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Anesthesia and Prader-Willi Syndrome by James Loker, MD Laurence Rosenfield, MD

Obesity- Obese individuals are more prone to obstructive apnea, pulmonary compromise, hypoventilation, and diabetes. Each of these should be taken into account when preparing for anesthesia. The individual may have altered blood oxygen or blood carbon dioxide levels that will change their response to medications including oxygen. Pulmonary hypertension, right-heart failure, and edema may necessitate evaluation by a cardiologist or pulmonologist prior to surgery. An ECG or echo to detect right ventricular hypertrophy may be beneficial to assess pulmonary hypertension. Frequently obese individuals with PWS may have significant body edema (extra fluid) that is not fully appreciated due to obesity. This should be carefully evaluated, and if necessary, diuretics used before and after the anesthesia. Airway management can be a particular problem when conscious sedation is used and appropriate safeguards should be in place.

High Pain Threshold- Individuals with PWS may not respond to pain in the same manner as others. While this may be helpful in post-operative management, it may also mask underlying problems. Pain is the body's way of alerting us to problems. After surgery, pain that is out of proportion to the procedure should alert the physician that something else may be wrong. Other possible signs of underlying problems should be monitored.

Temperature Instability- Because PWS is a disorder involving the hypothalamus, individuals may be either hypo- or hyperthermic. The parent or caregiver can be helpful in letting the anesthesiologist know what the individual's usual temperature is. Although there is no indication of a predisposition to malignant hyperthermia in PWS, depolarizing muscle relaxants (i.e., succinylcholine) should be avoided unless absolutely necessary.

Thick Saliva- A common problem in PWS is unusually thick saliva. This can complicate airway management, especially in cases of conscious sedation or during extubation (when a breathing tube is removed). Thick saliva also predisposes an individual to dental caries (cavities) and loose teeth. Oral hygiene should be evaluated prior to anesthesia.

Food-Seeking Behaviors- It is vitally important that any individual undergoing general anesthesia or conscious sedation have an empty stomach. This reduces the risk of aspiration of the stomach contents into the lungs. Individuals with PWS generally have an excessive appetite and may not tell the truth if they have eaten just prior surgery.

Any individual with PWS should be assumed to have food in the stomach unless it is verified by the caregiver that they have not eaten. A tube may need to be placed in the stomach to assure no food is present prior to attempting to place the breathing tube. Some individuals with PWS may ruminate (regurgitate some of their food) and are at higher risk of aspiration.

Hypotonia- The majority of infants with PWS are significantly hypotonic. This usually improves by 2-4 years of age. The majority, however, continue to have lower muscle tone than normal individuals. This may be a problem in the ability to cough effectively and clear the airways after use of a breathing tube.

Skin Picking- Habitual skin picking can be a significant problem in PWS. This can complicate healing of IV sites and incisional wounds. Usually if these remain well covered, they will be left alone. Depending on the individual's cognitive impairment, restraints or thick gloves may be needed to protect surgical wounds during healing.

Hypothyroidism- Although the incidence of hypothyroidism in PWS is not known, low levels of thyroid hormone could occur due to lack of thyroid stimulating hormone or thyroid releasing factor, not necessarily due to problems of the thyroid gland itself. If not already done, a check of thyroid hormone levels may be beneficial in the preoperative evaluation.

Central Adrenal Insufficiency- There are conflicting studies as to the incidence of CAI in PWS. Early papers reported a 60% incidence but more recent papers show a much lower rate (5-15%). In any patient with PWS that is having problems post-surgery, a cortisol level should be drawn and if appropriate, a stress dose of steroids given.

Difficult Access- Due to several problems including obesity and lack of muscle mass, individuals with PWS may pose difficulties with insertion of an intravenous line. Individuals with PWS may have smaller airways and veins than would be expected for their body size. A stable IV line should be present in any individual undergoing anesthesia.

Behavior Problems- Individuals with PWS are more prone to emotional outbursts, obsessive-compulsive behaviors, and psychosis. They may be on extensive psychotropic medication, and the possible interaction of these medicines with anesthesia should be appreciated.

Recovery Post Anesthesia- Drowsiness after anesthesia may be due to the underlying somnolence and a component of central apnea or hypoventilation. For typical outpatient procedures, consideration should be given to an overnight observation.

GI Motility- Individuals with PWS tend to have decreased GI motility and are prone to severe gastric distension, obstruction, and constipation that can be life threatening. Care must be taken when starting feeding after anesthesia. A GI algorithm is available from PWSA to help with assessing gastric distension in PWS.

Summary

In individuals with Prader-Willi Syndrome there are health issues that can alter the course of anesthesia. The majority of complications do not appear to come from general anesthesia, which is always closely monitored, but from poorly monitored conscious sedation. Any individual with PWS undergoing either general anesthesia, or conscious sedation should be considered a high - risk patient and appropriate safeguards put in place.

Edited 2/2

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Constipation in Children with PWS

Kathy Clark, Medical Coordinator (2017).

Reviewed by Ann Scheimann, MD

Difficulty passing bowel movements (BM) is a common problem in PWS, even during infancy. Very soft daily bowel movements are the goal – no bunny pellets, no liquid stools, no pain or discomfort. Some children will release just a small BM, unaware that there is a bigger load behind – so don't be afraid to ask to see what has been produced. Complete evacuation is the goal.

PWS Challenges

Poor motility in the entire GI tract - from sucking, chewing, and swallowing to stomach emptying, to finally pooping - things just don't move along in a typical pattern. There may be slow spots along this pathway, not just at the exit.

Low muscle tone (hypotonia) - movements such as crawling and walking help the passage of food, but are generally delayed skills for children with PWS.

Time - Parents and children are so busy with the many therapies and appointments that life is often too rushed to think about the last bowel movement or to take time for the potty.

Sensation - not feeling pain may also mean they miss the "full" signal that it is time to poop.

Gut microbes, probiotics, and fiber – gut microbes may not be typical in people with PWS, so a probiotic is worth trying. PWSA no longer recommend a high fiber/raw foods diet for persons with PWS because of the risks of fermentation if the digestive tract is not moving well. Fruits and vegetables, softened and in small pieces, are an essential focus of a healthy diet.

Top down, Bottom Up

If your child has had constipation, prevention should start at the "top" – over the counter medications that will make the food hang onto water, making the BM less likely to dry out. Miralax and milk of magnesia are examples of stool softeners. Stool softeners do not make the bowels contract or stimulate a bowel movement. Other oral medications, such as senna, activate the colon to propel a bowel movement along. Some families use these medications daily, and others add these only if things are not moving along. Taking these medications by mouth or feeding tube can take 1-3 days to produce results.

