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GUIDELINES AND GUIDANCE

Prader–Willi syndrome: guidance for children and transition into adulthood

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Abstract

Prader–Willi syndrome (PWS) is a rare orphan disease and complex genetic neurodevelopmental disorder, with a birth incidence of approximately 1 in 10,000–30,000. Management of people with PWS requires a multi-disciplinary approach, ideally through a multi-disciplinary team (MDT) clinic with community support. Hypotonia, poor feeding and faltering growth are characteristic features in the neonatal period, followed by hyperphagia and risk of rapid weight gain later in childhood. Children and adolescents (CA) with PWS usually display developmental delay and mild learning disability and can develop endocrinopathies, scoliosis, respiratory difficulties (both central and obstructive sleep apnoea), challenging behaviours, skin picking, and mental health issues, especially into adulthood. This consensus statement is intended to be a reference document for clinicians managing children and adolescents (up to 18 years of age) with PWS. It considers the bio-psycho-social domains of diagnosis, clinical assessment, and management in the paediatric setting as well as during and after transition to adult services. The guidance has been developed from

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information gathered from peer-reviewed scientific reports and from the expertise of a range of experienced clinicians in the United Kingdom and Ireland involved in the care of patients with PWS.

Keywords: Prader–Willi; hypogonadism; multidisciplinary team; scoliosis; psychosocial

Introduction

Prader–Willi syndrome (PWS) is a rare complex genetic disorder arising from the lack of expression of the paternally inherited imprinted genes on chromosome 15q11-q13. The most common causes are paternal deletion (65–70%) and maternal uniparental disomy (25–30%), with rare causes such as imprinting defects and translocations accounting for ~1% (1). The incidence of PWS is reported to be between 1 in 10,000–30,000 (2, 3).

Phenotypic manifestations vary according to the developmental phase in PWS. Hypotonia, poor feeding and faltering growth are dominant features in the neonatal period and whilst most infants are diagnosed early on, there still remains a delay in diagnosis for some patients (4). Nutritional and growth phases in children and adolescents (CA) with PWS are well described, with weight gain and hyperphagia leading to obesity later on in childhood if access to food is uncontrolled, with premature mortality primarily due to obesity-related complications in adulthood (5, 6, 7, 8).

CA affected by PWS can develop endocrinopathies due to hypothalamic dysfunction, such as growth hormone deficiency (GHD), and hypogonadotropic and hypergonadotropic hypogonadism. Central hypothyroidism and central adrenal insufficiency (CAI) are more rare. Other problems include scoliosis, which is related to hypotonia, respiratory difficulties, both central and obstructive sleep apnoea, as well as developmental delay and learning disabilities with temper tantrums, and skin picking (5, 9).

There is no effective medical treatment for the primary hyperphagia in PWS. Management therefore requires a lifelong multi-disciplinary approach, ideally through a multi-disciplinary team (MDT) clinic, with community support. The purpose of this article is to provide evidence-based expert consensus guidance on the management of CA with PWS.

Aims and objectives

- The specific areas in PWS which will be covered are:
- Management in infancy, childhood and adolescence.
- Initial diagnosis and investigations.
- The approach to diet and exercise.
- Initiation and monitoring of growth hormone (GH) including sleep studies and role of GH in young adulthood.
- Monitoring of puberty and the role of sex steroid replacement therapy.
- Monitoring of other endocrine issues including thyroid dysfunction, adrenal insufficiency and type 2 diabetes.
- Monitoring and management of scoliosis and bone health.
- Assessment of developmental, learning and behavioural issues, including management.
- Support through community care.
- Recognition of mental health conditions.
- Management of acute illness.
- Transition to adult services.

Scope and target population

This guidance document covers the management of (all) people (male and female) with PWS diagnosed before 18 years of age.

Methods

This guidance was developed in accordance with The Appraisal of Guidelines Research and Evaluation Instrument II (AGREE II) criteria (10), and the 2020 RCPCH Standards for Development of Paediatric Guideline (11). A consensus group was devised from clinicians with extensive experience in the management of PWS from the PWS specialist clinics in the United Kingdom and Republic of Ireland.

Searches relating to the diagnosis, management and transition of CA with PWS were conducted using a combination of text words and MeSH subject headings via the Ovid MEDLINE and the Cochrane Library. The initial literature search was conducted in March 2020 and repeated in Oct 2023. Papers were excluded from review if they were not written in the English language. The quality of evidence and risk of bias was assessed using the GRADE approach (12).

Guideline recommendations agreed by the entire group were made based on the highest level of evidence obtained. Where evidence was lacking or deemed too conflicting or inadequate to be able to make a recommendation, the authors then framed a recommendation.

Barriers, facilitators and resource implications

Development of this guidance was aimed at defining a standard of best practice. However, a significant proportion of the recommendations are based on low-quality evidence or expert consensus. Not all centres will have access to all of the MDT members recommended in this guidance for the care of CA

with PWS. This guidance aims to provide a standard against which such care can be audited to make a case for improving existing infrastructure and facilities.

Recommendations

Multi-disciplinary team

Parents and carers of CA with rare conditions commonly seek specific expertise and coordinated care that minimises the number of separate appointments (13, 14, 15). In CA with PWS, this multi-disciplinary care is, and most appropriately, coordinated by paediatric endocrinologists with support from dietitians and endocrine nurses, together with input from a variety of professionals including respiratory physicians, orthopaedic surgeons, psychologists and child/adolescent psychiatrists, physiotherapists, occupational, speech and language therapists and community paediatricians (Table 1) (5). MDT clinics should also work together as a coordinating link with the relevant specialists, schools, social workers, and child development teams as well as the provision of guidance and support to the family which may be required, particularly if behaviour problems are severe. PWS associations, including Prader-Willi Syndrome Association UK (https://www.pwsa.co.uk/), Prader Willi Syndrome Association Ireland (https://pwsai.ie) and the International Prader–Willi Syndrome Organisation (https://ipwso.org/), provide support and useful resources for the families, as well as for CA with PWS. PWSA UK may also be able to provide on-site outreach and remote support to PWS clinics, depending on their staffing resources. The increasing use of remote/virtual consultations may provide an opportunity to improve simultaneous joint working between teams.

An ideal model of care would be through a network of specialist PWS centres, together with those with an interest in PWS, often a paediatric endocrinologist, as similar multi-disciplinary models have successfully worked in other countries (e.g. Rare Diseases Center of Reference 'Prader-Willi Syndrome and Obesity with Eating Disorders' (PRADORT) in France), and for other conditions (e.g. Regional Networks for Paediatric Diabetes) (9). However, local health and social services should always remain involved so that they are able to provide regular support to the family at home if required and also manage emergencies when they occur due to serious physical or mental illness or because of placement breakdown, usually in relation to severe behaviour problems.

Genetic diagnosis

PWS results from the loss of expression of paternal genes in the region of chromosome 15q11-13, the most important being the genes of the *SNORD116* cluster. Diagnosis is confirmed by genetic analysis. PWS has several genetic subtypes: (i) deletion of the paternal copy of 15q11-13 (60–70% of cases), which includes type

Table 1 Role of health professionals in the management of PWS.

Health professional	Roles/problems in PWS
Community paediatrician	Development EHCP/links with school/AHPs/other services
Dentist	Poor enamel and increased dental caries
Dietitian	Food diary, calorie count recommendation Different phases of nutritional management
Endocrinologist (paediatric and adult)	Assessment of growth and puberty Initiation and management of growth hormone/sex steroid therapy Coordinator of Care
Geneticist	Counselling
Gynaecologist (if needed)	Adolescent/oestrogen replacement
Occupational therapist	Fine motor and sensory
Ophthalmologist	Strabismus, amblyopia and refractive errors
Orthopaedic/spinal surgeon	Risk of scoliosis in early childhood and late childhood/adolescence Assessment and management (bracing/surgery)
Psychiatry/psychology/CAMHS	Mental health and behavioural challenges
Respiratory physician	Central apnoea and obstructive apnoea – sleep disordered breathing problems Sleep studies/non-invasive ventilation
Social worker	Early help/child with disabilities team
Specialist nurse (endocrine/learning disability)	Advice and support
Speech and language therapist	Delayed eating and language disorder
Surgeon/urologist	Undescended testes and orchidopexy
Family support group (PWS associations)	Support and resources for families

I (BP1-III), type II (BP2-III), type III (BP3-IV) and type IV (BP4-V) deletions at least according to the breakpoints (BP); (ii) maternal uniparental disomy (mUPD) for chromosome 15 (in 20–40%); (iii) an imprinting centre defect or epimutation (<5%), and (iv) very rare cases of re-arrangement or translocation in the region of chromosome 15q11-13 or microdeletions in the key gene of PWS (e.g. *SNORD116* gene cluster) (<1%) (1, 16, 17). There is an increasing trend in maternal disomy with up to 50% of mUPD in children presenting now, possibly due to increased maternal ages (17, 18). In suspected cases, specific PWS genetic analysis should be requested, with genetic analysis initially assessing the methylation pattern of the SNRPN (small nuclear ribonucleoprotein polypeptide N) gene on chromosome 15q11-13. If this is abnormal, the diagnosis of PWS is confirmed, and when normal, PWS is excluded with 99% certainty unless a chromosomal re-arrangement, a microdeletion, or translocation is present, which can be assessed with a karyotype and comparative genomic hybridisation (CGH) microarray.

Genetic sub-typing of PWS is undertaken by assessment of deletions on chromosome 15 using fluorescent *in situ* hybridisation (FISH) or methylation-specific multiplex ligation-dependent probe amplification (MLPA). The underlying genetic sub-type may influence phenotype, notably with an increased risk of autistic/psychiatric features in mUPD. Different genetic mechanisms have been reported, including mosaicism (19). If no deletions are detected, mUPD can be assessed with samples of both parents (haplotype analysis). If no paternal deletion, mUPD, or chromosomal re-arrangement is detected, PWS is likely due to an imprinting defect, and assessment of mutations or deletions in the imprinting centre may be considered. While the recurrence risk of PWS in future pregnancies with a *de novo* paternal deletion or mUPD is generally low (<1%), chromosomal re-arrangements and imprinting centre abnormalities carry a high recurrence risk (20). It is therefore advised that patients and parents of PWS patients are seen by a medical genetics consultant at least once.

Initial investigations

A focussed medical history at the time of diagnosis is essential, and recommendations regarding key components of the history and examination are highlighted in Tables 2 and 3. The medical assessment should ensure likely complications of PWS are considered so that the appropriate management can be initiated in a timely fashion.

