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Spectrum of Hypogonadism and Its Management in Adolescents With Prader-Willi Syndrome: A Retrospective Cohort Study Over 35 Years

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ABSTRACT

Context: Adult data indicate that hypogonadism is underdiagnosed and undertreated in Prader-Willi Syndrome (PWS).

Objectives: We aimed to describe the spectrum of pubertal development, and the diagnosis and treatment of hypogonadism in paediatric/adolescent patients with PWS.

Design/Patients: A retrospective cohort study of patients with PWS aged 6–18 years seen at an Australian tertiary paediatric centre between 1 January 1990 and 31 May 2025 ($n = 65$).

Results: Spontaneous puberty onset was achieved in 63% females aged ≥ 8 years and 68% males aged ≥ 9 years with onset at a median age of 10.3 [8.9–12.5] years in females and 12.3 [11.9–14.3] years in males. By last visit, hypogonadism was diagnosed in 77% of females (95% central aetiology, 5% unknown) and 88% of males (73% central aetiology, 27% primary/mixed) at a median age of 14.1 [13.1–15.8] years in females and 15.3 [14.1–15.6] years in males. Pubertal hormone replacement therapy was initiated in 80% females and 60% males, with no significant change in proportion of patients with behavioural/psychiatric issues post treatment. Median femoral neck bone mineral density showed age-adjusted z-score of −1.5 [−2.2 to −0.8] and height-adjusted of −0.9 [−1.6 to 0.3].

Conclusions: Despite approximately two-thirds of adolescents with PWS entering puberty spontaneously, the majority demonstrated hypogonadism before transitioning to adult care, emphasising the need for ongoing pubertal assessment in this population. Aetiology is predominantly central hypogonadism, but there can also be a component of primary hypogonadism. Longitudinal controlled studies are required to determine optimal detection of hypogonadism and timing of pubertal hormone replacement in PWS.

1 | Introduction

Prader-Willi Syndrome (PWS) is a rare genetic disorder caused by the absence of paternally inherited, maternally imprinted genes at 15q11.2-q13, resulting in cognitive impairment, hyperphagic obesity and hypothalamic-pituitary impairment [1]. Hypogonadism is a common manifestation of the latter, with reported prevalence ranging from 50% to 100% in adults with PWS [2–5], presenting as incomplete or delayed pubertal development, genital hypoplasia and infertility [1, 6]. Despite this high prevalence, hypogonadism is reported to be underdiagnosed and undertreated in adults with PWS [2, 3]. While hypogonadism of PWS was historically conceptualised as entirely hypothalamic (central) in origin, it has emerged that primary hypogonadism also occurs in PWS [1–3, 7–10]. Mixed aetiology is also possible. In males with PWS, this has been

attributed to independent maturation of Leydig and Sertoli cells of the testes, while in females, an imprinting centre transcript only expressed in brain and ovarian tissue (as found in the mouse homologue of 15q11-13) may be implicated in combined aetiology hypogonadism with PWS [5, 11].

Osteoporosis or low bone mass is also observed in adults with PWS, largely attributed to hypogonadism [12–14]. Normal bone mineral density (BMD) in prepubertal children with PWS suggests that incomplete or delayed puberty interferes with acquisition of normal BMD by adulthood [15]. There is a paucity of research on pubertal hormone replacement therapy (HRT) and bone health in paediatric patients with PWS [15–18]. Furthermore, behavioural risks of pubertal HRT are commonly cited as clinical concerns for PWS care, but few published studies address this issue specifically [2, 3, 16].

Recent expert consensus statements endeavoured to outline treatment strategies for male and female hypogonadism in adults with PWS [2, 3]. However, there remains no evidence-based guidelines on the paediatric/adolescent population with PWS. In this 35-year retrospective cohort study at a tertiary paediatric hospital, we aimed to characterise pubertal development and hypogonadism (including treatment and outcomes) in PWS, as well as the impact of treatment on bone health and behavioural outcomes.

2 | Methods

Patients coded with a PWS diagnosis were identified using the electronic database of the Endocrinology Department at the Children's Hospital at Westmead. Patients were included if diagnosed with PWS, had ≥ 1 endocrine clinic visits at our hospital between 1/1/1990 and 31/05/2025, and aged 6–18 years inclusive between 1/1/1990 and 31/05/2025. The study was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee (2025/ETH00340).