The "bottom up" approach is helpful when there is already a backup of stool. Children quickly learn to "hang on" to a BM if it hurts to pass. Stimulating the anus can help release

the BM and may bring fast relief. A glycerin suppository, which has no medication, only a lubricant, will stimulate the rectum slightly and can be enough to prompt a BM. Dulcolax suppositories have medication which causes the rectum to squeeze and is a faster therapy. Neither one works unless it is touching the inside wall of the rectum – not stuck right into the BM. Grease up the anus with some Vaseline for your child's comfort in passing the large BM; this will also stimulate defecation. Have them lie on their side to insert the suppository, with their knees up to their chest. If they can wait 10 minutes to push, it is more likely to produce the best results. Drinking a glass of water before sitting on the toilet is also helpful – you may have to use your usual tricks to get them to drink.

Once a child has had lots of constipation bouts, they may lose the sensation that it is time to "go". They will have to retrain their bowels. Swallowing stimulates a reflex in the colon, so the best time to sit on the toilet is right after a meal. Make it a habit after breakfast. A chart with stickers can be a motivator!

Some parents find abdominal massage is helpful for any age child; there are YouTube videos explaining this technique. Blowing up a balloon or blowing bubbles can help a child relax their bottom muscles while sitting on the toilet. This is no time for speed or impatience. Bring a book to read together, or play music.

Toilet Tricks

Use statements rather than questions (e.g., "It is time to sit on the toilet", not "Do you need to use the bathroom?"). They may be unaware of the fullness in the colon.

You may need to reward the sitting, even without any results – think sticker charts.

Correct positioning on a toilet is very important for children – and adults. American toilets are poorly designed for good bowel elimination; we are designed to squat when pooping. For a child, or a short adult, the toilet height will never be ideal for good bowel health. The knees should be at least as high as the hips – a true squat is best to open up the muscles that release the BM. A small footstool at the toilet is a good investment – there are toilet footstools, such as the Squatty Potty, which may be very helpful - www.squattypotty.com

Keep their hands occupied so they cannot hold onto the toilet seat. This position can increase muscle tension of the pelvic floor and make it harder to pass the stool comfortably and completely.

Before adding any over the counter medication, call your health care provider to discuss the unique issues for your own child. These are just guidelines for a very common problem for children with PWS.

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Dental Health in Children and Adults with Prader-Willi Syndrome

Compiled and reviewed by B. Dorn, RN, M. Burr DNP, CPNP, and T. Hughes DDS

Individuals of all ages who have Prader-Willi syndrome (PWS) will eventually experience challenges with dental health. Research has identified a number of issues commonly experienced by individuals with PWS, including dental caries (cavities), gingivitis (inflammation of the gums tissue surrounding the teeth), reduced salivary flow, enamel erosion, and severe tooth wear.

It is critically important to address dental health at an early age to avoid lifelong complications. Further, proper dental habits and care, especially in adults with PWS, can help maintain overall health and prevent infections and tooth loss. Read on for additional tips.

DENTAL CARIES/CAVITIES, AND GINGIVITIS

The most common cause of dental caries and gingivitis is poor oral care. Mouth breathing is also a contributing factor in individuals who have PWS. Parents and caregivers should begin teaching and modeling good oral hygiene early to develop lifelong good habits. As time goes on, continue to monitor, and reinforce these skills.

Cleaning teeth should be done on regular basis 2-4 times a day.

- From birth to 6 months, or when the first tooth erupts, wipe the gums with a clean moist gauze pad or washcloth.
- Advance to using a very soft toothbrush or finger brush pad. This will help to establish good dental habits and assist with oral motor stimulation and strengthening.
- Wide brush handles often help to make brushing easier. A bicycle handle grip, rubber pencil grip or other special grip device (available from an occupational therapist) might be helpful.
- Always use a **soft** brush to minimize trauma to the gums.
- Typically, the parent or caregiver should assist in brushing teeth even up until early middle school if needed. Encourage and teach the child to do it, but the parent should finish it up with a “once over” to make sure all areas are reached. This is especially important if a person has braces and at bedtime, to make sure they don’t leave food along the gum lines.
- Solicit help from a dental hygienist to help teach and motivate the person receiving dental care. They might be more successful in achieving cooperation and successful mastery of the skill.
- Make tooth brushing fun.
    - Use fun tooth brushes; let the child or adult choose.
    - Use music or “tooth timers” to help with timing of how long to brush. Some toothbrushes light up and change colors to indicate proper brushing time.
    - Use battery operated or electric tooth brushes.
    - Use incentive charts.
    - Provide rewards – new toothbrush or sugar free gum

- Use good tasting toothpaste with fluoride. Always provide supervision with toothpaste to prevent the person from overeating it. Toothpaste in small amounts will not hurt you.
- White crusting around the mouth is often seen. Toothpaste and/or mouthwash designed for persons with dry mouth has been very effective. (for example, Biotene)
- Teach and encourage flossing. There are several flossing instruments available at most pharmacies and other stores.
- Limit sugar and use sugar-free products. When sugar combines with bacteria in the mouth there is increase acid production which can cause cavities and damage tooth enamel.
- Chewing sugar-free gum after eating can help increase salivation which could help prevent tooth decay. Limit to one piece and this does not substitute for brushing and flossing.
- Avoid food that is soft, sugary, and sticky like raisins, fruit snacks, or anything "gummy" that can contribute to creating cavities.

Dental examinations and cleanings should be done at least every 6 months.

- Do not be afraid to shop around. Get referrals from other parents in your community.
- Choose a dental team who is educated and experienced with patients with special needs or cognitive impairments.
- Consult an orthodontist between ages 6-9 to assess the palate and structure of the mouth. This can make it easier to keep teeth clean, preventing tooth decay, and periodontal disease.
- Finding dental professionals that accept Medicaid or other financial assistance can be very challenging, and reimbursement for dental services in these programs is often inadequate. Contact your state dental association for a list of providers.
- Some dental care providers have opted to donate their services in lieu of utilizing financial assistance.
- Community health clinics often have free or reduced-fee dental clinics. Special Olympics in some areas provide dental services. Watch for regional FREE dental clinics.
- Consider utilizing a Dental school for care.

REDUCED SALIVARY FLOW AND ENAMEL EROSION

Thick, sticky saliva is caused by reduced production of saliva and is commonly found in individuals who have PWS. Reduced salivary flow contributes to enamel problems, such as enamel erosion (the wearing down of the protective covering (enamel) of the teeth). When enamel wears down, microscopic channels in the tooth open up and become exposed. Most people with this problem complain of discomfort and pain. However, since persons with PWS have an altered pain response, they might not complain about this. Health conditions including gastric reflux, medications (aspirin, antihistamines, and some vitamins), as well as a diet high in sugars and acid contribute to enamel erosion.

In addition to good dental hygiene and care, there are additional steps that can manage and prevent these issues.

- Consult your dentist on use of sealants in preventing enamel erosion and tooth decay, even in adults.
- Drink water in moderation. Dehydration is often a contributing factor.
- Avoid beverages high in acid, such as soft drinks, sport drinks, juice, tea, and coffee.
- Swish mouth out with water or brush teeth after drinking beverages high in acid.
- Use a straw to keep acids away from teeth.

