draw upon a variety of the activities discussed throughout this book in order to stimulate the individual's various sensory systems on a regular and consistent basis. A trained physical and occupational therapist will be able to help you develop the right plan for your child, and to adjust it as his needs and abilities develop.

The effects of a sensory diet are both immediate and cumulative. In the short term, certain sensory activities can help a child to perk up or calm down within a given situation; however, in the long term these same activities can actually help to restructure your child's nervous system over time so that he will be able to integrate more appropriately to activities, develop a longer attention span, and handle transitions more easily.

As with other aspects of a child's education and development, a sensory diet should be based on the observations of the child's various caregivers and developed in collaboration with his treatment team — including parents, teachers, additional caregivers, and therapists. Sensory diets are a lifelong commitment requiring the correct recipe and consistent application, and they will often change over time. It's important therefore to make sure that all involved are kept up to date with any changes, and that the advice and observations of all parents and professionals are taken into account. Applied properly, the right sensory diet will have an important positive impact on your child's life and relationships.

On the following page is an example of a home sensory diet designed for an eight-year-old child in elementary school. A separate program would be devised for when the child was at school (including such activities as taking “movement breaks,” or providing crunch/chewing oral comfort while doing handwriting or listening to stories). Remember that every child develops differently, and should have his own unique program — you should always consult your therapists when developing a sensory diet for your own child.

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Sample Sensory Diet

In the Morning:

- **Massage feet and back** to help wake up.
- **Use vibrating toothbrush** or hairbrush.
- **Eat crunchy cereal** with milk.
- **Jump on mini trampoline.**

After School:

- **Go outside and play** on playground equipment.
- **Push grocery cart** or weighted laundry baskets (help with laundry or household chores).
- **Spinning** as directed.
- **Massage feet** to “reorganize,” use therapy putty, make body sandwiches.
- **Oral-motor —** use thick liquids through a straw, eat crunchy or chewy snacks or chew gum before table activities such as handwriting or coloring.

Dinnertime:

- **Help set table.**
- **Provide crunchy or chewy foods,** or add a bit of spice or tartness.

Bedtime:

- **Warm bath** with bubbles and calming essential oil.
- **Massage** during reading time.
- **Lights out** at same time every night.

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Parent and Therapist Resources/ Therapy Supply Catalogues

Abilitations
One Sportime Way
Atlanta, GA 30340
800-850-8602
www.abilitations.com

Beyond Play Early Intervention Products
877-428-1244

Oriental Trading Company
800-228-2269

Sammons Preston
An AbilityOne Company
P.O. Box 5071
Bolingbrook, IL 60440
800-323-5547 (Canada 800-665-9200
www.sammonspreston.com

Sensory Help Resources

Sensory Help Resources
Therapy Skill Builders
555 Academic Court
San Antonio, TX 78204-2498
800-211-8378
www.hbtpc

Therapy Works, Inc.
4901 Butte Place NW
Albuquerque, NM 87120
505-897-3478
www.alertprogram.com

Nutritional Guidelines:

Infants through Toddlers with Prader-Willi Syndrome

By
Melanie R. Silverman, MS, RD, IBCLC
Roxann Diez Gross, PhD, CCC-SLP

Prader-Willi
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NUTRITIONAL GUIDELINES: INFANTS THROUGH TODDLERS WITH PRADER-WILLI SYNDROME

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This information does not replace the advice from your pediatrician and other health professionals involved in your child's care. Please contact your local health care professionals for individual help for your child.

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Introduction

Feeding any newborn child is not an instinctive or simple experience. Babies born with Prader-Willi syndrome (PWS) have especially unique needs, and each child has their own set of abilities and challenges. Be patient with your baby and the slower pace of development that is common in this first year. It does get better.

In infancy, you will focus on making sure your baby is getting enough calories to grow and develop. It may take extra effort and timed feedings, or even tube feedings for a while. You will work closely with your feeding team. Parents will have to feed a baby who often does not act hungry. Well-meaning people may not always understand or approve. It is the beginning of your role in educating others about PWS.

After this year of coaxing your baby to eat, feeding your child will change significantly. Your child will enjoy eating and not need coaxing. Your role will be providing healthy, well-balanced meals, on a schedule. You will not be feeding your toddler as many parents do – when the toddler asks for food. By providing a predictable pattern and a planned diet, you will be supporting good behavior along with controlled weight gain.

PWSA | USA is here to help support and educate you. We hope you enjoy this booklet of general guidelines, working with your home team to make it fit your child. We are grateful to the authors for their time and dedication to children with Prader-Willi syndrome.

Sincerely,

Kathy Clark, RN, MSN, CS-BC
Coordinator of Medical Affairs for PWSA | USA

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Experts

Nutrition is important in children with PWS and you will read and hear advice from everyone on what and how you should feed your child. The information can be overwhelming and confusing. There are medical professionals, in addition to your pediatrician and endocrinologist, who can help you with your child:

• **Registered Dietitian (RD):** A dietitian, sometimes referred to as nutritionist, can evaluate your baby's growth and nutritional needs using growth charts and other measures. Dietitians also can advise what types of formulas and foods to introduce as your baby grows and can provide guidance on preventing obesity in later life.

• **International Board Certified Lactation Consultant (IBCLC):** A lactation consultant is an expert in breastfeeding and can offer techniques to enhance your breastfeeding experience. Some babies are too weak to nurse at birth, but a lactation consultant is skilled at helping moms maintain and/or increase milk supply. IBCLCs can also help teach you how to pump for your baby, if that is what you choose to do.

• **Speech and Language Pathologist (SLP) or Occupational Therapist (OTR):** Speech Pathologists are trained to evaluate swallowing function, including the esophageal phase, and to identify safe feeding methods. Occupational Therapists specialize in activities of daily living, which can include feeding. Depending on where you live, an SLT or OTR may be assigned to your child. These therapists can help with positioning your baby to feed, provide strategies for safe, efficient swallowing, and recommend special bottles or nipples to optimize feeding. Throughout this booklet, we will refer to these experts as feeding therapists.

• **Physical Therapist (PT):** A Physical Therapist specializes in gross motor skill development, which includes muscles that help children roll over, sit, crawl and walk. Because your child has low muscle tone, a Physical Therapist can be helpful to support physical development.

Contact your insurance company for detailed information about your policy for all the professionals that may be involved in your child's care. Most insurance policies require a written referral from your primary physician prior to starting any therapy. Your state may also have other financial programs available for your child such as Medicaid or a program called Children's Special Health Care Services. These programs have specific criteria for enrollment. Your child's therapist and dietitian may be familiar with the various insurance companies and availability of help in your area. Ask your doctor, therapist and/or dietitian to assist you with a phone call or letter, if necessary.

Your Newborn: Birth to four months

All babies with PWS have low muscle tone and that can affect how your baby eats, but not all babies with PWS have feeding problems. Talk with your doctors, dietitian and feeding therapist for evaluation and support if issues arise.

Growth

How do I know if my baby is gaining enough weight?
Babies will lose weight after they are born, sometimes as much as 7-10%. This is common, but it's important the baby gains the weight back by about two weeks of life. Weight gain is about 5-7 ounces per week for the first 6 months. The most important way to know if your baby is growing is to have him/her weighed on a scale and plotted on a growth chart in the pediatrician's office.

How often should I take my baby to the doctor to check growth?
Weight and length need to be monitored closely every 2-4 weeks for babies this age.

Should my baby's doctor use standard growth charts or are there special growth charts for children with PWS?
We have included charts (pages 28-29) for birth to age three years which show the growth patterns of children who have not been treated with growth hormone. Growth charts were published in 2016 which are specific to children with Prader-Willi syndrome from birth to age 18 years who are being treated with growth hormone (GH). {These are available on the PWSA | USA Web site under Medical – Medical Issues A-Z – Growth Charts}

These special charts can be very helpful for your health care providers, and we recommend you bring a printed copy to your next visit. The important role of the growth chart is marking the speed of changes over time, for both weight and length. Children do not grow smoothly, so one point in time is not as important as a pattern. Your doctor or nurse and dietitian can help you understand this in more depth. Children with PWS have low muscle tone and should be measured lying down until age three years, even if they can stand easily. Standard infant growth charts use length, not standing height, until that time. Babies born early need adjustments on a growth chart to account for this, which will be taken into account in assessing growth. Keeping your own copy of a growth chart can be very helpful to all the health care providers your child will see in these first years.

FEEDING

How do I know if my baby has feeding challenges?
Your feeding therapist can provide a swallowing diagnosis and help your baby to eat safely. There may be a feeding issue if your baby presents with these problems:

- Gains no weight or gains weight very slowly
- Closes mouth and turns away during feeding
- Eats very slowly (taking 30-45 minutes or more to finish a feeding)
- Has swallowing difficulty indicated by struggle coordinating the suck-swallow-breathe pattern, and/or frequent coughing, or choking
- Does not wake for feedings, or falls asleep early during the feedings
- Tires easily during feedings
- Is happy at the beginning of the feeding and then may become fussy or distressed before finishing the feeding
- Has larger amounts of milk or formula leaking from the mouth while feeding

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Can I breastfeed my baby?
You are encouraged to breastfeed your baby because nursing can increase oral strength, but if he or she cannot, there are ways to help your baby take advantage of the benefits breast milk offers. The first thing to do is locate an IBCLC (International Board Certified Lactation Consultant). An IBCLC may be available through your local hospital, pediatrician office or public health clinic. You can also find a lactation consultant at this website: http://www.ilca.org/why-ibclc/falc or you can call 1-888-452-2478.

IBCLCs can help you nurse and/or teach you how to pump your breast milk and give your baby a bottle. An IBCLC can also help you locate a breast pump to pump your milk. A feeding therapist may be called upon for help too. Your baby may need a special nipple attached to a bottle to help him/her feed.

What is a supplemental nursing system?
This is a small bottle filled with breast milk or formula that is connected to a small tube. The end of that tube is placed at mom's breast. As your baby nurses, he/she receives milk from the breast and from the supplemental nursing system. You can purchase the system online at www.amazon.com or Target.

What if I don't have enough breast milk to feed my baby?
There are a variety of excellent formulas that can be used to give your baby the nutrition he/she needs. A registered dietitian can help with the choice.

Which formula is best for my baby?
All feedings must be individualized. Standard infant formula is 20 calories per ounce, but your doctor or dietitian may recommend 24 or 26 calories per ounce to help with weight gain. It's important to follow the mixing directions you are given. If your baby has problems tolerating the formula, speak to your pediatrician or registered dietitian for advice.

Does my baby need vitamins and mineral supplements?
Newborns usually don't need vitamin or mineral supplements. Breast milk or formula usually provides enough vitamins and minerals. Pediatricians or dietitians may recommend Vitamin D in certain areas of the country and sometimes iron or fluoride. Speak to your pediatrician about supplements before you start any of them.

