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Guidance for the Clinician in Rendering Pediatric Care

Clinical Report—Health Supervision for Children With Prader-Willi Syndrome

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KEY WORDS
Prader-Willi syndrome, Prader-Labhart-Willi syndrome, uniparental disomy, genetic testing

ABBREVIATIONS
PWS—Prader-Willi syndrome
UPD—uniparental disomy
GH—growth hormone
IGF—insulin-like growth factor

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abstract

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This set of guidelines was designed to assist the pediatrician in caring for children with Prader-Willi syndrome diagnosed by clinical features and confirmed by molecular testing. Prader-Willi syndrome provides an excellent example of how early diagnosis and management can improve the long-term outcome for some genetic disorders. *Pediatrics* 2011;127:195–204

INTRODUCTION

Prader-Willi syndrome (PWS) (also Prader-Labhart-Willi syndrome) is a recognizable pattern of physical findings with significant cognitive, neurologic, endocrine, and behavioral abnormalities caused by lack of expression of genes from an imprinted region of the paternally inherited chromosome 15q11-q13, near the centromere. Originally described in 1958,[1] PWS was the first recognized disorder related to genomic imprinting in humans[2] and provides an excellent example of how early diagnosis and meticulous management can markedly improve the long-term outcome for people with some genetic disorders. PWS affects both genders equally and occurs in people from all geographic regions; its estimated incidence is 1 in 15 000 to 1 in 25 000 live births.[3,4] Affected infants uniformly have significant hypotonia, early feeding problems, and difficulty with weight gain. Later, a second phase of the disorder ensues with hyperphagia (excessive appetite for food), which leads to obesity and characteristic behavior problems. Without adequate weight control and management of eating behaviors, massive obesity and associated complications of diabetes, obstructive sleep apnea, and right-sided heart failure occur; death typically occurs in the fourth decade of life. With careful weight control, people with PWS can remain healthy well into older adult life, and some people are known to live into their seventh decade.

The findings of PWS are listed in Table 1. Clinical diagnostic criteria have been developed and validated[5] (Table 2), but now that reliable molecular testing is readily available, these clinical criteria should be considered guidelines to help define people for whom further diagnostic testing is indicated.[6] In general, PWS should be considered in any infant with significant hypotonia, particularly in the setting of poor feeding, reduced spontaneous arousal for feeding, and hypogonadism (undescended testes, small phallus, or small clitoris). In older children, the diagnosis should be considered when there is impaired satiety for food, especially with rapid weight gain. Likewise, poor linear growth, especially in the presence of excessive caloric intake, should also raise suspicion for PWS. Hypogonadism, hypotonia, developmental

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TABLE 1 Clinical Findings in PWS

Fetal
Breech position
Reduced fetal activity
Polyhydramnios
Growth
Short stature
Failure to thrive in infancy
Central obesity
Head and neck
Dolichocephaly
Narrow bitemporal diameter
Almond-shaped eyes
Strabismus
Up-slanting palpebral fissures
Myopia
Hyperopia
Thin upper lip
Small-appearing mouth
Down-turned corners of mouth
Thick, viscous (reduced) saliva
Enamel hypoplasia
Early dental caries
Dental crowding and malocclusion
Ocular
Strabismus
Nystagmus
Cataracts (rare)
Retinal hypopigmentation
Foveal hypoplasia
Hyperopia
Myopia
Respiratory
Hypoventilation
Obstructive sleep apnea
Central sleep apnea
Gastrointestinal
Feeding problems in infancy
Gastroesophageal reflux
Decreased vomiting
Genitourinary
Small penis
Scrotal hypoplasia
Cryptorchidism
Hypoplastic labia minora
Hypoplastic clitoris
Skeletal
Osteoporosis
Osteopenia
Scoliosis
Kyphosis
Small hands and feet
Narrow hands with straight ulnar border
Clinodactyly
Skin, nails, hair
Hypopigmentation
Blonde to light-brown hair
Frontal hair upsweep
Neurologic
Severe neonatal hypotonia that improves with age
Poor neonatal suck and swallow reflexes
Poor gross motor coordination
Poor fine motor coordination
Mild-to-moderate mental retardation
Learning disabilities
Increased risk of seizures
Global developmental delay
Speech-articulation problems
Hyperphagia