- Use fluoride toothpaste and an alcohol-free fluoride mouthwash. Use as a rinse and do not swallow. If needed, apply with a Q-tip.
- Report symptoms of Gastroesophageal Reflux Disease GERD) such as a sudden loss of tooth enamel, excessive belching and/or burping to your health care professional to identify if gastric reflux is present. This disorder has been identified in persons with PWS and can result in enamel destruction.

SEVERE TOOTH WEAR/GRINDING/BRUXISM

Teeth grinding or recurrent rubbing of the surfaces of the teeth can result in damage and severe tooth wear and other complications. This is often seen in children and adults with PWS. It occurs most often while sleeping.

- If a bite abnormality is identified a referral to an orthodontist is highly recommended.
- Mouth bite guard is recommended. It is best if it is individually fitted by dentist. It might require an incentive program for compliance.
- Discourage chewing on pencils, pens, or anything that is not food. Minimize chewing gum if present. The jaw muscles may become conditioned to clenching and increase likelihood of grinding teeth.

A Comprehensive Overview

Of GI Issues in Prader-Willi Syndrome

Ann Scheimann, M.D., M.B.A.

Dr. Scheimann is a Gastroenterologist and expert on PWS. Ann is a PWSA | USA medical consultant on PWS Gastrointestinal (GI) issues.

The prevalence of GI issues in persons with PWS of all ages is quite high. In addition to early feeding difficulties, reflux and aspiration symptoms are frequent problems in infancy. Problems with digestion affect approximately 35% of adults; constipation and diarrhea problems occur in 20-35%. Gastroesophageal reflux disease, GERD, is common.

Dr. Scheimann outlined suggestions to treat GERD in infants: use thickened feedings, avoid overfeeding, use more prone positioning, and eliminate all exposure to tobacco smoke. For older children and adults she recommended: avoid lying down after eating a meal, elevate the head of the bed, lose weight, avoid all tobacco, and avoid foods and medications that may cause reflux. Fundoplication is a surgical option when lifestyle changes and medications aren't enough.

Oral problems are common, including small mouths causing teeth crowding and enamel erosion. Salivary flow is generally far less than normal [dry mouth products such as Biotene can be helpful]. Factors predisposing someone to choking, a serious and not uncommon occurrence in persons with PWS, include hyperphagia (high drive for food), thick saliva, weak pharyngeal muscles, and reflux. Use of the "pace and chase technique for liquid consumption with meals is helpful in preventing the symptoms of esophageal dysphagia and choking. Dr. Scheimann advises all care providers to learn the Heimlich maneuver, treat reflux and gastritis symptoms, encourage chewing during meals, and, of course, supervise persons with PWS at all times.

Risk factors for developing gallstones, also not uncommon, include obesity, low fiber/high fat diet, and diabetes mellitus. 70-80% of normal adults in one study had no biliary symptoms when their gallstones were detected- the majority of healthy adults did not require treatment for gallstones unless symptoms arose such as right sided abdominal pain or pain after meals.

Constipation and encopresis (involuntary fecal soiling) are common problems. Factors that add to constipating conditions include developmental factors (cognition, genetics, fluid intake, etc.) and alter anatomy (low muscle tone, malrotation, etc.). Rectal ulcers can occur when there is chronic constipation. General guidelines to treat constipation in infancy include the careful use of glycerin suppositories or softening agents such as Karo syrup and the increase of fiber intake when solids are introduced. She cautioned against using enemas, suppositories and finger dilations unless recommended by the physician. For the school age child and adult, her suggestions included a cooked fiber-rich diet plus water and the continuous use of medications, such as Miralax with appropriate amounts of fluid on a daily basis rather than intermittent dosing.

Gastric motility (the rate at which the stomach empties) and an impaired vomit reflex (controlled by the central nervous system) contribute to serious stomach expansion and stomach rupture problems that can cause death. Warning signs and immediate hospitalization or ER evaluation for potential gastric rupture or gastric necrosis included a binge eating episode followed by abdominal discomfort, recent history of gastritis or ulcer.

While a variety of bariatric surgery techniques have been attempted in persons with PWS, the long-term results have been very poor. Research continues to explore viable treatment options, but bariatric surgery is not currently one of them.

Updated and reviewed by Dr. Scheimann on July 30, 2019

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Stomach and Intestinal Problems in Persons with PWS Some Answers . . . Many Questions

By Barb Dorn, R.N., B.S.N

We continue to learn more about health issues and Prader-Willi syndrome (PWS). Over the past few years, we have gained a greater understanding of various stomach and intestinal problems that appear to be somewhat more common in persons with PWS. We now know that symptoms of stomach distention or bloating can possibly be related to a condition called gastric dilatation, a life threatening condition. We may be beginning to have answers to other stomach and intestinal concerns; however, at the same time this knowledge is opening the door to more questions. It is our hope that we will gain a better understanding of these problems today so we can prevent them from ever occurring in children and adults with PWS tomorrow.

Gastroparesis, Gastric Dilatation/ Necrosis and PWS - What Do We Know?

PWSA | USA receives calls from around the country about people with PWS who are experiencing acute gastrointestinal problems. More and more children are being diagnosed with a problem called GASTROPARESIS (weakness of the stomach). This condition occurs when there is a delay or slowing in the contraction of the stomach. Because of this delay, stomach contents build up and abdominal distention can occur. The stomach is a muscle that contracts very much like our heart muscle. Unlike the heart, instead of pushing blood, the stomach pushes food out of its cavity into our intestine for further digestion. Feeling full is our body's mechanism for regulating the amount of food that the stomach can accommodate. When a person overeats, the stomach stretches. It may become "over stretched" or distended. We know that persons with PWS do not have the normal mechanism of registering fullness as they eat. They are at a very high risk of over distending their stomachs.

It is believed that if persons with PWS greatly distend their stomach, it can stretch to the point that it cuts off its blood supply, causing necrosis (the stomach tissue dies). This can be a life threatening condition if it is not quickly diagnosed and treated. Over the past few years, it has been discovered that many people with PWS have developed ACUTE IDIOPATHIC GASTRIC DILATATION WITH GASTRIC NECROSIS. Unfortunately, most of these cases have been diagnosed in a postmortem examination.

Acute = Sudden onset/severe **Idiopathic = Exact cause unknown** **Gastric = Stomach**
Dilatation = Expand, stretch, open **Necrosis = Death of tissue (stomach)**

Persons with PWS may be at higher risk for having gastroparesis. Some of the risk factors seen in both conditions are summarized below.

Risk factors for Gastroparesis	Risk Factors Seen in Persons with PWS
Diabetes – most common cause	Diabetes – many persons with PWS have diabetes.
Adrenal and thyroid gland problems	Many persons with PWS have been found to have low functioning of their thyroid gland.
Certain drugs weaken the stomach – many antidepressants and heart medications	Many persons with PWS take antidepressant medications as part of behavior management and some may be taking heart medications.
Neurologic or brain disorders such as Parkinson's, stroke and brain injury	We continue to learn the effects of PWS on brain functioning.