Data were retrieved from the hospital medical records at two main timepoints for each patient: (1) at ages 12 (range 11.5–13) or 13.5 (13–14.5) years for females and males respectively, and (2) the last visit at which pubertal assessment was documented. Data retrieved included: Tanner staging (within 12 months of timepoint), serum pubertal hormone biochemistry (6 months prior to/12 months post-timepoint), BMD, fractures before last visit, history of pubertal HRT, behavioural/psychiatric issues and potential adverse events reported by parents/carers and/or recorded by clinician while on pubertal HRT. BMD regions measured via dual-energy X-ray absorptiometry (DXA, GE Lunar DPX) included lumbar vertebrae 2–4 (L2-4), right neck of femur (NoF) and total body (TB). Low BMD was defined as a z-score of ≤ -2.0 based on local age and height-based reference data [19].

Behavioural and psychiatric issues were categorised into the following groups: psychotic features (including paranoia and delusion), mood disturbance (including labile mood and volatile behaviour), aggression (including violent behaviour), defiance (including argumentative behaviour and refusal to comply) and temper tantrums or emotional outbursts. Skin-picking and hyperphagia were excluded as these have not been flagged as major concerns of HRT, especially when compared to aggressive behaviour [6]. Additionally, there is already a high prevalence of these behaviours in PWS at baseline (50%–60% and 90%–100% respectively) [1].

Pubertal onset was determined by documented clinician diagnosis or by clinical notes documenting signs of pubertal onset, whichever was dated earlier. In males, this was defined as (a) testicular volume ≥ 4 mL (b) Tanner genitalia stage 2 (G2) with progressive increase in testicular volumes ≥ 3 mL, (c) Tanner G3 or greater or (d) biochemistry consistent with pubertal onset; and in females, (a) Tanner breast stage 2 (B2), (b) documented clinical pubertal progression or (c) biochemistry consistent with pubertal onset. Diagnosis of hypogonadism was established by documentation by the treating clinician or initiation of pubertal HRT (whichever occurred earlier). Aetiology was classified according to documentation by the treating clinician in the medical records (central, primary, mixed). When the aetiology was documented in the medical records as 'partial hypogonadism', or not documented, the clinical and biochemical findings were independently reviewed by the authors to determine the classification. Delayed pubertal onset was defined as $>$ age 12 years in females and >13.5 years in males [20].

At the Children's Hospital at Westmead, LH and FSH were performed using immunochemistry assays. Oestradiol (E2) and testosterone were previously performed by radioimmunoassay (RIA) and analysed via mass spectrometry for testosterone since July 2015 and for E2 since April 2019. External laboratory samples were analysed via RIA. Clinical decisions were based on the laboratory reference ranges for each assay.

Data were analysed using IBM SPSS Statistics Version 25. Independent *t*-test was used to compare normally distributed data in independent groups, Mann-Whitney *U* test in non-normally distributed data. Change in prevalence of behavioural or psychiatric issues after pubertal HRT was analysed using the McNemar test. Association between categorical variables was assessed using the Chi-Square test, or when minimum expected count was <5, using Fisher's exact test. Normally distributed data was presented as mean and standard deviation (SD); non-normally distributed data as median and interquartile range (IQR). Statistical significance was defined as $p < 0.05$.

3 | Results

Of the total 91 patients seen at the hospital during the study period, 65 met the inclusion criteria. Clinical characteristics of the study cohort are outlined in Table 1. Exact age of pubertal onset could not be ascertained in 12% (3/26) of females aged ≥ 12 years and 12% (2/17) of males aged ≥ 13.5 years. This was either due to loss to follow-up or prolonged interval between clinic visits.

3.1 | Female Adolescents

Tanner stages for females at the two study timepoints are outlined in Table 2. At 12 years of age, 56% (10/18) remained prepubertal (Tanner B1) and none were on pubertal HRT. By last staging (median age 15.7 years), all had at least reached stage B2, with 50% (10/20) being on pubertal HRT; however, neither of the two patients recorded to have Tanner stage B5 had

TABLE 1 | Clinical characteristics and pubertal milestones in the PWS cohort between ages 6–18 years.

Background characteristics		Females ($n = 37$)	Males ($n = 28$)
Age at last visit (years)		15.4 [11.2–17.9]	16.4 [10.1–18.0]
Anthropometrics at last visit	Height SDS	−1.09 [−2.12 to −0.48]	−0.60 [−1.45 to 0.28]
	Weight SDS	0.81 ± 1.16	1.27 ± 1.10
	BMI SDS	1.38 [0.57–2.12]	1.71 [0.93–2.22]
Growth hormone treatment		31 (84%)	24 (86%)
Genetic subtype	Deletion	12 (32%)	9 (32%)
	ICD	2 (5%)	0
	mUPD	16 (43%)	15 (54%)
	Abnormal methylation studies	4 (11%)	2 (7%)
	No information	3 (8%)	2 (7%)
Pubertal milestones		**Females age ≥ 8 years ($n = 30$)**	**Males age ≥ 9 years ($n = 22$)**
Adrenarche		27 (73%)	22 (79%)
Age adrenarche (years)		9.5 ± 2.4	10.7 ± 2.8
Premature adrenarche		9 (24%)	3 (11%)
Precocious puberty		3 (8%)	0
Spontaneous puberty at any age		19 (63%)	15 (68%)
Age at spontaneous puberty (years)		10.3 [8.9–12.5]	12.3 [11.9–14.3]
Achieved B3/G3+		15 (50%)	14 (64%)
Age at B3/G3+ (years)		12.6 ± 2.4	14.0 ± 1.4
Aberrant pubertal progress		**Females age ≥ 12 years ($n = 26$)**	**Males age ≥ 13.5 years ($n = 17$)**
Delayed pubertal onset		2 (8%)	2 (12%)
No spontaneous puberty		7 (27%)	4 (24%)
Hypogonadism		20 (77%)	15 (88%)
Pubertal hormone replacement		16 (62%)	9 (53%)