TABLE 1 Continued

Sleep
Snoring/obstructive sleep apnea
Central apnea during sleep
Excessive daytime sleepiness
Early-morning waking
Night-awakening for food-seeking
Voice
Hypernasal speech
Weak or squeaky cry in infancy
Endocrine
Hyperinsulinemia
GH deficiency
Hypogonadotropic hypogonadism
Diabetes mellitus (type 2)
Behavior/mental health
Skin picking
Rectal picking
Food related behavioral problems
Temper tantrums
Difficulty with transitions
Stubbornness
Obsessive behaviors
Perseverant speech
Obsessive-compulsive disorder
Psychosis
Elopement
Miscellaneous
Temperature instability
High pain threshold
Unusual skill with jigsaw puzzles

delays, speech-articulation defects, and characteristic physical appearance should all raise the index of suspicion. Significant neonatal hypotonia is present in essentially all children for whom molecular testing eventually confirms the diagnosis of PWS[7]; therefore, this history should be actively sought during evaluation of older children.

These guidelines are intended to be suggestions for health care providers when assisting in the provision of a comprehensive medical home for children and adults with PWS. They are based on a thorough review of the pertinent medical literature and incorporate experimental data and the experience of clinicians with expertise in caring for people with PWS. As with all chronic medical conditions, establishing a medical home is essential to the smooth and effective provision of care to the individual person and support to his or her family, which is best achieved when the primary care provider and consultants communicate effectively and clearly delineate their respective roles in the care of the person.

GENETICS AND GENOMICS OF PWS

PWS is associated with lack of expression of several genes on the paternally inherited chromosome 15. This region contains genes that are normally "imprinted," which means that they are differentially expressed (used to make RNA and proteins) depending on whether the chromosome was inherited from the father or the mother. On the maternally inherited chromosome 15, these genes are transcriptionally silenced by hypermethylation of their promoter regions. Therefore, only the paternally inherited chromosome produces the gene products. These changes are referred to as "epigenetic," because they do not involve a

TABLE 2 Suggested Criteria for Prompting Molecular Testing for PWS

Age at Assessment	Features Sufficient to Prompt DNA Testing
Birth to 2 y	Significant hypotonia with poor suck and difficulty with weight gain
2–6 y	Congenital hypotonia with history of poor suck; global developmental delay
6–12 y	History of congenital hypotonia with poor suck (hypotonia often persists), global developmental delay, and excessive eating (hyperphagia; obsession with food) with central obesity if uncontrolled
13 y through adulthood	Cognitive impairment, usually mild mental retardation, excessive eating (hyperphagia; obsession with food) with central obesity if uncontrolled, and hypothalamic hypogonadism and/or typical behavior problems (including temper tantrums and obsessive-compulsive features)

Adapted from Gunay-Aygun M, Schwartz S, Heeger S, O'Riordan MA, Cassidy SB. *Pediatrics*. 2001;108(5). Available at: www.pediatrics.org/cgi/content/full/108/5/e92.

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change in the sequence of the DNA but, instead, involve a change to the genomic structure that affects regulation of expression.

The part of chromosome 15 involved in PWS contains several segments of duplicated DNA that predispose to rearrangements, either deletion or duplication, of the PWS region. Absence of the paternally inherited contribution of the PWS region of chromosome 15 leads to lack of the gene products and causes the findings of PWS. In contrast, several other genes in the region are silenced by methylation on the paternally inherited allele. Absence of the maternally inherited contribution of this region causes Angelman syndrome, a completely different disorder caused by lack of expression of a single gene in the region (*UBE3A*).

A short sequence of DNA in the region called the "imprinting center" seems to control switching and maintenance of the imprinting pattern, which is critical, because half of a male's copies of chromosome 15 carry the silenced genes inherited from his mother. When he, in turn, passes copies of his mother's chromosome 15 to his own offspring, those genes must be reactivated, which "switches" the imprint.

It becomes clear, then, that there are multiple mechanisms by which a person may end up with no functional (transcriptionally active) copies of the genes in this critically important region of chromosome 15 and, thus, have PWS.

1. The most common situation (~70% of cases) is that the paternally inherited chromosome 15 contains a microdeletion of 3 to 4 megabases of genetic material spanning the PWS region.
2. In approximately 20% of cases, the affected infant has maternal uniparental disomy (UPD), which means that the child inherited both copies of chromosome 15 from the mother and no copy from the father.
3. Imprinting errors, which occur in 5% or fewer cases, involve a defect of the process of switching the imprint when the father passes on a copy of the chromosome 15 that he inherited from his mother.
4. Finally, PWS has been described as a result of a balanced translocation involving chromosome 15 that moves the genes in the region away from the imprinting center.