It has been found that people with PWS who have suffered from acute idiopathic gastric dilatation with gastric necrosis have had this occur shortly after a binge episode. It is not surprising to learn that persons with PWS who already have generalized low muscle tone may have poor muscle tone in internal muscles of their body.

The usual symptoms seen in gastroparesis include abdominal distention or bloating, abdominal pain, heartburn, vomiting and regurgitation of stomach fluid into the mouth. These symptoms can be very difficult to detect in persons with PWS. Any signs of acute abdominal illness should be evaluated by a health care professional.

If a person with PWS is experiencing gastrointestinal symptoms and problems, he/she may be referred to a specialist called a gastroenterologist (a doctor who specializes in disorders of the stomach and intestine), who will conduct tests to determine the cause of these problems. Optimally, gastroparesis is diagnosed through a gastric or stomach emptying test. Food that has been "marked" is given to the patient. A scanner then tracks the time it takes for food to leave the stomach. Another test that may be performed is an electrogastrogram (EGG). This is a test similar to the EKG test done on the heart. The EGG measures the electrical

waves that normally sweep over the stomach with each contraction. In gastroparesis, these electrical waves are slower than normal.

If caught early, gastroparesis can be treated. If there is an underlying medical condition, this needs to be treated. Diet and nutrition must also be adjusted. Since fats delay stomach emptying, foods high in fats should be avoided. High fiber food also stays in the stomach for a long period of time. They may need to be restricted if gastroparesis is severe. Liquids leave the stomach faster so they are encouraged. It has also been found that eating frequent small feedings 4-6 times a day may be helpful. In many cases, medications may be used to help stimulate the stomach to contract and empty more normally. It is important to follow the advice and recommendations of the health care professional and/or dietician that are most knowledgeable of that person's condition and needs.

QUESTIONS TO BE RESEARCHED: Is gastroparesis a common finding in children and adults with PWS? What should be done to diagnose and treat this condition? Are there any persons with PWS who seem to be at higher risk?

Many parents and caregivers also report that children or adults with PWS experience rumination (the regurgitation of undigested food from the stomach back up to the mouth). For so long, it was believed to be a behavioral issue. Could this problem be related to gastroparesis? Do we need to change our approach in its management? Is this problem a sign of gastroparesis?

Constipation – Could this Be a Problem for Persons with PWS?

Over the past year, PWSA | USA has been receiving an increased number of reports of constipation in children and adults with PWS. In many cases, this problem has been discovered by accident. Often, a large amount of stool has been noted in their intestines while having an x-ray or test done that is not specifically looking for this problem. So far, no research studies have been done to suggest or confirm if persons with PWS might be at higher risk. Intestines, like the stomach, are muscular organs which push its contents forward so that nutrients are broken down, absorbed and/or eliminated as part of the digestive process.

Constipation can be defined as infrequent passage of hard, dry stools or difficulty in evacuating stools. Ideally, a person should have a bowel movement every day or so, and it should be soft and bulky. There can be several causes for this problem. Some of the more common causes are summarized below.

Common Causes for Constipation
Lazy colon that does not contract properly and move the stool through the intestine (a "hypotonic" colon)
Thyroid deficiency
Low potassium level
Certain medications such as those used to manage mood/behavior, pain, diuretics (water pills)
Spastic colon
Tumors or advanced diverticulosis
Abuse of laxatives
Disruption in normal routine – often seen when a person travels

The longer stool remains in the colon, the greater the chance of it becoming hard and dry. As stool travels through the intestine, more and more water is absorbed, resulting in firmer, harder stool. When a person does not have adequate water intake, this can make this problem worse. Water and other fluids help to keep the stool moister and prevent this. If a person has a "lazy colon", it may be contracting; however, it may not be contracting strong enough to provide the person with adequate elimination of stool. In these situations, a person may be having a BM every day and still have a large quantity of stool remaining in their colon. This build-up can also cause over-distension of the colon. It can cause pressure – both forwards (toward the rectum) as well as backwards (toward the stomach). There has been a question as to whether this build-up of pressure in the colon may be adding to the problems in acute idiopathic gastric dilation and necrosis. Many persons who have suffered with this condition have also reported a problem with constipation.

The primary way constipation is diagnosed is by listening to a person's history and complaints. For many people with PWS, that reporting is often sketchy and incomplete. In the early years, parents may be assisting with toileting hygiene issues and see their child's stool. As they grow older and more independent, this is not the case. If a problem is suspected, the health care professional may perform a physical exam along with additional diagnostic testing. Blood testing may be done to rule out a thyroid or potassium deficiency. A barium x-ray may be performed; this is an x-ray using a contrast solution (barium) that is instilled with an enema into the lower intestine. Other tests such as a sigmoidoscopy or colonoscopy may be indicated. In both cases, a flexible lighted instrument is inserted into the rectum in order to view the intestine. The sigmoidoscopy allows the health care provider to view the rectum and lower descending colon. The colonoscopy is a more extensive test in which all of the large intestine can be viewed. If polyps (blood-filled growths that can often develop into cancer) are found, they can be removed and

biopsied. Growths may be one of the more serious causative factors that should be ruled out.

Treatment of constipation is dependent upon its cause. Once serious problems are eliminated, simple measures can be used.

Guidelines for Treating Constipation

- Eat regularly (not usually a problem for persons with PWS)
- Drink plenty of water and fluids daily (often difficult for persons with PWS)
- Encourage regular walking and/or exercise
- Use a bathroom when the urge to have a BM occurs. If needed, set aside 15 minutes after a meal to sit on the toilet.
- Eat a diet of high fiber, fruits and vegetables (fresh is often better)
- Use laxatives and/or enemas as recommended by your health care provider. There are different kinds of laxatives that work on the intestine in different ways. Your provider can assist you in choosing the correct one. Overuse of laxatives can cause the colon to become dependent upon them.

QUESTIONS TO BE RESEARCHED: Are persons with PWS at higher risk for constipation? Do they have a tendency to have a "lazy colon"? Are they effectively and adequately emptying the colon? Can people with PWS prevent issues with constipation? If yes, what appears to be the most effective form of treatment? Does constipation predispose the development of acute idiopathic gastric dilatation with necrosis?

Hemorrhoids and Anal Fissures – Could This Help to Explain Rectal Irritation and Picking?

Hemorrhoids are a common nagging disorder. They are dilated (enlarged) veins that occur in and around the anus and rectum. They may be internal (inside the rectal canal) or external (outside). They can cause some uncomfortable sensations and problems, including itching, irritation, bleeding and pain. If the hemorrhoids are external, they can often be seen as small protrusions from the anus. If they are internal, they may not be seen and a person may not be aware they have them. Conditions that can contribute to the development of hemorrhoids are poor bowel habits, constipation, diarrhea, obesity, pregnancy and straining during a bowel movement.