Note: standard deviation score (SDS), imprinting centre defect (ICD), maternal uniparental disomy (mUPD), Tanner breast stage 3/Tanner genitalia stage 3 or higher (B3/G3+). Abnormal methylation indicates diagnosis by methylation study with no other information found.

TABLE 2 | Tanner staging in the PWS clinic cohort at two study timepoints.

Study timepoint			Tanner stage[a]						
Females	**Age (years)**	**Pubertal HRT**	**B1**	**B2**	**B2-3**	**B3**	**B3-4**	**B4**	**B5**
At age 12 years ($n = 18$)	12.3 [12.1–12.4]	No HRT ($n = 18$)	10 (56%)	1 (6%)	1 (6%)	3 (17%)	1 (6%)	0	2 (11%)
		On HRT ($n = 0$)	—	—	—	—	—	—	—
Last staging ($n = 20$)	15.7 [14.2–16.7]	No HRT ($n = 10$)	0	0	1 (10%)	1 (10%)	4 (40%)	2 (20%)	2 (20%)
		On HRT ($n = 10$)	0	3 (30%)	0	3 (30%)	1 (10%)	3 (30%)	0
Males			**G1**	**G2**	**G2-3**	**G3**	**G3-4**	**G4**	**G5**
At age 13.5 years ($n = 13$)	13.7 [13.6–13.9]	No HRT ($n = 12$)	3 (25%)	2 (17%)	1 (8%)	5 (42%)	0	1 (8%)	0
		On HRT ($n = 1$)	0	1 (100%)	0	0	0	0	0
Last staging ($n = 15$)	17.3 [16.1–18.0]	No HRT ($n = 8$)	0	1 (13%)	0	2 (25%)	4 (50%)	0	1 (13%)
		On HRT ($n = 7$)	1 (14%)	0	0	2 (29%)	2 (29%)	2 (29%)	0

Abbreviation: HRT, Hormone replacement therapy.
[a]Tanner breast stage for females; genitalia stage for males.

received oestrogen replacement. Tanner ≥ B4 was not attained by 70% (7/10) of females treated with pubertal HRT, nor by 60% (6/10) of those not on oestrogen therapy. There was no significant difference in the age at which Tanner B3 was achieved by PWS patients compared to the general Australian population ($p = 0.98$) (Table 1) [21].

Of the cohort of females aged ≥ 12 years old, 77% were diagnosed with hypogonadism (Table 1). Two patients were noted to have regression of breast development and pubertal arrest after entering puberty at a normal age ≤ 12 years. Of those who entered puberty spontaneously, 32% (6/19) achieved spontaneous menarche during the study period. None were found to maintain regular periods before commencing pubertal HRT, though two initially had regular menses before progressing to infrequent or irregular menses.

Basal pubertal hormone levels in female adolescents with PWS are demonstrated in Figure 1. At age 12 years, basal luteinising hormone (LH) or follicle-stimulating hormone (FSH) were undetectable in 35% (7/20), with E2 being undetectable or at prepubertal levels, defined as < 40pmol/L, in 40% (8/20). On final blood tests (median age 17.1 years), 25% (5/20) had either undetectable or detectable prepubertal E2 levels and all females with undetectable basal gonadotropins (7/20) were diagnosed with hypogonadism.

3.2 | Male Adolescents

Tanner stages for males at the two study time points are outlined in Table 2. In the group staged at age 13.5 years, 23% (3/13) had Tanner G1 and the one patient on pubertal HRT had G2. At last staging (median age 17.3 years), 93% (14/15) had reached or surpassed G2 and 47% (7/15) were on testosterone therapy. Only one patient (who had received testosterone) attained G5. Tanner ≥ G4 was not achieved by 71% (5/7) of males on testosterone therapy and 88% (7/8) of those without pubertal HRT. Compared to the general Australian population, there was no significant difference in the age at which Tanner G3 was attained by male PWS patients ($p = 0.15$) (Table 1) [21].