What do I do if the baby is not gaining enough weight?
All of your baby's diet formula changes should be made under the supervision of your pediatrician or dietitian. Formulas come ready-tofeed, powder form or liquid concentrate. There are specific mixing instructions on the cans of formulas that should be followed closely. If you are giving breast milk, you can add a certain amount of formula to the breast milk to increase the calories.

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If you are giving formula, mixing instructions can be altered to increase calories. Adding cereal or other foods to your baby's formula or breast milk is not advised.

How much does my baby need to drink?
Babies with PWS often do not let you know when and how much they need to be fed so it's important to watch closely. On average, young babies need to be fed about 1½ to 3 ounces every 2-3 hours, but this can vary. This amount will increase as your baby grows. Some babies need more or less depending on their pattern of growth.

Should I wake my baby for feedings if he/she is very sleepy?
Usually, babies want to eat every 2-4 hours. Because babies with PWS are sleepy, you may need to wake your baby for feeding. Breast fed infants tend to eat more often than formula fed infants. Sticking to a schedule early on may be a good idea.

When can I let my baby sleep through the night?
Babies with PWS are very sleepy, but many are at risk for low blood sugar levels. Talk to your endocrinologist about feeding schedules and how often the baby should eat to make sure blood sugars 9 remain stable. During this period, babies usually eat every 2-3 hours, but should probably not go longer than about 4-5 hours.

How do I keep my baby awake long enough to finish a feeding?
A feeding therapist can help, but here are a few tips:

- Talk to your baby while feeding.
- Changing the baby's position during feeding, including breaks for burping.
- Diaper change just before feeding.
- Make sure baby is not bundled up and too warm. The coziness may make him/her fall asleep.
- Gently wipe baby's face with a wet cloth.
- Use cooler formula.
- Feed in an active, stimulating environment.
- Turn the lights on for nighttime feedings.
- You will learn over time what works best. Watch your baby closely and never force feed. Force-feeding can cause your baby to dislike feeding and develop an aversion.

Why can't my baby suck?
Low muscle tone and weakness includes the muscles used for swallowing. The tongue muscles "drive" sucking, and the lip muscles "seal" the mouth to the nipple. Breathing muscles and muscles in the throat and voice box are also important for swallowing, and they may need time and practice to strengthen and coordinate together.

How can I help improve my baby's ability to suck?

- The best thing for sucking and swallowing is practice. A feeding therapist will help you to find the best method to safely feed. Examples of available options include different bottle types and nipples, and/or evaluating different Nipples have a wider base that is more like the breast and can help positions, such as holding the baby more upright, side lying, or feeding in a bouncer chair.
- Oral motor stimulation such as providing pacifiers or toys can give "non-nutritive" sucking opportunities outside of feedings.

Nipples have a wider base that is more like the breast and can help to compensate for weak lip closure.

Here are examples of sip cups that can have a valve in place (for those who can coordinate the suck / swallow). The valve can be removed for those who don't have the coordination, strength or skill.

A specialty flow valve at the base of the nipple can help with poor lip seal and reduced suck (the valve does the work for the baby).

What is gastroesophageal reflux and is it harmful?

Babies with PWS have very low muscle tone throughout their bodies. They will sometimes experience problems with gastroesophageal reflux (GER) or the esophagus may be slow to transport food and liquid to the stomach. GER is the return of stomach contents back into the esophagus. It is usually caused by a weakness or relaxation in the muscles at the lower end of the esophagus, called the lower esophageal sphincter. GER or an esophageal phase swallowing problem should be addressed if it causes:

- slow or no weight gain.
- choking and/or coughing along with difficulty breathing.
- frequent upper respiratory tract infections or pneumonia.
- irritation of the esophagus; infants who experience pain ordiscomfort from GER or esophageal transport difficulty may limit their food intake or refuse to eat.

What can be done to treat GER or slow esophageal transport if it becomes a problem for my baby?

This is a situation that should be discussed with your pediatrician. There are medications available to help with GER. Offering smaller feedings may help as well. Taking breaks during feedings to suck on a pacifier may give time for the esophagus to clear as the baby swallows saliva.

TUBE FEEDING

How do I know if my baby needs to be temporarily fed by a tube?
Your baby's pediatrician, dietitian, and feeding therapist can help you decide, but there are some signs a tube may help your baby. If your baby…

- cannot take enough breast milk or formula to grow along his/her own growth curve.
- has swallowing difficulties that severely limit the amount that the baby can safely take.
- spends more than 30 minutes at most feedings during the day and almost always needs to be woken for feedings.

While it may be sad or frustrating to think of a feeding tube for your baby, the tubes can be extremely helpful and, over time, help parents feel much less stressed about feeding and meeting caloric goals. Also, there are ways tube feedings can be used to keep your baby taking some nutrition by mouth.

- • Your baby can breast or bottle-feed as much as he/she is able to and then the rest of the feeding can be given by tube.
- • Your baby may be able to feed during the day and need tube feedings only overnight from a small electric pump.

What is the difference between an NG and G-Tube?

- NG (nasogastric) tube: An NG tube is inserted through the nose to the stomach. The tube isn't in the mouth so it doesn't get in the way when a baby tries to suck. This type of tube doesn't require surgery. A doctor or nurse can teach you how to correctly insert the tube and teach you how to keep the tube clean.
- G-Tube (gastric tube): Gastric tubes require surgery for placement, but the advantage is they are hidden. These tubes may be recommended if tube feeding is needed longer than 2-3 months, but it varies child to child. If the tube is accidentally removed, reinsertion will have to be taken care of by a doctor.

How long will my baby need a feeding tube?
Your doctor, feeding therapist, and dietitian need to determine this answer. Feeding tubes provide a way to nourish your baby when he/she cannot eat enough from breastfeeding or bottle to grow and thrive. Usually, with close medical and nutritional attention, tube feedings are decreased as bottle or breast feedings are increased. During this time you will likely be required to bring your baby in for frequent weight checks to make sure the baby is gaining good weight as tube feedings are slowly discontinued. It's a gradual process that takes time. Feeding therapy can continue after the tube is out.

Should I try to breastfeed or bottle-feed my baby if he/she needs a G-tube?
Yes, it depends on your child's strength and safety in swallowing. Talk to your doctor or feeding therapist for advice.

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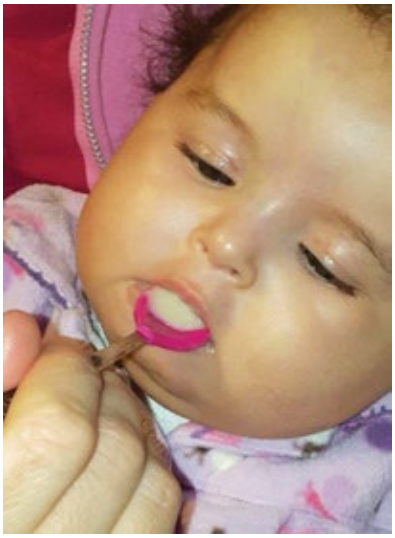
Your Older Infant: Four to twelve months


Ania

During this period of growth, your child will likely become physically stronger. Table foods will be introduced. Even though your child is still very young, habits formed are important.

GROWTH

How do I know if my older baby is growing normally?
Growth charts at the pediatrician's office are the best way to monitor your child's growth. Weight and length need to be monitored closely, every 2-4 weeks, for infants this age. Your doctor and dietitian should evaluate weight, length and head circumference frequently. Here are estimates of growth at various ages.

- Birth to 6 months: Weight gain is about 5-7 ounces (~140-200 grams) per week and ½" to 1 inch (1.5-2.5cm) per month.
- 6 to 12 months: Weight gain is about 3-5 ounces per week (~85-140 grams) and about 3/8" (1 cm) per month.

FEEDING

When should I introduce foods?
Your baby's readiness to accept solid foods depends on his/her ability to hold his/her head upright and steady without support. Your pediatrician will tell you when your child is ready to take solid foods safely.

What foods do I start with first?
For years, enriched rice cereal was the starting point in solid food introduction. This is not the case anymore. For example, you can start with pureed meats or vegetables.

How should I introduce solid foods?
It's a good idea to introduce one single-ingredient food at a time and wait 3 to 5 days before introducing another new food. The reason is to make sure your baby isn't allergic to the food. Also, when starting solids, your baby will be experiencing new flavors, textures and temperatures. Starting solids is easier for your baby if changes are made gradually. Make sure the baby is sitting up and is opening his/her mouth when the spoon comes at him/her. If he/she turns his/her head, do not force feed. You can always

talk to a feeding therapist if your child is not progressing during this phase.

What is the food consistency and texture supposed to look like?
This is a general guideline, but talk to your feeding therapist for help.

- Smooth pureed such as baby sweet potato: 4-6 months
- Thick pureed like pudding, or with mixed textures (small lumps) such as cottage cheese: 6-8 months
- Soft mashed table foods such as a baked potato: 7-9 months
- Soft, bite-sized table foods like cheese or cooked green beans: 9-12 months

How much does my older infant need to eat?
This is a great question, but a difficult one to answer. All babies are different. Below is a starting point; your baby may eat more or less. Offer these amounts and see how he/she does, but never force feed.

Food/Drink	4-6 months	6-8 months	8-12 months
Grains	**3-5 tbsp**	**3-5 tbsp**	**5-8 tbsp**
Vegetable	**1-2 tbsp**	**2-3 tbsp**	**2-4 tbsp**
Fruit	**1-2 tbsp**	**2-3 tbsp**	**2-4 tbsp**
Meat/Protein	**1-2 tbsp**	**1-3 tbsp**	**2-3 tbsp**
Milk	**28-32 ounces**	**26-32 ounces**	**24-32 ounces**

**tbsp = tablespoon*

What foods should I avoid giving my baby at this age?
Honey: It can cause botulism, a serious illness, if introduced before one year.
Cow's Milk: Stick with breast milk and formula; both are rich in iron, unlike cow's milk.
Choking hazards: large hard pieces of fruits, vegetables, meat or cheese, nuts, popcorn, raisins, gum, candy, hot dogs.

Should I give my baby juice?
No, it's not a good idea and nutritionally not helpful. Juice is full of sugar and there is no reason nutritionally that juice should be given at this age or as your baby grows into toddlerhood.

When should I change from breast milk or formula to milk?
Breast milk or formula is recommended throughout the first year of life. Once a child turns a year old, you can slowly switch the child to whole milk.

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When is the best time to introduce a cup?
It depends upon the skill of the child. If able to sit up, lift and hold the cup, some babies can begin to work on drinking from a cup around 7-12 months, but the introduction varies greatly. When your baby is first learning to use a cup, you may notice that he/she loses a good deal of liquid. This is normal as he/she learns to handle the amount of fluid in the mouth. There are many different types of age appropriate cups as shown.

Does my older baby need vitamin and mineral supplements?
Not all babies need vitamin and mineral supplements and this should be discussed with your dietitian or doctor. If your child is eating foods from all the food groups, there is no reason a multivitamin or mineral supplement is needed. It's a good question that can be asked again as your child grows and develops.