Several recent reports suggested that the essential PWS phenotype may be caused by loss of the imprinted HBII-85 cluster of small nucleolar RNAs (snoRNAs), which, if confirmed, will be one of the first developmental disorders shown to be caused by loss of microRNA.[8,9]

The PWS region of chromosome 15 is flanked by segments of duplicated DNA, which predisposes to deletion, or duplication, during recombination in meiosis. This seems to be the reason for the high frequency of the typical deletion in PWS and in some other recurrent microdeletions. It is important to recognize that the normal chromosome structure in the region plays a significant role in the development of the genetic defect; thus, PWS has been described as a "genomic disorder" to distinguish it from other genetic disorders that are specifically caused by an alteration in the sequence of the DNA.[10]

UPD is thought to result most often from meiotic nondisjunction that leads to trisomy for chromosome 15 and, thus, is associated with increased maternal age. Trisomy 15 is the most common trisomy at the time of conception but can only survive if there is a second mitotic division error after fertilization that eliminates 1 of the 3 chromosomes 15. If the paternally contributed chromosome is lost, the embryo will revert to having the normal 2 copies of chromosome 15, both of which originate from the mother. Alternatively, the sperm could have no copy of chromosome 15 as a result of a paternal meiotic error, and the resulting conceptus would have only 1 chromosome 15. Such an embryo would also be spontaneously aborted unless a second, mitotic error occurred after fertilization that duplicates the maternally contributed chromosome 15. In either case, an infant born from such a pregnancy would be missing the paternally contributed chromosome 15 and, therefore, would only have inactive, maternally imprinted copies of the genes in the PWS region.

The third mechanism, an "imprinting error," leads to a situation in which the imprinted (silenced) genes that the father inherited from his mother cannot be reactivated. The infant inherits 1 copy of chromosome 15 from each parent, but the PWS region is fully methylated on both copies of chromosome 15 and, thus, is silenced in both copies. This mechanism, although rare, is important to identify, because the inability to switch the imprint can be an inherited trait, which means that a man with an inherited imprinting defect has up to a 50% recurrence risk with each pregnancy to sire another child with PWS. The rare case of PWS attributable to a balanced translocation also may have an increased recurrence risk if the father carries the same translocation on the chromosome 15 he inherited from his mother. Neither deletion nor UPD is known to be associated with increased recurrence risk.

Although subtle differences have been shown between groups of people with deletions compared with UPD,[11–16] for the most part, there are no major differences in phenotype among the various causes. The exception is the finding of hypopigmentation, which is most notable in people with PWS who have a deletion of the *OCA2* gene (a

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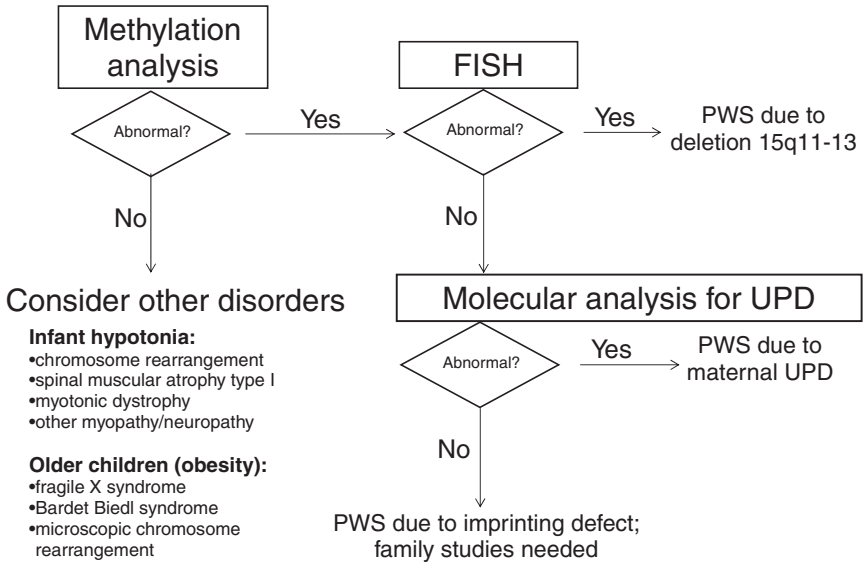

FIGURE 1
Flowchart of recommended molecular testing strategy for PWS.

nonimprinted gene in the PWS region of chromosome 15 associated with autosomal recessive oculocutaneous albinism type II).[17,18] Recently, some authors suggested that there may be subtle differences in neurocognitive development in children with deletions depending on the location of the proximal break point.[19] Others have not observed such a difference[13]; therefore, the clinical utility of defining the break points is not clear at this time.