Of the cohort of males aged ≥ 13.5 years, 88% were diagnosed with hypogonadism (Table 1). At age 13.5 years ($n = 13$), median testicular volume was 3.0 [1.6–7.3] mL, although 41% (7/17) of males aged ≥ 13.5 years had achieved pubertal testicular volume of ≥ 4 mL before age 13.5 years. History of cryptorchidism and/or orchidopexy was documented in 75% (21/28) of males.

Basal pubertal hormone levels in male adolescents with PWS are outlined in Figure 2. At age 13.5 years, basal gonadotropins were detectable in all males, except for one who had undetectable LH and had been diagnosed with hypogonadism. Detectable prepubertal testosterone levels, defined as < 1.0 nmol/L, were present in two males. On final blood tests (median age 17.7 years), no males had prepubertal testosterone levels and all males with undetectable basal gonadotropins (3/15) had been diagnosed with hypogonadism.

3.3 | Hypogonadism and Treatment

By last clinic visit (median age 17.5 years in females, 18.0 years in males), 81% (35/43) of adolescents (of eligible cohort females ≥ 12 years and males ≥ 13.5 years old) were diagnosed with hypogonadism (Table 3). Comparing females and males, there were no significant differences in hypogonadism prevalence (77% vs. 88%; $p = 0.86$), age at diagnosis (14.1 vs. 15.3 years; $p = 0.32$), number of hypogonadal patients treated with pubertal

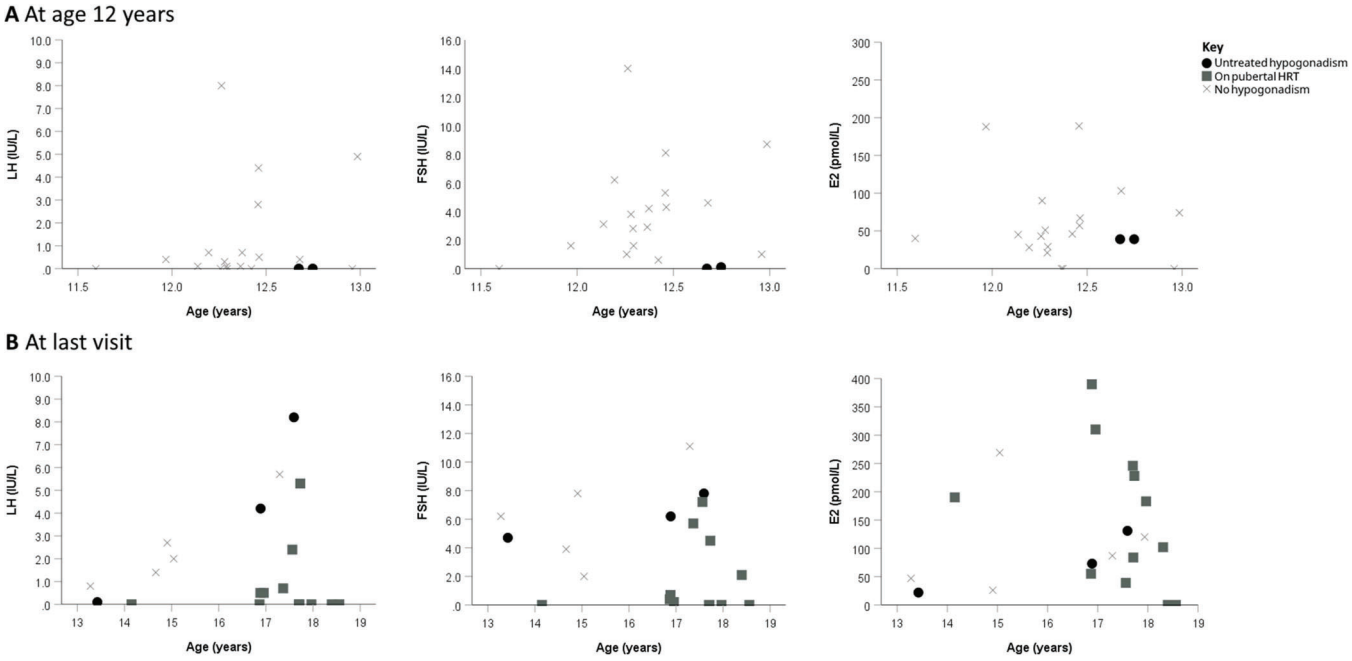

FIGURE 1 | Pubertal hormone levels in females with PWS. Undetectable hormone levels plotted as zero on y-axis. (A) Pubertal hormones at closest visit to age 12 years ($n = 20$, median age 12.4 [12.3–12.6] years). (B) Pubertal hormones on last blood test ($n = 20$, median age 17.1 [14.9–17.7] years). E2, oestradiol; FSH, follicle-stimulating hormone; LH, luteinising hormone; pubertal HRT, pubertal hormone replacement therapy.