Anal fissures are small tears in the lining of the anus. They can result from a dry hard bowel movement that causes this tissue to break. They are also seen when a person experiences bouts of diarrhea or irritation. A fissure can be quite painful during and following a bowel movement. Bleeding and itching may also be associated with these. They can become infected so that an abscess or ulceration may develop. In such cases, fever, drainage and swelling may also be present.

Diagnosis of any rectal problem is primarily done by examination by a health care provider. Because of the presence of bleeding, further studies may be done to make sure other more serious conditions (colitis, Crohn's disease, polyps, and tumors) are ruled out. Many of these problems resolve with no treatment. However, symptomatic treatment is often helpful in minimizing the discomfort associated with these problems. Stool softeners help to reduce the pain in passing the stool. Medicated creams and/or pads may decrease pain and itching. A sitz bath (soaking the buttocks in warm water) helps to relieve discomfort and promote healing. Medications such as antibiotics and/or suppositories may be prescribed. The health care professional may need to surgically open up an abscess to promote drainage and relieve pain. The itching, pain and irritation of hemorrhoids and other rectal problems can be very bothersome. In addition to discomfort, the problem can be compounded if a person is also experiencing rectal pressure often associated with severe constipation.

QUESTIONS TO BE RESEARCHED: Do persons with PWS have a tendency to have problems with hemorrhoids, anal fissures or other rectal problems? Is the start of rectal picking a result of persons with PWS experiencing these sensations and/or problems? Could this problem be prevented or decreased by paying closer attention to bowel habits, hemorrhoids, anal fissures and/or other rectal conditions?

Questions and Answers - Where Do We Go from Here?

We are just beginning to question and learn how the gastrointestinal system works in persons with PWS. In addition, we are starting to gain knowledge about some of the health concerns that are also being diagnosed. We don't have all the answers. What we do know is that we need to take a closer look at stomach and intestinal problems in people with PWS. We must learn what can be done to prevent serious health problems from occurring. We must proceed by encouraging and supporting more research. We must do everything to nurture the search for more answers.

Evaluation of Individuals with Prader-Willi Syndrome with GI Complaints

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Known or suspected binge, vomiting, lethargy, or abdominal pain/distension

Admit Patient for Observation

Is Patient stable and in no distress?

No

- NPO, and place NG. Urgent surgery consultation, CT abdomen
- Rectal exam
- Consider CBC, cortisol, CMP, amylase, lipase, lactate, ABG, PT/PTT, UA, BG

Yes

- Recommend NPO and KUB flat plate and upright
- Rectal exam for stool guaiac

Is there evidence of gastric distension or constipation / impaction / obstruction?

Free Air?

Evidence of gastric necrosis or perforation?

Yes

Emergent Surgery

There is no advantage to waiting for surgery.

No

- Admit to ICU for observation
- Surgical consultation
- Check plain film every 6–8 hours unless examination changes
- Assess for other etiologies

Constipation

- Stool cleanout regimen
- Check for impaction either digitally or with fleet enema prior to starting oral cleanout
- Calorie restricted clear liquid diet
- Check TFTs, electrolytes
- Consider GI or surgical consultation, especially if stool guaiac positive
- Reassess plain film in 12-24 hours
- Increasing distension or failure to clear stool may indicate impaction or obstruction. Further GI consultation should be considered

Gastric distension

- NPO
- NG for decompression
- Make surgery aware of Patient
- Reassess plain film in 6-8 hours unless condition worsens then urgent CT
- Consider GI consultation, especially if guaiac positive stool

Neither

- Check for UTI, pancreatitis, cholelithiasis, etc.
- RUQ ultrasound
- If patient vomiting consider esophageal obstruction or toxic ingestion

Note: Individuals with Prader-Willi syndrome have decreased muscle tone and pain response so clinical evaluation for acute abdomen is altered similar to a patient on steroids.

Credits: James Loker, M.D., Pediatric Cardiologist ● Ann Scheimann, M.D., M.B.A., Gastroenterologist ● PWSA (USA) Clinical Advisory Board Members
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Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome

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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	De Waele et al, 2008 (138)
		Decreased insulin secretion	Haqq et al, 2003 (139)
		Impaired glucose tolerance	Haqq et al, 2003 (140)
		Risk of cholesterol gallstones	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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Prader-Willi
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OSTEOPOROSIS EVALUATION AND THERAPY IN PRADER-WILLI SYNDROME

Consensus Statement of the PWSA | USA Clinical Advisory Board

Many individuals with PWS have osteoporosis (low bone mineral density). This condition is most often diagnosed in adolescence and adulthood. The cause(s) of the osteoporosis is not totally clear, but it is thought to be primarily due to the growth hormone and sex hormone deficiencies that occur in PWS. Hypotonia is probably a contributing factor as well.

Bone mass typically accumulates until around the age of 30, with the maximum accrual time for bone mineral density being in adolescence. Puberty is often delayed or incomplete because of a deficiency in sex hormones in individuals with PWS. This interruption of normal puberty in combination with growth hormone deficiency probably results in less bone mineral mass being accrued during adolescence in individuals with PWS compared to the normal population. However, the process may begin earlier than adolescence due to other hormonal abnormalities which affect bone mineral density.

Physical inactivity and limited weight bearing also play a role in the onset and exacerbation of osteoporosis. Exercise is an essential part of the life style for all individuals with PWS, and the health benefits of exercise must continue to be emphasized. Also, recent studies suggest that the use of psychotropic medications may play a role in the genesis or exacerbation of osteoporosis. It is well known that individuals receiving anticonvulsants for seizures or mood stabilization are at greater risk for osteoporosis. Adults receiving selective serotonin reuptake inhibitors (SSRIs) have greater bone loss and lower bone mineral densities. Children and adolescents receiving SSRIs are at risk for decreased bone mineral accrual and bone formation. Given the large number of individuals with PWS who are receiving psychotropic medications, extra care for evaluation and management of these individuals is required.

Osteoporosis is diagnosed with a dual-energy X-ray absorptiometry (DEXA) scan. A DEXA scan is a painless low dose X-ray procedure. DEXA scans of children and adolescents should be interpreted only by experts experienced in scoring these scans in pediatric patients. DEXA scans which are interpreted compared to adult standards (T-scores) often overestimate the presence of osteoporosis in children and adolescents. Although the normative pediatric databases are small, the interpretation of the DEXA scan should contain an age-, gender-, and race-matched Z-score. Frequently radiologists or other individuals who evaluate DEXA scans do not have access to this information. A Z-score (or T-score for adults) that is between 1 and 2 standard deviations below normal is considered osteopenia (weak bones), while a Z- or T-score that is more than 2 standard deviations below normal is considered osteoporosis. You should ask your physician to provide you with the Z-score (if you are under 18 years of age) or T-score (if you are an adult). DEXA scans should be monitored every one to two years in adolescents and adults with PWS.

Other assessments that are valuable for individuals with osteopenia or osteoporosis include measurements of serum calcium, phosphorus, magnesium, parathyroid hormone (PTH), alkaline phosphatase, 25-hydroxy-vitamin D levels (calcidiol), and 1,25(OH)2-Vitamin D (calcitriol). Many individuals in the United States are deficient in dietary intake of vitamin D and calcium. These nutritional deficiencies play a big role in the development of osteoporosis. Other laboratory measurements should include evaluation of thyroid function, prolactin, sex hormone levels, and growth hormone levels.