DIAGNOSTIC TESTING

Diagnostic testing for PWS, as outlined in Fig 1, should begin with methylation analysis to confirm the absence of paternally imprinted genes in the PWS region of chromosome 15. When only a maternal methylation pattern is seen, PWS is confirmed, but additional testing is needed to identify the specific cause, which allows for appropriate counseling regarding recurrence risk. The recurrence risk for spontaneous deletions or UPD is low (<1%), whereas the recurrence risk of imprinting mutations can be as high as 50%. If the methylation analysis is consistent with PWS and the karyotype and fluorescence in situ hybridization (FISH) reveal no evidence of deletion or balanced rearrangement, the next step is to obtain blood from the parents and the child to evaluate for UPD. If biparental inheritance is discovered in the face of abnormal methylation and normal FISH results, then, by process of elimination, the cause is assumed to be an imprinting defect. The possible role of testing for defects of the HBII-85 small nucleolar RNA cluster remains to be elucidated.

SPECIAL CONSIDERATIONS FOR THE INFANT AND CHILD IN WHOM PWS IS DIAGNOSED

Nutrition

Maintenance of adequate and appropriate nutrition is central to the care of people with PWS at every age. Infants may require support of feeding for several months. Caloric needs may be, but are not always, somewhat reduced in infants with PWS, and infants with PWS typically do not spontaneously demand feedings. Therefore, the infant's diet must be adjusted as needed to maintain appropriate weight gain as determined by frequent weight checks. Increased caloric density of feedings is often helpful. Later, after hyperphagia begins, the diet must be quite calorically restricted, often to as little as 60% of the calories that similarly sized children without PWS might require for adequate growth. This diet requires careful attention to the balance of essential nutrients, which is often best achieved by referral and regular follow-up with a dietitian who is knowledgeable about PWS.

Feeding Tubes (Nasogastric or Gastrostomy Tubes)

Infants with PWS have poor feeding because of weak suck, easy fatigability, and low muscle tone. The need for assisted feeding is nearly universal in the first 4 to 6 months; use of nursing systems with 1-way valves and manual assistance of sucking, originally designed for infants with cleft palate (eg, Haberman nipple, Pigeon feeder), can greatly reduce reliance on feeding tubes. Nasogastric tubes, when needed, are generally well tolerated and rarely required for more than 3 to 6 months. The use of a gastrostomy tube (generally with placement of a button-style device) can be avoided in most cases, but if, after considering the risks and benefits of both approaches, a decision to use a gastrostomy tube is made, the device should be promptly removed when no longer needed. Poor feeding is a transient problem in PWS, and the increased abdominal fat mass with reduced muscle that characterizes this disorder ensures a cosmetically disfiguring scar at the site of the gastrostomy tube (families sometimes refer to this as the "second belly-button"). These 2 factors, relatively specific to PWS, may significantly alter the risk/benefit analysis regarding the approach to tube feedings compared with the decision-making process for children with disabilities attributable to other causes.

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Endocrine Considerations and Recombinant Human Growth Hormone

Generalized hypothalamic insufficiency is characteristic of PWS and manifests as dysregulation of the hypothalamic-pituitary axis (including growth hormone [GH], thyroid function, and possibly regulation of the adrenal cortex), appetite, thermoregulation, and respiratory control. Recent work demonstrated the possibility that centrally mediated adrenal insufficiency may be an underrecognized contributor to premature deaths among people with PWS.[20,21] It is recommended that early-morning serum adrenocorticotropic hormone and cortisol concentrations be evaluated when the child is well and repeated during any severe illness. Consideration should be given to prophylactic therapy with hydrocortisone during rare episodes of critical illness in children with PWS, pending measurement of adrenocorticotropic hormone and serum cortisol. Discussion with a pediatric endocrinologist is helpful in determining whether provocative testing is indicated in early childhood.