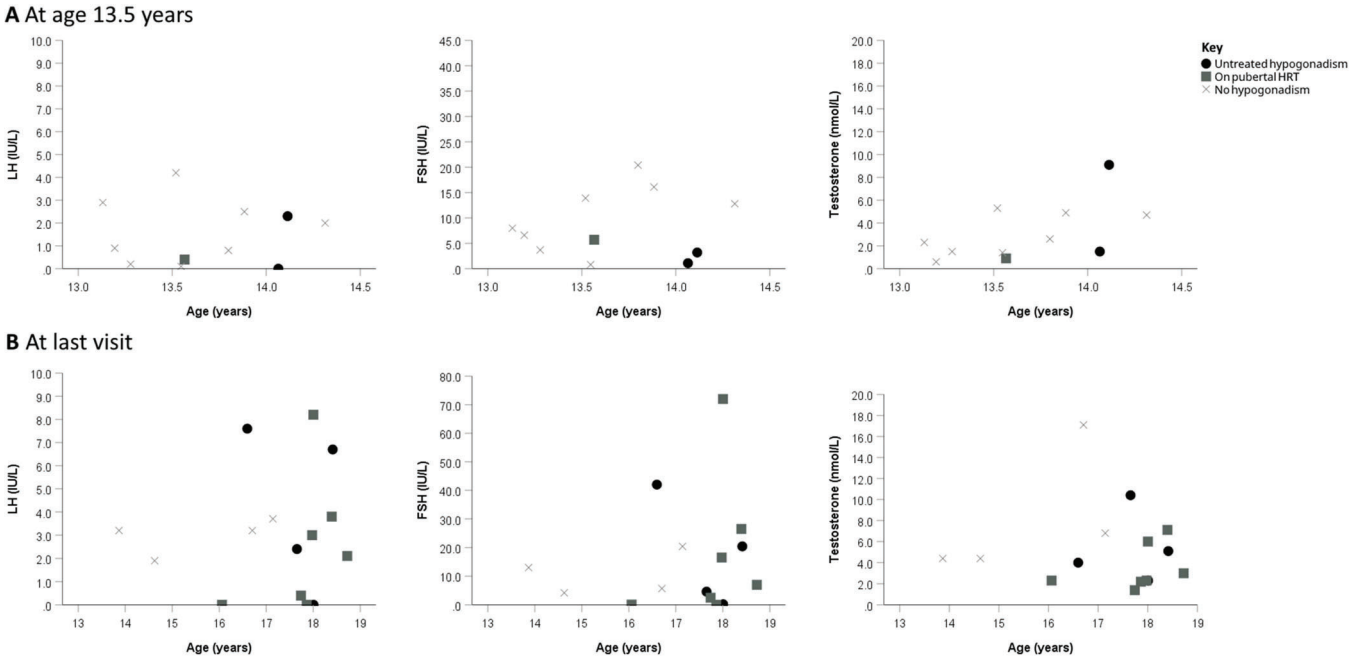

FIGURE 2 | Pubertal hormone levels in males with PWS. Undetectable hormone levels plotted as zero on y-axis. (A) Pubertal hormones at closest visit to age 13.5 years ($n = 11$, median age 13.6 [13.3–14.1] years). (B) Pubertal hormones on last blood test ($n = 15$, median age 17.7 [16.6–18.0] years). FSH, follicle-stimulating hormone; LH, luteinising hormone; pubertal HRT, pubertal hormone replacement therapy.

TABLE 3 | PWS patients diagnosed with hypogonadism.

		Female ($n = 20$)	Male ($n = 15$)
Age at hypogonadism diagnosis (years)		14.1 [13.1–15.8]	15.3 [14.1–15.6]
Aetiology	Central	19 (95%)	11 (73%)
	Primary	0	2 (13%)
	Mixed	0	2 (13%)
	Unknown	1 (5%)	0
Delayed onset of puberty		8 (40%)	6 (40%)
Received pubertal HRT		16 (80%)	9 (60%)
Age at starting pubertal HRT (years)		14.4 [13.2–16.5]	15.6 [14.6–16.9]
Months from diagnosis to pubertal HRT		0.0 [0.0–9.2]	0.0 [0.0–26.3]
Time on pubertal HRT until last visit (years)		1.9 [1.0–4.5]	1.7 [1.3–3.6]
Ceased pubertal HRT		2 (10%)	0

Abbreviation: HRT, Hormone replacement therapy.

HRT (80% vs. 60%; $p = 0.28$) and time to treatment in months (0.0 vs. 0.0; $p = 0.54$).

