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Hypothalamic and Gonadal Components of Hypogonadism in Boys with Prader-Labhart-Willi Syndrome

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Context: The specific form of hypogonadism in Prader-Labhart-Willi syndrome (PWS), central or peripheral, remains unexplained.

Objectives: The objectives of this study were to investigate the cause of hypogonadism in PWS and determine whether human chorionic gonadotropin (hCG) treatment can restore pubertal development.

Design: This was a clinical follow-up study, divided into two samples, over a duration of 1.5 and 4.5 yr.

Patients: Eight male infants and six peripubertal boys (age at start of observation, 0.06–0.93 and 8.1–10.8 yr, respectively) with genetically confirmed PWS were studied.

Intervention: hCG (500–1500 U twice weekly) was given from age 13.5 yr to the present.

Main Outcome Measures: Serum FSH, LH, inhibin B, and testosterone levels and pubertal development were the main outcome measures.

Results: Infants with PWS presented normal LH (2.3 ± 0.7 U/liter) and testosterone (2.5 ± 0.9 nmol/liter) levels (mean ± SEM at 5 months) compared with the reference range. However, two thirds of the boys displayed cryptorchidism. Inhibin B levels were at the lowest level of the normal range and decreased significantly between infancy and puberty (at 13 yr, 72 ± 17 pg/ml), whereas FSH secretion increased (9.9 ± 2.6 U/liter). Pubertal maturation stopped at an average bone age of 13.9 yr. hCG therapy increased testosterone (11 ± 2 nmol/liter) and reduced FSH (at 16 yr, 1.1 ± 0.9 U/liter) levels. Testicular volume (5.6 ± 1 ml) and inhibin B (26.5 ± 11.9 pg/ml) remained low.

Conclusion: Children with PWS display a specific form of combined hypothalamic (low LH) and peripheral (low inhibin B and high FSH) hypogonadism, suggesting a primary defect in Sertoli and/or germ cell maturation or an early germ cell loss. hCG therapy stimulates testosterone production and virilization. (***J Clin Endocrinol Metab* 91: 892–898, 2006**)

FIRST DESCRIBED IN 1956, the Prader-Labhart-Willi syndrome (PWS) is a complex neurodevelopmental disorder characterized by short stature, disturbed body composition, hypogonadism, cryptorchidism, and cognitive defect with extreme muscular hypotonia in the neonatal period (1–3). PWS is a rare syndrome (prevalence, 1:15,000–25,000) (4, 5), and diagnosis is often delayed until after infancy. It is caused by an absence of expression of paternally active genes in the PWS critical region on chromosome 15q11.2-q13.

Hypogonadism leading to hypogenitalism and early pubertal arrest is a central feature of PWS and is generally attributed to hypothalamic dysfunction. In male patients with PWS, some degree of gonadotropin deficiency was suggested by several reports of reduced gonadotropic function (3, 6–11) in the presence of prepubertally normal testicular histology (12–14). In addition, some patients may have primary hypogonadism with elevated basal and stimulated gonadotropin levels (13, 15–22) as well as abnormalities in testicular histology (6, 15, 17). These findings are usually interpreted as gonadal failure due to cryptorchidism and/or surgical intervention and indicate that gonadotropin deficiency is not complete in PWS (7, 20, 22). However, the absence of spermatogenesis was also described in descended testes (23), without indicating the origin of the testicular damage. The conflicting data on the pathophysiology of gonadal dysfunction in male individuals with PWS has still not been resolved.

Furthermore, it remains unknown to what extent GH deficiency contributes to impaired gonadal function. GH substitution was shown to potentiate the Leydig cell response to human chorionic gonadotropin (hCG) in patients with hypopituitarism (24, 25) or hypogonadotropic hypogonadism (26). Nevertheless, an arrest of gonadal development is observed in all boys at pubertal age despite otherwise efficacious GH treatment (27–30).

The aim of this study was to investigate the origin of hypogonadism in boys with PWS and to determine whether hCG treatment started at the time of pubertal arrest can restore Leydig cell function as well as pubertal development.