GH insufficiency is considered to be universal in PWS, so provocative diagnostic testing is not required in the face of reduced growth velocity. In the first year of life, reduced growth velocity may not be readily identified, but both controlled clinical trials[22,23] and clinical experience have demonstrated that there is often significant response to treatment with GH, primarily in improved lean mass, improved motor development, and normalization of body habitus. Decisions about use of GH therapy and management are best made in consultation with a pediatric endocrinologist. Although GH treatment has been approved by the US Food and Drug Administration for children with PWS older than 2 years with documented growth failure, clinical experience has suggested that treatment can begin at as early as 2 to 3 months of age. It is important that parents be thoroughly informed about the potential benefits and the potential for undesired effects. Specifically, there have been several deaths in children as young as 3 years with PWS within 6 months of initiating GH therapy. The role of GH in those deaths, if any, is not known. Adenotonsillar hypertrophy and obstructive apnea may occur during GH therapy; therefore, current recommendations for management include polysomnography (sleep study) before and 6 to 10 weeks after beginning GH treatment, regardless of age. Polysomnography results are frequently abnormal in people with PWS, and both central and obstructive hypopnea are common.[24] Evidence of obstructive sleep apnea should be managed according to accepted standards of care[25] (this American Academy of Pediatrics clinical practice guideline was published in 2002 and has not been updated) and, specifically, should lead to referral to an otolaryngologist for evaluation of airway, increased effort to reduce weight, and consideration of delaying (or stopping) GH treatment until polysomnography results improve. It has also been suggested that GH could be associated with unexpected death by increasing resting energy expenditure (through increased muscle bulk) in children with underlying abnormalities of central respiratory drive attributable to PWS, although there is a suggestion in the literature that treatment with GH may be associated with modest improvement in the central respiratory drive.[26]

There is mounting evidence from controlled clinical trials that GH therapy in children improves linear growth, lean mass and lean-to-fat ratio,[27] and respiratory drive,[26,28] and there has been suggestion of beneficial effects on bone density[27,29] and possible stabilization of behavior decline.[30] Studies are in progress to evaluate the use of GH in adults with PWS.[31] However, there is nothing to suggest that endogenous GH insufficiency improves in later life; therefore, it is reasonable to consider continuing therapy into adulthood. Pretreatment laboratory evaluation to document sequelae of GH insufficiency, to exclude other causes of slow linear growth in people with PWS, and to define baseline parameters related to potential complications of therapy often includes:

- polysomnography;
- measurement of plasma insulin-like growth factor 1 (IGF1), IGF-binding protein 3 (IGFBP3), thyroxine, and thyrotropin levels, a complete blood count, and a basic metabolic profile (with calcium); and
- left hand and wrist radiography for bone age (in older children).

Follow-up should include:

- repeat polysomnography 6 to 10 weeks after initiation of therapy (consider repeating in 1 year and any time at which there are new or worsening symptoms);
- monitoring of IGF1 at least twice yearly, dosing GH to keep IGF1 in physiologic range; and
- monitoring of head circumference at each visit, because GH treatment can cause abnormal growth of the head, especially if the fontanelles are open when GH is started.

Behavioral Food Controls

After the onset of hyperphagia, children with PWS may develop a wide range of food-related behaviors, including actively seeking food, eating nonfood items (eg, animal chow, spoiled food, decorative items that look like food, searching in garbage cans, etc), stealing money to buy food, and even running away from home to

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search for food in a wider area. Control of these behaviors is complex but centers on strategies to limit access to food (eg, locks on cabinets and refrigerators), limit exposures that make the child think about food (eg, birthday treats sitting on the teacher's desk during the school day), and instill confidence that the next meal will be served on time by scrupulously maintaining mealtime routines. Relatives and social contacts must be educated to realize that "sneaking" food to the child with PWS is not an appropriate method of demonstrating affection, and, in fact, undermines the child's nutritional regimen and sense of well-being.

Hypogonadism

Both males and females are affected, although the primary external manifestations in females (clitoral and labia minora hypoplasia) may not be obvious with cursory evaluation. A therapeutic trial of human chorionic gonadotropin (hCG) is indicated for treatment of undescended testes before surgery, because avoidance of general anesthesia is desirable for infants with low muscle tone and potential for underlying respiratory compromise. Added benefits of a course of hCG may include increased scrotal size and partial normalization of phallus length, thereby improving surgical outcomes for undescended testes and facilitating later standing micturition.

