Reviews in Endocrine and Metabolic Disorders (2019) 20:239–250
https://doi.org/10.1007/s11154-019-09502-2

Prader- Willi syndrome: An uptodate on endocrine and metabolic complications

Giovanna Muscogiuri[1] · Gloria Formoso[2] · Gabriella Pugliese[1] · Rosaria Maddalena Ruggeri[3] · Elisabetta Scarano[1] · Annamaria Colao[1] · on behalf of RESTARE

Published online: 7 May 2019

Abstract

Prader-Willi syndrome (PWS) is a genetic disorder characterized by short stature, low lean body mass, muscular hypotonia, mental retardation, behavioral abnormalities, dysmorphic features, and excessive appetite with progressive obesity. It is caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13. This genetic disorder has an estimated prevalence that ranges between 1/10,000–1/30,000. Hypothalamic dysfunction is a common finding in PWS and it has been implicated in several manifestations of this syndrome such as hyperphagia, temperature instability, high pain threshold, sleep disordered breathing, and multiple endocrine abnormalities. These include growth hormone deficiency, central adrenal insufficiency, hypogonadism, hypothyroidism, and obesity often complicated by type 2 diabetes. The aim of this manuscript is to overview the current literature on metabolic and endocrine complications of PWS, focusing on human studies and providing insights on the physio pathological mechanisms. A careful management of metabolic and endocrine complications can contribute to improve quality of life, prevent complications, and prolong life expectancy of PW patients.

Keywords Prader Willi syndrome · Hypotalamic dysfunction · Metabolic and endocrine complications

1 Introduction

Prader-Willi syndrome (PWS) is a genetic syndrome that is characterized by neonatal hypotonia and feeding difficulties in early infancy, short stature, behavioral problems, cognitive impairment, psychiatric illness, dysmorphic features (characteristic facial appearance like small mouth with downturned corners and thin upper lip with up-slanting palpebral fissures[1], small hands and feet, narrow hands with straight ulnar border, scoliosis), multiple endocrine abnormalities (hypogonadism, growth hormone [GH]/insulin-like growth factor I axis dysfunction, hypothyroidism, central adrenal insufficiency), early development of hyperphagia with food seeking behavior, and progressive development of severe obesity[2]. The typical obsessive compulsive behavior of these patients leads to skin picking that create different skin lesions (excoriations, scabs, scars, secondary milia) on the hands and the forearms [1]. This genetic disorder has an estimated prevalence that ranges between 1/10,000–1/30,000. PWS is the result of lacking expression of paternal genes from chromosome 15q11.2-q13. In fact in this region there are genes which are genomic imprinted and are normally active only from the paternally contributed chromosome 15 while those same alleles from the maternally chromosome 15 are inactivated through epigenetic mechanisms and are not expressed. Thus, the phenotype of PWS is determined by the lack of expression of one or more of the paternally inherited genes. The most common genetic mechanism responsible for PWS is deletion of a 5–6 Mb region from the paternally contributed chromosome 15 (found in 65–75% of affected individuals) followed by maternal uniparental disomy (UPD) 15 (found in 20–30%) and finally it could be due to a defect in the genomic region that controls the imprinting process, a so-called imprinting defect (ID; 1–3%) [3]. Hypothalamic dysfunction is the endocrinological core complication. The most dreaded complications of PWS are related

✉ Giovanna Muscogiuri
giovanna.muscogiuri@gmail.com

[1] Endocrinology Unit, Department of Clinical Medicine and Surgery, University Federico II, Via Sergio Pasini 5, 80121 Naples, Italy

[2] Department of Medicine and Aging Sciences; Aging and Translational Medicine Research Center (CeSI-Met), G. d'Annunzio University, Chieti, Italy

[3] Department of Clinical and Experimental Medicine, Unit of Endocrinology, University of Messina, Messina, Italy

to hyperphagia that is due to hypothalamic dysfunction and that leads to hyperphagia, temperature instability, high pain threshold, sleep-disordered breathing, and multiple endocrine abnormalities [3, 4]. In particular uncontrollable hyperphagia often results in severe obesity that requires more sophisticated dietary treatment [5] approach and that in turn increases the risk of developing Type 2 Diabetes Mellitus which has been reported in 25% of adult PW population [6]. Due to generalized hypothalamic dysfunction, children and adults with PWS are at risk for central adrenal insufficiency which has been detected in about 60% of cases [7]. Hypothyroidism is also a common finding (approximately 20–30% of children) in PWS and it is thought to be central in origin [8]. Moreover, individuals with PWS at birth often show clitoral and labia minora hypoplasia in females and micropenis with hypoplastic scrotal sac in males [3]. Further, hypogonadism represents a common finding leading to complete or partial pubertal failure due to insufficient secretion of the pituitary gonadotropins LH and FSH and gonadal sex steroids. Also, unilateral or bilateral cryptorchidism is detected in 80–90% of males [3]. Finally, short stature is one of the main characteristic of individuals with PWS that is almost always present by the second decade in the absence of GH replacement [3, 9]. Therefore, the aim of this review is to provide an overview on the current literature on metabolic and endocrine complications of PWS, focusing on human studies and providing insights on the physio pathological mechanisms.

2 Obesity and diabetes

PWS represents the most common cause of syndromal obesity, which is responsible for the increased metabolic complications and mortality observed in these subjects [10].

Overweight and obesity prevalence in PWS is approximately 82–98%. Unfortunately, to date, the exact mechanism of the development of obesity in PW patients is not fully understood (Fig. 1).

In these subjects, alterations in energy expenditure [11], food intake and hormone deficiencies [12], are attributed to a dysfunction in the hypothalamic satiety centre and to its hormonal circuitry.

Brain structure alterations, documented by preclinical studies and brain imaging studies conducted in mice, suggest that several brain areas play a crucial role in the abnormal food intake regulation. Examples of such alterations are an increased functional response of the hypothalamus to food stimuli, an involvement of the amygdala and a reduced interaction between the ventral striatum and the limbic structures [10, 13, 14]. Excessive eating has been observed in all genetic subtypes of the syndrome, and it has been defined as a hallmark of the disease. In the absence of rigorous supervision of food intake, many PW patients grow to weigh more than twice their ideal body weight. Aggressive and obsessive food seeking and storage are considered part of a broader abnormal behaviour and, according to Miller et al., the nutritional and eating behaviour of PW patients is characterized by seven successive phases with later stages, resulting in a persistent and inexorable hunger that causes wide problematic hunger-related behaviours [15].

Obesity in PWS has been thought to be related to abnormalities in the adipocyte-leptin-hypothalamic pathway. Although high leptin levels have been reported in PW patients, no difference has been observed in leptin concentration in PW patients as compare to healthy controls, after adjustment for BMI o fat mass content [16, 17]. Thus, there is no evidence that defective leptin production causes obesity in PWS, and leptin receptor deficiency is not a primary consequence of the gene defects leading to leptin resistance. Since ghrelin affects appetite as well as GH secretion, and both are abnormal in PWS, it has been hypothesized that this condition might involve ghrelin dysregulation. Elevated plasma ghrelin levels have been observed in patients with PWS, both before and after the development obesity and they are comparable to or higher than those reported to stimulate appetite and food intake during peripheral ghrelin administration in human [18–20].