If osteopenia or osteoporosis is present on DEXA scan, the primary treatment is maximizing vitamin D and calcium intake in the diet. A nutritional consult should be obtained to assess current dietary intake of calcium and vitamin D. Current recommendations for adults (note that pediatric standards vary according to age) are that dietary calcium for individuals with low bone mineral density should be at least 1,500 mg per day and vitamin D intake should be at least 600-800 IU per day. Some studies indicate that even these amounts may be inadequate to significantly improve bone mineral

density. Ideally, serum 25 vitamin D levels should be followed, with the desired concentrations being at least 30-32 ng/ml in order to improve bone mineral density.

In many cases the dietary intake is inadequate and supplementation of calcium and vitamin D is necessary. It is important to know that most calcium supplements are calcium carbonate which is only 40% bioavailable (meaning that a calcium supplement which contains 500 mg of calcium carbonate only provides 240 mg of elemental calcium which can be used by the bones). Vitamin D can be purchased over-the-counter without a prescription in 200 – 1,000 IU capsules or may be purchased at higher doses with a prescription. The best way to give calcium supplementation is with food, no more than 600 mg of elemental calcium at a time, and no more often than every 2 hours to allow maximal absorption.

Although medications called bisphosphonates (e.g., Fosamax, Actonel, and others) are commonly used in adults with osteoporosis, the use of these medications in adolescents and young adults remains controversial. Some experts in pediatric bone disease recommend that these medications not be started in young people with osteoporosis until they have had a fracture. The long term risks of these medications are unknown at this time. However, there have recently been reports of an increased incidence of jaw necrosis after dental procedures associated with these medications. Bisphosphonate therapy may be considered in adolescents or young adults once vitamin D and calcium supplementation are maximized. More research is needed to identify the long-term risks that may be associated with these medications in adolescents and young adults.

Other important treatment options for osteoporosis include hormone replacement therapy (such as estrogen, testosterone, thyroid hormone and growth hormone). These treatments have been shown to improve bone mineral density in individuals with PWS. Starting these therapies before adolescence, if possible, should be most beneficial. Supplementation of vitamin D, calcium, sex hormones and any other modality of treatment for osteoporosis should be monitored by a physician.

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PRADER-WILLI SYNDROME

MEDICAL ALERTS

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REVISED 2021

PRADER-WILLI SYNDROME

Prader-Willi syndrome (PWS) is a complex neurobehavioral genetic disorder resulting from abnormality on the 15th chromosome. It occurs in males and females equally and in all races. Prevalence estimates range from 1:12,000 to 1:15,000. Incidence in newborns is unknown.

PWS typically causes low muscle tone, short stature if not treated with growth hormone, cognitive deficits, incomplete sexual development, problem behaviors, and a chronic feeling of hunger that, coupled with a metabolism that utilizes drastically fewer calories than normal, can lead to excessive eating and life-threatening obesity.

It is felt to be a multistage disorder with decreased fetal movement prenatally and low birth weight. Infants have failure to thrive due to feeding problems and hypotonia. Toddlers have increased weight gain, then hyperphagia and obesity as they get older, if calories are not restricted. Most of the medical problems in Prader-Willi syndrome are related to the obesity, hypotonia, and hypothalamic dysfunction.

Some of the other factors that may cause difficulties include adverse reactions to medications, high pain tolerance, gastro-intestinal and respiratory issues, lack of vomiting, and unstable temperature. Adrenal insufficiency may also occur.

Severe medical complications can develop rapidly in individuals with PWS.

Members of the Clinical Advisory Board are available for consultation with physicians through the Prader-Willi Syndrome Association | USA.

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Mission

To enhance the quality of life of and empower those affected by Prader-Willi syndrome.

Table of Contents

MEDICAL ALERT

Important Considerations for Routine or Emergency Treatment

Obesity and its related complications is the major cause of morbidity and mortality in Prader-Willi syndrome. Keeping the individual at a healthy weight will minimize these complications but there are important medical and behavior problems unique to Prader-Willi syndrome regardless of weight status.

Medical professionals can contact PWSA | USA to obtain more information and be put in touch with a specialist as needed. Up-to-date has an excellent summary of the syndrome.

Central Adrenal Insufficiency in Individuals with Prader-Willi Syndrome

Several studies have shown CAI in individuals with PWS while others failed to show a deficiency. Stress dose of cortisol may be indicated if individual has problems after surgery or during times of stress. **http://www.pwsausa.org** and view Medical section under Adrenal Insufficiency.

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, or decreased movement of the extremity for more than a few days may warrant an x-ray.

Hyperphagia (Excessive Appetite)

Individuals with PWS must be constantly supervised in all settings to prevent access to food. In hospital settings, obtaining unguarded food can lead to rapid ingestion and fatal choking. 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 no treatments for this relentless hunger. Insatiable appetite may lead to life-threatening weight gain, which can be very rapid and occur even on a low-calorie diet.

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.

Pain Insensitivity

Lack of typical pain signals 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 Lesions and Bruises

Because of a habit that is common in PWS, open sores caused by skin picking may be apparent. Individuals with PWS also tend to bruise easily. These lesions can cause serious life-threatening infections. There are approaches to help mitigate picking. **h p://www.pwsausa.org/resources/medical-issues-a-z/** and view skin picking. Appearance of such wounds and bruises may erroneously lead to suspicion of physical abuse.

Swallowing and Choking

Persons with PWS are highly likely to have an undetected swallowing problem that places them at risk for asphyxiation of a food bolus (choking), and they require a specific type of swallowing evaluation. A clinical or bedside evaluation is not sufficient to detect dysphagia in this population. They frequently cannot tell if they cleared their airway after swallowing, increasing the risk for aspiration. Choking can also occur with rapid ingestion of unguarded foods and has led to many deaths in the PWS population.

http://www.pwsausa.org/resources/medical-issues-a-z/ and view Choking/Swallowing.

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. All individuals with PWS are at risk for mild hypothermia because of impaired peripheral somatosensory and central thermoregulation, poor judgment and cognitive inflexibility. Malignant hypothermia is a life-threatening problem occasionally seen in PWS. **http://www.pwsausa.org/resouces/medical-issues-a-z/** and view Temperature.

Vomiting – Lack of ability to vomit

Vomiting infrequently occurs in those 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 vomiting may signal a life-threatening illness and may warrant immediate treatment.**

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. Anti-diarrheal medications may cause severe colonic distension, necrosis and rupture and should be avoided.
http://www.pwsausa.org/resources/medical-issues-a-z/ and view Water Intoxication.