The oral route of administration was most prescribed both at initiation and last visit. At the last visit, oral route of pubertal HRT was used in 79% (11/14) females and 67% (6/9) males with PWS treated for hypogonadism, while transdermal HRT was used in 21% (3/14) females and 22% (2/9) males (Supporting Information S1: Table 1).

Among females treated for hypogonadism, 69% (11/16) were commenced on oestrogen-only replacement but by transition to adult care, 71% (10/14) on pubertal HRT at last visit had progressed to combined oestrogen-progestogen therapy. Treatment was ceased for two females; one due to mood disturbance, the other for undocumented reasons (Table 3). Another female patient originally stopped treatment due to adequate spontaneous pubertal development, but recommenced before last visit due to pubertal arrest off treatment. No males had pubertal HRT ceased during paediatric care within the study period.

Of those prescribed pubertal HRT during paediatric care, 25% (4/16) females and 55% (5/9) males had behavioural or psychiatric issues documented prior to pubertal HRT. After treatment, 31% (5/16) females and 55% (5/9) male patients were reported to have behavioural/psychiatric issues. Between pubertal HRT recipients and non-recipients, there was no significant difference in the proportion of patients with behavioural/psychiatric challenges reported during the overall study period in females aged ≥ 12 years (60% vs. 38%; $p = 0.42$) or males ≥ 13.5 years (100% vs. 89%; $p = 1.00$), nor when both groups were analysed together (78% vs. 56%; $p = 0.20$). There was also no significant change in proportion of patients with behavioural/psychiatric issues after HRT (36% vs. 40%; $p = 1.00$). Aggression was reported in one female patient on pubertal HRT after starting treatment. There were no significant differences in types of behavioural/psychiatric issues between males and females on pubertal HRT (Supporting Information S1: Table 2).

3.4 | Bone Mineral Density and Fractures

DXA was performed in 26 patients; all except two had a diagnosis of hypogonadism and all except one had a history of growth hormone (GH) treatment (Table 4). Low BMD for age was found at NoF, TB and L2-4 regions for 35%, 15% and 8%, respectively, and low BMD for height were found in 12%, 8%

TABLE 4 | BMD at last BMD study, stratified by treatment status for hypogonadism.

	All ($n = 26$)	Female ($n = 16$)	Male ($n = 10$)	*p*-value	Untreated ($n = 15$)	Treated[a] ($n = 11$)	*p*-value
Age	16.6 [14.7–17.6]	15.7 [14.3–17.4]	17.1 [16.4–17.8]	0.11	17.0 [14.8–17.9]	16.6 [14.2–17.5]	0.31
Bone age	16.5 [15.0–17.4]	15.3 [14.1–17.2]	16.9 [16.2–17.8]	0.06	16.6 [15.1–18.5]	15.6 [14.6–17.2]	0.27
Height SDS	−0.9 [−1.7 to −0.1]	−0.9 [−2.2 to −0.4]	−0.4 [−0.9 to 0.1]	0.06	−0.9 [−1.5 to −0.4]	−0.5 [−2.1–0.3]	0.44
BMD age z-score							
NoF	−1.5 [−2.2 to −0.8]	−1.2 [−2.2 to −0.6]	−1.9 [−2.3 to −1.0]	0.36	−1.4 [−2.2 to −1.0]	−1.5 [−2.5 to −0.7]	0.86
L2-4	−0.2 [−1.5 to 0.8]	−1.1 [−1.5 to 0.3]	0.0 [−0.9 to 1.3]	0.45	−0.1 [−1.1 to 0.8]	−1.4 [−1.6 to 1.0]	0.06
TB	−0.8 [−1.7 to 0.1]	−1.1 [−1.8 to 0.1]	−0.7 [−0.9 to −0.1]	0.75	−0.5 [−1.0 to 0.9]	−1.3 [−2.1 to −0.4]	0.02
BMD height z-score							
NoF	−0.9 [−1.6 to 0.3]	−0.6 [−1.2 to 0.6]	−1.4 [−2.0 to −0.7]	0.07	−0.9 [−1.2 to −0.6]	−0.8 [−2.3 to 0.7]	0.70
L2-4	0.1 [−0.6 to 1.2]	0.4 [−0.7 to 2.3]	0.1 [−0.7 to 0.9]	0.61	0.5 [−0.2 to 1.7]	0.0 [−1.4 to 0.7]	0.13
TB	0.2 [−0.4 to 1.0]	0.6 [−0.3 to 1.9]	−0.4 [−1.2 to 0.2]	0.05	0.3 [−0.3 to 1.1]	0.1 [−1.5 to 0.9]	0.24

Note: Bone mineral density (BMD), standard deviation score (SDS), neck of femur (NoF), lumbar vertebrae 2–4 (L2-4), total body (TB). Data presented as median and interquartile range.
[a]Pubertal hormone replacement therapy for hypogonadism.

and 0% respectively. The two PWS patients without hypogonadism who had DXA performed demonstrated normal BMD, both on age and height z-scores.

