IPWSO
International
Prader-Willi Syndrome
Organisation

Infants with Prader-Willi syndrome
Aged 0 to 3 years

Medical care: Overview
Medical Care: Evaluation

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MEDICAL CARE FOR INFANTS WITH PRADER-WILLI SYNDROME AGED 0 TO 3 YEARS
Evaluation, Guidance and an Overview for Healthcare Professionals

Prader-Willi syndrome (PWS) is a complex genomic imprinting disorder with extensive endocrine and neurodevelopmental manifestations as well as many potential medical complications. PWS is due to the loss of paternally inherited genetic information on chromosome 15, or the ability to express it, caused by one of three genetic changes (i.e., paternal deletion at chromosomal region 15q11.2-q13; maternal uniparental disomy 15; or an imprinting defect on chromosome 15). Genetic testing is available and essential to confirm the diagnosis and to define the genotype. A single genetic test, DNA methylation analysis, can conclusively make the diagnosis in >99% of cases.

The first 3 years of life are characterized by dynamic change. In the neonatal period there is severe hypotonia with poor suck and feeding difficulties and with most babies requiring some form of assisted feeding. Later in early childhood, the child begins to gain weight easily, which manifests a year or more before they display an increased interest in food. This can lead to excessive eating and the gradual development of severe obesity unless the access to food is tightly controlled to support normal weight gain. Motor milestones and language development are delayed. Early diagnosis and subsequent anticipatory guidance are crucial for the optimal development and treatment of the infant and young child with PWS. The earlier the diagnosis is made, the better informed the parents and the treatment team can be so that developmentally appropriate medical and behavioral interventions can be implemented.

IPWSO recognizes that access to health services and specialists vary considerably due to factors that include great distance, poor transportation, limited financial resources, or restricted availability. This document summarizes the recommendations for addressing the main health care needs of young children with PWS. While resources vary in different parts of the world, avoiding severe obesity is possible everywhere, when the needs for food control and personal support are accepted and carried out. The reader is directed to the other overview and evaluation guidelines in this series which includes Children with PWS (3-12 years of age), Adolescents with PWS (13 years of age and older), and Adults with PWS. The following are general observations and guidelines with other considerations warranted in some cases.

Perinatal:

- Decreased fetal movements and polyhydramnios or oligohydramnios are frequently observed.
- Increased ratio of head to abdominal circumference on fetal ultrasound.
- Abnormal hand and foot position frequently seen on fetal ultrasound & in newborns.

- Abnormal fetal position more often than typical.
- Increased need for assisted delivery or Caesarean section.
- Increased premature and postmature births.
- Birth weight is typically in the low to low normal range, and typically less than that of sibs.
- Hypotonia is typically evident in the first days after birth.
- The Apgar score in some cases is normal, and the newborn can seem clinically alert shortly after birth, in contrast to the hypotonic presentation in the next few hours and days.

Suspecting the Diagnosis:

- Any newborn with hypotonia, poor suck, weak or no cry and lack of appetite.
- Weak reaction to painful stimuli.
- Newborn males typically have undescended testes and a hypoplastic scrotal sac.
- Newborn females frequently have hypoplastic labia.
- Characteristic facial features (i.e., narrow bifrontal diameter, almond-shaped palpebral fissures, narrow nasal bridge, and/or thin vermilion border of the upper lip with down-turned corners of the mouth) may or may not be apparent at birth and may slowly evolve over time.

The differential diagnosis for the profound hypotonia of PWS in infancy is beyond the scope of this document, but can be found in Table 4 of the PWS GeneReview.

Establishing the Diagnosis

- Initially begin with DNA methylation analysis which will diagnose >99% of PWS.
- Also start with a chromosomal microarray (preferably an oligo-SNP array), which will pick up the deletion class and size, as well as microdeletions that include the "imprinting center" and *SNORD116* locus as well as 70% of uniparental disomy 15 (UPD) cases. (A chromosomal microarray can also pick up chromosomal abnormalities on other chromosomes.)

A positive test for PWS confirms the diagnosis in the vast majority of cases, but does not determine the underlying genetic change.