If my baby is underweight, should I force feed him/her to gain weight?
It's never a good idea to force feed your child, at any age, to help with weight gain. There are other, more gentle methods that a dietitian can provide. Supplements of powdered formula can be added to breast milk or formulas and made at higher concentrations to provide more nutrition for your baby. Food can be made higher in calories with oils and other additions. A dietitian can help maximize your baby's intake if weight gain is an issue.

What if my baby continues to refuse solid foods?
Decreased muscle tone, strength and control may affect your baby's ability to eat foods from a spoon. During the first year of life, breast milk or formula provides most of the nutrition that your baby needs. Solid foods can be placed gradually and increased based on your baby's development. Your feeding therapist can continuously assess, treat, and monitor your baby's progress and customize a plan.

If my baby is tube fed, how do I know when he/she is ready to wean from the feeding?
Weaning is a gradual process. The first step is the amount given by tube is decreased to hopefully cause an increase in appetite. If your baby responds by taking in more by mouth, tube feedings are decreased again. It's important to have your doctor and dietitian closely monitor your baby's weight during this transition.

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Alejandro

Your Toddler: One to three years

Feeding skills gradually improve throughout the toddler years so that feeding tubes are usually no longer needed. Table foods and cups replace baby foods and bottles.

The toddler years are important in establishing good dietary habits. How you handle food in your home and in social situations sets a pattern for behavior for the later years. Weight control is possible in PWS, but it requires careful attention to diet, the food environment, behavior and exercise.

Some children with PWS may start to become preoccupied with food during their toddler years. Meal planning, setting meal and snack times and expectations about behavior are crucial to develop positive lifelong habits around food.

Growth

How do I know if my toddler is growing normally?
During the second year of life, growth slows. Children between the ages of 1 and 3

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usually gain about 4-5 pounds per year and grow about 3-5 inches per year. The growth charts remain important to monitor. Weight and growth checks should be done every 1-2 months at this age and diet intake adjusted based on what is happening with weight-forlength for your baby on the growth charts.

When should I be concerned about my child's weight?
The growth chart gives you insight into how your child is growing. If your child is not gaining weight or growing slowly, he/she may need more calories. If your child is gaining excessive weight and crossing percentiles (from the 25th to the 50th or 75th in a very short amount of time), it may be important to adjust calorie intake.

Feeding

What is a healthy diet?
Fresh food is best and it's also important to offer a variety of foods too. Shopping the perimeter of the grocery store and visiting farmer's markets remains the best way to find fresh food. For farmer's markets near you visit:

www.ams.usda.gov/local-food-directories/farmersmarkets

What about food that comes in packages?
It's a good idea to learn how to read a food label to determine what is on the healthier side. Take a look at these two websites for help:

http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm274593.htm

http://www.eatright.org/resource/food/nutrition/nutrition-facts-and-food-labels/the-basics-of-the-nutrition-facts-panel

You also have to look at the ingredient lists. A good rule of thumb is that if you cannot recognize the ingredients on the lists, the food is probably not very healthy for you or your family. A dietitian can offer further help and answer more questions.

Landen

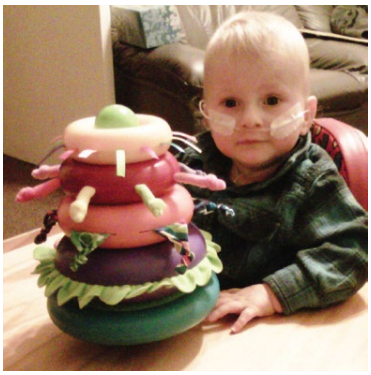
What are Carbohydrates, Protein and Fat?
Carbohydrates, protein and fat are the nutrients that give food their calories. Each has a different role in the body.

- Carbohydrates: provide energy and disease protection
- Protein: support growth and muscles
- Fat: provide energy and support vitamin metabolism

What are examples of Carbohydrates, Proteins and Fat?

- Carbohydrates: fruits, vegetables, brown rice, whole wheat pasta, whole wheat bread
- Protein: meat, fish, chicken, turkey, pork
- Fat: oils, butter

There are also foods that contain a combination of carbohydrates, protein and fat like milk and beans, which has all three. Eggs have protein and fat. Reading food labels will help you understand the makeup of foods.



Jason

I heard carbohydrates are bad for my child. Is that true?

Carbohydrates provide energy for growth and development and are rich sources of vitamins and minerals. That said, there are "good" carbohydrates and "bad" carbohydrates. When you serve your child carbohydrates, choose from the "good" suggestions. **"Good carbohydrates":** vegetables, fruits, whole grains bread/ crackers (>3 grams of fiber per serving), beans, peas, lentils, brown rice and quinoa. **"Bad carbohydrates":** candy, cakes, cookies, juices, muffins, white flour, white rice, white pasta, donuts, crackers.

Should I feed my baby a low fat diet to prevent future weight gain?

Fat is a very important part of a healthy diet for growth and development. Fat should not be avoided. Foods that contain fat are oils, avocado, nuts, cheese, eggs, fish and ground flaxseed. All should be part o a healthy diet.

What is the best way to offer healthy meals for my child?

At each meal and snack it's best to offer a source of carbohydrate, protein and fat. For example, egg, cheese and fruit would be a complete meal. Offering toast and cereal would not.

How much does my toddler need to eat every day?

Below is a starting point; your toddler may eat more or less. It's important to monitor overall growth and development and not worry i eating varies day to day. Offering a wide variety of fresh food is the most important goal for optimal nutrition.

Food Group	Amount	Serving/Equivalents/Notes
Milk	**2 cups (16 ounces)**	**1 ½ ounces cheese or 1 cup yogurt = 1 cup**
Meat	**2-4 ounches**	**¼ cup cooked beans = 1 ounce**
Fruit	**1 to 1 ½ cups**	**Soft and cut into small pieces-fresh or frozen is best**
Vegetables	**1 to 1 ½ cups**	**Soft and cut into small pieces-fresh or frozen is best**

Grains	**3-5 ounces**	**½ cup cooked oatmeal, ½ cup brown rice, 1 cup cereal (>3 grams of fiber per serving), 1 slice whole grain bread = 1 ounce**

Should I count calories for my child at this age?
Calorie counting can be cumbersome. Most toddlers need about 1000 calories per day, but this can vary widely. If your child starts to gain too much weight, a dietitian can look at your child's diet. Your dietitian should be able to review a food record you keep and reduce food that may be contributing to weight gain while making sure all nutrients are still met.

Can I have examples of breakfasts, lunches and dinners for my toddler?
Below are a few examples of healthy meals and snacks. Pay close attention to how well your child chews and swallows. For some toddlers, these foods need to be pureed and others will be able to chew the food.

Breakfast	Lunches	Dinners	Snacks
Scrambled Eggs Berries Milk	**Tuna Salad Fruit Vegetables**	**Chicken Broccoli Corn**	**Cheese Wheat Crackers**
Cottage Cheese Wheat Toast Apples	**Turkey Carrots Corn**	**Fish Mushrooms Asparagus**	**Sliced avocado Fruit Milk**
Oatmeal Ground Nuts Milk	**Lentil Soup Fruit**	**Beans Brown Rice Milk**	**Full Fat Yogurt Fruit**

What kind of milk should I give my child?
Once your child turns one year old, with permission from your pediatrician, you can gradually change to whole milk. You can speak to your dietitian about other options if you have questions.

I am worried about my baby's hydration. What can I do if he/she doesn't drink water?
There are ways to flavor water that may help. Soaking water with lemons/limes, apples/cinnamon sticks or oranges can help the water taste more interesting. In addition, drinking throughout meals and at the end of each meal should be taught because it can help to clear the esophagus.

My child is beginning to become preoccupied with food. What can I do?
One of the hardest tasks of parenting a child with PWS is controlling food intake. When our children tell us they are hungry, parents want to give them something to eat. To prevent obesity and the serious health problems that come along with it, parents need to ignore some natural parenting instincts. This is difficult. Meal planning and setting meal and snack times is crucial so your child knows what to expect when it comes to food.

Will my child try to eat nonfood items?

All toddlers are very curious and sometimes their curiosity leads them to taste non-food items. Toddlers with PWS may try to eat non-food items, just like any other curious child. You need to watch your child closely to make sure he/she is kept safe.

Sydney

How can I avoid my child overeating?

- Avoid using food as a reward for good behavior. Use praise, stickers, hugs, reading a book or special time together so as to avoid excess calories.
- Eat meals and snacks at scheduled times. A regular routine helps you monitor food intake and helps reassure your child that food is regularly available.
- Keep food out of sight and out of reach. If you have a kitchen door, you may find it helpful to keep the door closed and/or locked when the kitchen is not in use. A lock on refrigerators or cabinets may be necessary too.
- During mealtimes, supervise your child, especially when other children are present. Other children may offer your child food.
- Do not eat a snack in front of your child when they cannot eat.
- Remove dishes from the table immediately to prevent your child from eating extra portions or eating from other's plates.
- During meals, engage in pleasant conversations.
- Use smaller plates and cut food into smaller pieces to make it appear as if there is more.
- Encourage your child to eat slowly and help pace him/her to chew food thoroughly.
- Do not eat in front of the television or other technology.
- Post rules about behavior you expect at meals and explain to children they must abide by these rules.

Should I feed my baby in front of the television or tablet to distract him/her to eat?

The habits you form now will be important for a lifetime. What you feed your child is just as important as how you feed your child, and all family members need to follow the same rules. All meals and snacks should be eaten at a table, without technology, so your child can concentrate on the food that you provide for him or her. Televisions and tablets are distracting and don't allow anyone to tune in to their eating.

Jason1

What is Food Security?

Food Security means that your child can depend upon you to provide good nutrition with a plan for each meal, and no surprises such as extra snacks or substitutions for promised food. Reliability is the key here. Children are not expected to have to ask for food because it will be supplied as promised. It does not mean that children WON'T ask for more food or extra food – instead, a parent will always be in charge and prepared ahead of time for every snack and meal. Instead of feeding a child with PWS when they request food – which will lead to obesity and behavior problems – parents must be very organized to provide food security.

It's important to understand this concept early as your child grows and develops. These guidelines are essential to establish good food behaviors; it isn't just about controlling calories. Allowing children to be in charge of food will lead to significant challenges as they grow up.

The principles of food security are:

1. **No doubt** when meals will occur and what foods will be served – spontaneous changes are hard on children with PWS. Knowing what will be served makes them feel secure.
2. **No hope** of getting anything different from what is planned – no plate of tempting cookies on the counter, no buffet lines, no self-serving of portions.
3. **No disappointment** related to false expectations – if you promise ice cream, you must provide it.

What kinds of exercise should my child do during the toddler years?

Regular exercise is crucial and should not be underestimated, even in the early years. Once your child is mobile, avoid carrying them when possible. Move toys out of their reach to encourage movement. Avoid screen time as entertainment. Exercise helps control weight gain and improve muscle strength, but most importantly, it is essential for your child to learn, and for continued brain development. Involve your child in family games. Exercise should be fun and centered on play. PWSA | USA offers an extensive booklet "Therapeutic Interventions for the child with PWS" by Janice Agarwal, PT, CNDT which can guide parents and professionals with specific interventions.