Neonatal period

The neonatal period for parents of children with PWS can be particularly challenging. There is often a delay in diagnosis despite classical features being present (4). Admission to the Special Care or Neonatal Intensive Care Unit is generally required due to the degree of neonatal hypotonia with resultant feeding difficulties and/or respiratory issues. Such admissions are extremely stressful for parents of children with PWS, who are often overwhelmed by the equipment and technology, often rendering them fearful of touching or handling their infants. Maternal oxytocin levels, important for mother-child bonding, are reduced by stress (21). Every effort should be made by healthcare professionals to support parents and promote parent-child bonding in those with PWS. In addition, children with PWS have reduced oxytocin-producing neurons implicated in social development, feeding and also linked with autism spectrum disorder (ASD) features (22). There are promising reports of the effects of oxytocin treatment in the newborn period and there appears to be a critical window for the positive benefits of oxytocin, possibly <6 months of age (23, 24).

Babies with PWS have oropharyngeal hypotonia, leading to reduced sucking and often impaired swallowing. Nasogastric tube feeding is usually initially required, but gastrostomy is not usually needed. Feeding problems tend to improve sufficiently to allow adequate oral nutrition by 6–12 months of age. Assessment of sleep apnoea is essential in the neonatal period, as discussed later in the document.

Diet

Nutritional phases

There are complex nutritional phases within PWS. Historically, two distinct nutritional phases characterise PWS: significant feeding difficulties in infancy related to hypotonia with poor suck and hence slow weight gain, and later hyperphagia, leading to excess weight gain. However, clinical experience and a large US study have proposed a more gradual and complex range of phases (5, 6, 7, 8).

Growth assessment and monitoring

Assessment and monitoring should be undertaken using national/local growth charts, in our case, using UK WHO growth charts up to age 4 years and then national growth charts over 4 years. PWS-specific growth charts have been developed by some countries; however, these may not be applicable to all populations due to the small size of cohorts and data used. Body mass index (BMI) should also be monitored. However, given that body composition is altered in PWS with lower lean body mass (especially lower muscle mass) and higher levels of fat mass evident from infancy, BMI should be used with caution (25, 26). Regular and accurate growth monitoring is essential in PWS to avoid both under- and over-nutrition. Excessive weight gain should always be avoided. We recommend a stable weight trajectory aiming for weight gain along a centile in proportion with height. Accepting lower centiles for weight would

Table 2 Focussed history clinic review.

Item	Details
Pregnancy	Reduced fetal movements/ polyhydramnios
Delivery history	Type of delivery
	Place of birth
	Gestational age
	Birthweight
	Apgar
	Postnatal complications – hypoglycaemia
Genetics	Results of DNA analysis
Infancy	Feeding difficulties – faltering growth, tube feeding
	Growth
	Axial hypotonia
	Crying – abnormal/none
	Presence of small penis
	Presence of cryptorchidism
	hCG stimulation test results (if performed)
Skeletal/growth	Short stature
	Small hands/feet
	Scoliosis
Skin	Skin picking
	Erythema after a bath
	Easy bruising
Diet and nutrition	Hyperphagia
	Dental caries
	Obesity
	Sticky saliva
	Food behaviours – foraging, stealing and hoarding
	Food security
	Physical activity
Respiratory	Recurrent infections
	Sleep apnoea
	Hypoventilation during sleep
	Results of previous sleep studies
	Narcolepsy/cataplexy
CNS development	Developmental disorder/learning disabilities
	Behavioural issues
	Autistic/obsessional traits
	Audiology review
Education	Special educational needs
Social	Principal carers
	Receipt of Disability Living Allowance
Other professionals involved	
Medication	

be appropriate as long as the growth along the centile is maintained. NICE guidelines describing growth patterns where intervention may be required remain applicable in PWS patients, that is, NICE suggest action if normal birth weight and fall across >2 centiles (27). Input from a dietitian is important, particularly in the early years.

Table 3 Focussed examination at specialist clinic review.

Item	Details
Growth	Height
	Weight
	BMI
	Parents' height
Dental	Dental caries, sticky saliva
Skeletal	Scoliosis
Skin	Skin picking
	Easy bruising
General systemic	Cardiorespiratory, gastrointestinal, neurology – tone, power
Genitourinary	Position of testes/micropenis
Puberty	Tanner stage
Eyes	Strabismus
Development	Gross motor
	Fine motor and vision
	Hearing and speech
	Social/behaviour

Nutritional requirements

Children with PWS have the same micronutrient requirements as their peers; however, energy expenditure is considerably lower, attributable to the reduced muscle mass, together with hypothalamic dysfunction (28). Growth assessment will determine the estimation of energy requirements in this group. Additional consideration for requirements may be necessary during key periods of infancy, childhood, and adolescence. In infancy, tube feeding and feeding difficulties are common. To support appropriate weight gain and growth during this period, energy requirements may be increased. After infancy, usually before 2 years, energy requirements typically decrease, and careful growth monitoring is required throughout. In early childhood, weight gain may occur despite no increase in energy intake, attributable to reduced energy requirements possibly due to reduced muscle mass and reduced physical activity related to hypotonia. Subsequent weight gain also relates to the development of hyperphagia, which may occur between 4 and 8 years old (6, 28).

Energy requirements continue to reduce throughout childhood and adolescence to between 60% and 80% of the recommended daily requirements or 10–12 kcals per cm for weight maintenance and 6–8 kcals per cm for weight loss (29). Micronutrient requirements increase during adolescence in the general population, and teenagers with PWS are no different. Close monitoring of dietary intake to facilitate a nutrient-dense diet in the context of significant energy restriction is essential to support growth and prevent micronutrient deficiencies.

Adolescents with PWS are at increased risk of gaining weight for various reasons, including significantly reduced energy requirements, decreased physical

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activity, increased desire for independence and therefore unsupervised access to food, loss of routine and changing educational and home environments (30, 31, 32). Limited access to specialist MDT services, including community support and specialised residential placements, may also be contributing factors.

While some evidence suggests a high prevalence of obesity in PWS patients entering adulthood (82–98%) (33, 34, 35), there is evidence that early intensive and sustained intervention from infancy reduces the frequency and severity of obesity in adulthood (36).

Dietary supplements

Given the significant energy restriction necessary in the management of a child with PWS, an age-appropriate vitamin and mineral supplement should be recommended, either prescribed or over the counter (29). Several studies have been conducted on dietary patterns in people with PWS, suggesting several nutrient intakes that are commonly low (vitamin D, calcium, zinc and iron) that require attention (37, 38, 39, 40). Specific additional supplementation may be required on an individual basis following a careful dietetic assessment of micronutrient levels (41). Whilst we recognise some centres outside the UK and Ireland suggest the use of supplements such as medium-chain triglycerides (MCT), coenzyme Q10, and carnitine, the evidence to support them is limited and they are expensive, and so we do not recommend their routine use (9, 42).

Dietary strategies

Prevention of overweight and obesity is key in the management of a child with PWS. Excessive weight gain and its complications negatively impact both the child and family and incur a high degree of caregiver burden (43, 44). No studies of medications for obesity trialled in PWS have demonstrated long-term benefits without unacceptable side effects (45, 46, 47, 48). Thus, there are no licensed pharmacological agents available to treat hyperphagia in PWS (49), although clinical trials are ongoing. Clinical trials using diazoxide choline to help with severe hyperphagia have demonstrated promising results (50). Bariatric surgery has poor results in PWS with evidence of longer-term weight regain after 5 years and is not recommended in this disorder (51, 52). Similarly, there is no evidence to support the role of specific diets such as the ketogenic diet in PWS, and such diets have the potential to cause nutritional imbalance with long-term implications (53).

An energy-restricted, nutrient-dense diet together with increased energy expenditure is well recognised to maintain a healthy weight in PWS. From the start of weaning and prior to the onset of hyperphagia, it is essential to establish good eating habits with strict routines and controlled access to food. Different strategies can be used to achieve this, including portion control and calorie counting.

Food security

Hyperphagia and food-seeking behaviours associated with PWS begin in early childhood and persist throughout life. Food security practices must be implemented across all environments, in all settings. This can be in the form of physical interventions, such as locks on fridges and cupboards; indirect interventions, such as access to money; and behavioural interventions such as agreed consistent management of food requests outside of mealtimes. Complete approaches incorporating all aspects have been proposed, including the 'No Hope, No Doubt, No Disappointment' method (54). Food security is more than physical security – it is also making certain psychologically that the person with PWS knows that others will ensure that food is provided in the right amounts at the right times. Education and support for not only parents but also extended family/friends is also required, together with liaison with school staff.

Where access has occurred leading to excessive eating, the child should not be punished or made to feel this is their failure. Instead, there should be a discussion of how to learn from the error for future care. Such situations may arise because others have forgotten to lock cupboards or may not have acted in accordance with the agreed plan. This deviation by others from the agreed plan can cause distress for the person with PWS.

Providing independence is appropriate in terms of the transition from adolescence to adulthood. However, young adults with PWS are unable to independently make appropriate food choices, and therefore support for diet and access to food is required at all times throughout their lifespan. Even if individuals with PWS achieve food control for a period of time, the risk of relapse with increased food intake is high, often due to changes in their routine and environment. Helping people with PWS in childhood understand the need for support around food will help when they reach adult life, at which time it is normally expected that individuals have the right to make such decisions for themselves. The common element of success is a consistent approach balancing dietary intake, physical activity, and food security, ideally in partnership with the person with PWS.

Muscle function and exercise

A recent systematic review concluded that exercise was of benefit and should be optimised in PWS (55). Exercise in PWS reduces body mass by 2–12% via improved activity levels and cardiorespiratory fitness with no known adverse effects. Several strategies have been shown to positively influence continued participation in exercise for PWS children, including encouraging the individual to help choose the types of exercise (56).

As well as reduced muscle mass and strength, which leads to lower endurance; there are also structural and functional muscle abnormalities in PWS, together with impaired cortical motor signalling (57). Any form of

physical activity will improve this, and an exercise plan remains an essential part of management. Opportunities for physical activity must also be included in Education Health Care Plans (EHCP). Exercise may also be used as an activity to help distract from the desire to eat and preoccupation with food. However, exercise alone will not prevent weight gain and needs to be done in combination with calorie restriction. Growth hormone (GH) will have an additional benefit in improving muscle mass and function (58, 59).