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Abbreviations: BA, Bone age; CA, chronological age; hCG, human chorionic gonadotropin; pub-PWS, pubertal PWS; PWS, Prader-Labhart-Willi syndrome.

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We examined the pituitary-testicular axis in male infants with PWS as early as the diagnosis was established, because gonadal stimulation in boys during the first months of life is associated with subsequent testicular maturation (31, 32) and is reduced in congenital hypogonadotropic hypogonadism (33).

Subjects and Methods

Design

In a clinical follow-up study, children with PWS were observed for an average of 1.5 yr (infants) and 4.5 yr (peripubertal boys) in an outpatient center specializing in pediatric endocrinology (Institute Growth Puberty Adolescence, Zurich, Switzerland).

Study subjects

Infant group. To assess the function of the gonadal axis in PWS during infancy, eight boys with PWS (infant-PWS) were enrolled as soon as diagnosis was established and genetically confirmed (mean age, 5.2 months; range, 1–11 months). For one boy diagnosed immediately after birth, no biochemical data were available beyond the first 6 months of life. Therapy with daily injections of recombinant human GH (Genotropin, Pfizer, Duebendorf, Switzerland; 6 mg/m^2·wk, corresponding to ~0.025 mg/kg·d) was started in two patients at the age of 6 months and in three patients at the age of 12 months. Two patients were administered GH only after the age of 18 months. Data collected during GH treatment are specifically marked in Fig. 1. For ethical reasons, no age-matched control group consisting of healthy children was available. The hormonal data were therefore interpreted with the aid of normal ranges for children as reported below.

Peripubertal group. To assess gonadal function in males before and during puberty, data for six peripubertal boys with genetically confirmed PWS (pub-PWS) were retrospectively analyzed every 6 months from age 10–17 yr (in one early maturing boy from the age of 8.1 yr on). They were all receiving long-term daily treatment with recombinant human GH (6–7 mg genotropin/m^2·wk, corresponding to ~0.025–0.031 mg/kg·d), and their height and IGF-I levels had normalized. At a bone age of 13–16 yr, pubertal development and androgenization were sustained by administering hCG injections (Pregnyl, Organon, Pfaeffikon, Switzerland). For bone ages from 13–13.5 yr, 500 U hCG twice weekly, im, was administered; for bone ages from 13.6–14.5 yr, 1000 U twice weekly, im; and for bone ages exceeding 14.5 yr, 1500 U twice weekly, im, was administered.

This study was approved by the ethics committee of University Hospital of Zurich, and informed consent was obtained from the parents.

Clinical assessment

Height and weight were measured in all children using standard techniques (34), and pubertal stage was assessed every 6 months by the first author as suggested by Tanner (27). Testicular volume was measured using a Prader orchidometer and was indicated as the mean of left and right testicular volumes. Bone age was determined by x-ray (35) at 12- and 6- to 9-month intervals in prepubertal and pubertal boys with PWS, respectively and was interpreted by the first author. For comparability with the intermediate examinations, bone age was linearly interpolated between the previous and the following bone age.