Websites for reference and further reading

www.wholesomebabyfood.com | www.ellynsatterinstitute.org

www.kidshealth.org | www.mayoclinic.org | www.hopkinsmedicine.org

Acknowledgements

Melanie R. Silverman, MS, RD, IBCLC, is a registered dietitian and board certi ied lactation consultant. She received her Bachelor of Arts in Chemistry and Spanish from Indiana University and her Master of Science degree from Rush University, where she also completed her dietetic internship. She spent seven years in pediatric intensive care and outpatient clinics at the University of Chicago and has been in private practice since 2003 counseling families with picky eaters, food allergies, failure to thrive, tube feedings and obesity. She began her work with Prader-Willi syndrome in 2004. She is a speaker at national and international meetings. (www.melaniesilverman.com)

Roxann Diez Gross, PhD, CCC-SLP, has been an active researcher and a practicing speech-language pathologist for most of her career, and is frequently invited to lecture nationally and internationally on dysphagia (difficulty swallowing). Dr. Gross has published several scienti ic papers in peer-reviewed medical journals and has authored multiple clinical book chapters. Her primary area of research examines interactions between breathing and swallowing in individuals of all ages with neurological impairments and respiratory disease. She has the privilege of working with feeding expert, **Marybeth Trapani-Hanasewych, MS, CCC-SLP, and Patsy McMelleon, MA-CCC-SLP,** who provided advice and input into this booklet. Dr. Gross and other colleagues at The Children's Institute of Pittsburgh completed a PWSA | USA funded research study that characterized swallowing function in children and adults with PWS.

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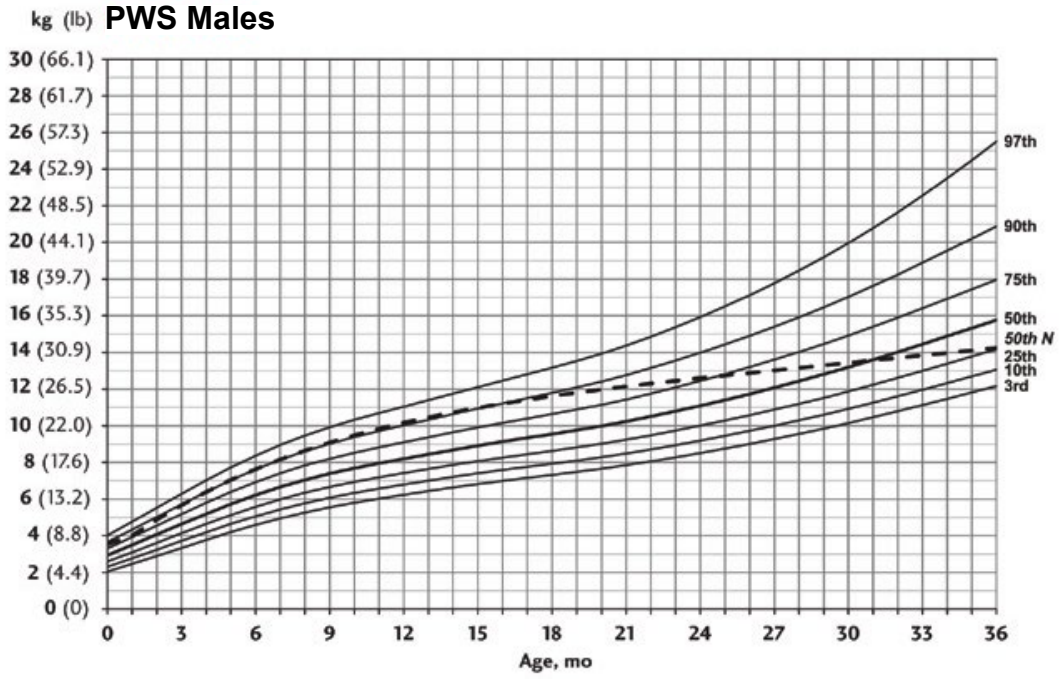
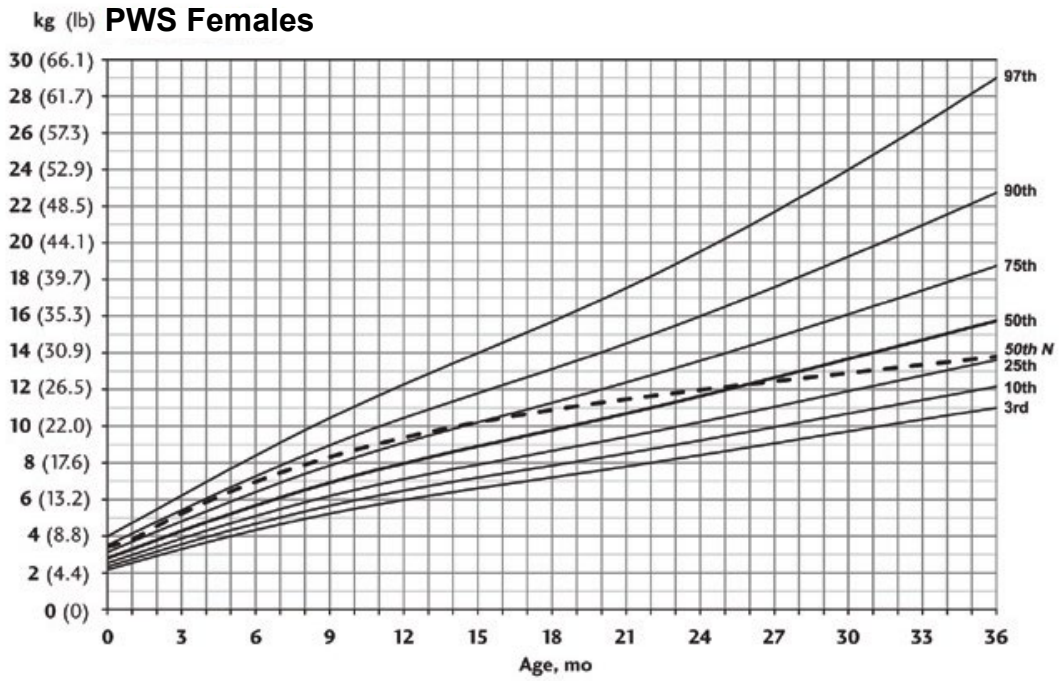
Weight of Infants with PWS
Compared with Normal Weight for Age





Standardized curves for weight of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line).

Weight of Infants with PWS
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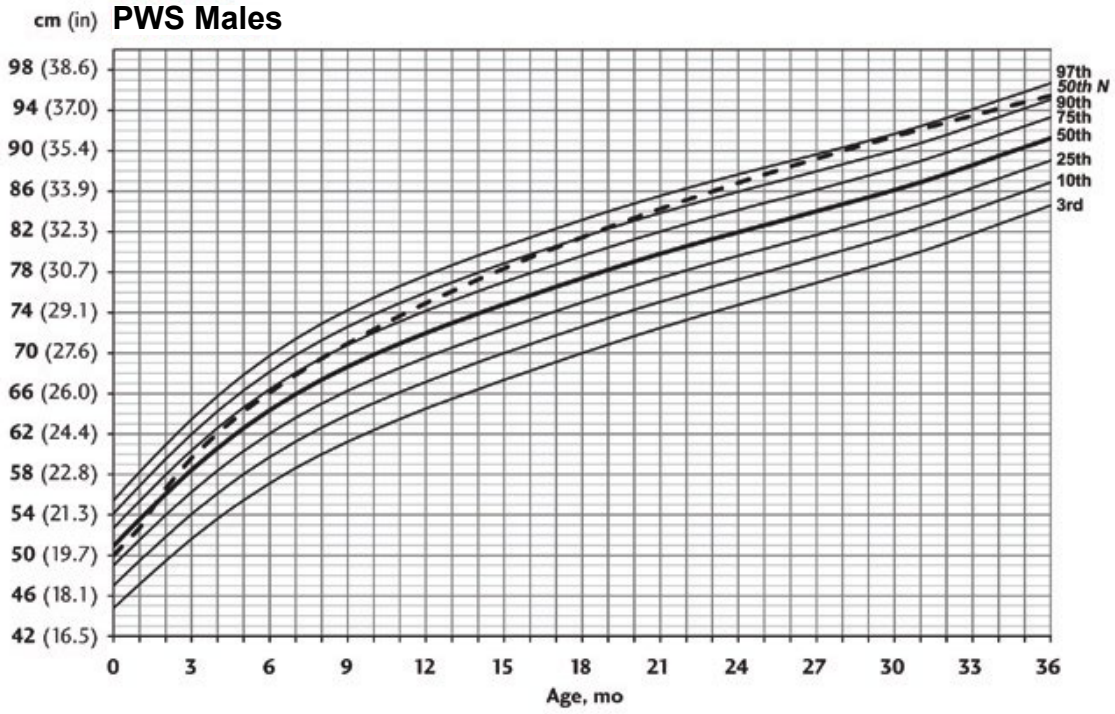

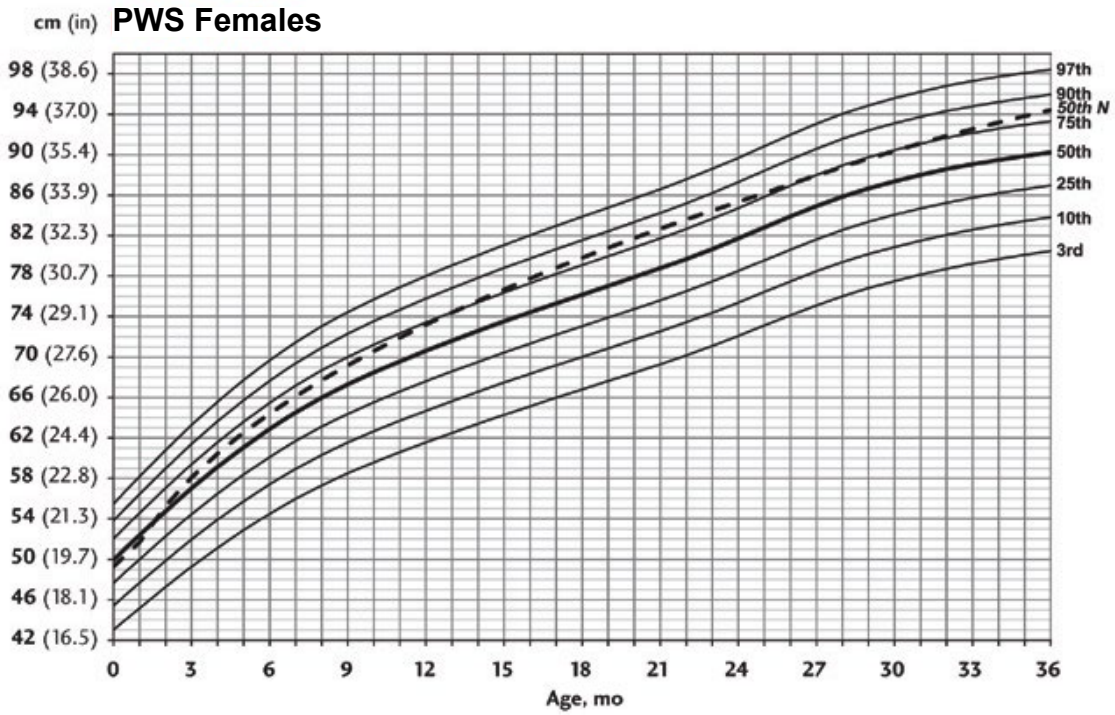

Standardized curves for length of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line).