Behavior Management

As the child with PWS ages, there is a progression of behavioral issues, many of which can be anticipated, identified early, and managed prospectively. Early childhood is often characterized by rigidity, particularly related to daily routines and long-term persistence of temper tantrums and oppositional behaviors typical of the normally developing 2-year-old. Later, perseverant speech and compulsive behaviors, particularly skin-picking, become prominent. In later childhood and the early adolescent years, food-seeking behaviors may increase and are often associated with lying, and occasionally stealing, to obtain food. Some teenagers with PWS have a disturbing tendency to sneak off to search for food, which is potentially quite dangerous and difficult to manage. Typical of the adolescent years, the teenager with PWS is often overly confident of his or her ability to handle risks and dangerous situations. It is important to recognize that teenagers with PWS deal with many of the same neurodevelopmental and hormonal issues that all adolescents encounter, and, similar to their typically developing peers, many of their behavioral issues seem to stabilize, although not disappear entirely, as they reach adulthood.

Management of the many complex behavioral issues is best accomplished through an active partnership of the parents, the primary care provider, and a developmental/behavioral specialist (pediatrician or psychologist). Behavioral management that focuses on rewarding desired behaviors and ignoring, when possible, undesirable behaviors seems to be most effective. Early recognition of developing behavior problems is critical for maximizing the effectiveness of such an approach. Parents should be counseled that offering food as a reward or withholding food as a punishment is almost always counterproductive and should be avoided. Positive reinforcers are generally not difficult to identify, and reward systems that use small, short-term goals that progress to larger goals are quite effective.

Finally, young adults with PWS seem to be prone to a variety of compulsive behaviors including smoking cigarettes, and some of them develop frank obsessive-compulsive disorder. Likewise, a significant minority of young adults with PWS develop depression, anxiety, and, in some cases, true psychosis. Parents should be counseled to identify early indicators of these processes to facilitate appropriate medical intervention.

HEALTH SUPERVISION FROM BIRTH TO 1 MONTH: NEWBORN INFANTS

Evaluation

- Confirm the diagnosis of PWS (Fig 1) and review the implications of the molecular testing results with the parents.
- Review history for:
  - growth and development;
  - feeding problems; and
  - symptoms of obstructive apnea.
- Physical examination should include evaluation of:
  - hypotonia, and
  - hypogonadism.

Anticipatory Guidance

- Review the phenotype, discuss the specific findings with both parents whenever possible, and talk about potential clinical manifestations associated with the syndrome; these issues may have to be reviewed again at a subsequent meeting.
- Point out both early and late feeding issues and the dichotomous nature of feeding problems (ie, too little as a neonate, too much as an older child), and, as appropriate, discuss use of nasogastric feedings with increased caloric-density formula to minimize volume and use of special nipples/feeders (eg, Pigeon feeder, Haberman nipple, other nursers designed to reduce work of sucking). Special attention should be paid to:
  - avoidance of prolonged oral feeding time (usually not >20 minutes per feeding);
  - transition from tube feeding;

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- maintenance of adequate caloric intake; and
- development of appropriate eating habits; discuss the importance of normal fat and calorie intake for brain development (some parents may start restricting too early).

- Refer infants to early-intervention services in the community.
- Discuss the importance of stimulating the infant, because he or she is likely to be undemanding.
- Inform the family of the availability of support and advice from the parents of other children with PWS.
- Supply contact information for PWS support groups (see "Resources for Parents").
- Point out the strengths of the child and positive family experiences.
- Discuss individual resources for support, such as family, clergy, and friends.
- Talk about how and what to tell other family members and friends; review methods of coping with long-term disabilities.
- Review the recurrence risk in subsequent pregnancies and the availability of prenatal diagnosis and genetic counseling.
- Give overview of the long-term management plan.

HEALTH SUPERVISION FROM 1 MONTH TO 1 YEAR: INFANCY

Evaluation

- Review and note clinical features and confirm diagnosis, if not done previously.
- Review routine health maintenance.
- Plot growth by using standard pediatric growth charts, and pay special attention to weight-for-length measurements.
- Monitor time/work of feeding and caloric density of foods to maintain appropriate growth.
- Perform developmental evaluation, and refer to early-intervention services (if not already done).
- Evaluate boys for undescended testes (or cryptorchidism) and inguinal hernia; consider trial of human chorionic gonadotropin injections (may be performed in conjunction with pediatric endocrinologist); refer to pediatric urologist or a urologist who has special expertise and experience with infants with disabilities if the infant's testes are abnormal.
- Check the infant's vision at each visit by using developmentally appropriate subjective and objective criteria; if evidence of strabismus or other concern arises, refer the infant to a pediatric ophthalmologist or an ophthalmologist who has special expertise and experience with infants with disabilities.
- Administer vaccines recommended for all children unless there are specific contraindications.
- Assess the emotional status of parents and intrafamily relationships; educate and support siblings and discuss sibling adjustments.