Obesity of PW subjects is metabolically different from simple obesity [3]. Indeed, PW subjects exhibit a lower amount of lean body mass and a higher level of fat mass as compared to obese subjects. The decrease in muscle mass is associated with reduced Resting Energy Expenditure (REE), with a normal relationship between fat-free mass and REE [21]. When corrected for lean mass, no differences between the PWS and obesity groups in the resting metabolic rate or in metabolic flexibility was observed [22]. Differently from the matched obese subjects, excessive fat mass in PW is typically distributed to the trunk and to the proximal extremity of the limbs, with a lower trunk-to-appendicular fat mass ratio and lower visceral adiposity. According to the latter, a higher insulin sensitivity (with lower fasting insulin and HOMA-IR) is generally observed in PW patients when compared to the obese population [23]. The possible explanation for this higher insulin sensitivity in PW could be identified in the prevalent subcutaneous and less visceral fat accumulation, in the higher ghrelin and adiponectin levels as well as in the lower GH hormone levels [24]. It is important to consider however, that data about insulin secretion and body composition in PWS are not univocal [25]. In a few studies, insulin levels and the degree of insulin resistance resulted to be similar in PW and in obese controls [23] with a similar proportion of abdominal subcutaneous and visceral fat accumulation observed in obese PW subjects as well as in BMI-matched controls [26]. On the basis of the aforementioned data, it definitely appears that further investigations are needed to analyse the metabolic profile of PW subjects and it is important to compare it with the

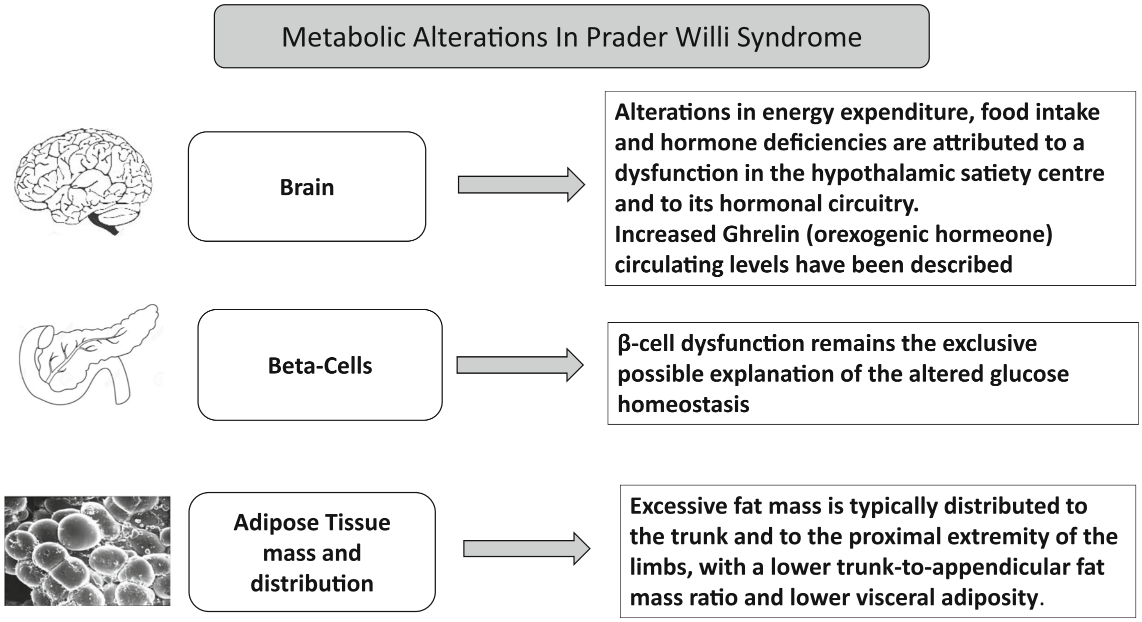

Fig. 1 Potential underling mechanisms in obesity and metabolic alterations in PWS

metabolic profile observed in patients with essential obesity. An interesting point will be the comprehension of the specific role on insulin resistance in the prediction of metabolic alterations in obese PW patients. This is because the mechanisms underlining the higher rate of glucose metabolism alterations (approximately 20%) observed in PWS, to date ascribable to the morbid obesity and insulin resistance, is still debatable [27]. The available data support the hypothesis that β-cell dysfunction remains the exclusive possible explanation of the altered glucose homeostasis in the PWS. Schuster et al. demonstrated that glucoregulatory mechanisms are different in obese PW versus non-PW subjects. The author showed that non-diabetic PW subjects manifest a deficiency in the 1st and 2nd phase of insulin release after glucose stimulation i.e. a significant increase in hepatic insulin metabolism (extraction) when compared with obese controls [25]. Possible causes of the β-cell dysfunction detected in the PWS are:

– a decreased GH secretion with a consequent reduced beta cell growth and response of insulin secretion;
– a reduced vagal parasympathetic tone to the pancreas which determines a decrease in insulin secretion [28].

A relative hyperadiponectinemia that may promote fatty acid oxidation and elevate inulin sensitivity [20]. As for non-PW diabetic/obese subjects, the therapeutic approach for diabetic/obese PW patients aims to aid weight loss and to the control blood glucose levels. This could be achieved by nutritional therapy together with an increase in physical exercise. However, education alone is not sufficient to obtain a lifestyle changes. Life style intervention should be associated with behavioral management technique in order to achieve short term attainable goal; this could help in sustaining motivation and compliance [29]. In PW patients not responding to the above interventions the therapeutic approach could by implemented with a pharmacological intervention using metformin, pioglitazone or even insulin, when needed. Recently, positive outcomes have been obtained with long acting Glucagon-like Peptide 1 Receptor agonists in terms of weight loss, glycaemic control, insulin secretion improvement as well as a reduction in plasma ghrelin [27, 30]. More wide and long term studies are however needed to further investigate the possible role of these drugs in the treatment of obese and/or diabetic PW patients .

3 Hypothyroidism

Hypothalamic dysfunction in PWS seems to be responsible of central hypothyroidism.

There are conflicting data in the literature regarding the prevalence of hypothyroidism in PWS: some studies report a prevalence of 2–4% in children and adult patients with PWS [31, 32] which is similar to that of the general population, while other authors report a prevalence of 20–30% [8, 33] or even of 72% in a study conducted on patients with PWS during the first 2 years of life [34]. Sharkia et al. performed a study in 23 new-borns with PWS; at the time of neonatal screening for congenital hypothyroidism, they found that TSH and total T4 concentrations were within the normal range and similar to those of controls [32]. In the same study, TSH response to thyroid-releasing-hormone in 21 children from birth to adolescence showed normal patterns except in one elder child with hypothalamic (tertiary) hypothyroidism [32]. However, Vaiani et al., studying the thyroid function of 18 children with PWS under 2 years of age, found low serum total T4 and/or free T4 levels without increments of serum TSH in 13 of 18 infant patients (72%) suggesting that hypothalamic-pituitary-thyroid axis dysfunction might be a common feature in PWS during infancy [34]. These studies suggest that central hypothyroidism may not be present at birth but may occur later, so neonatal screening is not enough to identify it and it is recommended to perform screening for hypothyroidism within the first 3 months of life and then yearly [35]. When hypothyroidism is diagnosed, treatment with levothyroxine at typical replacement doses should be used. In addition, as reported by Festen, particular attention should be given to thyroid function in patients starting GH therapy: in a study conducted on 75 PW children, a significant reduction of FT4 to low-normal levels, with normal TSH levels and relatively high or normal T3 levels, was observed during GH replacement therapy, suggesting that GH therapy could be responsible of an increased conversion of T4 to T3 [36]. Latter, in the literature there are also some anecdotal cases of congenital hypothyroidism in PW new-borns due to ectopic sublingual thyroid gland [37, 38] and fetalgoiter [39] (Table 1).

