

Infants with Prader-Willi syndrome Aged 0 to 3 years

Medical care: Evaluation, guidance and overview

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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 genetic disorder with endocrine and neurodevelopmental manifestations as well as many potential medical complications. 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 are characterized by dynamic change. In the neonatal period there is severe hypotonia with poor suck and feeding difficulties, with most requiring some form of assisted feeding. Later in early childhood the child begins to have easy weight gain followed by an increased interest in food which can lead to excessive eating and the gradual development of morbid obesity unless the eating is externally controlled. 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 may vary considerably due to factors that include great distance, poor transportation, limited financial resources, or restricted availability. This document summarizes the main health needs that are recommended in the context of available resources. 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. Other considerations may be warranted in some cases.

Perinatal:

- Decreased fetal movements and polyhydramnios or oligohydramnios frequently observed
- Increased ratio of head to abdominal circumference on fetal ultrasound
- Abnormal hand and foot position frequently seen on fetal ultrasound and in newborns
- Increased assisted delivery or C-section
- Increased premature and postmature births
- Birth weight typically in low and low normal range, and typically less than sibs
- Apgar scores usually normal since hypotonia not always recognized initially, but

hypotonia typically evident in the first days after birth

Suspecting the diagnosis:

- Should be suspected in any newborn with hypotonia, poor suck, weak cry and lack of appetite
- Newborn males typically have undescended testes and hypoplastic scrotal sac
- Newborn females frequently have hypoplastic labia
- The differential diagnosis for PWS in infancy is vast and beyond the scope of this document

Establishing the diagnosis:

- Start with DNA methylation analysis - will diagnose >99% of PWS
- 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
- Since the PWS region of the genome is very complex, and since most individuals with PWS will have one of three different changes (i.e., molecular 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 assure accurate diagnosis
- 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 *SNORD116* locus and 70% of uniparental disomy 15
- FISH, if chromosomal microarray not available, will confirm a deletion if present, but will not reveal size of the deletion and does not detect uniparental disomy 15 or an imprinting defect
- If DNA methylation and microarray are normal, consider *MAGEL2* mutation analysis for Schaaf- Yang syndrome, as well as mosaicism and other causes of congenital hypotonia
- Note that DNA methylation analyses by PCR are not typically quantitative and can miss mosaic conditions involving chromosome 15

Therefore, if the diagnosis is still suspected consider using a more quantitative method like MS-MLPA.

Genetic Counselling:

- Determine molecular class and subclass as soon as possible - see PWS GeneReviews at: <https://www.ncbi.nlm.nih.gov/books/NBK1330/>
- Medical Genetics should be consulted early to help establish the diagnosis, the molecular class and begin genetic counselling
- Advise regarding future recurrence risk (typically <1%, but can be as high as 50-100% in rare cases)
- Advise that prenatal diagnosis is available for future pregnancies

Nutritional Phases:

- Six nutritional phases have been described postnatally in PWS
- Individual variability seen in each phase

The first 3 phases 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 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
- 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 difficulty with feeding by mouth and will require assisted feeding
- Most require naso- or orogastric (NG/OG) feeding for the first few weeks to first few months
- Those that can feed orally will likely need special 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
- We are reluctant to put in gastrostomy feeding (G) tubes because there then tends to be an over reliance on G-tubes for feeding, there may be an increased risk of reflux, and a scar will be left
- G-tube placement is usually recommended for those needing assistance for >3months or

for other special reasons like parents feeling uncomfortable and insecure with an NG tube

- There is a risk of reflux and silent aspiration with a G-tube unless a Nissen fundoplication is also done
- Occupational (OT), Physical (PT) and Oral Motor Therapy should be involved early particularly with oral feeding
- Weight should be obtained 2-4 times per week
- Goal of 20-30 gram weight gain per day
- Most neonates will require a prolonged stay (weeks, rarely months) in the hospital until tolerating enteral feeds and at least limited oral feeds
- Concentration of the formula or fortification of the breast milk may be needed to ensure good nutrition in the first months of life
- Should not be discharged from the hospital without possible oral and physical therapy support at home
- Selected families can be taught to do NG feedings at home on a case by case basis
- Pediatric Endocrinology 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
- Risk of apnea is increased so the neonate should be monitored by pulse oximetry

Growth, Diet and Feeding Goals:

Need ongoing nutritional guidance:

- Initially aim for 10-25percentile weight for length (World Health Organization growth curve)
- Babies and children with PWS have more body fat than typically developing children
- Caloric needs are variable in the first year of life and should be adjusted as necessary by following the growth curve
- Weight, length, weight for length, and head circumference should be followed by the pediatrician initially every 2-4 weeks after the baby has been discharged from the hospital and then monthly
- Caloric needs (relative to typical children) begin to decrease usually after 15 months of age, but sometimes earlier
- Sometime after 15-18 months of age caloric needs are typically in the 60-80% range

for Recommended Daily Allowance (RDA)