Growth hormone

Growth hormone (GH) therapy is licensed for use in the UK and Ireland for children with PWS (https://www.nice.org.uk/guidance/TA188/) (60), with an increasing trend to prescribe it earlier due to accumulating evidence that this improves outcomes for final height and body composition (61, 62). True GH deficiency is identified in between 40 and 100% of PWS patients, depending on the GH stimulation test used (63). GH stimulation testing can therefore be performed, but it is not necessary in children before starting treatment. Those with clinical evidence of GH deficiency should be investigated as recommended for all children with GH deficiency, which would include pituitary imaging if appropriate, to exclude pituitary structural abnormalities, including tumours.

GH has a positive impact on final height, but the main reason for its use is an improvement in body composition (64), with additional benefits in motor development and cognition (65). Various randomised controlled studies have been performed investigating the effects of GH on cognition and behaviour. Some studies report GH therapy improves behaviour and cognition (66, 67, 68), whilst others report no improvement (69). GH-treated patients had higher scores in visuospatial and abstract reasoning (66, 70). The mechanism for this is unclear, though it is suggested that GH and/or IGF-1 has a direct effect on the brain. However, a recent meta-analysis demonstrated GH has a positive effect on motor development, but no evidence of benefit on cognition or behaviour (71). Although parents of children with PWS reported improvements in behaviour during GH therapy, this was not seen when assessed by standardised questionnaires (72). The effect of GH therapy on cognition and behaviour therefore remains controversial.

GH also, through its anabolic effects, increases lean body mass (LBM) and decreases fat mass in individuals with and without PWS (61, 73). In PWS, this results in improvements in both body composition and exercise capacity, as well as other benefits, such as improved lipid profiles (74). Starting GH therapy early, well before the onset of hyperphagia and the development of obesity, is recommended.

Age of GH initiation

Due to the potential benefits on cognition, language, and muscle tone, and the need to start GH treatment well before the onset of hyperphagia and obesity, the 2013 International Consensus Meeting recommended starting GH before the age of 2 years (75). In practice, however, GH therapy is usually started long started before then. We recommend starting GH therapy at the latest by the age of 1 year where possible. There is evidence to support starting GH earlier than 1 year in a few studies, and GH has been started as early as 3 months of age (66, 68, 76). There is no evidence of worsening sleep-disordered breathing when starting GH therapy before the age of 1 year compared to later (77). As indicated above, GH stimulation testing is not essential and should not delay the initiation of GH therapy.

Prior to GH initiation

GH therapy in children with PWS has been associated with sudden deaths, with the mechanism being thought to be due to respiratory issues, in particular, obstructive sleep apnoea (OSA), which may be caused by a combination of hypotonia, tonsillar hypertrophy, and obesity. Anatomical variants of the palate may also exacerbate this. Since unexpected premature deaths have also occurred in patients with PWS who were not on GH, this may not be a direct effect of GH therapy. However, GH treatment may, through elevated blood IGF-1 concentrations, increase adenoidal and tonsillar lymphoid tissue and so raise the risk of OSA (78, 79). Festen and colleagues reported no change in sleep-disordered breathing after 6 months of GH therapy, but it is important to monitor for symptoms of OSA, especially during respiratory illnesses (80). In patients with PWS and severe obesity and/or ongoing excessive weight gain, starting GH therapy may not be appropriate, especially in the presence of untreated or poorly managed OSA, poorly controlled type 2 diabetes mellitus (T2DM) and hypertension, and obesity-related complications. Once these complications are under control, GH can be reconsidered. In children who present late and already have severe obesity, GH therapy therefore will need to be considered on a case-by-case basis and used with caution. In summary, whilst there have been previous safety concerns about GH therapy, with regular and appropriate monitoring, it remains a safe treatment with improved outcomes even when starting GH in infancy (61, 62).

Sleep studies

Due to the potential respiratory changes associated with GH therapy, cardio-respiratory polysomnography is mandatory before the start of GH therapy through liaison with local respiratory services. Oxygen saturation studies are not sufficient. Infants with PWS may also have central sleep apnoea, and we suggest performing a baseline polysomnography in all patients with PWS as soon as the diagnosis is made, particularly if there is going to be a delay in starting GH therapy and even if GH therapy is not being

considered. If clinically significant central sleep apnoea is identified, the local respiratory team can advise if this needs to be treated with supplemental oxygen and/or, rarely, non-invasive ventilation (NIV) (81, 82). Central sleep apnoea should not delay GH therapy; indeed, GH may improve it (83).

Management of moderate/severe OSA is required before starting GH therapy, after discussion with local ENT and respiratory teams. Weight management strategies are essential, but adenoidectomy/tonsillectomy or NIV may also be required. A follow-up cardio-respiratory polysomnography should be performed 2–3 months after initiation of GH therapy, which is similar to what has been suggested by others (79). If there is mild OSA which does not require treatment (as guided by local respiratory services), GH can be started, with careful monitoring for symptoms.

If the repeat polysomnography is abnormal with evidence of worsening OSA, guidance should be sought from a respiratory paediatric sleep specialist. GH therapy should be discontinued if there is development of moderate/severe OSA until the OSA is treated.

Although there are limited data, we recommend as a minimum a cardio-respiratory polysomnography sleep study every 2–3 years in those under the age of 5 years on GH therapy, or sooner if there are clinical concerns suggestive of worsening OSA, even if the patients have had a previous normal sleep study. In those over the age of 5 years, cardio-respiratory sleep studies should be considered where there are clinical concerns, perhaps associated with significant weight gain, such as increased lethargy and acute changes in behaviour. Annual pulse oximetry/saturation studies may be considered as a screening tool in all ages. However, if there are concerns regarding OSA, a full cardio-respiratory polysomnography study needs to be performed as saturation studies are not adequate to completely exclude OSA (84). Close liaison and joint decision making with local respiratory specialists are needed in this situation.

Adults with PWS remain at risk of OSA, especially if obese, and there should be a low threshold for performing sleep studies in adulthood. However, once established on GH, repeated cardio-respiratory sleep studies or pulse oximetry/saturation studies are not necessary in adults without OSA, unless there is significant weight gain or development of symptoms suggesting the development of OSA, such as daytime somnolence or snoring.

GH dosing/monitoring

A starting dose of 0.5 mg/m^2 daily (9-15 µg/kg/day) is suggested, increasing the dose to 1.0 mg/m^2 daily (35 µg/kg/day) over a period of 3–6 months (75). We recommend using body surface area to avoid inappropriately high GH doses in overweight/obese individuals. Patients with PWS are known to be sensitive to GH therapy and can have blood total IGF-1 concentrations above the reference range on licensed doses. Free IGF-1 concentrations are not routinely measured in clinical practice, and total IGF-1 concentrations, which are measured by standard immunoreactive assays, do not correlate with IGF-1 bioactivity.

However, the bioavailable IGF-1, when assessed by the IGF-1 to IGFBP-3 ratio, is similar in PWS and GH-deficient (GHD) patients on GH therapy, and therefore, the potential risks of elevated free IGF-1 are similar (85, 86, 87). Younger patients with PWS appear to have higher IGF-1 bioactivity compared to older individuals with PWS (86). Patients with normal pre-treatment total IGF-1 concentrations and UPD seem to be at the greatest risk of elevated IGF-1 concentrations (88). *SNORD116* deletion may increase serum IGFBP7 concentrations and hence serum IGF-1 concentration (89).

As bioavailable IGF-1 may not be increased, higher total IGF-1 concentrations could be accepted within licensed GH doses, especially if the IGFBP-3 is also elevated. However, IGFBP-3 is not always routinely measured and is not available in all centres. Based on our combined clinical experience, modest elevations in IGF-1 should be reviewed in the context of potential complications of excess GH signalling such as hypertension, acromegalic features, or poor glycaemic control. IGF-1 concentrations more than twice the upper limit of normal should certainly be avoided and indicate the need for GH dose reduction. There are no reports of any adverse effects of high blood IGF-1 concentrations in children with PWS other than increasing the risk of OSA, especially if there is intercurrent upper respiratory tract infection (78, 79), although long-term data, especially in adults, are limited.

GH in adults

Since GH replacement is indicated in adults with PWS (see below), during the process of transition to adult services, it would be appropriate, after achieving adult height, to continue GH therapy and reduce the GH dose to usual adult doses. A recommended adult GH dose for GHD is initially 0.2 mg once daily (90). Higher final doses may be needed, especially for patients on oral oestrogen, while awaiting reassessment by adult endocrinologists, aiming for IGF-1 concentrations in the upper half of the age-related reference range; the use of a median final GH dose of 0.5 mg has been reported in PWS adults (91).

There is increasing evidence that GH therapy in adults with PWS is of benefit (92, 93, 94). Studies have demonstrated continued benefit from GH therapy in young adults with PWS, with statistically significant increases in LBM and decreases in percentage fat mass, improved muscle strength, and detrimental effects on fat mass and LBM when GH therapy is discontinued (95,

96, 97, 98). There are no consistent data regarding the effects of GH on lipids, echocardiography parameters, or bone health (97, 99, 100) One RCT has shown a decrease in low-density lipoprotein (LDL) (101), but other studies have not, although improvements in body composition were seen (96, 102). GH therapy in adulthood may be beneficial in terms of bone geometry, strength, and bone mass, but not necessarily bone mineral density (BMD), with sex steroid replacement being much more important in preventing the decline in BMD (100, 103, 104, 105, 106). Two studies have demonstrated improved mental and cognitive function with GH treatment in adults (107, 108), and one has shown that adults with PWS rated their quality of life and mental health better after the initiation of GH treatment in adulthood compared to before (109). Minor adverse events, including pretibial oedema, headache, and transient impaired glucose tolerance, have been reported (97).

GHD is not uncommon in adults with PWS, and evaluation of the GH axis at final height should be considered using GH stimulation testing after at least 1 month off GH therapy (97). Given the presence of obesity, a GHRH-arginine test may be the most appropriate test to perform as there are age- and BMI-related cut-offs (110), especially since insulin tolerance testing may be difficult because of poor venous access. Glucagon stimulation testing has poor specificity for adult GHD and so should be avoided. Due to current supply issues with GHRH, however, an oral macimorelin (growth hormone secretagogue) test could be considered, although this has not been studied in patients with PWS to date.