4 Adrenal insufficiency

Central adrenal insufficiency is a common finding in PWS. It has been reported that an undiagnosed and untreated dysregulation of hypothalamic-pituitary-adrenal axis could justify the high mortality rate of 3% per year reported in PW patients [40]. In fact in an autopsy study performed on four individuals with PWS, small adrenal glands by weight were found in three of them, suggesting that an unrecognized adrenal insufficiency (AI) may have contributed to their death [41]. For this reason, in recent years some studies have been conducted to highlight the real prevalence of the this disease, showing different results based on different testing methods used (0–60%) to detect adrenal insufficiency [7, 42–47]. In 2008, de Lind van Wjingarden et al. published the first cross-sectional analysis of adrenal insufficiency, conducted on 25 children with PWS using overnight single-dose metyrapone testing to measure ACTH response [7]. They found that 15 patients (60%) fulfilled the criteria of AI (ACTH response <33 pmol/l at 07:30 h), but conserved normal morning and diurnal cortisol values suggesting that there is a deficit in the reserve necessary for the stress response [7]. Subsequent studies conducted with other methods have led to less alarming results. Corrias et al. subjected 84 children with PWS to Low-Dose Tetracosactrin Stimulation Test (LDTST) 1 mcg, showing a sub-optimal response (defined as a peak cortisol response <500 nmol/l) in 14 of them (14.3%), which reconfirmed with the Standard Dose Tetracosactrin Stimulation Test (SDTST) in 4 patients (4.8% of the cohort) [42]. Similar results were obtained on 53 adult PW subjects, showing an abnormal cortisol peak after a LDTST in 15.1%, confirmed with a SDTST in 7.5% [43]. Beauloye et al. assessed AI using insulin tolerance test (ITT) and glucagon test (GT) in 20 PW children, reporting a prevalence of 5% [44], similar to that obtained in another retrospective study, using ITT, LDTST and SDTST [45]. Instead, some studies showed that the function of HPA axis was normal in PW subjects [46, 47]. Nyunt et al. reported normal cortisol response to stress in the entire cohort of 41 PWS children using LDTST to screen for AI [46]. Similarly Farholt demonstrated a normal response to SDTST or insulin tolerance test (ITT) in most of the patients, except one that showed an insufficient response to the first test not confirmed by the second one [46, 47]. The controversial results regarding to the prevalence of AI in PWS could be due to the different tests used to detect AI that have a different sensitivity and this prevent to draw final conclusions. Hypothalamic dysregulation has been hypothesized as a common mechanism underlying both stress-induced CAI and central respiratory dysfunction during sleep. PW children with CAI has been reported to have a higher central apnea index compared to those without. The administration of metyrapone in PW children resulted in an increase in the central apnea index which was particularly high in PW children with CAI [48]. However, these results were not confirmed by a retrospective study by Beauloye et al., that do not support a link between CAI and central respiratory dysregulation in PWS [44]. In conclusion, considering the risk of asymptomatic adrenal insufficiency which may manifest as severe intraoperative hypotension [49], we recommended to assess for AI by routine testing methods prior to any major surgery or anesthesia, using typical glucocorticoid replacement dose if AI is detected. However, glucocorticoids should be consider as prophylaxis or, at very last, be readily available, before or during surgery if normal adrenal function has not been documented. At the same time, chronic treatment with glucocorticoids should be consider with caution as it would increase the risk of bone demineralization and weight gain, already present in this syndrome (Fig. 2; Table 1).

5 Hypogonadism

Hypogonadism represents a common clinical feature in PW patients. Similar to other endocrine manifestations of the syndrome, hypogonadism has been classically thought to be central in origin, due to hypothalamic dysfunction and subsequent insufficient secretion of gonadotropins by the pituitary [3, 50, 51]. More recently, primary gonadal failure has been demonstrated as a major component of hypogonadism in both sexes [52–55]. Besides the fact that sexual hormones (testosterone and estrogens) are usually below normal range, studies have shown a

Table 1 Recommendations for monitoring and treatment of endocrine diseases in PWS patients at different ages of life

Endocrine disease	Age of life	Clinical and biochemical monitoring	Treatment
HYPOGONADISM	Early infancy	Clinical examination in males for -Undescended testes -Penilelength	-Human chorionic gonadotropin (hCG) -Short course of low-dose testosterone
	Childhood and mid-adolescence	- Clinical monitoring for initiation and progression of spontaneous puberty. -Careful monitoring of growth and skeletal maturation -If pubertal progression is delayed or stalls, assess hormone profile, including LH, FSH, testosterone/estradiol levels and inhibin B	Start testosterone/estrogens at graduated doses for initiation or continuation of stalled puberty
	Adult life	Assess Inhibin B levels for potential of fertility in females	Sex hormone replacement therapy (testosterone/ estrogens alone or in combination with progestin) Counsel for contraception in females
GROWTH HORMONE DEFICIENCY	Early infancy	- Checking for Born small for gestational age (SGA) status - Monitoring of growth - Assessing anthropometric measures (Use standardized anthropometric curves for non-GH-treated infants and children with PWS) - Assessing IGF-I concentration	Start GH therapy as diagnosis of PWS is made (standard dose: 1 mg/m2/daily or ~0.035 mg/kg/daily achieved within 1 month)
	Childhood and mid-adolescence	- Monitoring of growth and skeletal maturation - Monitoring pubertal development - Assessing anthropometric measures (Use standardized anthropometric curves for non-GH-treated infants and children with PWS) - Assessing IGF-I concentration	Start GH therapy as diagnosis of PWS is made (standard dose: 1 mg/m2/daily or ~0.035 mg/kg/daily achieved within 1 month)
	Adult life	- Assessing anthropometric measures - Measuring muscular strength - Assesing lipid and glucose profile - Aassesing IGF-I concentration	Restart GH therapy if GHD diagnosis is confirmed after achievement of final height (starting dose: 0.1–0.2 mg/daily)
HYPOTHYROIDISM	Early infancy	Clinical manifestations: -Poor feeding -Excessive sleeping -Weak cry -Constipation -Prolonged jaundice TSH, FT3, FT4 within three months of life	Levothyroxine at typical replacement doses
	Childhood and mid-adolescence	Clinical manifestations: -Slow growth -Delayed tooth development -Tiredness -Delayed puberty TSH, FT3, FT4 every year, or every 6 months if in therapy with GH	Levothyroxine at typical replacement doses
	Adult life	Clinical manifestations: -Fatigue, joint pain, muscle weakness -Constipation, weight gain -Cold intolerance -Menorrhagia -Sleep apnea and snoring -Dry skin, hair loss and thin nails -Decreased heart rate -Decreased exercise capacity -Cognitive impairment, memory loss TSH, FT3, FT4 every year, or every 6 months if in therapy with GH	Levothyroxine at typical replacement doses
ADRENAL INSUFFICIENCY	Early infancy Childhood and mid-adolescence Adult life	Classic manifestations of adrenal insufficiency including unexplained death and remembering that PWS individuals rarely develop fever or signs of illness including vomiting, because of hypothalamic dysfunction. Low-Dose Tetracosactrin Stimulation Test 1 mcg (n.v. ≥ 18,1 μg/ml)	Hydrocortisone at typical replacement dose prior to any stressful event, major surgery or anaesthesia, if AI is confirmed by test, or prophylactically if adrenal function has never been evaluated.