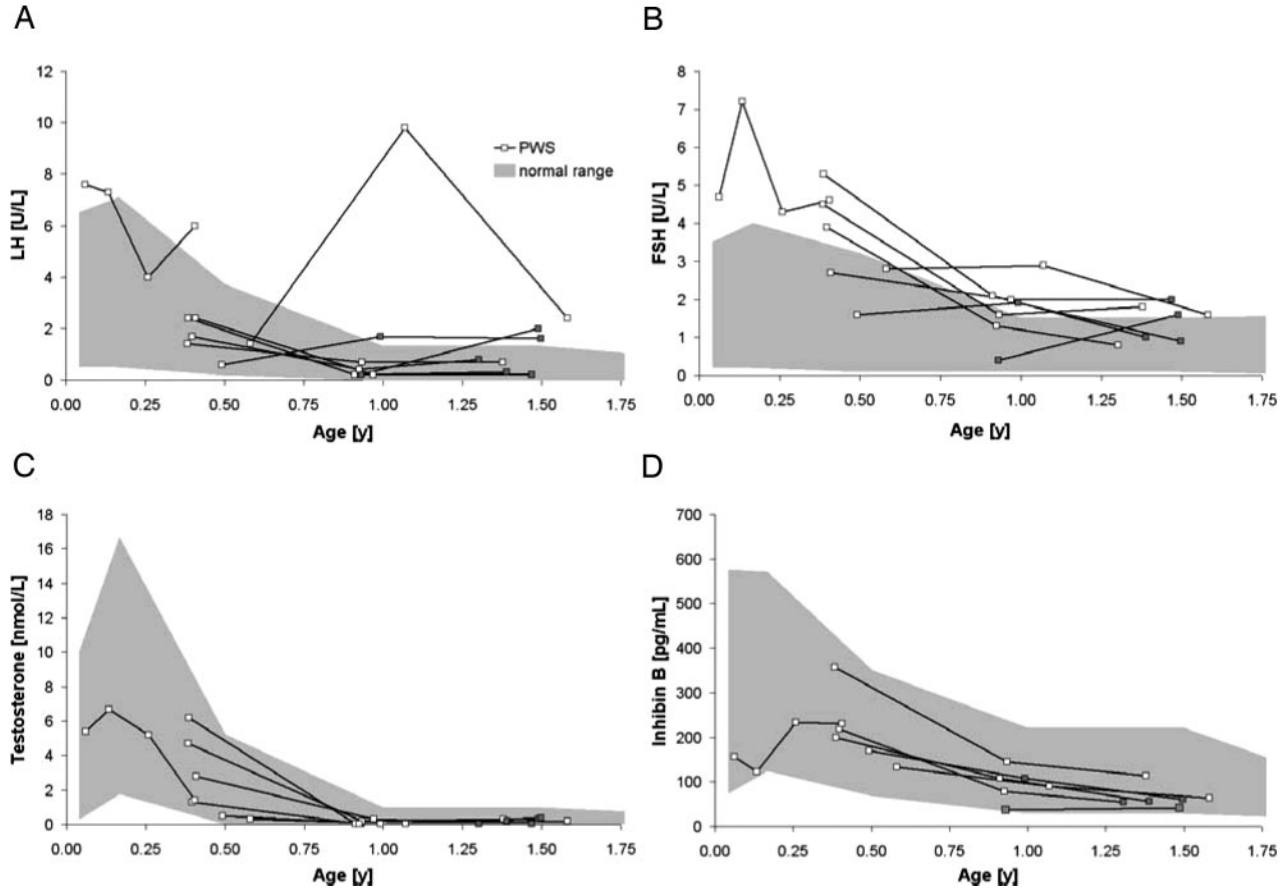

FIG. 1. A–D, Individual longitudinal levels of LH, FSH, testosterone, and inhibin B in male infants with PWS, before (□) or during (■) GH therapy. Reference ranges are marked with a *gray* background (36).

Hormone measurements

All hormone measurements are expressed in metric Systeme International units. Serum inhibin B was measured using a commercially available, double-antibody, enzyme immunoassay (Serotec, Oxford, UK) with a sensitivity of 7.8 pg/ml. The intra- and interassay coefficients of variation were less than 10%.

Serum LH and FSH were measured by a chemiluminescence immunoassay (Beckmann Access, Zurich, Switzerland) with a detection limit of 0.2 U/liter, and intra- and interassay coefficients of variation were less than 7%. The assay for LH had no cross-reactivity with hCG at a concentration of 500,000 U hCG/liter or with FSH at a concentration of 2000 U FSH/liter. In the FSH assay, the cross-reactivity of LH was 0.02% at a concentration of 2000 U LH/liter, and that of hCG was 0% at a concentration of 500,000 U hCG/liter.

Serum testosterone was measured by RIA (Cis Bio International, Gif-sur-Yvette, France) with a detection limit of 0.1 nmol/liter, and intra- and interassay coefficients of variation less than 8%.