If GHD is confirmed, adult GH replacement therapy as per current UK NICE guidance can be offered for the achievement of peak bone mass if under 25 years of age (60). However, neuropsychological symptoms, rather than body composition, are the NICE criteria for allowing the use of GH in adults with GHD over 25 years of age. The specific use of GH in adults with PWS has not been formally assessed by NICE and GH is not licensed for adults with PWS in the UK and Ireland unless they have confirmed adult GH deficiency (60). Continuing or starting GH beyond 25 years of age in PWS is complicated by the lack of validation of the Adult GHD Assessment (AGHDA) Quality of Life questionnaire in a neurodevelopmental syndrome like PWS. The ability to continue GH therapy in older individuals with PWS may therefore depend on local expertise and prescription guidelines, together with the wishes of the patient or family (92).

Even if GHD is not confirmed, adults with PWS may still benefit from GH treatment (92). In situations where there is a normal GH response to GH stimulation testing but a low IGF-1, the use of GH in adults with PWS is unclear and will again depend on local expertise.

GH should be considered only in adults with PWS in collaboration with specialist support. It should, however, be avoided or delayed in those with severe obesity, perhaps BMI > 40 kg/m^2, an increasing weight gain trajectory, poor glycaemic control (HbA1c > 58 mmol/mol, 7.5%) or uncontrolled hypertension.

Where GH therapy is used in adults, the dose should be titrated according to IGF-1 levels, aiming for a level between 0 and +2 SDS according to age- and sex-related cut-offs, as recommended for non-PWS GHD in adults (90). It is unknown if adults with PWS on GH are similar to children in having low free IGF-1 levels relative to their total IGF-1 levels. Therefore, it is unclear whether using normal adult IGF-1 reference ranges is entirely appropriate to guide GH dosing. Regular monitoring should be initiated, with particular emphasis on annual assessment for T2DM (HbA1c and non-fasting glucose), hypothyroidism (with measurement of both free thyroxine and TSH), and lipid profile. Adults with PWS have increased morbidity and mortality and often have additional undiagnosed health conditions. As such, they require regular monitoring and screening (36).

Puberty

Adrenarche

Premature adrenarche are common in children with PWS and do not usually require treatment (111, 112). Investigations may be considered if clinically indicated. Trials of aromatase inhibitors have been used off-license in Russell–Silver syndrome and PWS with adrenarche and have been shown to delay bone age advancement (113), but this is not routine practice at present, even for children with PWS.

Hypogonadism

Hypogonadism is a common feature in PWS. The degree of gonadal dysfunction varies, with both hypogonadotropic hypogonadism and primary gonadal failure reported (114).

Males with PWS

Males with PWS exhibit small testes and low serum testosterone concentrations, with falling inhibin B levels after puberty (115). Puberty may commence at a normal age, although cases of both precocious (116) and delayed puberty are reported, with some patients failing to enter puberty at all (114). Penile length is usually small-normal at birth and in childhood, but small in adulthood (117). Generally, boys with PWS have a normal appearance and development of pubic hair, reflecting unimpaired adrenal androgen secretion, and normal androstenedione and dehydroepiandrosterone sulphate (DHEAS) concentrations (118).

Undescended testes are reported in as many as 87% of boys with PWS (119). Early treatment with human

chorionic gonadotropin (hCG) has been used in some centres with variable doses and schedules. The use of hCG might improve surgical outcomes rather than aiding descent and may be considered in selected cases in discussion with local urologists, although there is no published evidence of benefit. hCG can result in complications including inflammation, pain, and penile growth, although no studies have been conducted in boys or men with PWS specifically (120). In boys who do enter puberty spontaneously, mid-pubertal arrest is the rule, with no correlation to type of cryptorchidism (unilateral or bilateral) (114).

First-line management is therefore to perform orchidopexy. Re-do orchidopexy is required in approximately 20% of cases compared to 5% of the general population (121). Orchidopexy in boys with PWS presents technical challenges due to the high rates of hypoplastic scrotum, short spermatic cord, and hypoplastic testes (121), and may not be indicated when the contralateral testis is *in situ* and viable (114). Given the difficulties and to improve outcomes, orchidopexy is recommended to be performed in a specialist centre by an experienced surgeon with expertise in laparoscopic surgery. The timing of orchidopexy should follow recommendations by the urologists as this may be slightly later than in cases without PWS.

In boys, testosterone replacement is encouraged to optimise bone and cardiovascular health as well as muscle strength. In boys who fail to enter puberty or exhibit mid-pubertal arrest, we recommend starting with transdermal 2% testosterone gel (e.g. Tostran) at low doses, increasing gradually, usually every 6 months, similar to British Society for Paediatric Endocrinology and Diabetes (BSPED) guidelines (122). Where transdermal testosterone is not available, low doses of injectable depot testosterone can be considered. When there is pubertal arrest, measurement of testosterone and sex hormone-binding globulin (SHBG) levels will guide the starting of testosterone therapy. Given the low lean mass, together with increased adiposity, this can lead to high testosterone levels and/or high oestradiol levels due to increased peripheral aromatisation which can result in gynaecomastia. Therefore, close monitoring of serum testosterone and oestrogen concentrations and free androgen index is required.

There is little evidence that testosterone therapy provokes challenging behaviour, provided it is increased slowly over time until an appropriate dose is reached (123). However, in those with known aggressive behaviour, it may be preferable to wait until this behaviour stabilises prior to commencing testosterone treatment. It may also be advisable to delay starting if there are any major upcoming social changes imminent that might be anticipated to cause behavioural problems, such as a change in schooling or residential placement.

Long-acting intramuscular (IM) depot preparations, such as testosterone undecanoate (Nebido©) have been used successfully in PWS (117), and may be preferred once the individual is established on a maintenance dose of a topical preparation. Using longer-acting preparations avoids the post-injection peaks that can occur with shorter acting preparations, such as testosterone enanthate or Sustanon© (testosterone decanoate/isocaproate/phenylpropionate/propionate). In our experience, lower doses of Nebido may often be sufficient in adults with PWS to achieve appropriate testosterone levels, i.e. normal post-pubertal levels. Thus Nebido© 0.5–0.66 g IM every 12 weeks may be preferable to the standard replacement dose of 1 g IM every 12 weeks, but this may depend on body size. Recommendations from an International Expert Panel for the management of hypogonadism in adult males with PWS have been recently published (124).

Females with PWS

Whilst the onset of puberty in females is usually normal, with cases of precocious puberty also reported, further pubertal development is often delayed and menarche may occur much later (114, 115, 125, 126, 127). Initiation of oestrogen therapy is recommended when there is either failure to enter puberty or mid-pubertal arrest.

For oestrogen replacement, 17β-oestradiol patches (e.g. Evorel©) are now the preferred choice for pubertal induction. Anecdotally, there are no reports of problems with skin picking in individuals treated with patches, and they seem to be well tolerated. The BSPED protocol for pubertal induction in primary ovarian insufficiency using patches can be used (128). The pubertal stage attained will determine which step in the pubertal induction scheme should be commenced initially. When withdrawal bleeds are achieved, a progesterone should be added as per BSPED guidelines. In adults, either 17β-oestradiol patches (e.g. Evorel©) or topical oestrogen gel (Sandrena©) are preferred, especially if there is severe obesity or hypertension. Oral options such as oestradiol valerate, or less preferably synthetic oestrogens such as ethinyloestradiol, are best avoided because of the increased risk of hypertension and venous thromboembolism. Available preparations can be found in the British National Formulary.

Oral progesterone (e.g. as part of a combined hormone replacement therapy such as Indivina© or Gedarel©, or alone as medroxyprogesterone or Utrogestan©) can be used intermittently if periods are acceptable, or continuously should periods not be desired, on an individual basis as discussed with the patient and family/carers. Utrogestan© has less androgenic action than older progestogens such as norethisterone. Combined oestradiol and progesterone patches (Evorel Conti© and Evorel Sequi©) are good options for those who had pubertal induction with oestradiol patches.

Depot progesterone injections alone can be problematic as the resulting hypo-oestrogenisation will impair bone health and is therefore not advised, though

they could be used in combination with transdermal or oral oestrogen. Recommendations from an International Expert Panel for the management of hypogonadism in adult females with PWS have been recently published (129).

Fertility and contraception

Although hypogonadism is a hallmark of PWS, there are several reported pregnancies in women with PWS, including in the UK (130, 131, 132). If the mother with PWS has a chromosome 15q11-13 deletion, the child would have a 50% chance of having Angelman's syndrome. The ability to care for the child would need to be assessed on an individual basis with social services, legal and community input.

To date, there have been no reported cases of fertility in males with PWS. A reduced number and immaturity of spermatogonia have been described (133), and this, in combination with the high rates of undescended testes and hypogonadism, is likely to contribute to this sub-fertility.

Young people with PWS have relationships that may include sexual activity, and advice on sexual health and contraception needs to be given. Due to their potential vulnerability, there have been safeguarding issues around sexual activity and exploitation in both sexes, and this should be considered as part of any social, residential, working, or educational placement. The PWSA UK has developed some helpful literature in consultation with people with PWS about sexual activity and identity that can be helpful (https://www.pwsa.co.uk/18---25-years).

Central adrenal insufficiency

Whilst one study has suggested a moderately high prevalence of central adrenal insufficiency (CAI) in PWS using an uncommon ACTH cut-off in the overnight metyrapone test (134), more recent multi-centre studies have suggested this is not the case, with a low prevalence in children and adults with PWS (only 1–2%) (135, 136). Morning cortisol levels in PWS children were similar to controls with no evidence of increased risk of CAI (137). However, a delayed cortisol response to ITT has been seen despite normal basal and peak cortisol levels, which some have postulated may indicate a risk of adrenal insufficiency during stress (138).

Various testing modalities for CAI have been used that differ in sensitivity and specificity, making it difficult to compare the results of the studies. The gold-standard insulin tolerance test (ITT) and overnight metyrapone test (measuring 11-deoxycortisol) are more sensitive indicators of the likely stress response compared to the ACTH tetracosactide test (standard or low dose). However, there are practical reasons why both tests might not be safe or available related to age, risk of side effects, poor venous access, and local test availability. In such cases, ACTH testing with either standard or low-dose synthetic ACTH (synacthen) can be used.

Studies published so far suggest adrenal insufficiency is rare in children with PWS (139, 140). There are differences in opinion about evaluation and management for CAI (112, 140, 141), and we feel there is currently insufficient evidence to change practice to routine screening and routine steroid cover during illness or anaesthesia/surgery. In the UK and Ireland, testing for adrenal insufficiency is recommended if there are symptoms (episodes of severe tiredness, dizziness, hypotension, unexplained weight loss, abdominal pain, nausea, hypoglycaemia), or a history of sudden decompensation during illness or surgery. Steroid cover for anaesthesia is not recommended routinely (136). However, again there is variation in practice with some international centres recommending steroid cover during intercurrent illness, some suggesting steroid cover during anaesthesia and major surgery, and others suggesting neither (112, 134, 142). If there are clinical concerns peri-operatively, assessment for CAI should be performed and treatment with hydrocortisone initiated.