Notes

Information in this publication is not intended to be, nor is it, medical or legal advice on the management or care of a person with Prader-Willi syndrome. It may not represent the opinions of PWSA | USA.

Any decision about treatment or legal options (including, but not limited to, medical, nutritional, educational services or psychiatric options) should be made in consultation with your own medical and legal team.

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and consultant experts

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INTRODUCTION

Characteristics and Common Medical Complications of PWS

This booklet was developed to alert medical practitioners in emergency departments, urgent care facilities and primary care practices to **severe medical complications that can develop rapidly in individuals with Prader-Willi syndrome (PWS).**

The booklet highlights medical issues that occur in some patients with PWS and hopefully assists in the recognition and management of problems that are uncommon in the general population but do occur with increased frequency among individuals with PWS. These findings may present at various ages and result in serious, sometimes urgent or even fatal outcomes. Common problems during hospitalization and medical procedures are also discussed.

The booklet also serves to alert families and other caregivers to potential PWS complications requiring specific management.

PWS is a variable and complex genetic neurobehavioral disorder resulting from an abnormality on chromosome 15. PWS occurs in approximately 1:10,000 to 1:15,000 births.

PWS affects the functioning of the hypothalamus and other aspects of the brain, and typically causes the following frequent findings:

- Generalized hypotonia evident prenatally and throughout life
- Decreased ability to suck in infancy leading to failure to thrive if not compensated. Swallowing abnormalities of oral secretions and food in all ages, often unrecognized
- Hyperphagia due to hypothalamically-driven lack of sense of satiety that can lead to dramatically excessive eating and, coupled with body composition abnormalities and metabolism with low caloric needs, can result in morbid obesity. Hyperphagia begins as early as ages 2-4 years and lasts throughout life. The presence of obesity can result in typical complications not usually present in those who are not obese, such as diabetes mellitus. Those with PWS who are not obese have had food intake carefully controlled by others.
- Short stature for the family if not treated with growth hormone
- Hip dysplasia, scoliosis, osteoporosis
- Delayed and incomplete sexual development
- Developmental delay and usually mild to moderate learning/cognitive deficits
- Chronic and significant problem behaviors; frank mental health conditions in some

In addition, some of the other common findings that may cause difficulties include:

- Adverse reactions to medications including anesthetics
- High pain tolerance leading to unsuspected issues such as fractures
- Gastrointestinal issues including decreased ability to vomit and chronic constipation. Occasional stomach necrosis and rupture often following binge eating
- Respiratory abnormalities such as hypoventilation or sleep disordered breathing in the form of obstructive or central sleep apnea
- Sleep problems such as excessive daytime sleepiness

- Temperature regulation abnormalities (hypothermia or hyperthermia)
- Misunderstanding or misinterpretation of information, necessitating clear and simple instructions

These findings are explained in more detail in the following pages, along with recommendations for evaluation and treatment for some of the problems in PWS. Information is based on literature review and experience of experts on PWS. The most emergent issues are discussed in the first section, inpatient, surgical and acute medical concerns in the second section, and additional medical issues and elaborations of some issues in the third section. A brief description of the genetic basis of PWS and how PWSA | USA can help in the event of death follow in sections IV and V.

Genetic testing is available for confirmation of diagnosis and to distinguish the three common causative genetic changes, which have a few distinctive findings (please see page 35 of this booklet, the section on Genetics.)

Recommended additional resources on medical issues in PWS include UpToDate® (www.uptodate.com) and GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1330/). Members of the PWSA | USA Clinical Advisory Board are available for consultation with physicians through the Prader-Willi Syndrome Association | USA.

I. Emergency and Acute Medical Issues

Obesity and its related complications are the major causes of morbidity and mortality in Prader-Willi syndrome (PWS). Keeping the individual at a healthy weight will minimize these complications, but there are important medical and behavioral/mental health problems unique to PWS regardless of weight status.

Note that people with PWS have cognitive disability, and though it is usually mild they may misinterpret what is asked of or told to them. Instructions should be kept clear and simple.

Medical professionals can contact PWSA | USA to obtain more information and be put in touch with a specialist, as needed. UpToDate® (www.uptodate.com) and GeneReviews (https://ncbi.nlm.nih.gov/books/NBK1330) have excellent summaries of the syndrome.

Severe Gastrointestinal Concerns

- **Vomiting – Decreased ability to vomit.** Vomiting occurs infrequently in many people with PWS. Emetics may be ineffective, and repeated doses may cause toxicity. This characteristic is of particular concern in light of hyperphagia and the possible ingestion of uncooked, spoiled, or otherwise unhealthful food items. **The presence of new onset vomiting or vomiting accompanied by loss of appetite or lethargy may**

signal a life-threatening illness and may warrant immediate treatment. (See below and pages 24-25 as well as foldout on the last page of this booklet for more information on this topic.)

- **Severe Gastric Illness:** Gastric problems are very common in PWS due to decreased motility and gastroparesis. Abdominal distension or bloating, pain and/or vomiting may be signs of life-threatening gastric dilation, inflammation or necrosis. Rather than localized pain, there may be a general or vague feeling of being unwell. Anti-diarrheal medications may also cause severe colonic distension, necrosis and rupture and should be avoided. Any individual with PWS with these symptoms needs immediate medical attention. An X-ray, CT scan or ultrasound can help with the diagnosis and confirm if there is gastric necrosis and/or perforation.

  If distension is noted, these individuals need close clinical monitoring on an ongoing basis, to be made NPO, and may need decompression with an NG tube. **Gastric necrosis or perforation is a medical emergency requiring exploratory laparotomy or emergent surgery. Individuals with PWS may not have tenderness, rigidity or rebound normally associated with an acute abdomen.** Please see additional information on Gastric Necrosis on pages 24-25 of this booklet and see *an algorithm for evaluation of GI complaints in people with PWS at the end of this booklet.* See also **http://www.pwsausa.org/resources/medical-issues-a-z/** and view GI Problems-stomach and intestines.

- **Constipation and Rectal Bleeding:** Although only 20% of adults with PWS report constipation, a recent study found that 40% of adults with PWS fulfilled the diagnostic criteria for constipation. Abdominal and rectal pain, rectal fissures, and rectal bleeding may occur in association with disordered defecation. Rectal ulcers have occurred in individuals with PWS as a result of localized deep rectal picking aggravated by rectal irritation from constipation/anal pruritus and can present with mucoid rectal discharge, bloody stools, rectal pain, and tenesmus suggestive of emerging inflammatory bowel disease and warranting gastroenterology consultation. **Colonic impaction** may also occur and needs to be addressed. See also Constipation on pages 25-26 and at **http://www.pwsausa.org/resources/medical-issues-a-z/**

- **Other GI issues**: Stomach pain can also be due to gallstones or pancreatitis. An ultrasound, chemistry analysis of the blood and CT of the abdomen will help with the diagnosis.

Swallowing Dysfunction and Choking

People with PWS are highly likely to have an undetected swallowing problem that places them at risk for asphyxiation by a food bolus (choking). Many people with PWS cannot tell if they have cleared their throat or airway after swallowing, increasing the risk for aspiration. As a result, assessment requires a special kind of evaluation, a videofluoroscopic swallowing study with an esophageal

sweep. A clinical or bedside evaluation is not sufficient to detect dysphagia in this population. Choking can also occur with rapid ingestion of food and has caused numerous deaths in the PWS population. For more information on this topic, please see **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Choking/Swallowing.

Respiratory Concerns

Individuals with PWS are at increased risk for respiratory difficulties. They have blunted ventilatory responses to hypoxemia and hypercarbia. This can cause problems related to anesthesia and sedation and complicate the diagnosis of obesity hypoventilation syndrome. Hypotonia, weak chest muscles, swallowing abnormalities, and central or obstructive sleep apnea are common. Anyone with significant snoring or other sleep problems, regardless of age or presence of obesity, should have a medical evaluation to look for sleep disordered breathing. This may include a sleep study. Infants commonly have central sleep apnea which generally improves spontaneously over time, but they may also have obstructive sleep apnea due to the hypotonia and other factors, as may individuals with PWS of all ages. Hypotonia can lead to diminished activity levels and low aerobic capacity. People with PWS at all ages are at risk for hypoventilation, which is central in origin. Hypersomnolence with or without cataplexy has been described in PWS.

In children with PWS, chronic stomach reflux and aspiration are emerging as common problems. Reflux should be considered in young children with chronic respiratory problems; videofluroscopy is the preferred test. Individuals with obstructive sleep apnea or obesity are at higher risk for reflux. At any age morbid obesity can be associated with obesity-hypoventilation syndrome. Children with PWS have been shown to have hypoventilation disproportionate to obstructive sleep apnea. (Please see pages 26-30 for recommendations for evaluation of breathing abnormalities associated with sleep disorders.)

Medications – Adverse Reactions

People with PWS may have unusual reactions to standard dosages of medications. Use extreme caution in giving medications, especially those that may cause sedation; prolonged and exaggerated responses have been reported. Metabolism of the drugs may be impaired in individuals with PWS. Abnormal body composition and metabolism may affect pharmacokinetics. In obese individuals, weight-based dosing guidelines often do not specify the use of actual body weight versus ideal or adjusted weight estimates, and multiple additional factors impacted by obesity must be considered for appropriate dosing. Consider additional focus on renal and hepatic function, medication lipophilicity, recommended dosing weight, and observability of medication effects. Special care should be taken with medications that have a narrow therapeutic window and for those in which the detection of harm may be delayed.

Pain Tolerance

A high threshold for sensing pain is common and may mask the presence of infection or injury. Someone with PWS may not complain of pain until infection is severe or may have difficulty localizing pain. Parent/caregiver reports of subtle changes in condition or behavior should be investigated for medical cause. Any complaint of pain by a person with PWS should be taken seriously.

Skin Picking and Bruises

Because of a compulsion that is common in PWS, open sores caused by skin picking may be apparent. Rectal picking/gouging is not uncommon. Individuals with PWS also tend to bruise easily. These lesions can cause serious life-threatening infections. Appearance of such wounds and bruises may erroneously lead to suspicion of physical abuse. There are approaches to help mitigate picking. Please see **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Skin Picking.