Anticipatory Guidance

- Review feeding issues (see above) and the infant's growth and development relative to other children with PWS.
- Review GH deficiency and review benefits and potential risks of GH therapy; consider referral to pediatric endocrinology specialist.
- Discuss:
  - need for careful dietary management later in childhood;
  - probability of mild-to-moderate cognitive impairment;
  - benefits of early behavioral monitoring and establishment of routines; and
  - importance of limit-setting and enforcement.
- At 6 to 12 months of age, review the psychological support and intrafamily relationships, including long-term planning, financial planning, and guardianship; reinforce need for parents to work in partnership, and discuss early relationship-counseling for parents if problems arise.
- Review early-intervention services relative to the strengths and needs of the infant and family.
- Review the family's understanding of the risk of recurrence of PWS and the availability of prenatal diagnosis.
- Discuss increased risk of seizures during childhood (5%–10% of those with PWS), which may be associated with fever and are generally responsive to monotherapy.

HEALTH SUPERVISION FROM 1 TO 5 YEARS: EARLY CHILDHOOD

Evaluation

- Obtain a history and perform a physical examination with attention to growth and developmental status. PWS-specific growth curves should only be used for children who are not treated with GH; regular curves should be used for children who are treated with GH.
- Feeding issues: monitor food intake and behaviors, and consider referral to dietitian who has experience with PWS; calorie needs must be based on growth rate and are usually less than those for similarly sized children without PWS.
- Annual hearing and vision screening evaluation before 3 years of age; refer the child to a pediatric ophthalmologist or ophthalmologist

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who has special expertise and experience with children with disabilities for a thorough evaluation for ocular findings during the second or third year of life or earlier if there is evidence of cataracts, nystagmus, or strabismus.

- Evaluate annually for scoliosis, and regularly assess muscle tone; refer to pediatric orthopedist for management of scoliosis as indicated.
- Discuss reduced salivation and increased caries risk by 1 year of age; refer to a pediatric dentist or a general dentist who has special training to manage children with special needs; consider need for more-frequent dental cleanings (every 3–4 vs every 6 months) because of the increased caries risk.
- Ask about symptoms related to obstructive sleep apnea, including snoring, restless sleep, and excessive daytime sleepiness; refer to a sleep or pulmonary specialist as indicated.

Anticipatory Guidance

- Review early intervention, including physical therapy, occupational therapy, and speech therapy, in the preschool program and discuss future school placement and performance.
- Assess the child's behavior, discuss behavioral management, and ask specifically about common behaviors seen in those with PWS (eg, skin-picking, temper tantrums, food-seeking, etc), which may begin during this period.
- Discuss sibling adjustments, socialization, and recreational skills.
- Encourage families to establish optimal dietary and physical exercise patterns to prevent obesity; schedule annual (or more often) meetings with dietitian to review caloric intake and suggest ways to provide less calorically dense foods.
- Discuss need for all family members, child care providers, and school staff members to learn about the disorder, the need for strict food management, and development of routines.
- Discuss future pregnancy planning, risk of recurrence of PWS, and prenatal diagnosis; remind parents of positive aspects for typically functioning children of having a sibling with special needs.

HEALTH SUPERVISION FROM 5 TO 13 YEARS: LATE CHILDHOOD

Evaluation

- Obtain a history, and perform a physical examination with attention to growth and developmental status; evaluate for scoliosis.
- Specifically evaluate for behavior issues that may arise in this age group, including binge-eating, running away, and worsening of skin-picking.
- Perform vision screening annually with attention to recurrence of strabismus.
- Perform thyroid-screening tests every 2 to 3 years or if symptomatic.
- Look for signs of premature adrenarche (which often occurs without progression of other aspects of precocious puberty; thus, reassurance is often the only intervention needed).
- Discuss management of skin-picking (primarily behavioral; medications, including topiramate, are used only in the most severe cases).