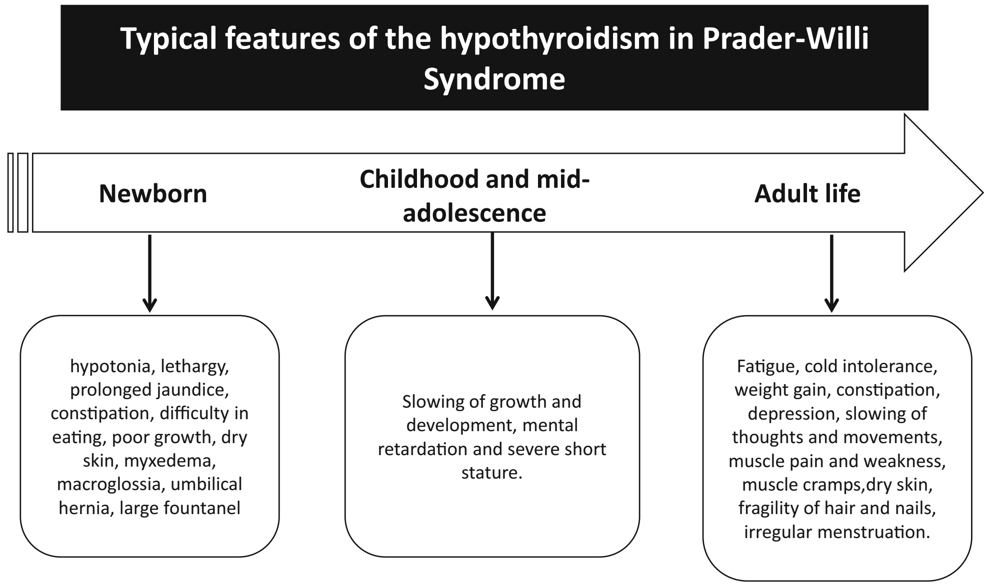

Fig. 2 Typical development of the hypogonadic phenotype in PWS

combined picture of hypogonadotropic hypogonadism with decreased levels of gonadotrophins, and primary hypergonodotropic hypogonadism with normal LH, low inhibin B and relatively high FSH levels [56, 57]. As a consequence, in both male and female PW patients there is a wide heterogeneity of the phenotype of hypogonadism (primary or central or both components) and its clinical presentation is extremely variable (Fig. 3; Table 1).

5.1 Male PW subjects

Hypoplastic scrotal sac may be evident at birth. Unilateral or bilateral cryptorchidism is a common finding, ranging from 66% to 100% of newborns [3, 57, 58]. Most PW patients require orchiopexy to reach a stable scrotal position, although early treatment with human chorionic gonadotropin (hCG) may result in an anatomically lower testis position and better outcomes, including complete scrotal descent, development of the scrotal sac and growth of penis length [59]. Despite micropenis (stretched penis <2.5 cm) may be evident at birth, penile length is within normal range at birth and in early childhood, but over time it falls near or below -2SDs compared to healthy subjects [60–62]. Smaller penile size associated with a large suprapubic fat may lead to difficult urinating while standing in young obese males.

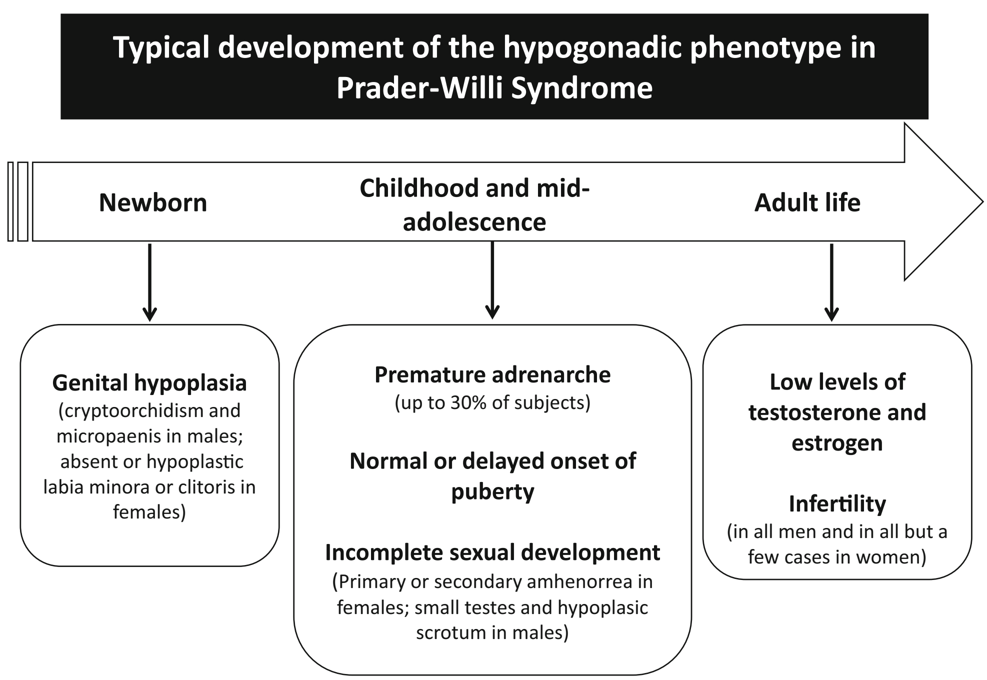

Fig. 3 Diagnosis, monitoring and treatment of hypothyroidism and adrenal insufficiency in PWS

In most PW males mini-puberty of infancy occurs normally, with a transient increase in gonadotropins and testosterone levels during the first few months of life [60]. At the onset of puberty, testosterone increases in comparison with pre-pubertal levels, but remain low. LH and FSH levels may vary according to the relative contribution of central and gonadal dysfunction. In males PW patients, primary gonadal dysfunction is common, while severe gonadotropin deficiency is rare. As a consequence, in most subjects LH levels remain within the normal range, while FSH increases and remains normal to high [57, 61]. Levels of Inhibin B (INB), a marker of spermatogenesis and Sertoli cell function, may be normal in infant boys, but are below the normal range in almost all PW adolescent and adult males [57, 63, 64]. Most studies report a normal age of onset of puberty in males, but early or delayed puberty may occur as well. Anyway, PW patients experience an incomplete pubertal development and testicular size remain small in adulthood [53, 57, 61, 64]. PWS males are generally infertile and no cases of paternity have been reported in the literature [51, 65].

5.2 Female PW subjects

The pattern of gonadal dysfunction in PW females is similar to that seen in males, that is a combination of various degree of primary gonadal defect and hypothalamic dysfunction, but it is usually less severe [53, 54, 63, 65]. Hypoplasia of the external genitalia is often evident at birth, with labia minora and clitoral hypoplasia seen in up to 76% of newbors [58]. Minipuberty is normal in infant girls and the onset of puberty typically occurs at a normal age [54, 55, 66]. However, pubertal progression is usually delayed and development impaired [54, 55, 67]. Most females with PWS have primary amenorrhea. However, up to 25% of PW girls undergo spontaneous menarche, which usually occurs late at an average age of 20 years; almost all subjects who progress to menarche have subsequent oligomenorrhea and secondary amenorrhea [54, 63]. After pubertal onset, serum estradiol levels are often in the normal early follicular range or low and LH levels are usually low or low-normal, while FSH levels may vary from low to normal to high, according to the different degrees of either primary or secondary gonadal failure [53, 63, 65]. INB, a measure of gonadal function, is reported to be low in most adult females with PWS, while the anti-müllerian hormone (AMH) is usually within normal values. Studies indicate INB levels>20 pg/mL correlate with the potential for fertility in PW females, though these levels are still frankly low in respect to healthy subjects [64, 67]. For this reason, INB is considered the most reliable marker of gonadal function and potential for fertility in female PW [65]. Indeed, despite maturation of follicles is impaired, maybe due to dysregulation of LH secretion, ovulation and thus conception cannot be ruled out in female adolescents with PWS [53, 65]. Pregnancies have been reported [68, 69] the most reliable marker of gonadal function and probably of fertility potential.