Falls and Fractures

Individuals with PWS may have significant fractures from simple falls and require X-rays even if they do not complain of pain. Persistent pain, swelling, guarding, limping, or decreased movement of an extremity for more than a few days may warrant an X-ray.

Water Intoxication

Water intoxication has occurred in relation to use of certain medications with antidiuretic effects, as well as from excess (binging) fluid intake alone. For additional information see **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Water Intoxication.

Temperature Abnormalities

Idiopathic hyperthermia and hypothermia can be noted in people with PWS. Hyperthermia may occur during minor illness and in procedures requiring anesthesia. Fever of unknown origin occurs. However, malignant hyperthermia does not appear to occur at increased frequency in PWS. On the other hand, fever may be absent despite serious infection. All individuals with PWS are at risk for mild hypothermia because of impaired peripheral somatosensory and central thermoregulation, poor judgment and cognitive inflexibility. Hypothermia is common in infants with PWS. See **http://www.pwsausa.org/resources/medical-issues a-z/** and view Temperature and Hypothermia.

Central Adrenal Insufficiency

Central adrenal insufficiency is a rare occurrence in people with PWS. A stress dose of cortisol may be indicated if the individual has problems after surgery or during times of stress. See page 34 in this booklet for more information. See also **http://www.pwsausa.org/medical-issues-a-z/** and view Adrenal or Cortisol Insufficiency.

Hyperphagia and Food Seeking

Individuals with PWS have a nearly constant drive to eat and must be continuously supervised in all settings to prevent access to excess food. In hospital settings, obtaining unguarded food can lead to rapid ingestion and fatal choking or gastrointestinal issues. Individuals who have normal weight have achieved this because of strict external control of their diet and food intake; these individuals are not less likely to ingest available food. There are currently no treatments for this constant urge to eat. Insatiable appetite may lead to life-threatening weight gain, which can be very rapid and occur even on a low-calorie diet.

II. Peri-Operative and In-Patient Issues

A. Hospital Experience and Pre-Anesthesia

Pre-Operative Preparation

When possible, pre-operative preparation to optimize nutritional status and address the common problems of diabetes control issues and constipation prior to significant elective surgical procedures should occur in patients with Prader-Willi syndrome.

Obesity Complications

A common finding in people with PWS, obesity can cause obstructive sleep apnea, pulmonary hypertension, diabetes, and right heart failure. These should be sought and addressed, as they affect illness, surgical and post-operative management.

Venous Access Difficulties

Many people with PWS will have difficult intravenous (IV) access due to increased fat mass and smaller than normal blood vessels. Ultrasound guided peripheral IV placement is helpful. IV lines are often more distressing to children with PWS than their actual surgery, therefore the lines need to be protected. In situations where hydration for more than 2-3 days is required, consider a peripherally inserted central catheter (PICC line) or tunneled central venous access, to avoid reinsertion.

Hyperphagia/Food Seeking

For people with PWS, complete safety from access to extra food is essential in any health care setting. Access to food storage or refrigerators should be prevented. Assume the individual has eaten unless verified by a caregiver. Complaints of hunger should not result in access to snacks or food. Patients in the hospital should have someone with them at all times. The individual may be on a calorie-restricted diet, and that should be conveyed to the nutritionist and kitchen. For elective procedures involvement of a dietician to help with pre-operative nutritional management along with planning for inpatient management of nutrition may be helpful. Patients with PWS should not be permitted to have "at your request" or "on demand" food ordering. A dietician should be involved in setting up the inpatient and discharge nutrition plans to ensure adequate protein intake along with appropriate vitamin/mineral supplementation to provide optimal healing.

Pain Tolerance

Unexplained tachypnea or tachycardia may be the only indication of pain. Behavior problems that are not typical for this person may also be evidence of pain. Individuals with PWS may not respond to pain in the same manner as others, masking the presence of underlying problems. Since pain may not be evident, other signs of underlying problems should be assessed.

Behavior Problems

Individuals with PWS are prone to emotional outbursts, obsessive-compulsive behaviors, and psychosis. These may be exacerbated by the stress of hospitalization or surgery. If possible, a pre-admission assessment should be performed, in part to consider 1-to-1 supervision in order to safeguard staff and the patient and prevent food foraging.

Psychosis

There is an increased risk of psychosis in individuals with PWS, which can be triggered by significant events such as changes in routines or serious illness. Prompt attention to hallucinations or reported change in typical behavior is essential. View Psychiatric Concerns at **http://www.pwsausa.org/resources/medical-issues-a-z/**

Skin Picking

Picking at sores and stitches is a common self-injurious behavior in PWS. It may complicate healing of IV sites and incisional wounds. Restraints or gloves may be necessary to protect wounds during healing. See Skin Picking at **http://www.pwsausa.org/resources/medical-issues-a-z/**

Temperature Instability

Low basal body temperature is typical in healthy individuals with PWS. Hypothalamic dysregulation can lead to poor temperature control during fever or hypothermia.

Respiratory Issues

The high incidence of central, obstructive and mixed apnea in people with PWS make it imperative to obtain a sleep study and/or pulmonology consultation prior to moderate or major surgical procedures in order to guide post-operative use of CPAP or BiPAP. The generalized hypotonia may include respiratory muscle weakness, which could complicate the ability to cough effectively and clear airways. See pages 26-30 in this booklet and **http:pwsausa.org/resources/medical-issues-a-z/** and view Breathing/ Respiratory concerns.

Cardiac Problems

Surprisingly, coronary disease is less in PWS than in individuals with similar obesity. Cardiac problems, if they do occur, usually are due to hypoventilation right heart failure, which can be associated with obesity. Non-pitting edema can often be seen in the obese individual even in the absence of heart failure and is treated with weight loss and ambulation. Diuretics are usually not very beneficial in treating the edema.

B. Anesthesia and Surgical Procedures

General Recommendations

Schedule procedures as early in the day as possible to prevent prolonged awake NPO status, so as to reduce patient anxiety and opportunities for food seeking behavior.

Anesthesia

People with PWS may have unusual reactions to standard dosages of anesthetic agents. Use caution in giving anesthesia. Outpatient procedures and conscious sedation may be especially problematic; the use of general anesthesia and airway management is often preferred but may warrant overnight observation for respiratory complications. Procedures done outside of the hospital settings should be carefully considered, with proper equipment for resuscitation immediately available. Ongoing assessment of breathing and oxygen saturation is critical in all outpatient procedures including dental work. Ongoing psychotropic medications may affect metabolism of anesthetic agents leading to shorter or longer duration of action. People with PWS may exhibit abnormal physiological responses to hypercapnia and hypoxia. There does not seem to be a higher incidence of malignant hyperthermia. Please see **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Anesthesia**.**

Narcotic Sensitivity

Individuals with PWS may have an exaggerated response to narcotics. Use the lowest possible dose to achieve the desired state of anesthesia. Many individuals with PWS have delayed gastric emptying that can be compounded with narcotics.

Airway Access

A small airway, high palate, and/or obesity (neck and pharyngeal adiposity) may complicate ability to intubate. It can also make bag-mask ventilation difficult (mask fit challenges, increased airway resistance and reduced respiratory system compliance). Outpatient procedures and general sedation may be especially problematic. Care must be taken during procedures done in or out of hospital settings, and assurance that proper equipment for resuscitation is immediately available if needed. The possibility of doing such procedures in an operating room should be discussed. Procedures where more than light sedation is used may warrant overnight observation, particularly since sensitivity to medications is also an issue in PWS (see below).

Saliva Abnormalities

Thick sticky saliva complicates airway management especially during conscious sedation. It also increases the risk of caries. Dried saliva may not be an indication of hydration status. Voluntary water drinking is minimal in the majority of individuals with PWS.

Oro-Pharyngeal Surgical Concerns

With a significant number of infants and children with PWS undergoing sleep assessments prior to growth hormone treatment and the potential consequent rise in surgical procedures (e.g., tonsillectomy) requiring intubation and anesthesia, it is important to alert the medical team about complications. These may include trauma to the airway, oropharynx or lungs due to possible anatomic and physiologic differences seen in PWS, including a narrow airway, underdevelopment of the larynx and trachea, hypotonia, edema, and scoliosis.

C. Post-Operative Period

General Recommendations

Patients with PWS who undergo deep sedation or general anesthesia should be recovered overnight in a monitored unit. Continuous monitoring of pulse-oximetry for 24 hours is important post-operatively, with attention to airway and breathing. Infants and children may require intensive care monitoring. A conservative approach to pain management should be used, limiting the use of narcotic agents. Consider direct supervision (1:1) for those patients at risk of food foraging post-operatively. Patients may exhibit altered temperature regulation, where fevers may be absent despite the presence of infection. Individuals with PWS are at risk for deep venous thrombi (DVT) and pulmonary embolism due to their hypotonia and obesity. DVT prophylaxis should be considered in all obese individuals with PWS, and prolonged bed rest is to be avoided. Please review the sections above under Hospital experience and Pre-Anesthesia (pages 12-15) and **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Post-operative Monitoring.

Respiratory Considerations

Pre-operative pulmonary assessment should guide the use of CPAP or BiPAP. Respiratory therapy may be indicated to prevent atelectasis and/or post-operative lung infections.

Pain Insensitivity and Narcotics

Individuals with PWS characteristically display a decreased outward response to pain. The only indications of pain may be behaviors that are not typical for that individual, or unexplained tachypnea/tachycardia. Lack of a typical pain response may mask the presence of underlying problems. Conversely, many post-surgical patients with PWS seem to experience less pain, and they can be comfortable with lower doses of narcotic medications or with a narcotic-free regime. Those who do need post-operative narcotics may benefit from methylnaltrexone to decrease the duration of the post-operative ileus.

Gastrointestinal Issues

Post-operative ileus is characteristically more profound and long lasting in patients with PWS. When indicated, sips of clear liquids may be started immediately after surgery, but the advancement of diet should be delayed until there are non-subjective signs of digestive recovery. One strategy for moderate to extensive surgeries on older children or adults is 2 ounces of clear liquids every 4 hours to start. If the patient tolerates intake and bowel sounds are present, the intake can be increased to 4 ounces every 4 hours. Abdominal radiographs are done daily to confirm normal gas patterns before advancing to a soft diet. Any abdominal bloating is an indication to discontinue diet.

Skin Picking

Skin picking may represent a severe threat to post-operative incisions. Restraints or gloves may initially be necessary, followed by physical barriers such as braces or casts to protect wounds during healing. Post-operative anxiety may cause patients without a history of skin picking to begin the habit.

Hypotonia Consequences

Generalized muscle hypotonia is a constant feature of PWS. It may complicate ability to cough effectively and clear airways, affecting post-operative recovery.

Pulmonary Embolism

Individuals with PWS are at increased risk for pulmonary embolism. Deep vein thrombosis prophylaxis should be considered in all obese individuals. Prolonged bed rest should be avoided.