Anticipatory Guidance

- Review the child's development and appropriateness of school placement and developmental intervention.
- Continue to stress the need for dietary management and daily exercise to avoid obesity.
- Discuss socialization, family status, and relationships, including financial arrangements and guardianship; begin discussion of adult living arrangements; advise parents to consider joining waiting list for placement in a group home specifically organized for people with PWS and recognize that placement may take several years (or more).
- Discuss the development of age-appropriate social and self-help skills and the development of a sense of responsibility.
- Discuss psychosexual development, physical and sexual development, menstrual hygiene and management, fertility, and contraception; explain that people with PWS often have strong feelings of desire for an infant.
- Discuss symptoms related to obstructive sleep apnea, including snoring and restless sleep, and evaluate for signs of excessive daytime sleepiness; refer to a sleep or pulmonary specialist as indicated.
- Discuss increased pain tolerance common in people with PWS, particularly with regard to evaluating for illness or injury; special attention should be given to risk of intestinal necrosis after binge-eating, because the high pain tolerance can mask symptoms and delay treatment, which can lead to death; people with PWS rarely vomit, so parents should be aware that vomiting after binge-eating can be an ominous sign.

HEALTH SUPERVISION FROM 13 TO 21 YEARS OR OLDER: ADOLESCENCE TO EARLY ADULTHOOD

Evaluation

- Perform physical examination with particular emphasis on evidence of:
  - heart failure;
  - peripheral edema;

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- skin-picking (perianal areas and intertriginous folds should be examined); and
- scoliosis.

- Evaluate diet, caloric intake, and exercise program, and stress obesity prevention; initiate weight-loss strategy if needed.
- Vision screening should be performed annually.
- Look for early signs of developing psychosis or increasing obsessive-compulsive behaviors seen in a minority of patients (risk is apparently higher in cases attributable to UPD than deletion, but may occur with either of them).
- Evaluate pubertal status and consider referral to pediatric endocrinology for discussion about pros and cons of sex hormone therapy.

Anticipatory Guidance

- Discuss skin care, especially in the presence of truncal obesity.
- Discuss issues related to transition into adulthood.
- Discuss possible compulsive behaviors, including use of tobacco.
- Discuss appropriateness of school placement, and emphasize adequate vocational training within the school curriculum while keeping in mind the special issues related to the need to scrupulously avoid exposure to opportunities to obtain food.
- Provide information on how to recognize the signs of psychosis.
- Discuss the need for gynecologic care for pubescent girls. Talk about the risk of Angelman syndrome (attributable to deletion of maternally inherited chromosome 15q11-13) with the patient and her family if she were to become pregnant; review the fact that there have been 2 case reports in which a woman has reproduced. Men with PWS are assumed to be infertile, although the possibility of fertility should always be considered.
- Discuss sexuality and socialization, the need for and degree of supervision and/or the need for contraception.
- Explain to the patient and her family the risk of genetic abnormalities if she were to become pregnant.
- Discuss group homes and independent-living opportunities specifically for people with PWS, workshop settings, and other community-supported employment (group homes specifically designed for people with PWS are desirable, but they often have long waiting lists, so applying during the adolescent years is helpful in securing a spot for the future).
- Discuss intrafamily relationships, financial planning, and guardianship.
- Facilitate transfer to adult medical care.

TRANSITION TO ADULT CARE

- Identify health care providers in the community who are willing to learn about the special situations of people with PWS; ideally, use providers with training or experience in the care of people with special needs.
- Regular evaluation is needed for:
  - weight control (maintenance or loss);
  - diabetes;
  - hypertension;
  - sleep apnea;
  - heart failure;
  - peripheral edema; and
  - behavior management, including the use of medications such as selective serotonin-reuptake inhibitors.
- Some providers may continue to care for the person with PWS through adult life (eg, the medical geneticist); when new providers are needed, the transferring physician should clearly communicate the person's needs, and care should overlap until all providers, as well as patients and their family, are comfortable with the care needed.

RESOURCES FOR PARENTS

Prader-Willi Syndrome Association, 8588 Potter Park Dr, Suite 500, Sarasota, FL 34238; telephone: 800-926-4797 or 941-312-0400; fax: 941-312-0142; Web: www.pwsausa.org

Foundation for Prader-Willi Research Canada (formerly Canadian Prader-Willi Syndrome Organization), 19-13085 Yonge St, Suite 370, Richmond Hill, Ontario, Canada L4E 0K2; telephone: 866-99-FPWRC (866-993-7972); Web: www.onesmallstep.ca

Foundation for Prader-Willi Research, 104 Hume Ave, Alexandria, VA 22301; telephone: 703-683-7500; fax: 703-836-0959; Web: www.fpwr.org

International Prader-Willi Syndrome Organisation, Web: www.ipwso.org

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