Hypothyroidism

Hypothyroidism has been reported in PWS (143), with thyroid dysfunction also commonly found in infancy (144). Some studies reported a similar incidence of hypothyroidism in PWS compared to the normal population (145), but more recent studies, which were primarily adults with some children, reported hypothyroidism in up to 16% of patients, with the majority of hypothyroidism being central in origin (146, 147). Annual monitoring of thyroid function with both TSH and free thyroxine levels is suggested with a low threshold to initiate treatment.

Type 2 diabetes mellitus

T2DM often occurs in adults with PWS, with up to 25% affected and increasing further with age (148, 149, 150). However, T2DM has been reported in children and adolescents with PWS, as young as 11 years old, together with impaired glucose tolerance (148, 149, 151, 152, 153). The risk factors for the development of T2DM are similar to the general population, with obesity being the greatest risk factor (148, 152). Ethnicity also seems to be a factor, with an earlier onset of T2DM reported in Japanese and Korean patients with PWS (152, 153), and from personal experience, those of South Asian heritage, or with a family history of T2DM, similar to T2DM in young people without PWS (150).

Although obesity is a major risk factor, the pathophysiology of T2DM in PWS seems to be different from those with primary obesity (149). Individuals with PWS have a lower insulin resistance, and a more

favourable adipocytokine and inflammatory profile, for their degree of obesity, which may be related to reduced visceral adiposity (154, 155, 156). GH therapy does not appear to be associated with an increased risk of T2DM (152), but glycaemic control should be optimised before starting GH replacement, and consideration should be given to GH treatment being discontinued when T2DM is diagnosed and only restarted once T2DM is well controlled.

Weight loss and increasing physical activity remain the mainstay of treatment, with metformin being the first pharmacological agent in the management of T2DM in PWS. Currently, the only other non-insulin drug licensed for the treatment of T2DM in patients < 18 years of age is the GLP-1 agonist liraglutide, but there is no evidence of a positive effect of liraglutide in T2DM in patients with PWS (157). Anecdotally, the use of thiazolidinediones such as pioglitazone can also be helpful if there is obesity-related insulin resistance. Combination therapy with glucagon-like peptide 1 (GLP-1) agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors can be considered if monotherapy with metformin is insufficient in adults (149). Liraglutide and exenatide can improve glycaemic control in adolescents/adults with T2DM (46). However, there is no evidence from a randomised double-blind placebo-controlled trial that the GLP-1 analogue liraglutide (even at an obesity dose of 3.0 mg daily) is helpful for weight loss in children and adolescents with PWS without T2DM (157). However, a systematic review together with some case reports suggests potential benefits in terms of weight loss in adults with PWS using liraglutide and exenatide, although data remain limited (46, 158). There are also no published data in PWS on the benefits of the latest generation GLP-1 analogue semaglutide or combined GLP-1/GIP receptor agonist tirzepatide. Sodium–glucose cotransporter-2 (SGLT-2) inhibitors are often used in adults with T2DM, promoting weight loss as a result of energy loss through increased glycosuria, and are now also recommended for the treatment of T2DM in CA (159). There have been case reports of SGLT-2 inhibitors being used in PWS to help improve glycemic control (160, 161), though there can be an increased risk of genitourinary tract infections, including thrush. In addition, due to communication issues, it is important to be aware of the risk of normoglycaemic ketoacidosis. If escalation to insulin therapy is needed, care should be taken to avoid hypoglycaemia which prompts increased food intake, for example, by using just long-acting insulin rather than including short-acting insulin.

Appropriate screening for T2DM-related complications such as retinopathy, nephropathy, and neuropathy should follow standard guidelines, as there are no data on people with PWS being at altered risk. However, they do appear to have a reduced risk of fatty liver disease and hyperlipidaemia for their degree of adiposity (155, 162, 163).

Management of T2DM is more challenging in patients with PWS compared to the general population, and prevention of weight gain and excess food intake, especially during adolescence, remains vital. Control of the food environment to reduce access to, and hence intake of, excess food, especially carbohydrates, is also vital in the management of T2DM. Targeting unrecognised food intake can often improve poor glycaemic control, and any worsening of blood glucose concentrations should prompt investigation for possible open or surreptitious access to excess food, rather than just escalation of T2DM medications.

Temperature regulation

Other features of hypothalamic dysfunction can also be seen in PWS, such as problems with thirst and temperature (9). A normal rise in temperature due to an intercurrent illness may not be seen. Appropriate measures also need to be taken during extremes of temperature, such as suitable clothing and the need for additional fluids during physical activity (9). Poor fluid intake can exacerbate constipation in PWS.

Gastro-intestinal problems

Gastroesophageal reflux (GOR) is common in young children. The FPWR Registry (https://pathforpws.com/study-information/) showed (patient reported) reflux in 45% of patients < age 2 years, improving to 20% of those > 2 years (164). Not many studies have formally assessed GOR in PWS, but a small number showed a high prevalence of GOR in both children and adults with PWS (165). GOR may lead to silent aspiration and is therefore important to recognise and treat (166). GOR management should be as per usual guidelines (167).

Decreased ability to vomit is commonly reported in PWS, both in children and adults (168). Although, the reasons for this are not completely known, diaphragmatic, abdominal, and intercostal muscle hypotonia may be contributory. Choking may occur frequently and has been reported as a cause of death in 8% of older children and adults, according to family-collected data. Predisposing factors for choking were hyperphagia, thick saliva, weakness of pharyngeal muscles, and GOR (169). More recently, videofluoroscopy in patients with PWS aged 5–35 years showed dysphagia with food residue in the pharynx and oesophageal stasis in almost all patients (170). Videofluoroscopy in infants with PWS (<6 months of age) also showed pharyngeal stasis in 13/16 babies (24).

Delayed gastric emptying is a commonly reported feature in adults with PWS (171), and has also been seen in children with PWS (172). There are some case reports of severe gastric dilatation in children and young people as young as 5 years (173). Abdominal hypertension and shock can occur as a result of gastric dilatation, which

can be life-threatening (173, 174). Gastric necrosis and rupture have been described in young adults. Symptoms may include vomiting, which is otherwise rare, abdominal pain, and occasionally haematemesis. In a survey of 154 patients with PWS who had died, 3% were due to gastric rupture related to overeating, the youngest patient being 17 years of age (169). In a large cohort of patients with PWS in the US who died during the period 1973–2015 which included babies, children, and young people, gastrointestinal-related problems such as perforation, distension, or obstruction were the causes of death in 10%, with equal distribution over the ages (8).

Constipation is known to occur more frequently in obese children than in those without obesity. There are no data in children with PWS, but 20–40% of adults with PWS are reported to have constipation (33, 175). In a small cohort of 21 adults with PWS (aged 17–47), 40% fulfilled criteria for constipation, and the majority had a faecal mass in the rectum (compared to 12% in patients without PWS) and delayed gastro-intestinal transit time (from 1.6 to 2 days and even >3 days in 24% of patients) (176). Management of constipation in PWS should be as per local/NICE guidelines (177). In our experience, probiotics (such as Biokult©) can be helpful for managing constipation and abdominal bloating. Encouraging a good fluid intake is important to help avoid constipation. Lactulose should be avoided as a laxative because of the risk of bacterial overgrowth with gut dysmotility in neurodevelopmental disorders.

Dental

As previously mentioned, there is reduced production of saliva, which is very viscous (178), which also increases the risk of dental caries, and regular dental reviews are recommended.

Ophthalmology

Eye and vision problems are frequent in PWS, with most identified before the age of 5 years, and strabismus (related to muscle hypotonia) being the most common (179, 180, 181). Surgery for strabismus is more often required in PWS children compared to the general population (179, 180). Myopia, hyperopia and astigmatism are also frequently seen, with the prevalence of myopia and astigmatism higher in those with deletions compared to mUPD (179). It is important that children with PWS are screened for visual problems and deficits corrected early on.

Bone health

The combination of poor muscle tone, reduced physical activity, hypogonadism and GHD in children with PWS may have a profound outcome on bone health. Studies have been performed investigating the effect of GH on bone mineral density with no significant impact long term (182). GH therapy alone does not improve bone health and sex steroid replacement therapy is more important (106, 183).

It is important to optimise bone health through sex steroid replacement, vitamin D/calcium supplementation and physical activity. Dual energy X-ray absorptiometry (DXA) scans should be considered at the point of transition to adult services to assess bone health after treatment (or not) of GHD and hypogonadism. Although bone mineral density is stable in young adults, it has been shown to decline in men with PWS, probably related to inadequate sex steroid replacement, as well as sedentary lifestyle and reduced calcium intake (99, 183). Assessing bone mineral density (BMD) of the lumbar spine (L1–L4) is most reliable in the paediatric population. BMD needs to be adjusted for the patient's size. Reference values for BMD and bone mineral apparent density (BMAD) for children are available (184).

Hip dysplasia

Due to reduced fetal movements, there is an increased incidence of hip dysplasia ranging from 8–30% (185). A hip examination needs to be performed at birth, and only if abnormal, further investigations are required. A hip X-ray at the same time as the first spinal X-ray at around 12–18 months can also be performed. If hips are normal, no further hip imaging is required.

Scoliosis

Scoliosis, kyphosis and kyphoscoliosis, are commonly seen in children and adolescents with PWS – the exact cause is not completely clear (186, 187). The scoliosis seen in PWS is usually lumbar or thoracolumbar, unlike idiopathic scoliosis, which is typically thoracic (1, 186). Prevalence rates are uncertain, but over 40% is a consistent finding, with peaks in the preschool and early adolescent age groups (186). There is no evidence that GH therapy causes or worsens scoliosis, as the onset and progression of scoliosis are similar in GH-treated PWS individuals and controls (188, 189). Rapid growth, which can also occur during puberty, has been associated with the onset of scoliosis and/or progression. Exercises to help develop core strength and muscle tone, including swimming and ballet, are useful for general motor development and metabolic status and are thought to protect the spine. We would advise against getting the infant to sit if they have significant hypotonia, as it would result in them being slumped in the chair. It would be better to encourage tummy time to improve core tone/strength (185). Regular clinical examination, at least annually, is important, although it can be difficult to assess scoliosis in the presence of underlying obesity.