5.3 Premature adrenarche

There is a high prevalence, up to 30%, of premature adrenarche in both males and females with PWS. It is commonly associated with pubic or axillar hair, but it is typically not progressive and not associated with other signs of central puberty. Increased growth velocity and advanced bone age have been reported in some cases, although presence of obesity may also contribute to skeletal advancement [50, 70]. Premature adrenarche is generally thought to be benign, and further investigation or treatment is not usually warranted. Nevertheless, careful clinical assessment is necessary to exclude/demonstrate further testicular enlargement as a first sign of puberty in males (testicular volume greater than 4 ml using a Prader orchidometer) and breast development Tanner stage II as the first sign of puberty in females with PWS [50, 51].

The laboratory diagnosis of hypo gonadotropic hypogonadism in PW patients relay on the identification of very low circulating total testosterone or estrogens levels, associated with variable gonadotrophins (low to normal to high) and low to low-normal and inhibin B levels. Hormone profile assessment is recommended in each patient before considering sex hormone replacement therapy, mainly in females.

Even though the beneficial effects of hormone replacement on bone density and muscle mass, body image and quality of life are well known [71–73], no consensus statement exists as to the most appropriate regimen of sex hormone treatment in PW patients. Androgen replacement should be always considered in hypogonadal PW males, mostly in boys in mid-adolescence [50, 51]. The choice of the hormone replacement therapy protocol aimed at virilising the patient will depend on age at diagnosis and local practices. [50, 51, 73]. However, there is agreement that dosing and timing should reflect the normal process of puberty. Usually, replacement with testosterone is recommended in PW males if pubertal progression is delayed or stalls, by age 14–16 years [64, 65]. In general practice, injectable testosterone enantathe is preferred for reasons of convenience and cost. It should be started as low as 25% of the recommended normal adult dose, that is at t a dose of 50–100 mg given every 28 days, with gradual increase towards typical adult male doses (200–250 mg), to keep low-normal serum testosterone levels [65, 73]. Once males are at adult doses, other forms of testosterone administration can be considered including testosterone patches or gel, although these forms require daily administration, raising problems of adherence. Caution must be taken in individuals with skin picking behavior. Careful monitoring of growth and skeletal maturation is needed to avoid unfavorable effects of final height. Also, potential increase of aggressiveness may occur under testosterone treatment, even if it has not been clearly demonstrated [50].

Hormone replacement in PW women should be individually tailored depending on sexual development, hormonal profiles, bone density and individual needs. In girls with delayed or incomplete puberty, if no breast development occur by age of 13 years or no menarche by age 16 years, oral oestrogens at graduated doses should started for initiation or continuation of stalled puberty. Oral oestrogen in combinations with progestin should be used after the first menstrual bleed has occurred. Counselling about the risk of pregnancy and contraception (contraceptive pills) should be considered in those women who may have the potential for fertility (normal INB levels at serial measurements) [50, 51] (Table 1).

6 Growth hormone deficiency

Growth hormone deficiency (GHD) is the most frequent and studied endocrinopathy in PWS with a prevalence ranging from 40 to 100% [12, 32, 74].

In PWS GH 24-h secretion is decreased along with a reduction of IGF-I production and a lower response of GH to stimulation tests [32, 75]. Some factors influence GH secretion in these patients [76, 77]:

- age: there is a progressive decline of GH secretion with age;
- body mass index (BMI): PW obese patients have lower GH levels;
- genetics: GH response to test is lower in patients with maternal uniparental disomy for chromosome 15 (UPD15) than in patients with paternal deletion of 15q11-q13 (del15).

In consequence of such altered GH/IGF-I secretory patterns which indicates the presence of GHD in PW paediatric patients, current guidelines suggest that GH testing is not required before starting GH therapy in children with PWS [34, 78]. On the other hand, several studies indicate that GHD is not present in all adult PW patients, therefore performing dynamic tests after the attainment of final height may be beneficial in adult [78].

Moreover, some pituitary morphological abnormalities were found in 63–74% of patients with PWS despite there is no correlation with hypopituitarism [8, 79].

Short status is typical of PWS [80] and this is one of the clinical features due to GHD together with growth deceleration, reduced pubertal spurt, increased body fat, decreased lean body mass, reduced muscle strength, impaired bone mineral density and psychological impairment [12, 51, 80].

GH treatment in children with PWS has the aim to achieve a final height within normal range and to compensate for metabolic disorders caused by GHD [81]. Metabolic benefits of GH treatment support the continuation of therapy also during transitional age and adult age and in adult PW patients previously untreated [82]. In fact, in adult patients who discontinued GH therapy were observed an increase in visceral adipose tissue and decrease of muscle mass and an alteration of IGF-I status and lipid profile [83–86].

It is recommended to start therapy as soon as possible just the diagnosis of PWS is made (often around 3–6 month of age) [82, 87], before the onset of obesity and in order to obtain better improvements in motor and cognitive developments [81, 88].

Starting GH dose recommended by guidelines for PW children is 0.5 mg/m^2/day gradually increased to 1 mg/m^2/day based on IGF-I levels in order to avoid side effects [87]. In adult the initial dose is 0.1–0.2 mg/day [34]

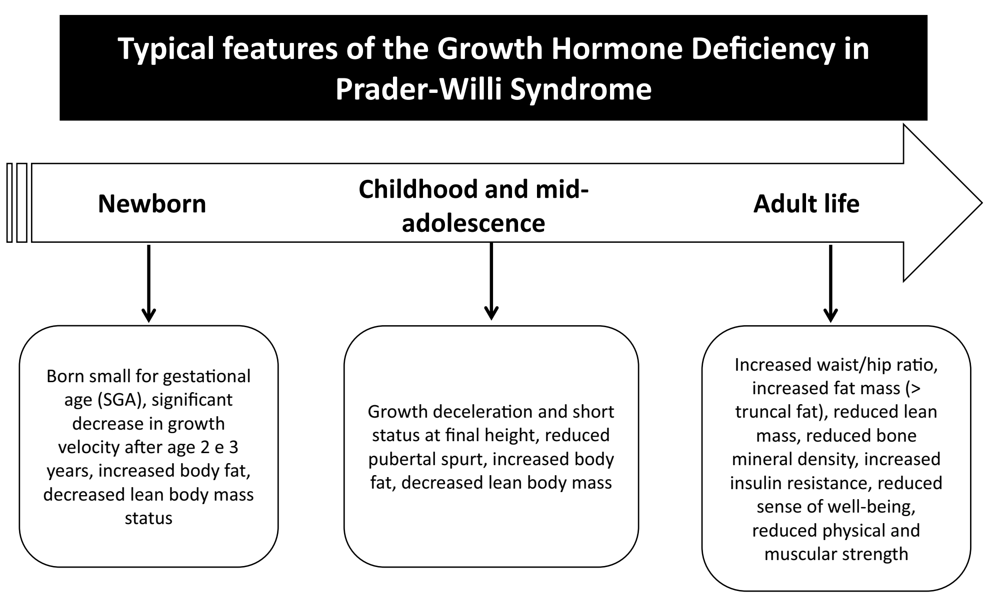

Fig. 4 Diagnosis, treatment and monitoring of Growth Hormone Deficiency (GHD) in PWS

which may be gradually increased maintaining IGF-I levels within the upper half of the reference range [89].

In children GH treatment has beneficial effects on final height, body composition, increasing lean mass and reducing fat mass, adaptive communication, cognitive skills, language [84, 88–90] motor development, energy expenditure, BMD and cardiovascular health [88, 91, 92]. There is also an improvement in ventilation and breathing pattern which may reduce the risk of sleep apnoea [81]. Positive effects on body composition, energy expenditure, BMD, hearth and respiratory functions are observed in adulthood too [51, 82, 93]. In these patients there is also an improvement in quality of life and behavioural and psychologic functioning [87].