The hormonal data of PWS children were compared with previously published age-dependent reference ranges in infants (36) or peripubertal boys (37), applying identical methods (inhibin B and testosterone in infants) or assays resulting in similar normal ranges for adult men as the methods used in our study, namely, for LH and FSH a fluoroimmunometric assay (DELFIA, Wallac/Perkin-Elmer, Turku, Finland) with detection limits of 0.06 and 0.05 U/liter, respectively, and for testosterone in peripubertal boys an RIA (Coat-a-Count, Diagnostic Products Corp., Los Angeles, CA) with a detection limit of 0.2 nmol/liter.

Statistical methods

All data were processed by GAS 5.0.19 (Institute for Medical Informatics, Zurich, Switzerland). Individual hormone profiles are shown in Figs. 1 (infants) and 2 (peripubertal boys); group data in the tables are presented as the mean ± SEM.

Endocrinological data usually show a skewed distribution and should be log-transformed before additional analysis, but our small sample did not allow for a reliable assessment of distribution. Nevertheless, we performed a log-transformation [log(x + 1)] of the hormonal data. Note that Manasco *et al.* (38) successfully applied a log transformation to FSH, LH, inhibin, and testosterone and obtained approximately normally distributed data with constant variance.

Seven of the eight infants in the group infant PWS had measurements taken at the ages of 5 (4–7), 12, and 18 months. The results obtained at 5, 12, and 18 months were compared by ANOVA for repeated measurements, allowing tests for changes in hormone levels between the ages of 5, 12, and 18 months (time factor) to be performed, and Greenhouse-Geisser corrections were applied. $P < 0.05$ was considered significant.

In peripubertal boys, measurements were taken at different points in time. To analyze the effects of hCG treatment, the difference between the mean of the first four measurements taken after beginning treatment and the mean of the last four measurements without treatment was calculated for each child on a log scale. The mean of the differences in means was then calculated, and a paired t test was performed to test significance. By exponentiating these quantities (the individual mean differences and the mean of all the mean differences), estimates of a post-treatment/pretreatment ratio was obtained for every hormone, which characterized the effect of hCG (Table 3).

Pearson correlations among the four hormones were calculated on a log scale for each measurement (infants) and each period (peripubertal boys). Due to the very small sample size, however, only correlations above 0.76 (infant PWS) or 0.82 (pub-PWS), were significant at the 0.05 level.

Results

Infants

The individual profiles of LH, testosterone, and inhibin B secretion were generally within the normal range (Fig. 1 and Table 1), except for increased FSH in five infants with PWS. Between 5 and 18 months of age, a clear decrease in the levels of FSH, testosterone, and inhibin B (time factor in the ANOVA, $P < 0.0001$) and a trend ($P = 0.08$) for a decline in LH concentration were observed (Table 1).

During the study, there were no significant differences in hormone levels between PWS boys with spontaneous descent of testes or with cryptorchidism or orchidopexy, although testes were not completely descended in four infants with PWS up to the 12th month of life (one infant with unilaterally and three with bilaterally maldescended testes), and in three infants up to the 18th month (one infant with unilaterally and two with bilaterally maldescended testes).

There were no significant associations between hormones in infants with PWS.

Peripubertal boys

Onset of puberty. In prepubertal boys with PWS, bone age (BA) was slightly advanced (Table 2); the mean difference between BA and chronological age (CA) was 1.22 yr (range, 0.3–2.4), whereas this was no longer found after pubertal arrest [mean difference (BA minus CA), 0.33 yr; range, −0.9 to 1.6]. Testicular volume spontaneously increased at the CA of 11.2 yr (BA, 12.5 yr). At this age, pubic hair was adequately developed (median pubic hair stage 3; range, 1–3.5; data not shown). All boys with PWS had a history of cryptorchidism, but their testes were descended at that time after surgical