Orthopedic Concerns

Musculoskeletal manifestations, including scoliosis, hip dysplasia, fractured bones (which may be undetected), osteoporosis, and lower limb alignment abnormalities, occur at significant frequency in people with PWS. Care of this patient population from the orthopedic surgeon's

perspective is complicated by other clinical manifestations of PWS. Please see also **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Orthopedic Issues**.**

Behavioral Disorder and Psychosis

People with PWS are prone to emotional outbursts, obsessive-compulsive behaviors, and in some cases psychosis. Psychosis can be triggered by significant events such as changes in routines and serious illness. Prompt attention to hallucinations, disorientation or reported change in typical behavior is essential. View mental health issues at **http://www.pwsausa.org/resources/medical-issues-a-z/** under Psychiatric Concerns.

Summary of Post-Operative Management

Patients with PWS are known to have increased morbidity after surgery due to:

- Abnormal physiological response to hypercapnia and hypoxemia
- Untreated central and/or obstructive sleep apnea
- Hypotonia
- Narrow oropharyngeal space
- High incidence of central, obstructive and mixed apnea
- Thick secretions
- Obesity
- Increased incidence of scoliosis with decreased pulmonary function

- Prolonged exaggerated response to sedatives
- Increased risk for aspiration
- Decreased pain sensation
- Possible challenges with compliance to pre- and post-operative treatment procedures due to:
  - Extreme food seeking behavior and hyperphagia
  - High incidence of gastroparesis and slow motility of the intestinal tract
  - Severe skin picking which may interfere with wound healing
  - Altered temperature regulation – fever may be absent in the presence of infection
  - The possibility of central adrenal insufficiency

Therefore, the following are recommended for post-operative management:

- Patients with PWS who undergo deep sedation and general anesthesia should be recovered overnight in a monitored unit. Infants and children may require intensive care monitoring.
- Continuous monitoring of pulse-oximetry for 24 hours post-operative with attention to airway and breathing.
- A conservative approach to pain management and use of narcotic agents.
- Full assessment of return of gastrointestinal motility prior to initiation of intake by mouth, often with abdominal radiographs, because of the predisposition to ileus after surgery.

- Scheduling procedure as early in the day as possible to prevent prolonged time period where food seeking could take place.
- Direct supervision (1:1) to prevent foraging post-operatively and exclusion from ad lib patient ordering of food from hospital dietary services.
- Monitor for picking at wounds and/or incisions. These may require additional dressings and other barriers including full time sitter to prevent access to surgical site and medical devices
- Close observation of wound for signs of infection
- Airway clearance to prevent atelectasis and/or post-operative lung infection.
- Due to the hypotonia and obesity, individuals with PWS are at risk for deep venous thrombi (DVT) and pulmonary embolism. Patients should be under the guidelines for DVT prophylaxis.

Please see also **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Post-operative/Surgery.

III. Evaluation and Treatment of Special Issues

Risk of Stomach Necrosis and Rupture

A Cause of Death from Sepsis, Gastric Necrosis or Blood Loss

Signs and symptoms of stomach necrosis and rupture:

- **Vomiting-**Atypical vomiting accompanied by decrease in appetite or lethargy is unusual in PWS
- **Loss of appetite** (ominous sign)
- **Lethargy**
- **Complaints of pain, usually non-specific.** Pain sensation appears to be abnormal in PWS due to high pain threshold; affected people rarely complain of pain
- **Pain** is often poorly localized
- **Peritoneal signs** may be absent
- **Abdominal/stomach bloating** and **gastric dilation**
- **Fever** may or may not be present
- **Guaiac positive stools (chronic gastritis)**

An algorithm for Emergency Room evaluation of an individual with PWS and abdominal complaints is on a foldout page at the back of this publication.

History may include:

- History of **binge eating** within the week. Hyperphagia and binge eating are characteristic of people with PWS, regardless of whether obese or slim. This frequently occurs at holiday or social occasion with less supervision of intake
- History of **gastroparesis**, which is common in PWS, though often undiagnosed
- History of significant **obesity followed by weight loss**, which may leave the stomach wall thinned.
- See also **http://www.pwsausa.org/resources/medical-issues-a-z/** under GI Problems**.**

Constipation

Constipation is a common problem in individuals with Prader-Willi syndrome (PWS). Although only 20% of adults with PWS report constipation, a recent study found that 40% of adults with PWS fulfilled the diagnostic criteria for constipation. It takes longer for food to move through the GI system (gastroparesis) in Prader-Willi syndrome. This slower passage of food can lead to serious issues similar to the ones seen related to the stomach. Outpatient methods used to clear constipation in non-PWS patients may be ineffective due to poor fluid intake and hypotonia. Inpatient regimens frequently use large volumes of fluid which may cause problems. Reliance on these methods may lead to life-threatening conditions such as necrosis and perforation of the colon and subsequent sepsis. Due to decreased muscle tone and altered pain response, individuals with

PWS may not have the same clinical exam that a non-PWS patient would have. A heavier reliance on imaging may be necessary. Individuals with PWS may be at higher risk for impaction. Rectal examination and enema may be required in addition to oral cleanout regimen. This may also be problematic in some, leading to rectal picking.

Patients with PWS having constipation and receiving repeated regimens of oral PEG (polyethylene glycol) solution for bowel cleansing should be monitored closely for abdominal distention and retention. Use of laxative agents with sweeter flavoring, such as lactulose or chocolate-flavored senna preparations, should be avoided if possible.

Failure of standard constipation protocols to clear the stool in a timely manner, especially in the face of increasing abdominal distention, vomiting, decreased appetite, stoppage of food consumption, and/or abdominal pain, warrants surgical or GI consultation. Emergent surgical or colonoscopic intervention may be necessary.

Breathing Abnormalities Associated with Sleep

Problems with sleep and sleep disordered breathing have long been known to affect individuals with PWS. The problems have been frequently diagnosed as sleep apnea (obstructive [OSA], central or mixed) and/or sleep related hypoventilation with hypoxemia. Disturbances in sleep architecture (delayed sleep onset, frequent arousals and increased time of wakefulness) are also frequent. Sleep

problems in people with PWS are often underrecognized as they do not exhibit the most common symptoms such as snoring, witnessed apneas, etc.

Factors that seem to increase the risk of sleep disordered breathing include young age, severe hypotonia, narrow airway, morbid obesity, and prior respiratory problems requiring intervention such as respiratory failure, reactive airway disease and hypoventilation with hypoxemia. Due to a few fatalities reported in individuals with PWS who were on growth hormone therapy (GH), some physicians have also added this as an additional risk factor. One possibility (that is currently unproven) is that GH could increase the growth of lymphoid tissue in the airway thus worsening already existing sleep disordered breathing. Nonetheless, it must be emphasized that there is currently no definitive data demonstrating that GH causes or worsens sleep disordered breathing. However, to address this concern, as well as the historically well documented increased risk of sleep-related breathing abnormalities in PWS, **the Clinical Advisory Board of the PWSA | USA makes the following recommendations:**

1. **A sleep study or a polysomnogram** that includes measurement of oxygen saturation and carbon dioxide for evaluation of hypoventilation, obstructive sleep apnea and central apnea should be contemplated for all individuals with Prader-Willi syndrome. These studies should include sleep staging and be evaluated by experts with sufficient expertise for the age of the patient being studied.

2. **Risk factors that should be considered to expedite the scheduling of a sleep study should include:**
   - Severe obesity – weight over 200% of ideal body weight (IBW).
   - History of chronic respiratory infections or reactive airway disease (asthma).
   - History of snoring, sleep apnea or frequent awakenings from sleep.
   - History of excessive daytime sleepiness, especially if this is getting worse.
   - Before major surgery including tonsillectomy and adenoidectomy.
   - Prior to sedation for procedures, imaging scans and dental work.
   - Prior to starting growth hormone or if currently receiving growth hormone therapy.

Additional sleep studies should be considered if patients have the onset of one of these risk factors, especially a sudden increase in weight or change in exercise tolerance. **If a patient is being treated with growth hormone, it is not necessary to stop the growth hormone before obtaining a sleep study unless there has been a new onset of significant respiratory problems.**

Any abnormalities in sleep studies should be discussed with the ordering physician and a sleep specialist knowledgeable about treating sleep disturbances to ensure

that a detailed plan for treatment and management is made. Referral to a pediatric or adult sleep medicine specialist is strongly encouraged for management of the respiratory care.

In addition to a calorically restricted diet to ensure weight loss or maintenance of an appropriate weight, a management plan may include modalities such as:

- Supplemental oxygen
- Continuous positive airway pressure (CPAP) or Bilevel positive airway pressure (BiPAP)
- Oxygen should be used with care as some individuals may have hypoxemia as their only ventilatory drive and oxygen therapy may actually worsen their breathing at night.
- Behavior modification therapy is sometimes needed to gain acceptance of CPAP or BiPAP.
- Medications to treat behavior may be required to ensure adherence to the treatment plan.

If sleep studies are abnormal in the morbidly obese child or adult (>200% IBW), the primary problem of weight should be addressed with an intensive intervention — specifically, an increase in exercise and dietary restriction. Both are far preferable to surgical interventions of all kinds. Techniques for achieving this are available from clinics and centers that provide care for PWS and from the national parent support organization [PWSA | USA]. Behavioral problems interfering with diet and exercise may need to be addressed simultaneously by people experienced with PWS.

If airway related surgery is considered, the treating surgeon and anesthesiologist should be knowledgeable about the unique pre- and post-operative problems found in individuals affected by Prader-Willi syndrome.

Tracheostomy surgery and management present unique problems for people with PWS and should be avoided in all but the most extreme cases. Tracheostomy is typically not warranted in the compromised, morbidly obese individual because the fundamental defect is virtually always hypoventilation, not obstruction. Self-endangerment and injury to the site are common in individuals with PWS who have tracheostomies placed.

At this time there is no direct evidence of a causative link between growth hormone and the respiratory problems seen in PWS. Growth hormone has been shown to have many beneficial effects in most individuals with PWS including improvement in the respiratory system. Decisions in the management of abnormal sleep studies should include a risk/benefit ratio of growth hormone therapy. It may be reassuring for the family and the treating physician to obtain a sleep study prior to the initiation of growth hormone therapy and after 6-8 weeks of therapy to assess the difference that growth hormone therapy may make. A follow-up study after one year of treatment with growth hormone may also be indicated.

Endocrine Abnormalities

Hypothalamic dysfunction and its resultant hormone deficiencies are the presumed origin of many features of PWS.