Respiratory Concerns

Individuals with PWS are at increased risk for respiratory difficulties. Hypotonia, weak chest muscles, swallowing abnormalities and sleep apnea are common. Anyone with significant snoring, regardless of age, should have a medical evaluation to look for obstructive sleep apnea. Infants commonly have central sleep apnea which generally improves over time but may also have obstructive sleep apnea due to hypotonia and other factors. Hypotonia can lead to diminished activity levels and low aerobic capacity. Hypoventilation may be central in origin.
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 apnea or obesity are at more risk for reflux.

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

PWSA | USA Clinical Advisory Board Consensus Statement - 12/2003

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 is 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.

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 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 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.

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.

Growth Hormone Treatment and Prader-Willi Syndrome

PWSA | USA Clinical Advisory Board Consensus Saemen - 6/2009
PWSA Inernational Consensus Saemen 2013

Both statements are found at **http://www.pwsausa.org/resources/medical-issues-a-z/** and view Growth Hormone.

In-Patient Considerations

Access difficulties – venous and airway

Obesity and poor muscle tone may complicate line placement. A small airway, high palate, and/or obesity may complicate ability to intubate. Saliva is often thick and sticky. Many persons with PWS will have difficult IV access due to increased fat mass and smaller than normal blood vessels. Outpatient procedures and general sedation may be especially problematic. Care must be taken during procedures done in out of hospital settings, and that proper equipment for resuscitation is immediately available and consideration for doing these procedures in an OR should be discussed. Procedures where more than light sedation is used may warrant an overnight observation.

Anesthesia

People with PWS may have unusual reactions to standard dosages of anesthetic agents. Use caution in giving anesthesia. Serious problems occur during conscious sedation, if it is not well monitored, rather than from the use of general anesthesia and airway management. Ongoing assessment of breathing and oxygen saturation is critical in all outpatient procedures including dental work.

http://www.pwsausa.org/resources/medical-issues-a-z/ and view Anesthesia.

• Anesthesia and Prader-Willi Syndrome: James Loker, M.D., Laurence Rosenfield, M.D.

• Anesthesia Concerns for Patients with PWS: Winthrop University

Behavior problems

Individuals are prone to emotional outbursts, obsessive-compulsive behaviors, and psychosis. Psychotropic medications may affect metabolism of anesthesia leading to shorter or longer duration of action.

Cardiac problems

Surprisingly, coronary disease is less in PWS than in individuals with similar obesity. Cardiac problems usually are due to hypoventilation right heart failure. Edema can often be seen in the obese individual

even in the absence of heart failure and is treated by weight loss and ambulation. Diuretics are usually not that beneficial in treating the edema.

Food seeking behaviors/Relentless hunger

Complete safety from access to food is essential in any health care setting. Assume individual has eaten unless verified by 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 caloric restricted diet and that should be conveyed to the nutritionist and kitchen.

Hypothalamic dysfunction – Pituitary deficiencies

Hypothyroidism- Risk of central (TSH deficiency) hypothyroidism is 20-30% and may be undiagnosed prior to surgery.

Growth hormone deficiency - All individuals should be considered to be GH deficient.

Hypothalamic dysfunction is also the presumed origin of many other unique problems including temperature regulation, hunger, ventilatory effort, behavior patterns.

Hypotonia

This muscle weakness may complicate ability to cough effectively and clear airways.

Narcotics

Individuals may have an exaggerated response to narcotics. Use the lowest possible dose to achieve the desired state of anesthesia. Many individuals have delayed gastric emptying that can be compounded with narcotics.

Obesity

Consideration for obstructive apnea, pulmonary hypertension, diabetes, and right heart failure should be addressed.

Pain insensitivity

Unexplained tachypnea or tachycardia may be the only indication of pain. Behavior problems which are not typical for this person may be evidence of pain. Individuals with PWS may not respond to pain in the same manner as others and it may mask the presence of underlying problems. Since pain may not be present, other signs of underlying problems should be monitored.

Pulmonary embolism

Individuals with PWS are at risk for pulmonary embolism. DVT prophylaxis should be considered in all obese individuals. Prolonged bed rest is to be avoided.

Psychosis

There is an increased risk of psychosis in individuals with PWS, which can be triggered by significant events such as changes in routines and serious illness. Prompt attention to hallucinations or reported change in typical behavior is essential. View mental health issues **http://www.pwsausa.org/resources/medical-issues-a-z/** under Psychiatric concerns.

Saliva abnormalities

Thick sticky saliva complicates airway management especially during conscious sedation and increases the risk of caries. Dried saliva may not be an indication of hydration status. Water drinking is minimal in the majority of individuals with PWS.

Skin picking

May complicate healing of IV sites and incisional wounds. Restraints or gloves may be necessary to protect wounds during healing.

Temperature instability

Low basal temperature is typical in healthy individuals with PWS. Hypothalamic dysregulation can lead to poor control during fever or hypothermia. There is no known predisposition to malignant hyperthermia, but depolarizing muscle relaxants should be avoided if possible.

Surgical and Orthopedic Concerns

With the increasing number of infants and children with PWS undergoing sleep assessments prior to growth hormone treatment and the potential rise in surgical procedures (e.g., tonsillectomy) requiring intubation and anesthesia, it will be important to alert the medical team about complications that may include trauma to the airway, oropharynx, or lungs due to possible anatomic and physiologic differences seen in PWS. They can include a narrow airway, underdevelopment of the larynx and trachea, hypotonia, edema, and scoliosis.

Musculoskeletal manifestations, including scoliosis, hip dysplasia, fractured bones (which may be undetected), osteoporosis and lower limb alignment abnormalities, are described in the orthopedic literature. However, care of this patient population from the orthopedic surgeon's perspective is

complicated by other clinical manifestations of PWS. **http://www.pwsausa.org/resources/medical-issues-a-z/** view Orthopedic Issues.

Postoperative Monitoring of Patients with Prader-Willi Syndrome

Patients with PWS are known to have increased morbidity after surgery due to:

- Abnormal physiological response to hypercapnia and hypoxia
- 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 postoperative treatment procedures due to:
  - Extreme food seeking behavior and hyperphagia due to hypothalamic dysfunction
  - High incidence of gastroparesis and slow motility of the intestinal tract

– Extreme skin picking which may interfere with wound healing
– Altered temperature regulation – fever may be absent in the presence of infection. There does not seem to be a higher incidence of malignant hyperthermia
– The possibility of central adrenal insufficiency

RECOMMENDATIONS:

- 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 postoperative with attention to airway and breathing.
- A conservative approach to pain management and use of narcotic agents.
- Full assessment of return of GI motility prior to initiation of intake by mouth 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 postoperatively.

- 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.
- Utilization of respiratory therapy interventions to prevent atelectasis and/or postoperative 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.

http://www.pwsausa.org/resources/medical-issues-a-z/ and view Postoperative Monitoring.

Severe Gastric Intestinal Concerns

Vomiting – Lack of ability to vomit

Vomiting infrequently occurs in those 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 vomiting may signal a life-threatening illness and may warrant immediate treatment.**

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. 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 monitoring, 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.

In addition to gastric distension, colonic impaction may also be present and need to be addressed. 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.