Serial DXA scans were available for 11 patients. Of these, six had received pubertal HRT between the first and last scans (median time between scans 2.8 [1.7–4.5] years, median treatment duration until final scan 1.0 [0.8–2.5] years), while three remained treatment-naïve until last scan and two patients had started pubertal HRT before their first scan. BMD parameters before and after HRT ($n = 6$) are included in Supporting Information S1: Figure 1.

History of fractures were documented in medical records for 18% (12/65; 6/37 females and 6/28 males) of all patients by last clinic visit, 17% (2/12) of whom were diagnosed with hypogonadism before sustaining a fracture.

4 | Discussion

There are few studies investigating puberty and bone mineral density in adolescents with PWS. In this retrospective study, the majority of adolescents with PWS demonstrated hypogonadism by transition to adult care, consistent with studies reporting high prevalence of hypogonadism in adults with PWS [2, 3]. This is despite two-thirds of the cohort entering puberty spontaneously (at any age), supporting the notion that hypogonadism in PWS is predominantly a disorder of incomplete puberty or pubertal arrest than complete gonadotropin deficiency [5, 22–24].

Males with PWS were found to have predominantly central, but also primary and mixed forms of hypogonadism, contrasting with past publications reporting predominantly testicular failure in males with PWS [2, 7, 25]. Lack of increase in testicular volumes despite advanced genital stage and/or pubertal testosterone levels, indicate mixed hypogonadism. Serial FSH and inhibin B levels may help detect evolving primary hypogonadism when there is failure of expected progression in testicular volume in adolescent males with PWS. Inhibin B may be one of the earliest markers of primary testicular failure in PWS, reported to decline between age 10–15 years with corresponding FSH rise [7]. As inhibin B was not ordered routinely for our cohort, it is possible some patients diagnosed with central hypogonadism had coexisting early stages of testicular dysfunction, not detectable on gonadotropin levels alone. Future studies may examine the role of inhibin B as an early marker for hypogonadism in PWS and the optimal threshold for initiating treatment.

In our female paediatric cohort, hypogonadism was solely central in aetiology, also differing from literature illustrating occurrence of primary ovarian dysfunction in female adolescents and adults with PWS [3, 25, 26]. AMH was inconsistently measured in our cohort, thus not analysed. While low or undetectable inhibin B levels may indicate early stages of ovarian failure [26], other studies have found inhibin B within normal ranges in adolescent females with PWS [23]. In contrast to males, the correlation between inhibin B and FSH in females with PWS remains unclear [7, 26, 27]. In our female cohort PWS, FSH was mildly elevated in some but none met the ≥ 25 IU/L threshold for primary ovarian failure [28]; most were accompanied by pubertal E2 levels, which may be elevated by

aromatisation in adipose tissue with concomitant obesity [29]. It has been proposed that females with PWS have a weaker FSH response due to greater negative feedback by inhibin B than in males [26]. Further research on the utility of AMH and inhibin B for detecting primary ovarian failure onset in adolescent PWS patients is warranted. It is also postulated that ovarian dysfunction occurs more gradually than testicular failure in PWS, which may explain the absence of overt primary hypogonadism in our younger adolescent cohort contrary to adult women with PWS [3, 25]. Slower progression of gonadal failure in females with PWS than males may also explain reports of pregnancies in females with PWS while no males with PWS has ever been recorded to have fathered a child [6]. Some authors propose that the aetiology of hypogonadism in PWS cannot be determined before age 20 years [25]. The relative contribution of obesity in functional hypogonadotropic hypogonadism is unclear, but likely to be a minor component.

In females, Tanner staging was less frequently documented after pubertal onset. This may be attributed to difficulty in assessing breast development in context of concomitant obesity or limiting examination out of respect for patients. However, considering some participants had regression in breast development and were found to have pubertal arrest after entering puberty spontaneously at a normal age, infrequent staging may miss the onset of hypogonadism. While lack of increase in testicular volume can signify evolving primary gonadal dysfunction in males, there is no equivalent bedside parameter in females. Hormone assays and pelvic ultrasound form important adjuncts to clinical pubertal assessment in females with PWS. A Scottish paediatric study [27] found 52% of males > 13 years old with PWS received testosterone therapy while only 21% of females > 14 years old with primary amenorrhoea started oestrogen therapy. Although the percentage of males treated with testosterone was similar in our cohort, 80% of female patients with hypogonadism in our cohort were treated with oestrogen replacement, highlighting the clinical practice variability at different centres. While it has been suggested to treat hypogonadism in PWS at a physiological age [6, 18], applying this in practice is difficult, as puberty may begin spontaneously and clinicians often need to wait until mid-pubertal stage for clinical signs of stalled puberty or biochemical changes to diagnose hypogonadism. However, even those treated did not have advanced clinical pubertal stage by last visit, which may suggest clinician reluctance to escalate doses appropriately through adolescence. This mirrors adult data demonstrating undertreatment of hypogonadism as a common occurrence due to behavioural concerns [2].