GH treatment seems to be generally safe and well tolerate [51]. Although GH treatment could result in an increase in fasting plasma glucose and insulin resistance, usually it does not increase the onset of diabetes which seems to be most influenced by obesity [85, 87, 89]. Moreover, because of reports of unexpected mortality in PW patients during GH treatment, it is recommended to monitor breathing problems and sleep apnoea [94]. Other potential side effects include joint pain, oedema, scoliosis and intracranial hypertension [51]. So, it is recommended to perform polysomnography before starting treatment and periodically after, monitoring glucose profile and IGF-I levels, and monitoring development and/or progression of scoliosis during growth [51, 81].

Regarding exclusion criteria for GH therapy in PWS, the presence of severe obesity, untreated severe sleep apnoea, active cancer, active psychosis and uncontrolled diabetes contraindicates GH treatment [93]. However, long-term surveillance of benefits and risk of GH treatment in PWS at any age is required because of the lack of data (Fig. 4; Table 1).

7 Conclusions

PWS genetic disorder characterized by dysfunction of the hypothalamic -pituitary axis. Endocrine disorders such as hypogonadism, growth hormone [GH]/insulin-like growth factor I axis dysfunction, hypothyroidism and central adrenal insufficiency are common findings and are often untreated. Further research is needed on frequency and management of these endocrine diseases in PWS in order to lead to a significant improvement in health and developmental outcomes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Kanaka-Gantenbein C, Kogia C, Abdel-Naser MB, Chrousos GP. Skin manifestations of growth hormone-induced diseases. Rev Endocr Metab Disord. 2016;17(3):259–67.
2. Crinò A, Fintini D, Bocchini S, Grugni G. Obesity management in Prader-Willi syndrome: current perspectives. Diabetes Metab Syndr Obes. 2018;11:579–93. https://doi.org/10.2147/DMSO.S141352 eCollection 2018.
3. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genet Med. 2012;14(1):10–26. https://doi.org/10.1038/gim.0b013e31822bead0.
4. Butler MG. Prader-Willi syndrome: obesity due to genomic imprinting. Curr Genomics. 2011;12:204–15.
5. Fitch A. Effective dietary therapies for pediatric obesity treatment. Rev Endocr Metab Disord. 2009;10(3):231–6.
6. Butler JV, Whittington JE, Holland AJ, Boer H, Clarke D, Webb T. Prevalence of, and risk factors for, physical ill-health in people with Prader-Willi syndrome: a population-based study. Dev Med Child Neurol. 2002;44(4):248–55.
7. Lind van Wijngaarden RF, Otten BJ, Festen DA, Joosten KF, de Jong FH, Sweep FC, et al. High prevalence of central adrenal insufficiency in patients with PraderWilli syndrome. J Clin Endocrinol Metab. 2008;93:1649–54.
8. Tauber M, Barbeau C, Jouret B, Pienkowski C, Malzac P, Moncla A, et al. Auxological and endocrine evolution of 28 children with Prader-Willi syndrome: effect of GH therapy in 14 children. Horm Res. 2000;53(6):279–87.
9. Angulo MA, Castro-Magana M, Lamerson M, Arguello R, Accacha S, Khan A. Final adult height in children with Prader-Willi syndrome with and without human growth hormone treatment. Am J Med Genet A. 2007;143A(13):1456–61.
10. Zhang Y, Wang J, Zhang G, et al. The neurobiological drive for overeating implicated in Prader–Willi syndrome. Brain Res. 2015;1620:72–80.
11. Butler MG, Theodoro MF, Bittel DC, Donnelly JE. Energy expenditure and physical activity in Prader–Willi syndrome: comparison with obese subjects. Am J Med Genet A. 2007;143A:449–59.
12. Burman P, Ritzen EM, Lindgren AC. Endocrine dysfunction in Prader–Willi syndrome: a review with special reference to GH. Endocr Rev. 2001;22:787–799.2.
13. Dimitropoulos A, Schultz RT. Food-related neural circuitry in Prader- Willi syndrome: response to high- versus low-calorie foods. J Autism Dev Disord. 2008;38(9):1642–53.
14. Pujol J, Blanco-Hinojo L, Esteba-Castillo S, Caixàs A, Harrison BJ, Bueno M, et al. Anomalous basal ganglia connectivity and obsessive-compulsive behaviour in patients with Prader-Willi syndrome. J Psychiatry Neurosci. 2016;41(4):261–71.
15. Miller JL, Lynn CH, Driscoll DC, Goldstone AP, Gold JA, Kimonis V, et al. Nutritional phases in Prader Willi syndrome. Am J Med Genet A. 2011;155(5):1040–9.
16. Goldstone AP, Holland AJ, Butler JV, Whittington JE. Appetite hormones and the transition to hyperphagia in children with Prader-Willi syndrome. Int J Obes. 2012;36(12):1564–70.
17. Butler MG, Moore J, Morawiecki A, Nicolson M. Comparison of leptin protein levels in Prader-Willi syndrome and control individuals. Am J Med Genet. 1998;75(1):7–12.
18. Lim CT, Kola B, Korbonits M. The ghrelin/GOAT/GHS-R system and energy metabolism. Rev Endocr Metab Disord. 2011;12(3):173–86.
19. Wren AM, Seal LJ, Cohen MA, Brynes AE, Frost GS, Murphy KG, et al. Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab. 2001;86(12):5992.