Determining the underlying genetic cause is particularly important for recurrence risk determination and can aid in prognosis and management considerations.

Individuals with PWS will have one of three different genetic changes (i.e., genetic classes) in this region as a cause for their PWS:

- paternal deletion in chromosome 15;
- maternal uniparental disomy 15; or
- An imprinting defect.

It is recommended that at least two different genetic tests be performed to ensure an accurate diagnosis and to determine the genetic class.

Additional or alternative testing:

- **Fluorescence in situ hybridization (FISH):** If chromosomal microarray is not available, will confirm a deletion if present, but will not reveal the size of the deletion and does not detect a UPD or an imprinting defect.
- **If DNA methylation and the microarray are normal:** Consider *MAGEL2* sequence analysis for Schaaf-Yang syndrome, a specific microdeletion of the *SNORD116* locus (which should be picked up by most high-resolution chromosomal microarrays), as well as mosaicism and other causes of congenital hypotonia.

Note that DNA methylation analyses by Polymerase Chain Reaction (PCR) are not typically quantitative and can miss mosaic conditions involving chromosome 15.

Therefore, if a PWS diagnosis is still suspected consider using a more quantitative method like Methylation-Specific Multiplex Ligation-Dependent Probe Amplification (MS-MLPA) or quantitative DNA methylation analysis.

- **MS-MLPA** can also be an excellent first test since it can economically identify abnormal DNA methylation at multiple sites as well as detect deletions in the region, although not as precisely as a chromosomal microarray.
- Note that **Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS)** can also diagnose PWS if a trio (patient and both parents) is done, but WES and WGS will miss the imprinting defect epimutation subclass and some of the UPD cases. It is recommended to follow up both positive and negative results with WES and WGS with DNA methylation analysis for confirmation.

Genetic Counseling:

- Determine genetic cause as soon as possible - see Figure 1 in the PWS GeneReview
- Medical Genetics should be consulted early to help establish the diagnosis, the genetic class/type, and begin genetic counseling.

- Advise regarding future recurrence risks (typically <1%, but can be as high as 50% in rare cases, and as high as 100% in very rare cases if the mother has a 15;15 Robertsonian translocation).
- Confirmation of the cause of imprinting defects is critical because inherited deletions of the imprinting center have a high recurrence risk (50%), while imprinting defects by epimutations carry a <1% recurrence risk for the parents.
- Advise that prenatal diagnosis is available for future pregnancies.

Nutritional Phases:

Six nutritional phases have been described postnatally in PWS.

Individual variability can be seen in each phase.

The first 3 phases typically occur before 3 years of age.

- Phase 1a – hypotonia with difficulty feeding and decreased appetite.
- Phase 1b – improved feeding, appetite and growth.
- Phase 2a – weight begins to increase inappropriately on the appropriate growth curves without an overt increase in appetite or calories (generally begins around 18-36 months, but can be as early as 12 months) if on a typical toddler diet.

Energy (caloric) needs in PWS are often lower than typical babies and infants because of lower lean body mass and less movement/motor activity, especially after age 6-12 months when typical babies move much more.

Neonatal Period:

Virtually all neonates with PWS have an immaturity of the breathe-suck-swallow reflex resulting in difficulty with oral feeding that requires assisted feeding.

- Most require nasogastric (NG) feeding for the first few weeks to first few months.
- Those that can feed orally will likely need special bottle nipples and extra time to feed.
- Limit duration of oral feeds to no longer than 25-30 minutes per feed to limit risk of aspiration.

There is a well-documented risk of aspiration when feeding the infant with PWS, without the child coughing (silent aspiration) due to low muscle tone in the larynx and slow esophageal transit which can lead to the risk of a lung infection.

The presence of a possible laryngeal cleft can also contribute to silent aspiration and require otolaryngologic evaluation of the airway with correction under anesthesia.

Please be reluctant to place a gastrostomy feeding (G) tube because there then tends to be an over-reliance on the G-tube for feeding, potentially an increased risk of reflux, and a greatly increased risk of complications with G-tubes versus an NG tube.

G-tube placement is not recommended unless the infant needs feeding assistance for >3 months or for other special reasons like parents feeling uncomfortable & insecure with an NG tube.