TABLE 1. Hormone levels (mean ± SEM) in infants with PWS and reference data

Group	Age (yr)	LH (U/liter)	FSH (U/liter)	Testosterone (nmol/liter)	Inhibin B (pg/ml)
PWS 5 months[a]	0.43 ± 0.03	2.3 ± 0.7	3.6 ± 0.5	2.5 ± 0.9	239.9 ± 34.4
No.	8	7	7	7	7
Normal range	0.33–0.66	0.2–3.7	0.1–3.2	0.05–5.2	70–350
PWS 12 months[a]	0.97 ± 0.02	1.9 ± 1.3	1.7 ± 0.3[b]	0.1 ± 0.0[b]	111.1 ± 21[b]
No.	8	7	7	7	7
Normal range	0.75–1.5	0.01–1.3	0.1–1.5	0.05–0.97	30–220
PWS 18 months[c]	1.44 ± 0.04	1.1 ± 0.3	1.4 ± 0.2[b]	0.21 ± 0.05[b]	91.9 ± 28.1[b]
No.	7	7	7	7	7
Normal range	0.75–1.5	0.01–1.3	0.1–1.5	0.05–0.97	30–220

Reference data and normal ranges are from Lahlou *et al.* (36).

[a] One infant with unilaterally; three with bilaterally maldescended testes.

[b] Significant decrease in hormones between the fifth and 18th months of life ($P < 0.0001$, by ANOVA for repeated measurements; refer to text).

[c] One infant with unilaterally; two with bilaterally maldescended testes at 18 months.

TABLE 2. Clinical and biochemical data of pre- or pubertal children with PWS before and during hCG therapy compared with reference data

	CA (yr)	BA (yr)	Tvol (ml)	LH (U/liter)	FSH (U/liter)	Testosterone (nmol/liter)	Inhibin B (pg/ml)
Prepubertal stage							
PWS[a]	10.1 ± 0.4	11.3 ± 0.3	1.8 ± 0.2	0.2 ± 0.1	2.4 ± 0.4	0.7 ± 0.1	58.5 ± 5.2
No.	6	6	5	6	6	6	5
Normal range	6.7–12.4, Tanner 1		1–3	0.05–0.99	0.25–2.55	0.2–0.9	35–182
Pubertal arrest							
PWS[a]	13.5 ± 0.3	13.9 ± 0.3	4.0 ± 1.0	1.2 ± 0.6	9.9 ± 2.6	2.3 ± 0.9	71.8 ± 16.5
No.	6	6	6	6	6	6	6
Normal range	10.6–15.5, Tanner 2		3–11.6	0.11–2.97	0.07–4.39	0.2–13.4	62–338
6 months after onset of hCG therapy							
PWS[b]	14.0 ± 0.3	14.4 ± 0.4	5.0 ± 0.6	0.2 ± 0.8	1.8 ± 0.7	7.3 ± 1.4	41.5 ± 10.8
No.	6	6	6	6	6	6	6
Normal range	11.7–15.8, Tanner 3		5.4–15.0	0.51–5.42	0.94–9.68	0.9–21.2	78–323
>1.5 yr during hCG therapy							
PWS[c]	15.9 ± 0.1	15.6 ± 0.5	5.6 ± 0.8	0.2 ± 0.1	1.1 ± 0.9	11.4 ± 2.0	26.5 ± 11.9
No.	4	4	4	4	4	4	3
Normal range	12.8–18.0, Tanner 4		10–23	1.11–5.89	1.98–6.88	7.7–26.5	67–304

Tvol, Testicular volume. Reference data and normal ranges are from Andersson *et al.* (37).
[a] One boy with cryptorchidism and testicular descent during hCG; all other PWS children after surgical correction of cryptorchidism.
[b] hCG dose, 1333 ± 211 U/wk in the midpubertal phase.
[c] hCG dose, 2250 ± 250 U/wk in the late pubertal phase.

correction, with the exception of one boy with impalpable testes.