20. Irizarry KA, Miller M, Freemark M, Haqq AM. Prader Willi syndrome: genetics, metabolomics, hormonal function, and new approaches to therapy. Adv Pediatr. 2016;63:47–77.
21. Bekx MT, Carrel AL, Shriver TC, Li Z, Allen DB. Decreased energy expenditure is caused by abnormal body composition in infants with Prader-Willi syndrome. J Pediatr. 2003;143(3):372–6.
22. Purtell L, Viardot A, Sze L, Loughnan G, Steinbeck K, Sainsbury A, et al. Postprandial metabolism in adults with Prader-Willi syndrome. Obesity (Silver Spring). 2015;23(6):1159–65.
23. Brambilla P, Crinò A, Bedogni G, Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology (ISPED), et al. Metabolic syndrome in children with Prader-Willi syndrome: the effect of obesity. Nutr Metab Cardiovasc Dis. 2011;21(4):269–76.
24. Goldstone AP, Thomas EL, Brynes AE, et al. Visceral adipose tissue and metabolic complications of obesity are reduced in Prader-Willi syndrome female adults: evidence for novel influences on body fat distribution. J Clin Endocrinol Metab. 2001;86(9):4330–8.
25. Schuster DP, Osei K, Zipf WB. Characterization of alterations in glucose and insulin metabolism in Prader-Willi subjects. Metabolism. 1996;45(12):1514–20.
26. Talebizadeh Z, Butler MG. Insulin resistance and obesity-related factors in Prader-Willi syndrome: comparison with obese subjects. Clin Genet. 2004;67(3):230–9.
27. Fintini D, Grugni G, Brufani C, Bocchini S, Cappa M, Crino A. Use of GLP-1 receptor agonists in Prader-Willi syndrome: report of six cases. Diabetes Care. 2014;37:e76–7.
28. Berthoud HR, Powley TL. Morphology and distribution of efferent vagal innervation of rat pancreas as revealed with anterograde transport of Dil. Brain Res. 1991;553:336–41.
29. Fitch A, Bock J. Effective dietary therapies for pediatric obesity treatment. Rev Endocr Metab Disord. 2009;10(3):231–6.
30. Sze L, Purtell L, Jenkins A, Loughnan G, Smith E, Herzog H, et al. Effects of a single dose of exenatide on appetite, gut hormones, and glucose homeostasis in adults with Prader-Willi syndrome. J Clin Endocrionl Metab. 2011;96:E1314–9.
31. Butler MG, Theodoro M, Skouse JD. Thyroid Function Studies in Prader–Willi Syndrome. Am J Med Genet A. 2007;143A:488–92.
32. Sharkia M, Michaud S, Berthier MT. Thyroid function from birth to adolescence in Prader-Willi syndrome. J Pediatr. 2013;163:800–5.
33. Diene G, Mimoun E, Feigerlova E, Caula S, Molinas C, Grandjean H. Endocrine disorders in children with Prader-Willi syndrome – data from 142 children of the French database. Horm Res Paediatr. 2010;74:121–8.
34. Vaiani E, Herzovich V, Chaler E, Chertkoff L, Rivarola M, Torrado M, et al. Thyroid axis dysfunction in patients with Prader-Willi syndrome during the first 2 years of life. Clin Endocrinol. 2010;73:546–50.
35. Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M. Recommendations for the diagnosis and management of Prader-Willi Syndrome. J Clin Endocrinol Metab. 2008;93(11):4183–97.
36. Festen D, Visser T, Otten B, Wit J. Thyroid hormone levels in children with Prader–Willi syndrome before and during growth hormone treatment. Clin Endocrinol. 2007;67:449–56.
37. Bocchini S, Fintini D, Grugni G, Boiani A, Convertino A, Crinò A. Congenital hypothyroidism due to ectopic sublingual thyroid gland in Prader-Willi syndrome: a case report. Ital J Pediatr. 2017;43:87.
38. Sher C, Bistritzer T, Reisler G, Reish O. Congenital hypothyroidism with Prader-Willi syndrome. J Pediatr Endocrinol Metab. 2002;15:105–7.
39. Insoft RM, Hurvitz J, Estrella E, Krishnamoorthy KS. Prader-Willi syndrome associated with fetal goiter: a case report. Am J Perinatol. 1999;16:29–31 14.
40. Whittington JE, Holland AJ, Webb T, Butler J, Clarke D, Boer H. Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region. J Med Genet. 2001;38:792–8.
41. Stevenson DA, Anaya TM, Clayton-Smith J, Hall BD, van Allen MI, Zori RT, et al. Unexpected death and critical illness in Prader-Willi syndrome: Report of ten individuals. Am J Med Genet A. 2004;124:158–64.
42. Corrias A, Grugni G. Assessment of central adrenal insufficiency in children and adolescents with Prader-Willi syndrome. Clin Endocrinol. 2012;76:843–50.
43. Grugni G, Beccaria L, Corias A, Crino A, Cappa M, de Medici C, et al. Central adrenal insufficiency in young adults with Prader-Willi syndrome. Clin Endocrinol. 2013;79:371–8.
44. Beauloye V, Dhondt K, Buysse W, Nyakasane A. Evaluation of the hypothalamic-pituitaryadrenal axis and its relationship with central respiratory dysfunction in children with Prader-Willi syndrome. Orphanet J Rare Diss. 2015;10:106.
45. Connell, Paterson WF, Wallace AM, Donaldson MDC. Adrenal function and mortality in children and adolescents with Prader–Willi syndrome attending a single centre from 1991–2009. Clin Endocrinol. 2010;73:686–8.
46. Nyunt O, Cotterill AM, Archbold SM, Wu JY, Leong GM, Verge CF, et al. Normal cortisol response on low-dose synacthen (1 microg) test in children with Prader Willi syndrome. J Clin Endocrinol Metab. 2010;95:E464–7.
47. Farholt S, Sode-Carlsen R, Christiansen JS, Ostergaard JR, Hoybye C. Normal cortisol response to high dose synacthen and insulin tolerance test in children and adults with Prader-Willi syndrome. J Clin Endocrinol Metab. 2011;96:E173–80.
48. de Lind van Wijngaarden RFA, Joosten KFM, van den Berg S, Otten BJ. The relationship between central adrenal insufficiency and sleep-related breathing disorders in children with Prader-Willi syndrome. J Clin Endocrinol Metabol. 2009;94(7):2387–93.
49. Barbara DW, Hannon JD, Hartman WR. Intraoperative adrenal insufficiency in patients with Prader-Willi syndrome. J Clin Endocrinol Metab. 2008;93:1649–54.
50. Angulo MA, Butler MG, Cataletto ME. Prader Willi syndrome: a review of clinical, genetic, and endocrine findings. J Endocrinol Investig. 2015;38:1249–63. https://doi.org/10.1007/s40618-015-0312-9.
51. Heksch R, Kamboj M, Anglin K, Obrynba K. Review of Prader-Willi syndrome: the endocrine approach. Transl Pediatr. 2017;6(4):274–85. https://doi.org/10.21037/tp.2017.09.04.
52. Vogels A, Moerman P, Frijns JP, Bogaert GA. Testicular histology in boys with Prader-Willi syndrome: fertile or infertile? J Urol. 2008;180(1800–1804):113.
53. Siemensma EP, de Lind van Wijngaarden RF, Otten BJ, de Jong FH, Hokken-Koelega AC. Testicular failure in boys with Prader-Willi syndrome: longitudinal studies of reproductive hormones. J Clin Endocrinol Metab. 2012;97:E452–9 114.
54. Eldar-Geva T, Hirsch HJ, Rabinowitz R, Benarroch F, Rubinstein O, Gross-Tsur V. Primary ovarian dysfunction contributes to the hypogonadism in women with Prader-Willi syndrome. Horm Res. 2009;72(3):153–9 120.
55. Eldar-Geva T, Hirsch HJ, Benarroch F, Rubinstein O, GrossTsur V. Hypogonadism in females with Prader-Willi syndrome from infancy to adulthood: variable combinations of a primary gonadal defect and hypothalamic dysfunction. Eur J Endocrinol. 2010;162(2):377–84 121.
56. Radicioni AF, Di Giorgio G, Grugni G, Cuttini M, Losacco V, Anzuini A, et al. Multiple forms of hypogonadism of central,