Risk of reflux and silent aspiration with a G-tube should lead to discussion and individualized decision making about a Nissen fundoplication at the time of G-tube placement.

A Nissen fundoplication can increase the risk of dumping syndrome and hypoglycemia. Alternatively, a transpyloric gastrojejunal tube can be used for bypassing the stomach for enteral feeds without a Nissen fundoplication.

There also is a higher risk of overfeeding with a G-tube. Both regular weighing to support appropriate growth and timely discontinuation of G-tube feeding are necessary.

- Providing early Occupational (OT), Physical (PT), and Oral Motor Therapy are particularly important with oral feeding.
- Weight checks should be obtained daily while still in the hospital and weekly when at home.
- The goal is a 20-30 grams (¾ -1 ounce) of weight gain per day.

Once the diagnosis is confirmed, the discharge can be planned with the likely expectation for tube feeding support at home. Most neonates will require a prolonged stay (days, weeks, rarely months) in the hospital until tolerating enteral feeds and at least limited oral feeds.

Early training in the hospital of families to provide adequate nutritional support at home is crucial.

Concentration of the formula or fortification of the breast milk may be needed to ensure good nutrition in the first months of life.

Discharge planning must include training the family for safe tube feeding, therapy to support improved oral feeding, and close follow up to monitor the energy (caloric) needs and advice regarding advancing oral feeding.

Families can be taught to do NG feedings at home on a case-by-case basis.

- Pediatric Endocrinology services should be consulted after the diagnosis to discuss future hormonal therapy.
- Appropriate nutritional intake should be in place prior to the start of growth hormone therapy.

- Both central and obstructive sleep apnea (OSA) are common in infants with PWS, so the neonate should be monitored initially by pulse oximetry with the duration of the monitoring based on the infant's needs and symptoms.

Growth, Diet & Feeding Goals:

Ongoing nutritional guidance is imperative.

- Initially aim for 10-25 percentile weight for length (World Health Organization growth curve).
- Babies and children with PWS have more body fat than typically developing children.
- Energy (caloric) needs are variable in the first year of life and should be adjusted as necessary according to the growth curve.
- Weight, length, weight for length, and head circumference measurements should be followed by the pediatrician initially every 2-4 weeks after the baby has been discharged from the hospital and then monthly.

Energy needs (caloric needs relative to typical children) begin to decrease usually after 15 months of age, but sometimes much earlier, especially if the child is very hypotonic, does not move as much as other children, or the weight increases too rapidly.

- Be careful to ensure enough fluid if energy intake must be diminished.
- Sometime after 15-18 months of age energy (caloric) needs are typically in the 60-80% range for Recommended Daily Allowance (RDA) of typically developing infants.
- As the weight begins to increase, decrease the calories to keep the child in the 25-50% weight for length.
- Nutritional counseling is important to ensure appropriate protein and micronutrient intake.
- It is important to introduce high quality foods early, but ensure appropriate amount of fats for good brain growth.
- When introducing solid foods, it is recommended to base the decision on the baby's motor development. This is usually at 6 months of developmental age once you are sure the baby can hold their head up and their ability to chew and swallow is appropriate.
- Avoid low nutritional quality food (e.g., fried food, simple carbohydrates and sugars).
- Encourage cooked vegetables, but only in small pieces when the child is able to chew sufficiently well due to the risk of aspiration.
- Restrict fruit to those low in sugar (caloric) content and to two small servings a day.

- It is important to introduce water as a beverage when starting solid foods. It can be a challenge for some children to accept plain water, so zero/low calorie flavored water is acceptable.
- Ongoing consultation with a pediatric dietitian is desirable after 1 year of age.
- Supplementation of 10 micrograms (400 IU) of vitamin D should be given daily for all breast milk fed, and those formula fed infants until they are taking a total of 28-32 ounces (830-950 ml) day of formula which is vitamin D fortified.
- Encourage healthy eating and exercise as a family.