- As the weight begins to increase, decrease the calories to keep the child in the 25-50% weight for length
- Nutritional counselling important to ensure appropriate protein and micronutrient intake
- Important to introduce high quality foods early, but ensure appropriate amount of fats for good brain growth
- Avoid low nutritional quality food (e.g., fried food, simple carbohydrates)
- Encourage vegetables and fruit low in sugar content
- Ongoing consultation with a pediatric dietitian is desirable after 1 year of age
- Vitamin supplementation is essential with a low-calorie diet, as well protein prioritization
- Encourage healthy eating and exercise as a family

Medications:

Growth hormone therapy (GHT) should begin in the first year of life once child has appropriate nutritional status:

- Dosing should be monitored carefully by an endocrinologist
- Before starting GHT a baseline modified sleep study should be done, if possible, and then repeated after approximately 6-8 weeks to assess for worsening obstructive sleep apnea
- Consider referral to an Otolaryngologist before and after starting GHT to assess lymphoid tissue in the throat

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 hypoplastic scrotal sac and cryptorchidism and often small penis
- Trial of human chorionic gonadotrophin (HCG) in males under the supervision of a pediatric endocrinologist may be beneficial prior to orchiopexy
- Orchiopexy should be done between 6-12 months of age

Labs:

- Newborn screening labs per standard newborn protocol
- Thyroid function tests (freeT4 and TSH) annually and prior to the start of GHT

- IGF-1 and IGFBP-3 if receiving GHT
- Early morning cortisol prior to GHT and any surgical procedure requiring anesthesia, as well as during episodes of severe illness
- 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, Physical and Speech Therapies
- Use of Ankle-Foot-Orthoses (AFOs) 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

Orthopaedic Concerns:

- Scoliosis – 40% of children with PWS will develop scoliosis, and half of those will start during infancy
- Do not sit children upright until they are able to pull to sit on their own
- Having them sit in the typical slouched position may help initiate a spinal curve
- Have children with PWS screened for scoliosis by sitting radiograph once they can sit independently
- A clinical examination rarely catches curves in infants with PWS in 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 to the developmental milestones and 10% of children with PWS have hip dysplasia
- Hip dysplasia should be monitored and treated with 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 at the same time the screening spine radiographs are obtained
- Many children with PWS will have hypotonic pes planus (flat feet), making gait less efficient
- A brace, either a UCBL (University of California, Berkeley Laboratories) or SMO (Supra Malleolar Orthosis), will be helpful in supporting the feet as well as helping to hold the feet with growth

Behavioral Management:

- Start setting strict limits early and use verbal praise for appropriate behavior
- Regular eating times and only at the table
- No eating off other's plates or random snacking

Routine Health Maintenance:

- Health maintenance and vaccine administrations - scheduled same as a typical young child
- Check for strabismus and treat accordingly
- Fluoride varnish with eruption of teeth

Acute situations in PWS:

Many can have infections (even severe) without fever

- Small children with PWS can have elevated body temperature especially in hot weather, without being ill, but careful medical examination is recommended whenever temperature is elevated
- Coughing can be weak especially in the youngest and pneumonia can be overlooked - only symptoms could be weakness, loss of appetite, and tachypnea
- Airway 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
- Most infants with PWS are unable to vomit when they have a gastrointestinal infection. 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 should be taken seriously and evaluated by a physician
- Older children, in particular, are at risk of bingeeating and then subsequently developing severe gastric distention and necrosis
- Signs and symptoms of illness can be more subtle than typically developing children - parents can be helpful historians who can provide valuable insights when their child is not "acting right"

General 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 the quality of

life.

PWS is due to absence of paternally inherited 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. It is very strongly recommended that the clinical diagnosis be confirmed through genetic testing. Other conditions can overlap in signs and symptoms with PWS. A DNA methylation analysis confirms the diagnosis in >99% of cases, but does not provide the specific genotype. A medical geneticist can order the appropriate genetic testing to determine the specific genotype. IPWSO can 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: <http://www.ipwso.org>.

Sources of detailed information about PWS are:

Pediatrics: www.pediatrics.org/cgi/doi/10.1542/peds.2010-2820

GeneReviews: <https://www.ncbi.nlm.nih.gov/books/NBK1330/>

PWSA (USA) Medical Alert Booklet:

<https://www.pwsausa.org/wp-content/uploads/2015/11/newMAbookfinal.pdf>