peripheral or combined origin in males with Prader-Willi syndrome. Clin Endocrinol (Oxf). 2012;76:72–7 115.
57. Eiholzer U, l'Allemand D, Rousson V, Schlumpf M, Gasser T, Girard J, et al. Hypothalamic and gonadal components of hypogonadism in boys with Prader-Labhart-Willi syndrome. J Clin Endocrinol Metab. 2006;91:892–8.
58. Crinò A, Schiaffini R, Ciampalini P, Spera S, Beccaria L, Benzi F, et al. Genetic obesity study Group of Italian Society of pediatric endocrinology and diabetology (SIEDP). Hypogonadism and pubertal development in Prader-Willi syndrome. Eur J Pediatr. 2003;162(5):327–33.
59. Bakker NE, Wolffenbuttel KP, Looijenga LH, Hokken-Koelega AC. Testes in infants with Prader-Willi syndrome: human chorionic gonadotropin treatment, surgery and histology. J Urol. 2015;193(1):291–8.
60. Fillion M, Deal CL, Van Vliet G. Normal minipuberty of infancy in boys with Prader-Willi syndrome. J Pediatr. 2006;149(874–876):117.
61. Hirsch HJ, Eldar-Geva T, Benarroch F, Rubinstein O, Gross-Tsur V. Primary testicular dysfunction is a major contributor to abnormal pubertal development in males with Prader-Willi syndrome. J Clin Endocrinol Metab. 2009;94(7):2262–8.
62. Hirsch HJ, Eldar-Geva T, Erlichman M, Pollak Y, Gross-Tsur V. Characterization of minipuberty in infants with PraderWilli syndrome. Horm Res Paediatr. 2014;82(230–237):118.
63. Brandau DT, Theodoro M, Garg U, Butler MG. Follicle stimulating and leutinizing hormones, estradiol and testosterone in Prader-Willi syndrome. Am J Med Genet A. 2008;146A(5):665–9.
64. Hirsch HJ, Eldar-Geva T, Bennaroch F, Pollak Y, Gross-Tsur V. Sexual dichotomy of gonadal function in Prader-Willi syndrome from early infancy through the fourth decade. Hum Reprod. 2015;30(11):2587–96.
65. Gross-Tsur V, Hirsch HJ, Benarroch F, et al. The FSH-inhibin axis in Prader-Willi syndrome: heterogeneity of gonadal dysfunction. Reprod Biol Endocrinol. 2012;10:39. https://doi.org/10.1186/1477-7827-10-39.
66. Hirsch HJ, Eldar-Geva T, Erlichman M, Pollak Y, Gross-Tsur V. Characterization of minipuberty in infants with Prader Willi syndrome. Horm Res Paediatr. 2014;82(230–237):118.
67. Eldar-Geva T, Hirsch HJ, Pollak Y, Benarroch F, Gross-Tsur V. Management of hypogonadism in adolescent girls and adult women with Prader-Willi syndrome. Am J Med Genet A. 2013;161A:3030–4.
68. Akefeldt A, Tornhage CJ, Gillberg C. A woman with Prader-Willi syndrome gives birth to a healthy baby girl. Dev Med Child Neurol. 1999;41(789–790):122.
69. Schulze A, Mogensen H, Hamborg-Petersen B, Graem N, Ostergaard JR, Brondum-Nielsen K. Fertility in PraderWilli syndrome: a case report with Angelman syndrome in the offspring. Acta Paediatr. 2001;90(455–459):123.
70. Schmidt H, Schwarz PS. Premature adrenarche, increased growth velocity and accelerated bone age in male patients with Prader-Labhart-Willi syndrome. Eur J Pediatr. 2001;160(69–70):124.
71. Butler MG, Haber L, Mernaugh R, Carlson MG, Price R, Feurer ID. Decreased bone mineral density in PraderWilli syndrome: comparison with obese subjects. Am J Med Genet. 2001;103(216–222):127.
72. Vestergaard P, Kristensen K, Bruun JM, Østergaard JR, Heickendorff L, Mosekilde L, et al. Reduced bone mineral density and increased bone turnover in Prader-Willi syndrome compared with controls matched for sex and body mass index—a cross-sectional study. J Pediatr. 2004;144(5):614–9 128.
73. Young J. Approach to the male patient with congenital hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2012;97:707–18.
74. Bridges N. What is the value of growth hormone therapy in Prader Willi syndrome? Arch Dis Child. 2014;99:166–70.
75. Petriczko E, Horodnicka-Józwa A, Szmit-Domagalska J, et al. Aspekty endokrynne zespołu Pradera i Williego u dzieci i młodzieży. Pediatr Pol. 2008;83(5):522–8.
76. Cohen M, Harrington J, Narang I, Hamilton J. Growth hormone secretion decreases with age in paediatric Prader-Willi syndrome. Clin Endocrinol. 2015;83:212–5.
77. Di Giorgio G, Grugni G, Fintini D, et al. Growth hormone response to standard provocative stimuli and combined tests in very young children with Prader-Willi syndrome. Horm Res Paediatr. 2014;81:189–95.
78. Deal CL, Tony M, Hoybye C, et al. Growth hormone in Prader Willi syndrome clinical care guidelines workshop participants. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in PraderWilli syndrome. J Clin Endocrinol Metab 2013. 2013;98:E1072–e87.
79. Miller JL, Goldstone AP, Couch JA, Shuster J, He G, Driscoll DJ, et al. Pituitary abnormalities in Prader-Willi syndrome and early onset morbid obesity. Am J Med Genet A. 2008;146A:570–7.
80. Cassidy SB, Schwartz S, Miller JL, et al. Prader Willi syndrome. Genet Med. 2012;14:10e26.
81. Góralska M, Bednarczuk T, Rosłon M, Libura M, Szalecki M, Hilczer M, et al. Management of Prader-Willi Syndrome (PWS) in adults - what an endocrinologist needs to know. Recommendations of the Polish Society of Endocrinology and the Polish Society of Paediatric Endocrinology and Diabetology. Endokrynol Pol. 2018;69.
82. Grugni G, Marzullo P. Diagnosis and treatment of GH deficiency in Prader-Willi syndrome. Best Pract Res Clin Endocrinol Metab. 2016;30(6):785–94.
83. Lafortuna CL, Minocci A, Capodaglio P, et al. Growth hormone therapy improves exercise capacity in adult patients with Prader-Willi syndrome. J Endocrinol Investig. 2008;31(9):765–72.
84. Siemensma EP, de Lind van Wijngaarden RF, Festen DA, et al. Beneficial effects of growth hormone treatment on cognition in children with Prader-Willi syndrome: a randomized controlled trial and longitudinal study. J Clin Endocrinol Metab. 2012;97:2307–14.
85. Höybye C, Thorén M, Böhm B. Cognitive, emotional, physical and social effects of growth hormone treatment in adults with Prader-Willi syndrome. J Intellect Disabil Res. 2005;49(Pt 4):245–52.
86. Sode-Carlsen R, Farholt S, Rabben KF, et al. One year of growth hormone treatment in adults with Prader-Willi syndrome improves body composition: results from a randomized, placebo-controlled study. J Clin Endocrinol Metab. 2010;95(11):4943–50.
87. Deal CL, Tony M, Höybye C, Allen DB, Tauber M, Christiansen JS, et al. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab. 2013;98:E1072–87.
88. Festen DA, de Lind van Wijngaarden R, van Eekelen M, et al. Randomized controlled GH trial: effects on anthropometry, body composition and body proportions in a large group of children with Prader-Willi syndrome. Clin Endocrinol (Oxf). 2008;69:443–5.
89. Bakker NE, Kuppens RJ, Siemensma EP, Wijngaarden RF, Festen DA, Bindels-de Heus GC, et al. Eight years of growth hormone treatment in children with Prader-Willi syndrome: maintaining the positive effects. J Clin Endocrinol Metab. 2013;98:4013–22.
90. Colmenares A, Pinto G, Taupin P, Giuseppe A, Odent T, Trivin C, et al. Effects on growth and metabolism of growth hormone

treatment for 3 years in 36 children with Prader-Willi syndrome. Horm Res Paediatr. 2011;75:123–30.
91. Myers SE, Whitman BY, Carrel AL, Moerchen V, Bekx MT, Allen DB. Two years of growth hormone therapy in young children with Prader-Willi syndrome: physical and neurodevelopmental benefits. Am J Med Genet A. 2007;143A:443–8.
92. Carrel AL, Myers SE, Whitman BY, Allen DB. Benefits of long-term GH therapy in Prader-Willi syndrome: a 4-year study. J Clin Endocrinol Metab. 2002;87:1581–5.
93. Passone CBG, Pasqualucci PL, Franco RR, Ito SS, Mattar LBF, Koiffmann CP, et al. Prader-Willi syndrome: what is the general pediatrician supposed to do? A review. Rev Paul Pediatr. 2018;36(3):345–52.
94. Van Vliet G, Deal CL, Crock PA, et al. Sudden death in growth hormone-treated children with Prader-Willi syndrome. J Pediatr. 2004;144:129–31.