FSH started to rise after the CA of 9.3 yr (BA, 10.5 yr; data not shown), before the clinical appearance of pubertal signs (testicular volume, <3 ml), and reached clearly elevated levels at pubertal arrest, with a mean CA of 13.5 yr (Fig. 2B and Table 2). Pubertal arrest was evidenced by testicular volume remaining stable at about 4.0 ml, lack of an additional tes-

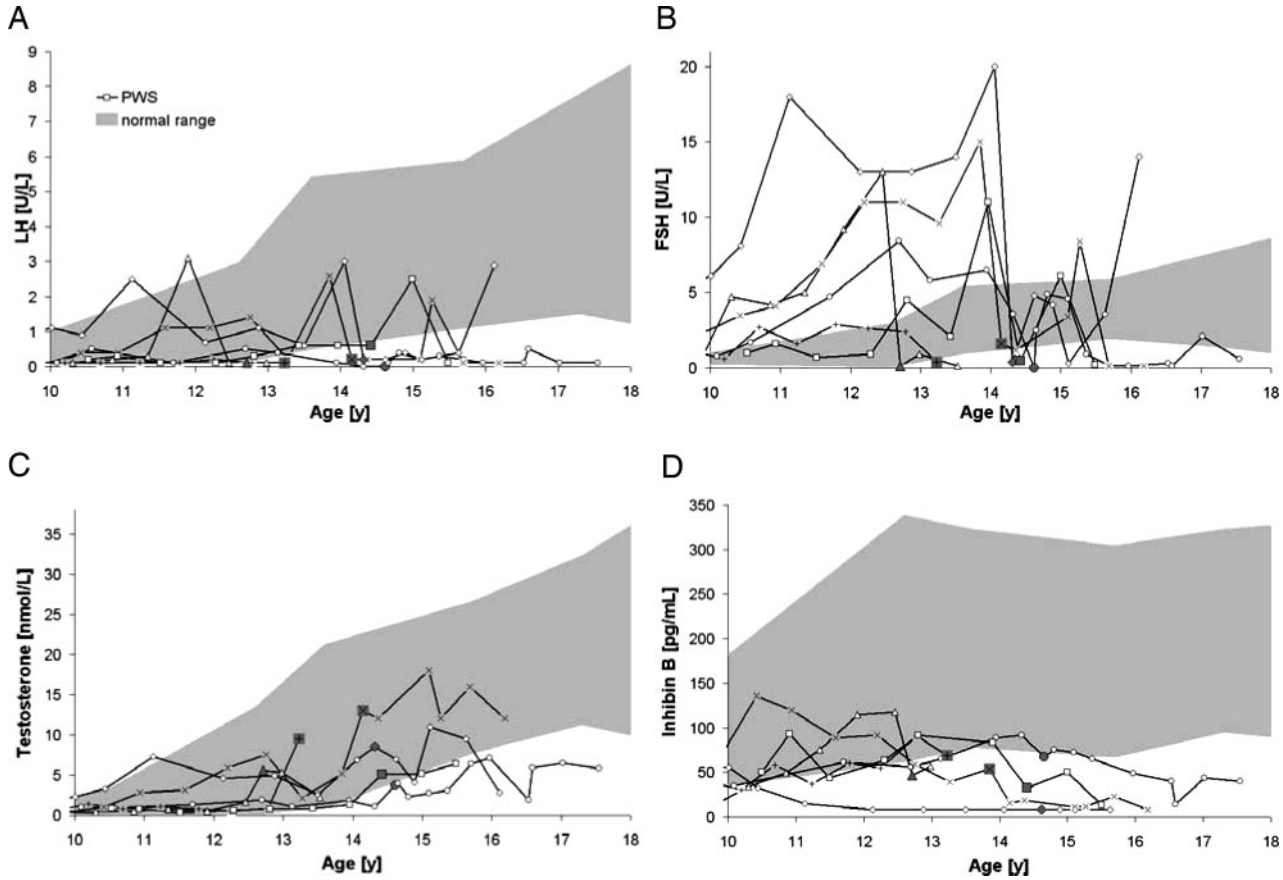

FIG. 2. A–D, Individual longitudinal levels of LH, FSH, testosterone, and inhibin B in peripubertal boys with PWS (□ and ○; X, designates individual patients separately). The first control during hCG treatment is marked in *gray*. Reference ranges are marked with a *gray* background (37).

tosterone increase (2.3 ± 0.9 nmol/liter; Fig. 2C), and arrest of bone maturation at an average BA of 13.9 yr (Table 2). At this time, pubic hair was fully developed in most boys (median pubic hair stage 5; range, 3–5). Inhibin B levels (Fig. 2D) were below the normal range in most boys with PWS after the age of 12 yr. LH and testosterone levels were in the lower normal range up to the age of about 13 yr (Fig. 2, A and C, and Table 2). During this period, LH was correlated with testosterone (pub-PWS: r = 0.86: $P < 0.05$) and FSH (pub-PWS: r = 0.86; $P < 0.05$).