Spinal X-ray examination is useful, together with Cobb angle measurements. It is recommended to obtain a postero-anterior radiograph of the whole spine to assess for scoliosis. Lateral radiographs may be required to assess kyphosis. Spinal X-rays should be performed every 2 years once the child is able to sit independently until the age of 5 years, together with an annual clinical examination. The frequency could increase if the deformity is progressive. Annual clinical examination review should continue, with spinal radiographic examination being performed again in late childhood/early puberty, around the age of 10 years. Spinal radiographic examination should be performed at least every 2 years during puberty, and more regularly if clinically indicated, until the cessation of growth. Obesity readily inhibits the ability to detect scoliosis on clinical examination and so, spinal radiographic examination will be needed.

If there is evidence of scoliosis (Cobb angle >10°) on initial or follow-up X-rays, referral/discussion with the local paediatric spinal team should be undertaken for their opinion, as there can be rapid progression in the scoliosis depending on the stage of growth. A Cobb angle exceeding 25° requires urgent referral to the paediatric spinal team for further assessment and management. If there is any doubt regarding the diagnosis, a referral to the paediatric spinal team is advised. Of note, bone mineral density is inversely associated with Cobb angle in patients with PWS, and this should therefore also be considered by clinicians when assessing scoliosis (189), although there is no need for standard bone mineral density scans until after puberty.

The treatment of scoliosis may involve bracing and surgical intervention depending on the age, degree and magnitude of progression of the scoliosis (186). Children who develop kyphosis also require review by the spinal team.

Learning, cognition and development

There is considerable complexity and interplay between cognition, neurodevelopment, and behaviour in PWS. In practice, these have daily and ongoing implications at home, in educational, and other settings, requiring recognition and understanding.

Cognition

General cognitive abilities are usually in the mild to moderate learning disabilities (LD) or intellectual disabilities (ID) range, or are more severe in a minority. Specific cognitive difficulties are common; these may include poor short-term memory and poor mathematical skills (190), slow processing of verbal information, speed of response, and decision making (191), slow switching of attention from one task to another, difficulty doing more than one task at the same time, and in responding to two possibilities or choices (192). Areas of strength may include the ability to persist at tasks, and some individuals, especially with a deletion, have strong visuospatial skills (193).

The two main genotypes (deletion and mUPD) can have other differences in cognitive and behavioural feature; the mechanisms for which are unclear (194, 195). Those with mUPD tend to have better verbal abilities and impaired coding ability (193).

Speech, language, oro motor skills and swallowing

Feeding and oro-motor skills are delayed and swallowing may continue to be dysfunctional (166, 170).

There is great variability in speech and language development, but most children with PWS have some degree of speech and/or language deficit, ranging from individuals who are nonverbal to those who develop normal speech and language skills over time. Speech sound deficits, dysfluency, reduced oral motor skills and language deficits are common (196). The majority of children have some degree of receptive and expressive language deficits (196, 197, 198). Those with mUPD may have higher expressive than receptive language abilities (199).

Language and communication disorders affect social development, learning and behaviour. Speech and Language Therapists have an important role from an early age and throughout the lifespan as part of multidisciplinary care (196).

Motor development

PWS causes ongoing abnormalities in muscle function (57), including decreased endurance and hypotonia, plus joint laxity. Hypotonia in infancy may be severe. Early gross motor development is usually markedly delayed, which tends to affect other aspects of development. The early use of GH may benefit the development of walking (200). Both physiotherapy advice and consideration of growth hormone from infancy onwards are therefore important interventions. Most children with PWS walk unaided by 24–30 months, but a small minority walk later. It may be helpful for parents to know that gross motor delay taken alone is not an indicator of the degree of cognitive impairment. Joint laxity is common and necessitates supportive footwear and review and may require ankle-foot orthoses, which need to be updated by physiotherapists as a child grows. Parents, schools, and colleges should be advised to anticipate possible excessive tiring in extended physical activities and that there may be mild to moderate difficulties with fine motor skills, coordination or planning of movements (201, 202). Physiotherapists and Occupational Therapists have important assessment and advisory roles, not only in the child's early years.

Social development

Most children with PWS display social interest but have weaknesses in interpreting and responding to social information (203). There is overlap between behavioural characteristics seen in PWS and in autism spectrum disorder (ASD); therefore, the diagnosis of ASD in PWS can be challenging and may become clearer with age. The current estimated prevalence of ASD in PWS ranges between 12% and 41% (204). However, future studies of prevalence need to investigate sufficiently large numbers and employ state-of-the-art diagnostic measures for ASD (205). Children with PWS with mUPD are reported to be at a higher risk of ASD (66, 206) and candidate genes for autism have been located within the 15q11-q13 chromosomal region (207). Furthermore, there is some evidence that 'autistic behavioural problems' may be more severe in mUPD than in those with the deletion (208). There is a growing tendency for autistic behavioural problems, to manifest themselves later in adolescence (208).

In practice, the characteristics of ASD may become more or less apparent with time (205) and therefore referral for assessment may be required at differing ages. Social impairment, with and without a diagnosis of ASD, requires adapted support and should be included in school Education Plans (Fig. 1).

Behavioural issues

PWS has a characteristic neuro-behavioural and cognitive phenotype (209, 210). An international consensus defined the behavioural characteristics as hyperphagia, sudden and sustained so-called temper outbursts, anxiety, obsessive-compulsive behaviour, repetitive and ritualistic actions, rigidity and inflexibility, impaired social cognition and skin picking (204). Sudden and sustained emotional outbursts, skin picking, repetitive questioning, transition difficulty and non-compliance are the most commonly reported problematic behaviours (211). Outbursts occur particularly around access to food, changes to schedule and expectations or demands (192). A study of 101 participants with PWS found that temper outbursts decreased in frequency with age, while the duration of outbursts increased (212). Provocations fitted into three themes: goal blockage, perceived social injustice, and difficulty dealing with change. Lying and stealing to gain access to extra food, often clandestine, are also commonly described as a child gets older.

The most effective external approaches are the appearance of calm, waiting and not overreacting, and only later attempting to identify possible triggers and factors that may predispose or maintain these behaviours including any physical contributors such as hunger, tiredness or the consequences of sleep apnoea. Psychotropic medications alone for behavioural outbursts without any other underlying mood disorder are unlikely to be effective.

Skin picking

Skin picking is frequently seen in PWS (213). Sepsis secondary to skin ulceration is a known cause of death in older patients (8). Keeping nails short and using moisturisers, covering minor skin lesions, together with distraction techniques may help to reduce this in the first instance. Identifying the circumstances in which skin picking happens, such as boredom, lack of engagement, and anxiety, may contribute to developing preventative strategies. Precise reasons for the high incidence are unknown. Skin picking is considered to be a consequence of an interaction between a biological vulnerability and environmental circumstances (213).

In practice, a combination of interventions is required as often no single approach is successful. These include addressing environmental circumstances and behavioural and psychological techniques and advice, rather than medication, although there is limited evidence about this. One open-label study using N-acetylcysteine has shown some benefit for skin picking (214), with a starting dose of 600 mg once daily in children, and 600 mg twice daily in adults. The frequency can be increased to three times daily if tolerated, but in our experience, increasing the doses in children does not seem to alter the outcome. Mild gastrointestinal side effects can sometimes be an issue with N-acetylcysteine. Diaries should be completed before and after starting therapy to ensure that there is a clear benefit of N-acetylcysteine.

Although topiramate has been used for skin picking, the evidence is again limited, and given its side effect profile, it is not routinely recommended (215, 216). Topiramate has been used with some success in reducing hyperphagia in PWS in 2 small uncontrolled studies but was not always tolerated (217, 218). Whilst topiramate with phentermine is approved by the FDA for the management of obesity in non-PWS adults, it is not licensed in the UK and Ireland for this indication.

Guanfacine extended release demonstrated improvement in symptoms of skin picking, aggression/agitation and attention deficit hyperactivity disorder (ADHD) in one study of patients with PWS, but it was not effective in psychosis (219).

Patients with PWS may also display rectal picking, which may lead to ulceration and rectal bleeding, masquerading as inflammatory bowel disease (220). Treatment for this is difficult and is mostly based on tools for behavioural change although mainstream treatment of constipation is also paramount.

It has been proposed that improvements in behaviour are mediated through afferent and efferent vagal projections and their effects on the functioning of the autonomic nervous system. A small study found transcutaneous vagal nerve stimulation (t-VNS) to be an effective, novel, and safe intervention for chronic temper outbursts in adults with PWS (221), however this is not available in routine clinical practice, and further research is required.

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Introduction:

PWS is a rare genetic condition which affects a child's growth, development and learning, physical health, behaviour, and sometimes mental health. These have important implications for the child's care, and their social and educational development.

Medical issues:

Hyperphagia: i.e. increased hunger, lack of appetite regulation, and food seeking. Potential for food-related anxiety and behavioural difficulties. Risk of greater emotional and behavioural difficulties, and severe obesity if not managed consistently.

Implications for school: responsibility for supervising all access to food (including others' lunchboxes, classroom food items), for consistency in meal and snack routines, and the child's expectations in liaison with parents/carers. More information and advice is available from the child's paediatric clinic/dietician and on PWSA websites. Choking is an increased hazard, particularly if food intake is rapid or if food is dry, and requires heightened awareness and encouragement of water with meals.

Reduced awareness of pain; inconsistent recognition of temperature:

Implications for school: supervision of activities, incidents and clothing requirements.

Lower muscle tone and physical endurance ± mild co-ordination difficulties:

Implications for school: daily exercise is important; children often tire more than peers as day progresses, and this needs to be anticipated, e.g. activities involving a lot of walking.

May have ankle foot orthoses (AFOS) because of low tone. Seek Physiotherapy and Occupational Therapy advice.

Speech and language: delay or disorders are common, ranging from nonverbal to complex disorders, speech sound deficits, receptive or expressive language deficits, and transient delay. Slow processing of speech and delay in response is common.

Implications for school: awareness of possibilities. Seek Speech and Language Therapy (SALT) advice.

Learning: usually mild-moderate learning disabilities, sometimes more severe. Specific cognitive difficulties are common.

Implications for school: will require detailed assessment at some stage. Learning potential may be masked.

Specific cognitive and behavioural characteristics: which may affect learning and general behaviour. Often social interest but deficits in social understanding and reciprocity, inflexibility, need to control, literal interpretation, fixations/obsessions, repetitive questions, perseveration, difficulties with transitions, need to complete tasks, anxiety, emotional regulation difficulty and outbursts, skin picking.