Medications:

- It is recommended to begin growth hormone therapy (GHT) in the first year of life once the child has attained appropriate nutritional status and ongoing management is in place.
- Dosing and follow-up should be monitored carefully by an endocrinologist or a physician with expertise in GHT.
- A sleep study (polysomnography/PSG) is recommended if a past sleep study or several pulse oximetry recordings have been abnormal, if there are any symptoms of OSA, excessive daytime sleepiness, significant behavior changes, or an increase in obesity.
- Consider referral to an Otolaryngologist if there has been an abnormal sleep study or if otolaryngologic issues (e.g., laryngeal cleft, silent aspiration) are suspected. Infants with PWS may also develop sleep-related breathing disorders over time. An annual checkup is recommended and referral to a Sleep study lab (if the facilities are available).

Genital Exam:

- Both males and females have hypogonadism, but it is more obvious in males.
- Females frequently have hypoplasia of the labia majora, minora and clitoris.
- Males typically have a hypoplastic scrotal sac and cryptorchidism, and often a small penis.
- Early trial of human chorionic gonadotrophin (hCG) for treatment of cryptorchidism under the supervision of a pediatric endocrinologist may be beneficial prior to orchiopexy.
- Orchiopexy, if needed, should be done between 6-12 months of age if the infant is in suitable health for surgery and anesthesia, but ideally no later than 18 months due to the increased risk of future testicular cancer in undescended testicles. Preserving fertility is not an issue since no male with PWS has been known to be able to reproduce.

Laboratory Tests:

- Newborn screening labs per standard newborn protocol.
- Thyroid function tests (free T4 and TSH) annually and prior to the start of GHT.
- IGF-1 and IGFBP-3 if receiving GHT.
- Early morning cortisol prior to any surgical procedure requiring anesthesia, as well as during episodes of severe illness (cortisol deficiency is present in up to 5% of children with PWS) due to concerns of central adrenal insufficiency.

Note that morning cortisol levels are lower in children receiving GHT, though still within the normal reference range.

- Routine pediatric labs.

Developmental Milestones:

- Delayed – the time of the individual milestones is generally double those of a typical child. Will need early interventions – Occupational (OT), Physical (PT), and Speech and Language Therapies (SPLT).
- Hypotonia – early intervention with OT, PT, and SPLT is essential to increase sensory feedback to the brain. Sensory stimulation increases alertness and improves neurocognitive maturation that is dependent on motor experience for learning.
- In children with delayed independent weightbearing past 16-18 months, consider use of Ankle-Foot-Orthoses (AFOs) which will stabilize the hypotonic foot and ankle, allowing for earlier standing and walking.

Braces may be reduced or discontinued once the child is an accomplished ambulator. A brace to stabilize moderate or severe pes planus (University of California Bioengineering Laboratory or Supramalleolar Orthosis, UCBL or SMO respectively) helps improve balance and gait tolerance and may prevent long standing foot deformity.

Orthopaedic Concerns:

- Scoliosis: 60-70% of children with PWS will develop scoliosis with curve onset occurring in nearly 25% before 4 years of age, and the remainder during adolescence.
- Kyphosis with or without scoliosis will also start in infancy in around 25% of the patients and is often underdiagnosed.
- Do not place the children in an upright sitting position until they are able to pull to sit on their own. Therefore, infants should be placed in the prone position as often as possible, while awake.
- Avoid having babies sit in the typical hypotonic slouched position as that may initiate a spinal curve.

- Have children with PWS screened for scoliosis by sitting radiograph once they can sit independently.

Clinical examination rarely catches spinal curvatures within the optimal treatment range.

- The earlier growth hormone can be started, the better, in terms of protecting against severe scoliosis.
- Hip development is delayed in parallel with the developmental milestones and 10% of children with PWS have hip dysplasia. This dysplasia is not always apparent in the first months of life, so routine hip X-rays should be obtained on a regular basis through early childhood.
- Hip dysplasia should be monitored and treated with the child's increased activity and weight bearing, rather than bracing or surgery, except in cases of lack of improvement with growth or subluxation (where the femoral head is slipping out of the socket).
- Obtain a supine anteroposterior and frog leg pelvis radiographs around age one year at the same time as the screening spine radiographs.
- Many children with PWS will have hypotonic pes planus (flat feet), making gait less efficient.