- **Hypothyroidism** (thyroid stimulating hormone deficiency) has been reported to occur in up to 20%-30% of individuals and may be undiagnosed prior to surgery. Central and primary hypothyroidism can be seen in individuals with PWS. Levothyroxine treatment should not be routinely prescribed in children with PWS unless confirmed by thyroid function testing. Both plasma thyroid stimulating hormone (TSH), T_4 and free T_4 (FT_4) are low in central hypothyroidism, whereas TSH is elevated in primary hypothyroidism. It is recommended that baseline thyroid function testing (T_4/FT_4 and TSH) be done during the first 3 months of life (unless the newborn screening was normal) and annually thereafter, especially if the patient is receiving GH therapy. Please see Hypothyroidism at **http://pwsausa.org/resources/medical-issues-a-z/**

- **Growth hormone deficiency** is also related to hypothalamic dysfunction. All individuals with PWS should be considered to be growth hormone (GH) deficient. Currently, growth hormone is being used as early as one month of life with overall beneficial effect on body composition and growth. The recommended dose is 0.18 to 0.24 mg/kg of ideal body weight divided 7 days a week. The lowest dose is recommended in infants. Benzyl alcohol free-GH products such as Genotropin Miniquick should be first choice whenever possible during the first 6 months of life. Bone age, growth velocity, plasma IGF-1, $IGFBP_3$, glucose, HbA1C, insulin, and thyroid function testing should be monitored during GH treatment.

  Overall, GH therapy is generally safe and well tolerated in PWS children and adolescents. Extreme caution, however, is recommended during 3-12 weeks after initiating GH due to possible development of increased intracranial pressure, manifested by headache and papilledema. It resolves by stopping GH and restarting thereafter with low GH dose with gradual increase. Due to possible development of obstructive sleep apnea, polysomnography should be obtained prior to initiating treatment, within 3-6 months after starting GH therapy, and then annually. Scoliosis is not a contraindication for GH treatment.

  While GH is typically discontinued once bone maturation is achieved at a bone age of 14.5 and 16.5 in girls and boys, respectively, it is the consensus of experts that GH remains beneficial throughout the lifespan. An adult GH stimulation test is necessary to consider adult GH treatment. GH dose in adults is 0.2 to 1.2 mg daily. Lower extremity edema is the most common side effect, but it subsides after decreasing the GH dose. The same blood work as for children is needed to monitor GH treatment in adults, with bone mineral density instead of bone age. See Growth Hormone at **http://pwsausa.org/resources/medical-issues-a-z/**

- **Hypogonadism** occurs in both sexes. Both central or hypogonadotropic (low LH/FSH) and primary or hypergonadotropic (ovarian failure) hypogonadism have been reported in PWS.

Cryptorchidism is virtually universal in males with PWS. Although human chorionic gonadotropin (hCG) is only effective in 24% of infants, this modality of treatment should be considered before a surgical approach. Early treatment with hCG may result in better outcomes including improved development of the scrotal sac, growth of phallus length and muscle tone. The improved muscle tone may decrease the need for gastrostomy tube feeding and facilitate circumcision and orchidopexy.

The increase in onset of pubic and/or axillary hair before age 8 years in girls and 9 in boys is most commonly the result of premature adrenarche and should not be confused with an early sign of puberty. Testicular enlargement (4 ml) in boys and breast development in girls is the first sign of puberty.

No consensus exists as to the most appropriate regimen for sex hormone replacement in PWS. However, most experts recommend intramuscular testosterone replacement in males starting at a dose of 25-50 mg given every 28 days, usually by age 14 years, with gradual increase towards typical adult male doses. Behavior should be monitored during treatment. Other modalities of androgen therapy include daily patches or gel as well as testosterone enanthate, which is administered subcutaneously once a week, typically administered by the parents. Oligomenorrhea or amenorrhea is typical for females with PWS. In girls, usually by age 12-13 years, low-dose oral estrogens with gradual increase are recommended, with combined oral contraceptive pills used after the first vaginal bleeding has occurred. Monitoring of sex hormone replacement therapy should include LH, FSH and sex hormones (testosterone or estrogens).

Although rare, there have been six documented pregnancies in females with PWS. Therefore, counseling on reproductive health and contraceptive practices is warranted for all females with PWS. See Puberty/Sex Hormones at **http://pwsausa.org/resources/medical-issues-a-z/**

Central Adrenal Insufficiency

The possibility has been raised of unrecognized adrenal insufficiency as the responsible cause of unexplained death in some individuals with PWS. However, subsequent studies based on various means of dynamic testing revealed low rates of central adrenal insufficiency in PWS, ranging from 0 to 14.3%. It is currently considered rare.

In general practice, the first step in evaluating patients for possible central adrenal insufficiency is measuring a morning (8 to 10 a.m.) basal cortisol level. Dynamic testing should be considered if repeat cortisol is still below normal range. None of the dynamic stimulation tests can be considered completely reliable for establishing or excluding the presence of central adrenal insufficiency. Consequently, clinical judgment remains one of the most important issues for deciding which patients need assessment or reassessment of adrenal function.

IV. Genetic Basis of PWS

PWS is due to a genetic abnormality that, in the vast majority of cases, results from a new genetic change in the person with PWS. It is caused by lack of expression of a group of genes on the proximal long arm of chromosome 15 (15q11.2-q13). In about 2/3 cases, this expression deficiency is due to absence (**deletion**) of a segment of the chromosome 15 contributed to the affected individual by the father. In most of the remaining cases it is due to the presence of two maternally-contributed and no paternally-contributed chromosome 15 (**maternal uniparental disomy**). Normally the relevant genes in the PWS 15q region are only expressed when inherited from the father and not when inherited from the mother, a process called genomic imprinting. The third, least common cause is a defect in the imprinting center such that both parental copies of the relevant genes in the PWS region of chromosome 15 are suppressed (an **imprinting defect**).

Although most of the manifestations of PWS are the same regardless of the cause of absent expression of these genes, a few problems occur more frequently in the presence of one or the other of the genetic causes leading to somewhat different prognosis. Recurrence risk can also vary with genetic cause. All three of these genetic causes will result in an abnormal DNA methylation test, though determination of the exact genetic cause requires additional testing. Further discussion of the genetics of PWS and the manner in which they can influence medical problems is beyond the scope of this brochure but can be found in numerous sources including Gene Reviews: **https://ncbi.nlm.nih.gov/books/NBK1330/**

V. In the Event of Death

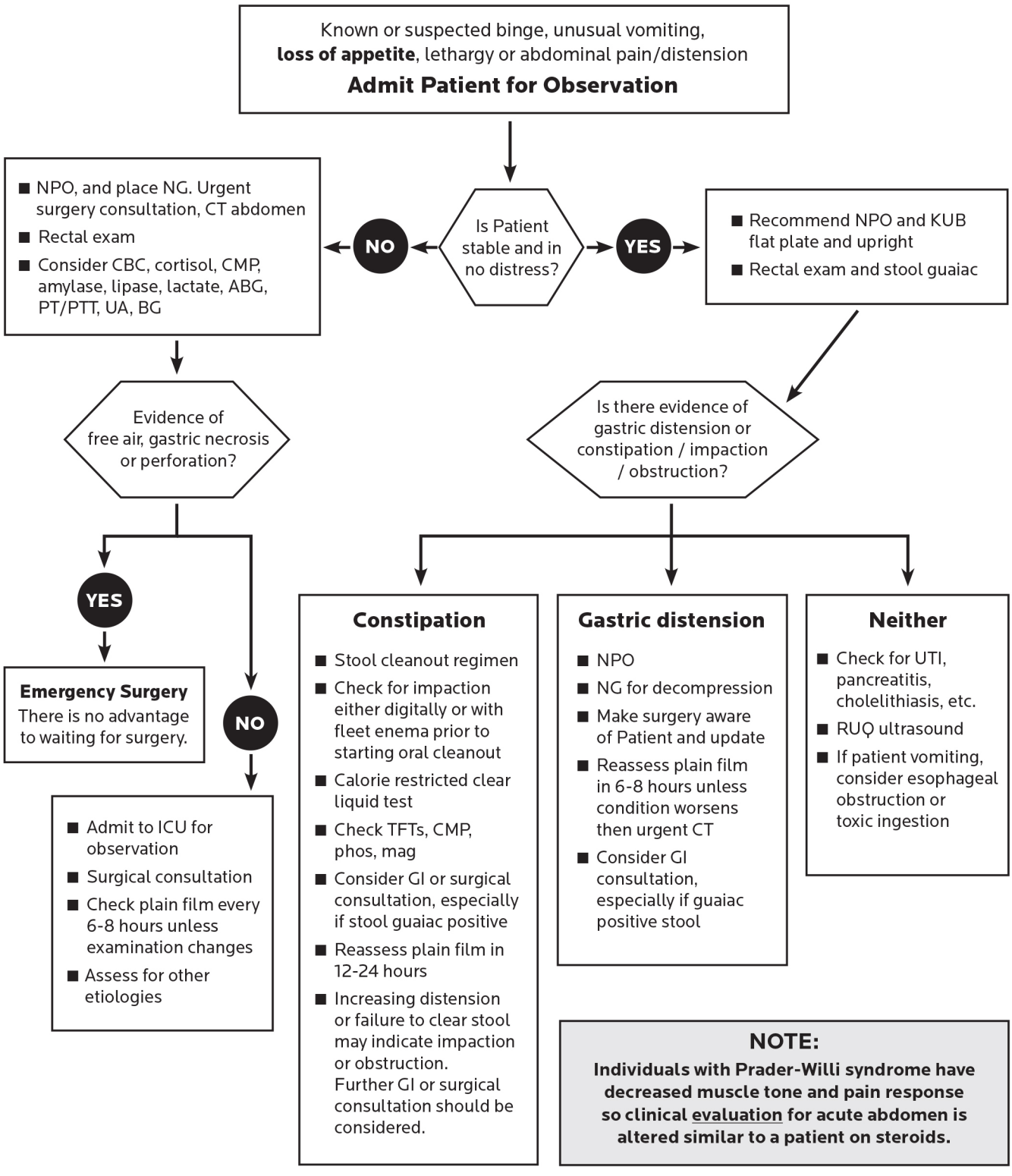
PWSA | USA collects information on mortality to help advance knowledge about causes of death. That knowledge can lead to future research and address critical areas of need for advancing treatment development and quality of life/longevity for those with PWS. We also partner with Autism BrainNet to facilitate the collection of postmortem brain tissue to identify new and effective treatments.

When the death of a loved one is near or has occurred, families may call Autism BrainNet's 24-hour, seven-day-a-week hotline to begin the donation process:

877.333.0999 or PWSA | USA **941.312.0400**

PWSA | USA also provides bereavement support to families who have lost a child with PWS. Please call PWSA | USA to report a death so that the family can receive grief counseling. Please contact Family Support (**941.312.0400**) in the event of death/near-death of an individual with PWS.

Evaluation of Individuals with Prader-Willi Syndrome with New GI Complaints



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Prader-Willi SYNDROME ASSOCIATION | USA
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Prader-Willi Syndrome Medical Alerts
by
Clinicians of the PWSA | USA Clinical Advisory Board
and consultant experts

This life-saving Medical Alerts Booklet is dedicated to ***Janalee Heinemann, MSW*** *in appreciation for a lifetime of service to the PWS community and the truly thousands of lives that were saved and transformed by her skill, compassion, and dedication.*

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