Implications for school: anticipate. A positive behavioural approach, and avoid negatives and confrontation. Advice for schools is freely available on PWSA websites or telephone helplines.

Figure 1

Suggested headings and content of health reports for Education Plans.

Behavioural advice for families, schools and colleges

Families and carers need well-informed PWS-specific behavioural advice and help to develop strategies that aim to reduce the incidence and severity of behaviours, to manage incidents optimally, and to deal with lower-level behaviours, such as repetitive questioning and perseveration. Local services, including child and adolescent mental health services (CAMHS), or psychologists and behaviour specialists attached to neuro-developmental services or PWS clinics, should provide these assessments and advice. The rarity and complexity of PWS behaviours can be challenging for local CAMHS services, and the level of cognitive impairment may not reach local intellectual disability (ID) CAMHS criteria, but responsibility remains and is defined in NICE guidance (222). Additional external or tertiary specialist PWS advice may be required. In England and Wales, a paediatric PWS behaviour and mental health multidisciplinary clinical service at the Maudsley Hospital in London has been nationally commissioned but can be accessed only through local CAMHS.

All CA with PWS may develop problematic behaviours due to emerging mental illness, and should be able to access either local LD/ID CAMHS or mainstream CAMHS services in a timely manner. A recent coroner's report has highlighted the consequences of insufficient support from local authorities and mental health services with underestimation of disease burden and the need for multidisciplinary care and multi-agency working (223). This case illustrates that failure to do so can have a severe impact on their lives and that of their families.

Education and Learning Plan

Some children with PWS attend mainstream primary schools with additional support, while others need more specialised schools from the start. By secondary school age, i.e. age 11 years plus, we find that most children attend schools for children with special educational needs because of widening academic and social expectations. Mainstream secondary schools have the added challenges of greater access to food, money, and of potential social isolation, which have to be managed consistently by the school.

Intellectual abilities may also be masked by their social development and behavioural difficulties. A UK population-based sample of people with PWS found that levels of academic achievement were lower than would have been predicted on the basis of IQ. The authors propose that this may be due to the failure to recognize

and address their specific learning needs in the context of relatively mild ID (224).

All children with PWS need individualised support at school based on a detailed understanding of their educational, health, social, and behavioural needs. Most children require a statutory education plan that has been agreed upon by their Local Authority, i.e. an Education Health Care Plan (EHCP) in England, Additional Learning Needs (ALN) in Wales, Additional Learning Provision (ALP) in Scotland, and Co-ordinated Support Plan (SEN EHCP) in Northern Ireland. Applications for these plans can be made by pre-school special needs services, schools, or parents. In Ireland, at the primary school level, additional school resources are allocated either under the 'General Allocation Model' or through application via a Special Educational Needs Organiser (SENO) and the National Council for Special Education (NCSE), who allocate additional resources to schools on a case-by-case basis (225).

The rarity and complexity of PWS means that schools may be unfamiliar with the implications of the different aspects of the condition for the child in school. The child's clinicians are responsible for providing this health and developmental information in their reports to schools, and parents, and for educational plans (226). The lead PWS hospital paediatrician needs to communicate with the developmental disciplines, including a community (developmental) paediatrician, as well as psychologists or CAMHS if involved, to ensure that reports are holistic. Reports may need to be updated at later stages, particularly at transition to and from secondary school. Suggestions for the content of Education Plan Health Reports are given in Fig. 1.

Nurseries and schools may be unaware of sources of additional information about PWS and should be directed to these (PWSA UK, PWSA-I). If there are difficulties accessing educational plans or resources, parents may be directed to charities such as Independent Parental Special Educational Advice (IPSEA) in the UK (https://www.ipsea.org.uk/), in Ireland NCSE (https://ncse.ie/), disability law experts (https://dls.org.uk/) or local legal advocacy.

Mental health

Adolescence and adulthood may be associated with increased rates of mood disorders and anxiety compared to their peers, the anxiety commonly being situational and associated with change. Whilst medications such as selective serotonin reuptake inhibitors (SSRIs) have been used successfully to help with anxiety and repetitive and ritualistic behaviours, they must be used with care. Bipolar disorder has also been described, and hypomanic mood swings may occur as a result (227, 228).

There is concern about the inappropriate use of anti-psychotics, particularly in adults with PWS. There are no randomised trials of the use of anti-psychotics in PWS, and if they are to be used, a clear evaluation of their positive and negative outcomes should be undertaken (9, 229). In PWS, anxiety is the most typical psychiatric diagnosis, occurring in over half of individuals. Skin picking, repetitive questioning, transition difficulty, and non-compliance are the most commonly reported problematic behaviours. Thus, anti-psychotics should be reserved for debilitating relevant formal psychiatric diagnoses (e.g. a psychotic illness) rather than for problematic behaviours, which are often food-related, and managed through control of the food environment and a consistent day-to-day regime. Training of family and carers, with the support of well-informed mental health professionals, would be more helpful, especially given the adverse metabolic effects of such medications (5). Any psychotropic medication should be started at low doses and initiated by a referral to a specialist CAMHS team led by a mental health professional, ideally with expertise in learning disabilities (230) or the quaternary referral CAMHS specialist services in England for PWS (https://slam.nhs.uk/service-detail/service/service-for-complex-autism-and-associated-neurodevelopmental-disorders-scaand-281/) and (https://www.psychiatry.cam.ac.uk/ciddrg/).

The mUPD genetic subtype of PWS is strongly associated with the development of affective psychosis (231). In a UK-wide sample of 119 adults with PWS, 62% of those with mUPD had a diagnosis of psychotic illness compared with 17% of those with a chromosome 15q11-q13 deletion (228). Other studies have demonstrated a lower prevalence; however, this was a much younger cohort compared to the UK study (72). In addition to the onset of hallucinations and delusions, atypical symptoms such as hypersomnia, confusion, and motor symptoms were seen, and the initial diagnosis made may be that of a confusional disorder (delirium) with no clear physical illness identified. Whilst assessing the physical state of someone with PWS who presents with the onset of an abnormal mental state is important, the cause of such changes is more commonly the onset of severe mental illness. Follow-up studies have reported that those with mUPD who have developed a psychotic illness had a more severe, difficult-to-treat illness with a poorer outcome compared to those with a deletion (228). However, once stability has been achieved in psychotic illness, recurrence rates are low (232). In the acute phase of a psychotic illness, urgent referral to the local psychiatric services, such as CAMHS, is essential.

Mental capacity

From the age of 16 years, in England and Wales, the Mental Capacity Act 2005 and in Scotland, the Adults with Incapacity (Scotland) Act (2001) will apply if someone with PWS is considered to lack the capacity to make a specific decision. In the Republic of Ireland, new legislation is being considered. If there is uncertainty,

adolescents with PWS may need to be assessed to determine whether they have the capacity to make specific decisions, particularly with regard to access to food and money.

Many young people and adults with PWS will be found on assessment to lack capacity to make decisions about aspects of their welfare, health, finances, access to food, and accommodation, especially where these decisions impact on, or are affected by, hyperphagia and eating behaviour; however, there will be exceptions.

Family and caregiver support

There is increasing evidence that the impact of children's behavioural and mental health issues on parents, siblings, and carers can be considerable even compared to other neuro-disability syndromes. This may be underestimated by those unfamiliar with PWS, and support services are reportedly limited (43, 211, 233, 234, 235, 236).

In one PWS study, disruption of routines, restricted social activities, and psychological difficulties increased caregiver burden (43). Two studies reported a strong positive correlation between caregiver burden and increasing hyperphagia and age. Younger children aged 0–4 years with PWS posed care-related burdens on parents, whereas older PWS individuals' anxiety, temper tantrums, and oppositional behaviour conferred higher caregiver burden (236, 237).

A child having PWS may affect their siblings' quality of life (QoL). In one study, mothers and siblings reported decreased QoL, increased family conflict and behavioural distress, and siblings reported moderate-to-severe symptoms of stress disorder (234). A PWSA UK parent and carer open access national survey in 2015 identified moderate to high levels of stress in over half of the respondent families.

Strategies to support and mitigate caregivers' and families' stress may include providing information and behavioural advice about PWS from early years onwards (some PWS clinics have a parent advisor), early identification of difficulties by clinicians, and referral for support and other interventions. Annual multi-agency reviews of Educational Plans provide an opportunity to identify and address needs. Multidisciplinary networking meetings and communication between clinicians, schools and other services can be helpful. PWS organisations provide information and support to parents and professionals and sometimes contribute to meetings.

Transition in adolescence and adulthood

Transition through adolescence and into adulthood can be problematic because of the increasing demand for independence, which abuts the need for rigorous control of the food environment, with the risk that in its absence severe and life-threatening weight gain will occur. This is a particular issue for those with higher cognitive abilities, who are more independent in their daily activities. For young adults, access to social care support and learning disability services, as well as the availability of community, educational, and work opportunities, is limited and varies significantly between different areas. In many countries, including the UK and Ireland, there is a limited number of adult endocrinologists/physicians with a special interest and experience in PWS.

Despite international consensus publications about adults with PWS, care for PWS remains sub-optimal, with a large proportion having underlying health problems which are not diagnosed, in particular sleep apnoea (36). Ongoing multidisciplinary care, as well as ongoing GH therapy, is beneficial and should ideally continue into adulthood (94). Young adulthood is also the age at which mental illness may develop for the first time. Management will very much depend on the local situation, but paediatric endocrinologists should be encouraged to engage with their adult colleagues to develop transition and adult PWS clinical and community services, as adult care requires specialist input with multidisciplinary support and a physician such as an endocrinologist acting as a core healthcare professional (36). Teams with expertise in adult learning disability should be involved early in the transition process to help identify needs and management, e.g. social worker, psychology, and psychiatry. The 'Ready-Steady-Go' transition program may be useful to fill gaps in knowledge for parents and family members and to prepare the young person for transition, as the program also contains a version for young people with learning disabilities (https://www.readysteadygo.net/rsg.html).

Specialist PWS residential care providers in some countries (e.g. USA, UK, Netherlands) can be especially helpful in the medical management of PWS, for the achievement of weight loss or maintenance into adulthood, by providing a secure food environment, appropriate physical activity, meaningful peer social interaction, and vocational opportunities (36, 55). In our experience, though more expensive, they are usually more successful in this regard than supported living or non-specialist residential group homes, and long term weight and health have been shown to be better in dedicated hostels compared to the family environment (238). Specialist residential placements are not always available for all individuals and also not in all countries, and therefore it is important to provide knowledge and expertise to all those looking after individuals with PWS. Even in the UK and Ireland, there can be difficulties obtaining funding from the NHS in addition to social care, especially when the current need is to prevent weight gain rather than achieve weight loss. The UK and Irish PWS Associations are an excellent point of contact for the availability and utility of specialist community PWS respite and residential care providers around the UK and Ireland.