Effects of hCG treatment

hCG treatment was started after pubertal arrest was evident, at a mean BA of 13.9 yr, and induced significant changes in all boys with PWS (Fig. 2). Testosterone increased 2.8-fold (Table 3), but remained in the lower normal range (Fig. 2C and Table 2); after the age of 15 yr, testosterone was clearly decreased in three of four boys. FSH dropped 3-fold in all patients (Table 3), below the normal range (Fig. 2B). LH was suppressed due to hCG therapy. Rebounding of FSH and LH levels indicated the need to increase the dose of hCG (Fig. 2, A and B). Clinical signs of androgenization improved during hCG treatment, *e.g.* deepening of voice and genital development to adult size, without adverse side effects concerning sexual or social behavior. However, there was no correlation between hCG dose and testosterone levels. Testicular volume slightly increased, but remained subnormal. Inhibin B remained well below the normal range (Table 2 and Fig. 2D).

Discussion

In the present study we longitudinally analyzed levels of the hormones of the pituitary-testicular axis in boys with PWS during infancy and puberty. According to our data, at the age of 5 months infants with PWS have normal LH and testosterone and slightly elevated FSH levels, revealing sufficient gonadotropic stimulation and normal Leydig cell function during infancy. Inhibin B levels are significantly decreased in PWS from infancy onward, suggesting a primary testicular defect affecting the tubular compartment. This decrease in inhibin B is associated with increased FSH, but not LH, secretion. Midpubertal LH levels do not rise, and pubertal maturation stops. hCG therapy promotes pubertal development through an increase in serum testosterone levels and reduces FSH levels, whereas inhibin B secretion does not increase. These findings question the traditional assumption of a hypothalamic defect as the unique cause of hypogonadism in PWS and imply that there is an additional important peripheral defect in gonadal development at puberty.

TABLE 3. Hormonal changes induced by hCG treatment in boys with PWS, expressed as ratios after/before hCG treatment (refer to *Subjects and Methods*)

Parameter	Patient no.						Median	*P*
	1	2	3	4	5	6		
LH (U/liter)	0.97	0.69	0.57	1.21	0.68	1.17	0.85	0.25
FSH (U/liter)	0.49	0.31	0.17	0.65	0.16	0.47	0.33	0.005
Testosterone (nmol/liter)	1.67	2.51	1.5	6.63	2.87	4.32	2.84	0.006
Inhibin B (pg/ml)	0.95	0.25	1	1.19	0.61	0.42	0.65	0.14

The levels of FSH, LH, and testosterone in PWS infants were well within the normal range. Because in most infants with PWS, the diagnosis was made only after the expected peak of gonadotropin secretion, which occurs during the second month of life, early postnatal gonadotropin secretion could not be analyzed in most of our patients. However, one infant with complete testicular descent was nevertheless investigated from the first month on and displayed a fully normal gonadotropin surge. In addition, four boys at the age of 4 months showed serum testosterone levels compatible with a possible residual elevation after the postnatal gonadotropin peak. In contrast, inhibin B levels gradually decreased in the presence of normal or even increased FSH levels. These data suggest that the formerly assumed gonadotropin deficit in infants with PWS is not complete and, above all, does not involve FSH secretion.