At our centre, DXA is clinically indicated for hypogonadism and performed at endocrinologist discretion, leading to insufficient BMD data in PWS without hypogonadism as a control group in this retrospective study. A Dutch study demonstrated significant BMD decline in PWS from age 11 in females and 14 years in males, yet mean TB and lumbar spine BMD SDS remained above −1.0, not dissimilar to our cohort's median height and age z-scores [18]. However, a subsequent study showed 15% of young adults with PWS at adult height (mean age 17.2 years) have TB BMD < −2.0 SDS, consistent with our findings, while also demonstrating that TB BMD in their cohort was significantly lower compared to healthy peers [17]. Although not a site traditionally preferred in paediatrics, the proximal femur is an alternative when reference data is available [30]. Typically, the NoF site reaches peak BMD earlier in adolescence than in the lumbar spine. In contrast, our PWS cohort demonstrated lower age and height z-scores for BMD at NoF than for the L2-4 region. Given scoliosis is associated with PWS and artefacts from scoliosis surgery can artificially raise TB and L2-4 BMD, the NoF region may play a role in assessing BMD in this context [31, 32]. Longitudinal data will help determine potentially differential BMD accrual throughout the body in the PWS population and its relationship to scoliosis surgery. While the trajectory of BMD on HRT appeared better corrected for height than age in our cohort, due to the small numbers, we were unable to conclude whether BMD on HRT is better corrected for height than age. We were also not able to assess for the effect of GH therapy on BMD in our PWS cohort as all but one of the patients who had DXA were treated with GH therapy. A large paediatric retrospective study showed GH therapy improved lumbar BMD [13]. On the other hand, another randomised controlled trial in PWS patients found GH alone did not protect young adults with hypogonadism from BMD decline after achieving adult height, but pubertal HRT improved BMD, independent of GH therapy [17].

Behavioural/psychiatric issues reported were not found to be associated with pubertal HRT in either sex in this study. Also reassuringly, the proportion of males with behavioural challenges remained unchanged after testosterone replacement. However, selection bias is possible if HRT was not initiated in those with severe behavioural concerns at baseline. Additionally, if testosterone doses were not increased appropriately with pubertal induction, it may diminish differences between treatment groups. Supporting our findings, a Japanese prospective study also demonstrated an improvement in BMD and lean body mass with testosterone replacement in adult males with PWS without change in aggressive behaviour [16]. Standardised clinical care and titration protocols may assist in overcoming the clinician reluctance in escalation of treatment and facilitate further data collection towards evidence-based care.

Consistent with the literature, we also documented high prevalence of premature adrenarche in children with PWS, speculated by some to arise from premature development of the zona reticularis [22, 33]. Precocious puberty is also a paradoxical but recognised occurrence in PWS, as seen in three females in our cohort [34]. In our male cohort, 75% had cryptorchidism, but evidenced by published histological data of the testes at surgery, this may not be associated with the development of hypogonadism in PWS males [35].

Inherent to the retrospective design of this study, limitations include missing data (especially in DXA scans and female pubertal staging), variable timing of hormone assays and incomplete temporally corresponding staging and biochemistry. Diagnosis on the aetiology of hypogonadism also depended on clinician documentation rather than dynamic testing. Small subgroup analyses were limited by insufficient power.

5 | Conclusions

Most adolescents with PWS demonstrate evolving hypogonadism by the time of transition to young adult care, usually after spontaneous pubertal onset at a normal age. However, there

remains a reluctance to diagnose and treat hypogonadism in PWS despite its presence in the great majority by young adult life. The optimal time to intervene for long term bone and psychosocial health is unclear. Further studies are required to determine the best biomarker for early and timely diagnosis and treatment of hypogonadism in PWS. While lack of significant adverse behavioural/psychiatric changes with pubertal HRT in our cohort is reassuring, there remains the need for a standardised protocol for the use of pubertal HRT in adolescents with PWS.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Author Declaration Form Clinical Endocrinology. **Figure S1:** BMD z-scores in hypogonadal patients before and after pubertal HRT. **Table S1:** Modalities of pubertal hormone replacement therapy (HRT) used in PWS patients with hypogonadism. **Table S2:** Potential adverse events and adherence issues with pubertal hormone replacement therapy.