Management of acute illness in PWS

Immune function is normal in PWS, but the increased prevalence of T2DM and respiratory problems (particularly in adults) means that there is a greater risk of hospital admissions due to acute illness and infections. Cognitive difficulties may make it difficult for individuals with PWS to give a complete medical history. In addition, many have a high pain threshold, rarely vomit, and may not develop a high temperature from infections and inflammation as a result of hypothalamic dysfunction. This means they may appear relatively unaffected by significant injuries, infections, or gastrointestinal problems, and this must be taken into account in investigation plans.

People with PWS appear particularly at risk of gastrointestinal perforation and delayed gastric emptying and should have a low threshold for imaging and diagnostic intervention, particularly if pain is reported or the person has vomited (169, 172). When these occur, it may well be an indication of a life-threatening physical illness that has until that point gone unnoticed. Treatment plans may need to take into account differences in body composition; otherwise, managing acute illness in PWS should not differ from the rest of the population.

If an individual with PWS is admitted to the hospital, including elective admission, staff must be aware of dietary needs and the need to manage access to food. They should take into account their learning disability, for example, allowing relatives or carers to be present on the ward and ensuring that issues are explained in an appropriate manner. Plans to support behaviour and reduce anxiety may be needed, for example, making sure staff are aware of the importance of telling them well in advance what is going to happen, avoiding changes in plan, signposting, and procedures requiring fasting are scheduled as 'first on list' to minimize distress and ensure food is not on display on the ward. Reasonable adjustments (first on list, anaesthetic pre-assessment, signposting/timelines for day events) may minimize the potential for challenging behaviour to disrupt or cancel planned surgical or interventional activity.

Anaesthetic issues in PWS may include increased BMI, obstructive or central sleep apnoea, complex airway management (poor dentition, micrognathia and limited neck mobility), restrictive respiratory physiology due to kyphoscoliosis, behavioural challenges, gut issues, thermoregulation, and glucose/stress response. Specific anaesthetic guidance can be found on the PWSA UK website or the Orphanet anaesthesia site (239).

Conclusion

Children and adults with PWS can experience multiple medical, cognitive, behavioural and emotional issues and problems, some of which are potentially life-limiting. Adults with PWS are unfortunately still dying from hyperphagia and obesity-related complications. It is important that clinicians supporting these individuals are aware of all of these possibilities and have access to the various specialists required in their care. Lifelong monitoring and management of individuals' care are needed (Table 4).

This document has drawn together published evidence, where available, on the multi-disciplinary care of

Table 4 Recommendations for screening in patients with PWS at diagnosis and throughout life.

Item		Diagnosis	Childhood	Transition
Endocrine	Growth hormone stimulation test	No	No	No[a]
	Adrenal function testing	No	Only if clinical suspicion	Only if clinical suspicion
	Thyroid function	Yes	Annually	Annually
Cardiorespiratory	Full sleep study	Yes	2–3 months after initiation of GH Every 2–3 years	If concerns
	Overnight pulse oximetry	No	Annual	No
Bone	Spinal X-ray	Yes	Every 2 years (once sitting) until age 5 years and at age 10 years and during puberty	Yes
	DXA bone scan	No	No	Yes
Blood monitoring	IGF-1, TFTs, FBC, nutrition screen[a], PTH, renal function, liver function, bone profile, vitamin D, FSH[c], LH[c], testosterone/oestrogen[c] (IGF-BP3 and inhibin B[c] – where available)	Yes	Annual	Annual

[a]This will vary depending on local centres; [b]Evaluation of the GH axis can be considered in adult services; [c]When age appropriate.

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Table 5 Executive summary.

Domain	Recommendation
Structure of healthcare team	Young people with PWS require multidisciplinary care, ideally through a network of specialist centres.
Genetic analysis	The diagnosis of PWS should be confirmed by genetic analysis, and young people with PWS should be referred for review by Clinical Genetics after genetic confirmation.
Growth	Height and weight should be measured at every clinical visit and plotted on standard growth charts for children and young people.
Nutrition	Children with PWS have the same micronutrient requirements as their peers, and multivitamins and minerals should be prescribed as appropriate.
	Caloric requirements are generally reduced, related to reduced energy expenditure secondary to hypotonia, but will vary depending on their age and growth. Input from experienced dietitians should be sought soon after diagnosis.
	Measures must be undertaken to ensure food security throughout life, together with encouraging physical activity.
Growth hormone	Due to the potential upper respiratory changes associated with GH therapy, a level 2 (cardio-respiratory) sleep study is mandatory before the start of GH therapy through liaison with local respiratory services.
	Where an appropriate sleep study has been obtained, GH should be recommended to start prior to the age of 1 year.
	A starting dose of 0.5 mg/m^2 daily (9–15 µg/kg/day) is suggested, increasing the dose to 1.0 mg/m^2 daily (35 µg/kg/day) over a period of 3–6 months.
	Body surface area should be used to avoid inappropriately high GH doses in overweight/obese individuals.
	Serum IGF-1 concentrations may be higher in PWS, but levels more than twice the upper limit of normal should be avoided and indicate the need for GH dose reduction.
	Evaluation of the GH axis at final height should be considered using GH stimulation testing after at least 1 month off GH therapy via a GHRH-arginine test.
	GH may be used in adults with PWS up to the age of 25 years, but thereafter the data supporting this intervention are sparse.
Hypogonadism	Premature adrenarche are common in children with PWS and do not require treatment.
	Hypogonadism is a constant feature in PWS and may require treatment with testosterone or oestradiol/progesterone, as appropriate.
Other endocrine dysfunction	No routine screening is required for adrenal insufficiency in PWS.
	Screening for hypothyroidism should be undertaken regularly.
Sleep studies	We recommend as a minimum, a full level 2 (cardio-respiratory) sleep study every 2–3 years in those under the age of 5 years on GH therapy, or sooner if there are clinical concerns suggestive of worsening OSA, even if the patients have had a previous normal sleep study.
	In those over the age of 5 years, cardio-respiratory sleep studies should be considered where there are clinical concerns, perhaps associated with significant weight gain, such as increased lethargy and acute changes in behaviour.
Muscle function	Exercise is an essential part of management in PWS and should be recommended at all stages as an adjunct to preventing obesity.
Bone health	It is important to optimize bone health through sex steroid replacement, vitamin D/calcium supplementation, and physical activity.
	Dual energy X-ray absorptiometry (DXA) scans should be considered at the point of transition to adult services.
Spine	Annual clinical examination of the spine should be undertaken.
	Spinal x-rays should be performed every 2 years once the child is able to sit independently until the age of 5 years.
	Thereafter, repeat X-rays are recommended at 10 years and then at least every 2 years during puberty, and more regularly if clinically indicated, until the cessation of growth. If there is evidence of scoliosis (Cobb angle >10°) on initial or follow-up X-rays, referral/discussion with the local paediatric spinal team should be undertaken.
	A Cobb angle exceeding 25° requires urgent referral to the paediatric spinal team for further assessment and management.
Learning, cognition, and development	Additional support for learning, cognition, and development may be required from a range of professionals, including educational psychology, occupational therapy, physiotherapy, and speech and language therapy.
	Individualised education and healthcare plans (EHCP) should be developed for all children with PWS to trigger statutory channels of support via the local education authority (LEA) and children's services.

(Continued)

Table 5 Continued.

Domain	Recommendation
Parent/Caregiver support	PWS confers high levels of caregiver and family burden. The PWSA-UK, PWSA-I, IPSWO, and other national PWS charities offer advice and support for PWS families, education, and social services professionals. This includes introducing respite care for families sooner rather than later.
Mental health and behaviour	All CA with PWS with associated behavioural problems should be sign-posted to PWS associations for information and guidance, and if appropriate, should be able to access either local LD or mainstream CAMHS services. Respite care is very valuable where available.
Transition to adult services	Transition to adult PWS clinical and community services should involve multi-disciplinary support and a physician such as an endocrinologist acting as a core healthcare professional.

children and young adults with PWS, with, for the first time, the clinical expertise from the specialist PWS paediatric clinics across the UK and Ireland.

PWS is a rare orphan disease with no effective pharmacological treatment currently available for hyperphagia. In practice, CA and adults with PWS, their families, and carers have variable access to clinical and coordinated PWS expertise. Families and carers report unmet needs to the PWSA UK and Ireland. Increased knowledge and education about PWS are vital for all health and social care professionals alongside the development of multidisciplinary expert clinical networks and commissioning.

Greater availability and easier access are needed for adult specialist PWS residential services providing food security, meaningful activities, and meaningful activities and well informed support. Increased funding is required for specialist clinical and residential services and for the national PWS associations, which provide vital support, advice, and training.

There have been considerable advances in the understanding and management of PWS over the last 20 years, and the future of young people is potentially different from many previous reports. With improved management, the clinical phenotype has also changed, with reduced obesity and fewer resultant co-morbidities. However, for optimal progress, their requirements include access to expert clinical knowledge and coordinated multidisciplinary health and social care, together with family support, and these are not yet guaranteed.

This paper provides guidance and background information on the multidisciplinary care of children and young adults with PWS in the UK and Ireland. It focuses on best practices for children and the transition to adulthood. It is based on available evidence and expert opinion. An executive summary can be found in Table 5.

Declaration of interest

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Useful links

Foundation for Prader-Willi Research:
https://www.fpwr.org/
Foundation for Prader-Willi Research 'PATH for PWS' registry:
https://pathforpws.com/study-information/
Prader-Willi Syndrome Association Ireland:
https://pwsai.ie/
Prader-Willi Syndrome Association United Kingdom:
https://www.pwsa.co.uk/
International Prader-Willi Syndrome Organisation:
https://ipwso.org/
Prader-Willi Syndrome Association USA:
https://www.pwsausa.org/

Author contribution statement

MGS developed the PWS Network consensus group and led the group meetings and drafting of the guideline. TB, NB, RC, EFG, APG, AH, SK, RK, AK, EAL, AKLH, CM, SP, ER, CS, and SS formed the consensus group and were responsible for literature searching, discussion of available data, and revising and redrafting the manuscript. All authors contributed equally and are therefore listed in alphabetical order. They have all approved the final draft of this manuscript.

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