Constipation in Individuals with Prader-Willi Syndrome

James Loker, M.D., Pediatric Cardiologist
Ann Scheimann, M.D., M.B.A., Gastroenterologist
PWSA | USA Clinical Advisory Board Members

Constipation is a common problem in individuals with Prader-Willi syndrome (PWS). It takes longer for food to move through the GI system 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. Failure of standard constipation protocols to clear the stool in a timely manner, especially in the face of increasing abdominal distension, vomiting, decreased appetite, stoppage of food consumption and/or abdominal pain warrants surgical or GI consultation. Emergent surgical or colonoscopic intervention may be necessary.

Kuhlmann, et al. (2014) A descriptive study of colorectal function in adults with Prader-Willi syndrome: high prevalence of constipation.* ***BMC Gastroenterology*, Apr 4; Vol 14: page 63

Prader-Willi Syndrome | USA ALERT! Risk of Stomach Necrosis and Rupture

Possibly Related to Chronic Gastroparesis

A Cause of Death from Sepsis, Gastric Necrosis or Blood Loss

Signs and symptoms of stomach necrosis and rupture:

- **Vomiting-** Any vomiting is unusual in Prader-Willi syndrome
- **Loss of appetite-** (ominous sign)
- **Lethargy**

- **Complaints of pain, usually non-specific-** Pain sensation is abnormal in Prader-Willi syndrome due to high pain threshold; 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**
- **Temperature regulation** is altered in Prader-Willi syndrome
- **Guaiac positive stools (chronic gastritis)**

An algorithm for ER evaluation of an individual with PWS and abdominal complaints is on a foldout page in the back of this publication.

These Signs should raise suspicion of STOMACH NECROSIS/RUPTURE as a possible diagnosis which can be LIFE-THREATENING!

History may include:

- **History of binge eating within the week**
- **Hyperphagia and binge eating are characteristic** of Prader-Willi syndrome, regardless of whether obese or slim

- **Frequently occurs** after holiday, or social occasion with less supervision of intake
- **History of gastroparesis-** Common in Prader-Willi syndrome, though often undiagnosed
- **Often slim or history of significant obesity followed by weight loss-** May leave the stomach wall thinned
  http://www.pwsausa.org and view Medical A-Z under GI Problems.

IN THE EVENT OF DEATH

In the case of a death or impending death, please call PWSA |USA immediately **at 1-800-926-4797** for support and advice.

Reporting of Deaths

The Prader-Willi Syndrome Association | USA has created a research database of reported deaths of individuals with PWS. Although most premature deaths are attributable to morbid obesity, cases unrelated to obesity have been noted. PWSA | USA has a formal investigation of causes of death.

PWSA | USA also provides bereavement support to families who have lost a child with PWS. Please call PWSA | USA to report a death and so the family can receive grief counseling.

Organ Donation for Research

When a child or adult with PWS dies, the family may wish to consider donation of organs for research. PWSA | USA has established a procedure for such donations.

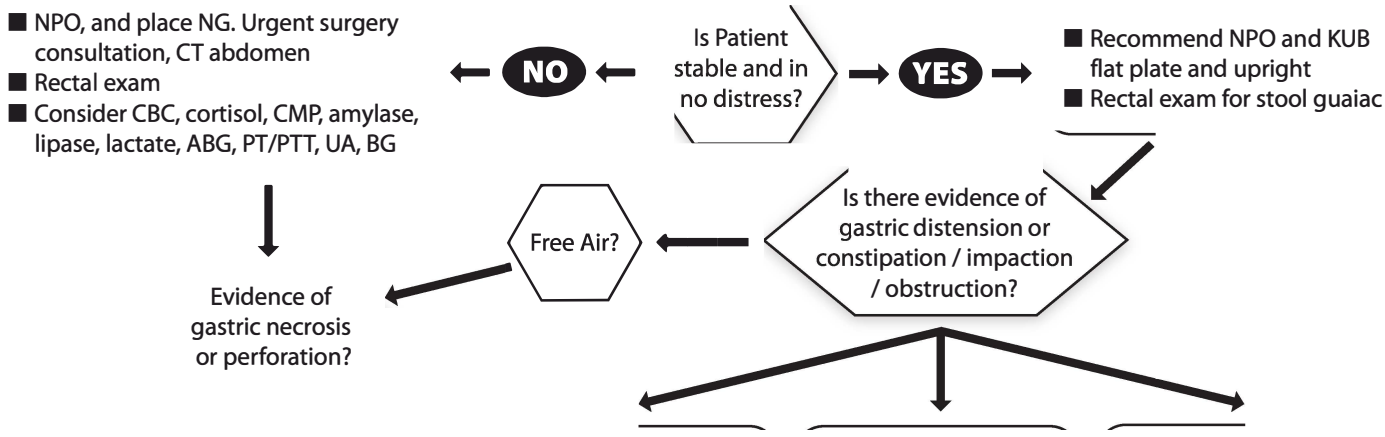
For donating brain tissue, contact Autism BrainNet 877-333-0999.

http://www.pwsausa.org and view Brain Tissue Donation.

Important Notes

Evaluation of Individuals with Prader-Willi Syndrome with GI Complaints

Known or suspected binge, vomiting, lethargy, or abdominal pain/distension
Admit Patient for Observation



YES

Emergent Surgery
There is no advantage to waiting for surgery.

NO

- Admit to ICU for observation
- Surgical consultation
- Check plain film every 6–8 hours unless examination changes
- Assess for other etiologies

Constipation

- Stool cleanout regimen
- Check for impaction either digitally or with fleet enema prior to starting oral cleanout
- Calorie restricted clear liquid diet
- Check TFTs, electrolytes
- Consider GI or surgical consultation, especially if stool guaiac positive
- Reassess plain film in 12-24 hours
- Increasing distension or failure to clear stool may indicate impaction or obstruction. Further GI consultation should be considered

Gastric distension

- NPO
- NG for decompression
- Make surgery aware of Patient
- Reassess plain film in 6-8 hours unless condition worsens then urgent CT
- Consider GI consultation, especially if guaiac positive stool

Neither

- Check for UTI, pancreatitis, cholelithiasis, etc.
- RUQ ultrasound
- If patient vomiting consider esophageal obstruction or toxic ingestion

NOTE:
Individuals with Prader-Willi syndrome have decreased muscle tone and pain response so clinical evaluation for acute abdomen is altered similar to a patient on steroids.

Prader-Willi
SYNDROME ASSOCIATION | USA
SAVING AND TRANSFORMING LIVES

Credits: James Loker, M.D., Pediatric Cardiologist • Ann Scheimann, M.D., M.B.A., Gastroenterologist PWSA|USA Clinical Advisory Board Members

www.pwsausa.org

Important Notes

Prader-Willi Syndrome Medical Alerts
by
Medical Specialists in Prader-Willi Syndrome

This life-saving Medical Alerts Booklet is dedicated to
Janalee Heinemann in apprecia ion for a life ime 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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