The findings in our patients with PWS differ from the situation in infants with hypogonadotropic hypogonadism (33) or cryptorchidism as well as from infants with Klinefelter's syndrome. In infants with prenatal diagnosis of Klinefelter's syndrome, levels of FSH and inhibin B were normal, but testosterone was decreased (36). In boys with cryptorchidism, hormonal data, including inhibin B, were in the normal range (39, 40). The normal androgen levels observed in the present study during infancy explain neither the high incidence (67%) of cryptorchidism in boys with PWS nor the hypogenitalism found in other children with the syndrome. The lack of abdominal pressure in the presence of the extreme muscle hypotonia might be an alternative explanation for disruption of testicular descent in PWS (41).

Bone maturation before puberty is generally slightly advanced in children with PWS due to obesity-related endocrine alterations (42, 43), with a slight elevation of adrenal androgens. As a consequence, boys with PWS entered puberty at an adequate or even early age with normal levels of LH and testosterone, but bone maturation and testicular development slowed down after BA 13 yr, as it is typical for hypothalamic hypogonadism (44).

hCG therapy was started when pubertal arrest was recognized. Leydig cells responded to hCG therapy. Testosterone rose, although levels remained in the lower normal range, and LH secretion decreased. In the long term, testosterone levels dropped below the normal range again and did not correlate with the dose of hCG. This therapy induced complete testicular descent in one boy with undescended testes. However, testicular volume, on the average, did not increase to more than 6 ml, probably because of the lack of spermatogenetic activity (45, 46). The steep decline in FSH levels during hCG treatment confirmed a previous anecdotal report (18) and was similar to that found in boys with cryptorchidism after hCG administration. It was explained to be mediated by the increase in testosterone secretion and subsequent aromatization to estrogens (39). These data suggest that in PWS, the hypothalamic-pituitary negative feedback of the FSH and LH axes works.

In contrast, levels of inhibin B were low not only during childhood, but were further decreased during puberty in our patients with PWS. It is assumed that during puberty in

healthy boys, high intratesticular testosterone levels activate germ cells and initiate inhibin B production (32, 37, 39, 47). In the present study inhibin B remained invariably decreased despite the significant rise of testosterone during hCG therapy. The lack of inhibin B response to hCG as well as the low basal inhibin B levels from infancy imply some form of Sertoli cell hypofunction, a primary defect of the tubular epithelium (32), and/or a disturbed interaction between Sertoli and germ cells. Cryptorchidism does not seem to be exclusively responsible for this damage, because inhibin B levels are normal in healthy boys with cryptorchidism (39, 40) and, in the infants of the present study, independent of testicular descent. Furthermore, the hypothesis of a primary gonadal defect in PWS is substantiated by the findings of absent germ cells in gonadal biopsies of descended testes of adult males with PWS (15) even in descended testes (23).

Nevertheless, there is no doubt that the hypothalamic defect is responsible for the absence of the pubertal LH rise in PWS. This suggests that the two axes (FSH and LH) are dissociated in this syndrome at puberty, with FSH reflecting a peripheral and LH a central hypogonadism.

hCG treatment and subsequent testosterone increase were well tolerated without behavioral side effects. In male adolescents with PWS, a substitution with sex hormones seems mandatory to induce normal pubertal development, prevent osteoporosis, and improve body composition. A typical male appearance is important to avoid additional stigmatization due to high voice, gynecomastia, and other signs of eunuchoidism. Because testosterone deficiency in males with PWS further aggravates the inborn decrease in lean mass, it represents an additional factor for reducing energy expenditure and enhancing fat accumulation. Hypogonadism in PWS children should be treated at puberty. hCG administration can be controlled and adapted on a short-term basis, preventing significant fluctuations in testosterone levels. However, Sertoli cell/tubular function is not restored by this treatment.

In summary, children with PWS display a specific form of combined (central and peripheral) hypogonadism involving deficiency of LH and testosterone secretion at puberty and primary damage of the tubular compartment, resulting in reduced inhibin B levels and FSH elevation. Furthermore, the response of testosterone to hCG therapy is inadequate. This condition may be caused by a defect in Sertoli cell maturation and/or germ cell depletion. In adolescents with PWS, hCG therapy ensures male appearance without side effects, but testicular volume remains subnormal, and fertility is not achieved.

Acknowledgments

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