A brace, either a UCBL or SMO, will be helpful in supporting the feet as well as helping to hold the feet with growth.

Behavioral Modification:

- Start setting strict limits early and use verbal praise for appropriate behavior.
- Regular eating times and only at the table.
- The child should always know that they only eat what is provided at meal and snack time.
- No eating off other's plates or random snacking.
- During early childhood, the parent should determine what foods are offered, and the child can decide whether to eat all of it or not.
- Children with PWS should not be rewarded with food or punished by withholding food in the home and preschool setting.

Routine Health Maintenance:

- Health maintenance and vaccine administrations should be scheduled the same as a typical young child.
- Check for strabismus and treat accordingly.

- Dental referral is suggested at the eruption of the first tooth. Parental application of a fluoride toothpaste the size of a grain of rice is recommended until the child is able to swish and spit the toothpaste so as to prevent fluorosis.

Slow intestinal motility leads to accumulation of stool throughout the colon in essentially all people with PWS at some point.

- Attention to good bowel habits to maintain one to two soft stools per day, with softeners as needed, is important. Intermittent bowel cleanses (clean outs) may be needed if signs of constipation such as abdominal discomfort, leaking of liquid stool in underwear, or difficulty evacuating the rectum develop.

Acute situations in PWS:

Many children can have infections (even severe) without fever or a fever without an infection.

Small children with PWS can have elevated body temperature especially in hot weather, without appearing ill.

Careful medical examination is recommended whenever the temperature is elevated. Likewise, some children feel warm during cool weather and prefer to dress more lightly than other children.

Coughing can be weak especially in the youngest and pneumonia can be overlooked – the only symptoms may be weakness, loss of appetite, stridor, tachypnea and intercostal retractions during labored breathing.

Respiratory infections are the most common cause of deaths in infants with PWS.

- Hospital admission in case of pneumonia in a child with PWS is warranted to monitor oxygen saturation and risk of prolonged apnea. Be aware that high oxygen supplementation can suppress respiration in PWS due to a poor sensitivity to carbon dioxide.
- Recurrent pneumonias warrant assessment for occult dysphagia/swallowing dysfunction as a contributor.

Many infants with PWS are unable to vomit when they have a gastrointestinal infection. A nasogastric tube in these cases can sometimes be lifesaving.

Individuals with PWS typically have slow gastric emptying and an increased pain threshold. Therefore, any episodes of vomiting and/or abdominal pain and distention should be taken seriously, and parents should have a low threshold to have the child evaluated by a physician.

Older children, in particular, are at risk of binge eating and then subsequently developing severe gastric distention and necrosis, which are life threatening and need emergent evaluation.

Signs and symptoms of illness can be more subtle than in typically developing children. Parents can be helpful historians who can provide valuable insights when their child is not "acting right".

- Choking problems are more common in children with PWS and should be closely monitored while eating. Thus it is recommended that the child slows down the speed of taking bites and takes a sip of liquid between bites (i.e., "Pace and Chase").

Summary remarks:

This document is designed to address the medical problems typically encountered in infants and young children with PWS in an effort to reduce serious complications and improve their quality of life.

Other conditions can have signs and symptoms which are similar with PWS. It is therefore very strongly recommended that the clinical diagnosis be confirmed through genetic testing.

PWS is due to absence of paternally inherited expressed genetic information on chromosome 15q11.2-q13 due to one of three genetic mechanisms: deletion, maternal uniparental disomy, or imprinting defect. The latter can be associated with familial recurrence risk. A DNA methylation test confirms the diagnosis in >99% of cases, but does not provide the specific genetic class. A medical geneticist can order the appropriate genetic testing to determine the specific genotype and provide the appropriate genetic counseling. IPWSO offers free genetic screening for individuals living in countries where this is not available and can also be of assistance in identifying sources of testing.

Please also see medical and other information (most of which is written for a lay audience) on the International Prader-Willi Syndrome Organisation (IPWSO) website which includes information about family support organizations in over 100 countries.

Additional sources of detailed information about PWS are:

1) PWS GeneReview
2) Prader-Willi Syndrome Association | USA – Medical Issues A-Z